Massoud Mahmoudi
Editor

Allergy and Asthma

Practical Diagnosis and Management

Second Edition

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To memory of my father Mohammad H. Mahmoudi and to my mother Zoherh, my wife Lily, and my sons Sam and Sina for their support and encouragement.

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Chapter 1
Introduction to Immune System

Massoud Mahmoudi

The human body is constantly exposed to a variety of external elements. These foreign materials find their way into the body via inhalation, ingestion, and penetration. As we inhale to get our required oxygen from the air, we also inhale fumes, smoke, dust, pollens, particles, molds, bacteria, viruses, and their by-products. Another way we expose our bodies to foreign invaders is through trauma and injury. The system responsible to defend us against these foreign substances is our *immune system*, and our protective status, natural or acquired, is known as *immunity*. The two types of immunity are *innate immunity* and *acquired or adaptive immunity*.

Innate Immunity

Innate immunity is a natural immunity against microbes and other nonmicrobial substances that exist before exposure to these substances. The various components of the innate immune system are primarily activated by the recognition of a small number of molecular patterns that are present on nearly all pathogens. This system consists of various defensive mechanisms that work collaboratively to eliminate foreign invaders (Table 1.1). The first defensive tool of this system is the skin, a physical barrier that protects the body from the invasion of organisms. Bodily secretions that moisturize the skin and mucous membranes also play a role in preventing

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Table 1.1 Features of innate and adaptive immunity

Features	Innate immunity	Adaptive immunity
Host memory to foreign antigens	–	+
Specificity	–	+
Barriers to foreign antigens: skin, mucous membranes, bodily secretions	+	–
B-cell and T-cell participation	–	+
Cell-mediated immunity	–	+
Antibody production	–	+
NK cells	+	–
Phagocytosis	+	–

colonization of bacteria, by washing them off or destroying them. For example, tears wash the eyes, remove the loose foreign bodies, and may destroy some organisms by enzymatic reactions; sweat contains lactic acid that has an acidic pH, creating an unsuitable environment for most organisms; and gastric juices are acidic and can destroy acid-labile organisms. In addition to skin and bodily secretions, several other defense strategies, such as coughing, sneezing, or ciliary movements of the respiratory epithelium, help remove foreign objects and organisms.

Another major mechanism of the innate immune system by which the body gets rid of organisms and foreign invaders is phagocytosis. This is an engulfing mechanism that host cells use to surround, engulf, and lyse materials with various hydrolyzing enzymes. The cells assigned to perform such activity are termed *phagocytes* and consist primarily of neutrophils and macrophages. Neutrophils are multilobed nucleated cells originating from the bone marrow, where they mature and stay for a short while before being released into the circulation. They contain various granules that carry destructive enzymes and chemical substances that can destroy engulfed organisms. Macrophages are derived from monocytes, which form in the bone marrow and are released into circulation. These kidney-shaped nucleated cells comprise 1–6 % of all nucleated blood cells. After 1 day of circulation in the blood, they move to various tissues; in the tissues, they are named macrophages or histiocytes. Macrophages of different tissues are named differently, although their basic mechanisms are the same. For example, the ones that reside in liver and lung tissues are known as Kupffer cells and alveolar macrophages, respectively.

Natural Killer Cells

Viruses can infect the host cells and replicate causing general infection. To prevent viral replication, the body needs to intervene and remove such infected cells. Natural killer (NK) cells are large granular lymphocytes that do just that; they are members of the innate immune system, and they function by recognizing and killing the infected cells. NK cells also activate macrophages to kill phagocytosed microbes. NK cells have granules that contain *perforin* and *granzymes*. Perforins create pores in target cells, and granzymes cause apoptosis of the target cells.

How Are Virus-Infected Cells Recognized?

Recognition of virus-infected cells relies on two sets of receptors, the *inhibitory* and *activating* receptors on NK cells. Inhibitory receptors bind to class 1 major histocompatibility complex (MHC) receptors found on most normal cells; this inhibits activation of NK cells and therefore prevents the killing of normal host cells. But virus-infected cells decrease class 1 MHC expression, thereby eliminating the inhibitory signal sent to the NK cells. Because NK cell activation is now unopposed, the activating receptors can bind to and kill the virus-infected cells.

Complement System

The complements are a group of plasma proteins. They are an important part of the innate immune system and engage in the destruction of microbes via three different pathways: *classical*, *alternative*, and *lectin* pathways. Complement activation causes inflammation and lysis of invading microorganisms (see Chap. 23).

Adaptive Immunity

Adaptive immunity, also known as acquired immunity, serves as an organism-specific protective system. The components of this immunity retain memory of specific exposures to deter against subsequent invasion of the same organisms (Table 1.1).

There are two types of adaptive immunity: *humoral immunity* and *cell-mediated immunity*.

Humoral Immunity

This system is responsible for the production of antibodies against bacteria. The major players of this system are *B cells*, a class of lymphocyte.

B Cells

B cells mature in the *bursa* of *Fabricius* in birds and in the fetal liver and bone marrow in humans. Pluripotent stem cells differentiate in the bone marrow and give rise to lymphocytes and other cells (Fig. 1.1). B cells comprise 10–15 % of lymphocytes. The released mature B cells have a short lifespan of several days. Upon invasion of bacteria, these cells are activated and undergo several cycles of division and proliferation, and they give rise to two types of cells, *memory* B cells and *effector* B cells or *plasma cells*. Memory B cells live for years. Their job is to remember the exposure to specific

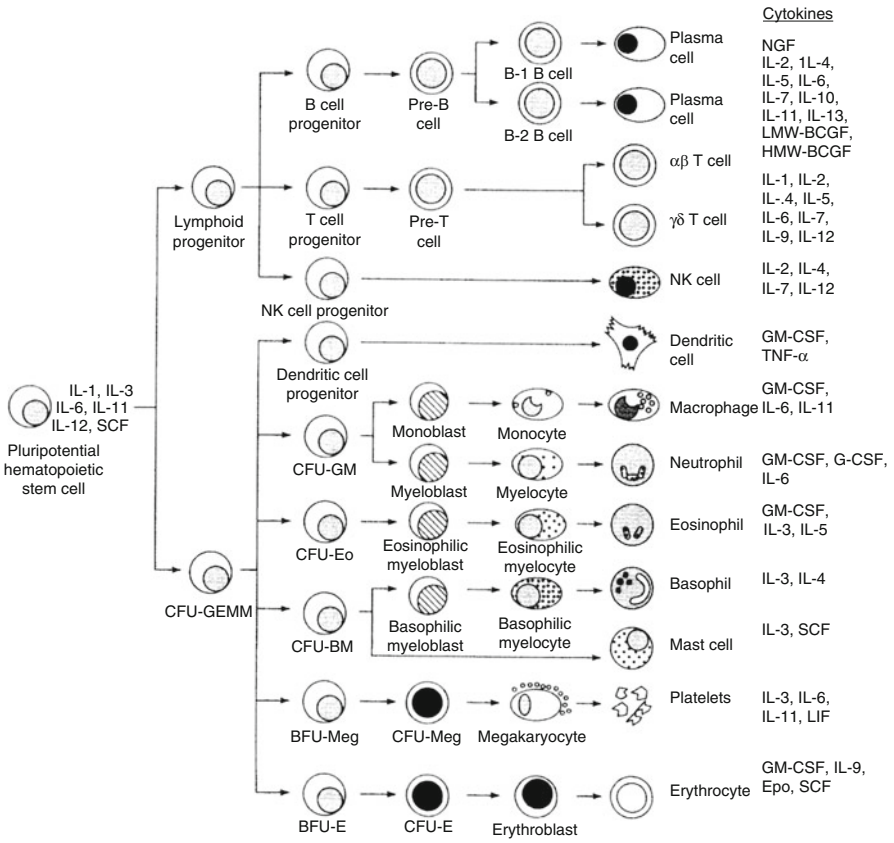

Fig. 1.1 Schematic differentiation of hematopoietic cells (Reproduced with permission, from Lewis and Harriman [10])

organisms and then in subsequent encounters to expedite the recognition of and antibody production against these organisms. The effector B cells are in charge of antibody or immunoglobulin production to fight against the invading bacteria. Mature B cells express immunoglobulins on their cell surface but do not secrete them, whereas effector B cells produce immunoglobulins in their cytoplasm and secrete them to their environments. The plasma cells survive for days to weeks to produce antibodies and die thereafter, whereas memory cells survive for many years.

Cell-Mediated Immunity

This system is responsible for recognizing and destroying intracellular microbes such as viruses, *Mycobacteria*, and *Leishmania*. The major players of this system are T cells. They encounter and destroy infected cells by either activation of macrophages that lead to destruction of phagocytosed microbes or by direct killing of the infected cells.

T Cells

These cells are "thymus derived"; their precursors are originated from the bone marrow but later they migrate to the thymus. In the thymus, T-cell precursor cells mature and learn to recognize self from nonself and are then released into the circulation as naive T cells. T cells represent 80 % of the lymphocytes in peripheral blood circulation. Like B cells, on exposure to antigen, naive T cells differentiate and give rise to effector and memory cells. Those that do not confront antigens eventually die by programmed cell death known as *apoptosis*. The two major subsets of T cells are the T helper cells, designated as CD4+ T cells, and cytotoxic or cytolytic T cells, designated as CD8+ T cells. These cells are involved in interacting with intracellular organisms, for example, infected cells (see section "Type IV: Cell-Mediated Hypersensitivity"). T cells express antigen-specific receptors known as T-cell receptors. There are two types of T-cell receptors; one type has α and β chains, Tαβ, and the other type has γ and δ chains, Tγδ. These receptors are antigen specific, and T cells only recognize those antigens that are presented by *antigen-presenting cells*. Antigen-presenting cells have proteins on their surfaces known as the *major histocompatibility complex* (*MHC*) that binds to the antigen. It is the combination of this complex and the antigen that is recognized by T cells.

In addition to T-cell receptors, many surface proteins are expressed on T lymphocytes with assigned functions. These receptors participate in various roles, such as antigen recognition and T-cell activation, among others.

Interaction of Antigens and Antibodies

We are vulnerable to invasion by millions of different antigens. Is our body prepared to defend and fight against such vast numbers of structurally different antigens? We have clones of B and T lymphocytes that have unique antigen receptors for specific antigens; on exposure and contact to an antigen, the specific lymphocyte clones are recognized and selected, *clonal selection*, by the antigen and are activated. This activation stimulates the lymphocyte clones to proliferate, *clonal proliferation*, and produces high numbers of the same lymphocytes; this is called *clonal expansion*. In the next step, some of these lymphocytes differentiate to two groups of cells; one is the group capable of producing antibodies, the effector B cells, and the other group is cells that do not produce antibody but remember the antigen exposure and live for many years, also known as memory B cells. A similar process occurs with T cells. Some T cells become effector T cells and combat pathogens; others become memory T cells to remember the exposure in case of future infection. The nondifferentiated cells eventually end up dying (apoptosis).

B Cells: Responsible for the Production of Antibodies

Antibodies, also known as immunoglobulins, are glycoprotein molecules with a distinct structure (Fig. 1.2). Each molecule is made of an identical pair of heavy chain molecules held together by a disulfide bond and an identical pair of light chains. A disulfide bond also holds the light and heavy chains together. Each heavy and light chain contains a variable region (V) and a constant region (C). The variable regions of heavy and light chains form a unique antigen-binding site. Each antibody molecule has two such sites. Each antigen-binding site has three hypervariable regions that are complementary to the bound antigen. What makes each antibody unique is the structure of these hypervariable regions. These regions are also known as *complementarity-determining regions*, designated as CDR1, CDR2, and CDR3. The immunoglobulins are either membrane bound or secretory; the membrane-bound immunoglobulins act as receptors on B cells where they recognize a specific antigen. The immunoglobulins are produced by plasma cells, also known as B lymphocytes. Immunoglobulins are synthesized in the cytoplasm and stored in Golgi complexes. Immunoglobulin molecules are designated as *IgA*, *IgG*, *IgM*, *IgD*, and *IgE*. Each immunoglobulin molecule or isotype is unique in function and biological properties. The most common type of immunoglobulin, IgG, has subclasses of IgG1, IgG2, IgG3, and IgG4, each with unique biological properties. Immunoglobulin A also has two subclasses, designated as IgA1 and IgA2. Table 1.2 summarizes the features of immunoglobulins.

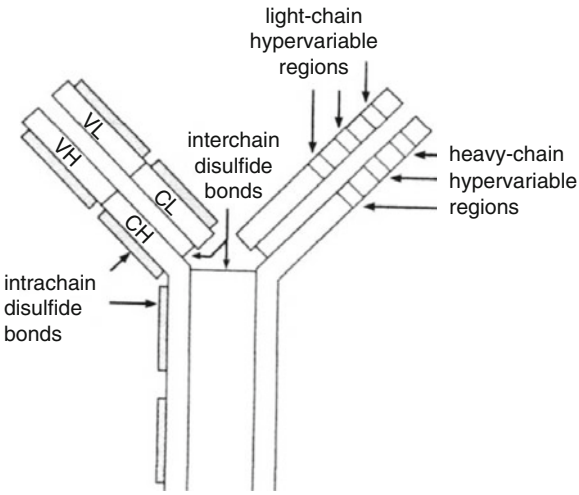

Fig. 1.2 Schematic depiction of an IgG molecule showing the approximate locations of the hypervariable regions (Reproduce with permission, from Parslow [11])

Table 1.2 Immunoglobulins: features and characteristics

Immunoglobulins (Ig)	Molecular weight (d)	Serum concentrations	Half-life (days)	Subclasses	Complement fixation	Placental transfer	Immediate hypersensitivity	Other characteristics/ functions
IgA	170,000 or 350,000 (secretory)	1.4–4 mg/ml	6	IgA1, 2	–	–	–	Involved in mucosal immunity
IgD	160,000	0–0.4 mg/ml	3	–	–	–	–	Membrane-bound antigen receptor of B-cell surface
IgE	180,000	17–450 ng/ml	2.5	–	–	–	+	Immediate hypersensitivity, defense against parasitic infection
IgG	160,000	8–16 mg/ml	23	IgG1, 2,3, 4	IgG 1, 2, 3	+	–	Involved in type II hypersensitivity
IgM	900,000	0.5–2 mg/ml	5	–	+	–	–	Membrane-bound antigen receptor of B-cell surface, involved in type II hypersensitivity

Autoimmunity

The role of our immune system is to defend against invading microorganisms and foreign antigens. The body is capable of differentiating between "self" and "non-self"; in other words, under normal conditions, the immune system does not react against self-antigens. This is the basis of *self-tolerance*. When self-tolerance is compromised, the immune system turns against itself; this response is the basis for autoimmune disease. Autoimmunity, such as in the case of Graves' disease, is related to an antibody against thyrotropin receptors or T-cell autoreactivity. To maintain self-tolerance, the autoreactive T or B cells need to be controlled by elimination or suppression to spare autoreactivity against self. When there is a defect in such a control system, upon activation, autoreactive T or B cells can cause tissue injury.

Genetic predisposition plays an important role in the development of autoimmune diseases. The genes involved are MHC or non-MHC genes. In addition, environmental triggers, infectious agents, and noninfectious triggers such as drugs and loss of regulatory cells may contribute to autoreactivity. Figure 1.3 summarizes the steps proposed in the pathogenesis of autoimmune diseases. CD4 Th1 cells play the central role of T-cell tolerance. Activated autoreactive CD4 Th1 cells are able to cause cell-mediated tissue damage; they can also induce CD8 cells and lead to tissue injury.

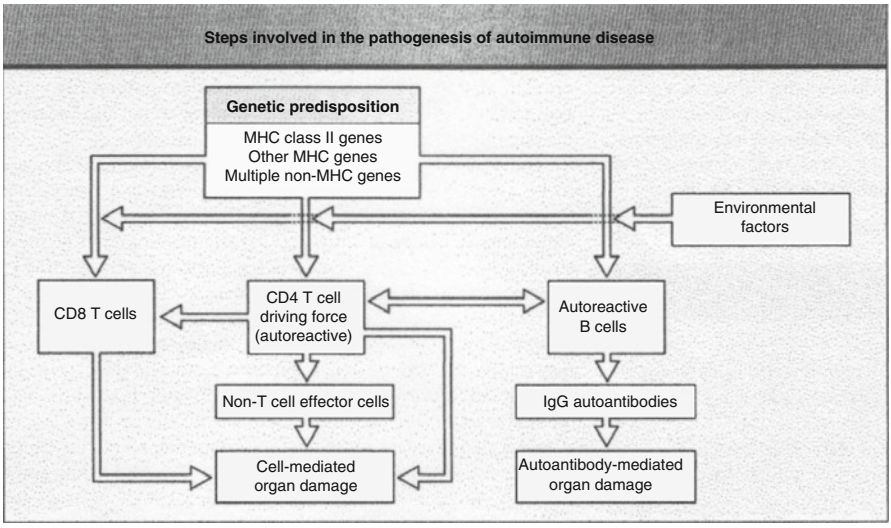

Fig. 1.3 Steps involved in pathogenesis of autoimmune diseases (Reproduced with permission, from Kotzin [5])

T Cell–Antigen Interaction

The steps leading to T-cell–antigen interaction are as follows:

1. Antigen-presenting cells, such as monocytes, macrophages, dendritic cells, or B lymphocytes, process foreign antigens to form peptides.
2. Peptide antigens bind to a complex of protein known as major histocompatibility complex (MHC), either MHC I or II.
3. The complex is later expressed on the surface of antigen-presenting cells.
4. There are two subsets of T cells: T helper cells, designated as CD4+ T helper cells, and cytotoxic or cytolytic T cells, designated as CD8+ T cells. CD4+ T cells recognize and bind to the antigen–MHC II complex, whereas CD8+ T cells recognize and bind to the antigen–MHC I complex of antigen-presenting cells.
5. The result of T-cell–MHC I complex interaction is the destruction of infected cells. The result of T-cell–MHC II complex interaction is activation of CD4+ T helper cells to promote further immune functions, such as providing stimulatory signals to B cells to produce immunoglobulins.

T-Helper-Cell Regulation

On exposure to antigens, naive T cells activate, proliferate, and then differentiate to T helper 1 (Th1) or T helper 2 (Th2) cells. Differentiation of activated cells to Th1 or Th2 effector cells depends on the presence of certain cytokines. For example, in the presence of interleukin 12 (IL-12), secreted by macrophages, activated T cells differentiate to Th1 cells, whereas in the presence of interleukin 4 (IL-4), produced by cells such as mast cells, activated cells differentiate to Th2 cells. When one pathway is under way, the other pathway is suppressed (Fig. 1.4). The cytokines involved in such regulations are interferon (IFN)-γ and IL-10. IFN-γ produced by Th1 cells not only promote Th1 differentiation but also inhibit the proliferation and production of Th2 cells. In contrast, IL-10 produced by Th2 cells blocks Th1 production.

Differentiation of activated cells to Th1 or Th2 effector cells also depends on the types of presenting antigens. For instance, intracellular bacteria such as *Listeria monocytogenes* and *Mycobacterium tuberculosis* or certain parasites stimulate Th1 response, whereas allergens and helminths trigger Th2 response.

Cells of the Immune System

Mast Cells

In addition to their role in defense against bacteria and parasitic invasion, mast cells play a role in allergic responses. These important effectors of hypersensitivity originate from the bone marrow and mature in tissues. There are two types

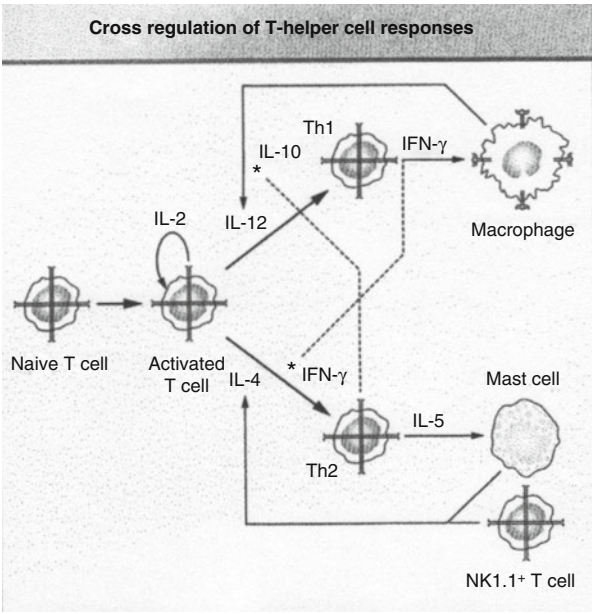

Fig. 1.4 Cross-regulation of T-helper-cell responses. Stimulation of naïve (TH0) T cells with antigen in the presence of IL-12 (macrophage produced) or IL-4 (produced by either NK1.1+ T cells or mast cells) leads to a Th1 or Th2 response, respectively. IFN-γ production by Th1 cells inhibits the activity of IL-4, thereby limiting Th2 production. IL-10 production limits Th1 responses by blocking the production of IL-12 by macrophages. Thus, the expression of Th1 and Th2 cytokines also serves to reinforce the production of similarly differentiated T cells (Reproduced with Permission, from Eager et al. [3])

of mast cells: the connective and the mucosal type. They have prominent nuclei and cytoplasmic granules that contain various mediators, some preformed and some newly synthesized. Mast cells carry high-affinity receptors on their surface, namely, FcεRI. These receptors have high affinity for the Fc portion of IgE. The binding of Fc and FcεRI is needed for mast cell activation (see section "Type I: Immediate Hypersensitivity or Anaphylactic"). Based on their cytoplasmic granule contents, human mast cells are divided into those that contain tryptase only, known as MCt, and those that contain chymase, carboxypeptidase, and cathepsin G in addition to tryptase, known as MCtc. The MCt cells are abundant in intestinal mucosa, lung alveolar walls, and nasal mucosa, whereas MCtc are more abundant in the skin, intestinal submucosa, and blood vessels. MC cells are characterized as immune system related and increased in allergic diseases, parasitic diseases, and chronic immune deficiency diseases and acquired immune deficiency syndrome (AIDS). The MCtc cells, in contrast, are nonimmune system related, and their numbers do not increase in allergic or parasitic disease or in AIDS and chronic immune deficiency. Their numbers, however, increase in fibrotic diseases.

Basophils

These cells are also important effector cells in hypersensitivity and comprise less than 1 % of white blood cells; they measure 8–10 μm and stain blue with Wright's stain. The precursor cells of basophils are in the bone marrow, where they mature before being released into the circulation. Like mast cells, they have a high-affinity receptor on their surfaces, FcεRI, that binds to the FC portion of IgE. Upon stimulation of basophils, the contents of granules are released; like mast cells, some mediators are preformed and some are newly synthesized.

Eosinophils

These cells are 12–17 μm and have bilobed nuclei and cytoplasmic granules that are unique when stained or seen under an electron microscope. Eosinophils contain cytoplasmic primary granules that lack a core and a group of membrane-bound specific granules that contain electron-dense crystalline cores. These granules contain four major cationic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO). The function of these proteins ranges from the destruction of parasites to the killing of microorganisms and tumor cells. In addition to granule cationic proteins, eosinophils have various lipid products, cytokines, and chemokines that participate in various functions. Eosinophils participate in various immune functions and are increased in parasitic infections and allergic diseases.

Defective Immune System

Deficiencies and defects in any components of the immune system can result in immunodeficiency. The diagnosis of immunodeficiency starts with patients' complaints and a series of diagnostic evaluations. Some of these laboratory tests include a complete blood count with differentials, immunoglobulin concentration, human immunodeficiency virus (HIV) testing, evaluation of B- and T-cell function, NK cell evaluation, and analysis of gene defects, among others (see Chap. 32).

Hypersensitivity Diseases

Repeated exposure of the body to an allergen makes susceptible individuals *sensitized* to that allergen. At some time, the body may overreact and become *hypersensitive* to the exposed allergen and cause tissue injury and damage. Diseases resulting from this type of reaction are immunologic and known as *hypersensitivity diseases*. The hypersensitivity diseases are traditionally classified in these four distinct types:

Table 1.3 Hypersensitivity reactions

Type	Reactions	Mechanism	Onset of action	Examples
Type I immediate hypersensitivity or anaphylactic	IgE mediated	Degranulation of mast cells and release of histamine and other mediators	Minutes to hours	Urticaria, allergic rhinitis, food allergy
Type II antibody-mediated hypersensitivity	Non-IgE (IgG or IgM) mediated	Interaction of antibody with cell surface antigens leading to complement activation and lysis or phagocytosis	Days	Hemolytic anemia, Hashimoto's thyroiditis, transfusion reaction
		Autoimmune reactions		
		Antibody-mediated cytotoxicity		
Type III immune complex-related hypersensitivity	Immune complex mediated	Formation of immune complex and deposition on various sites such as blood vessels	10–21 days	Serum sickness; systemic lupus erythematosus (SLE)
Type IV cell mediated	Cell mediated	Secreted cytokines from CD4+ and CD8+ cells activate macrophages leading to inflammation and tissue injury	2–4 or more days	Mantoux reaction, allergic contact dermatitis
		Direct killing of affected cells by CD8+ T cells		

Type I: Immediate hypersensitivity or anaphylactic
Type II: Antibody-mediated hypersensitivity
Type III: Immune complex-mediated hypersensitivity
Type IV: Cell-mediated hypersensitivity

Table 1.3 summarizes the features of a hypersensitivity reaction.

Type I: Immediate Hypersensitivity or Anaphylactic

An immediate hypersensitivity reaction occurs within minutes of exposure to an allergen in a previously sensitized person. The reaction is a result of a chain of events that starts with exposure to an allergen (Fig. 1.5a). These steps are summarized as follows:

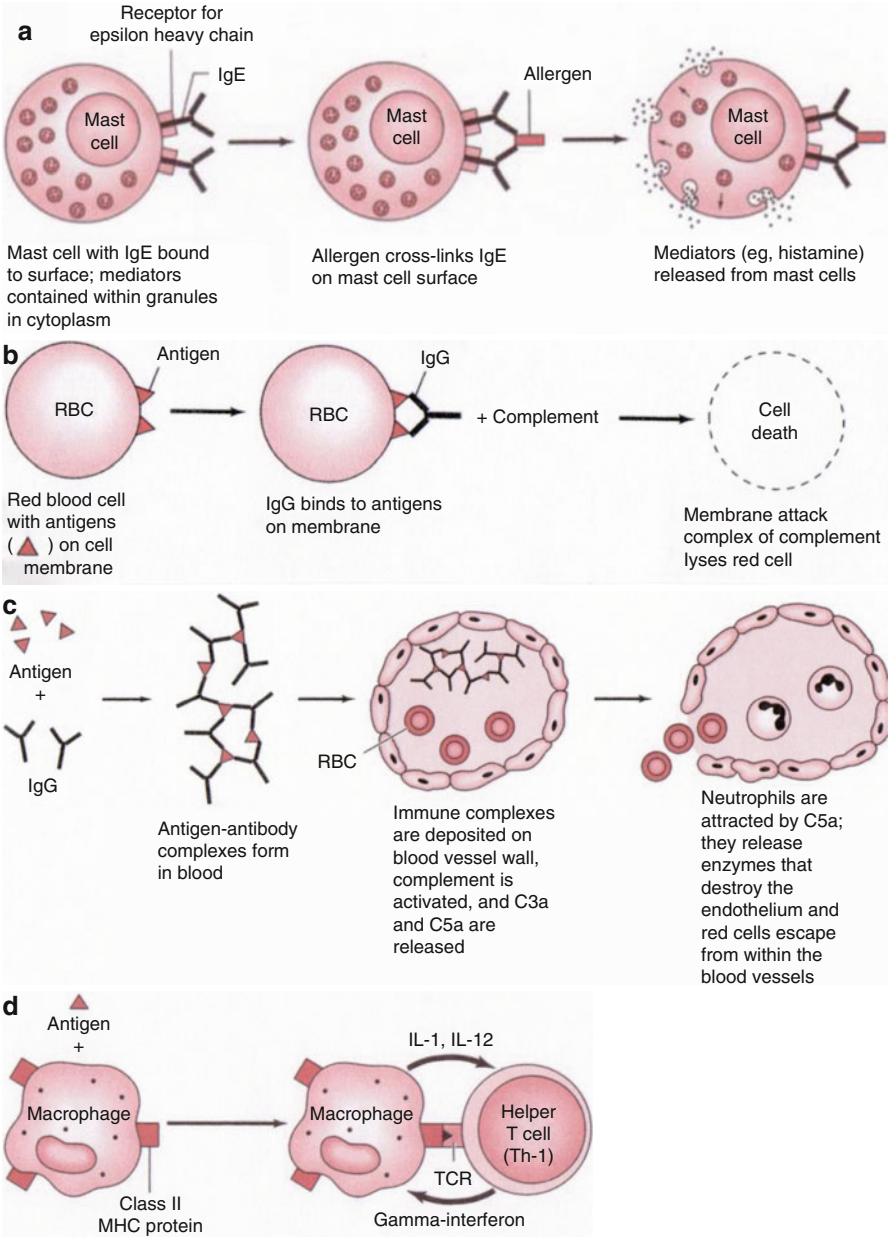

Fig. 1.5 Four types of hypersensitivity diseases (Reproduced with permission, from Levinson [13]). (**a**) Type I hypersensitivity (immediate or anaphylactic). (**b**) Type II hypersensitivity (antibody mediated). (**c**) Type III hypersensitivity (immune complex-mediated). (**d**) Type IV hypersensitivity (cell-mediated)

1. Initial encounter with the allergen.
2. Binding of antigen-presenting cells (APCs) to the allergen.
3. Antigen processing by antigen-presenting cells. The result of this process is antigen-bound MHC protein on the surface of APCs. Such cells then are capable of binding to T cells via T-cell receptors.
4. Activation of T helper cells after binding with APCs.
5. Activation of B cells by activated T helper cells.
6. Differentiation of B cells to plasma cells.
7. Production of IgE by plasma cells.
8. Binding of IgE to mast cells (sensitization step). This binding is a result of linking between Fc portions of IgE with the high-affinity Fc receptor, known as FcεRI, on the surface of mast cells.
9. Subsequent exposure to the same allergen stimulates the sensitized mast cells to degranulate (i.e., opening the granules and releasing various mediators); the mediators so released cause the immediate hypersensitivity reaction.

Type II: Antibody-Mediated Hypersensitivity

This type of hypersensitivity reaction involves the interaction of non-IgE antibodies (i.e., IgM or IgG) with cell surface antigens or matrix-associated antigens. The mechanisms of tissue injury may involve opsonization of cells by antibody (i.e., binding of antibody to tissue antigen) that leads to complement activation and phagocytosis, leukocyte activations, in which their products cause the tissue injury (Fig. 1.5b), or by *antibody-dependent cell-mediated cytotoxicity* (*ADCC*). In this type of reaction, the antibody binds to the infected cells. Then NK cells recognize and bind to the antibody-coated infected cells and destroy them. A known example of type II hypersensitivity, transfusion reaction, is briefly discussed later.

A transfusion reaction is a result of a blood transfusion from a noncompatible donor to a receiver. This reaction may occur as a result of ABO blood group or rhesus (Rh) factor antigen incompatibility of donor and receiver. An example is blood transfusion from a donor with blood group A to a receiver with blood group B. Individuals with blood group A have antigen A and anti-B serum antibody, whereas individuals with blood group B have B antigen and anti-A serum antibody. Transfusion of blood from a donor with blood group A to a receiver with blood group B causes rapid hemolysis of donor blood cells. Rhesus (Rh) factor antigen is also a cause of hemolytic reactions; this occurs when an Rh-negative mother, who lacks the Rh antigen, carries an Rh-positive fetus. Blood crossing the placenta from the fetus to the mother can stimulate the mother to produce anti-Rh antibody. Maternal antibody crossing the placenta to the fetal circulation can destroy the fetal erythrocytes. Also, during a subsequent pregnancy, such anti-Rh antibody from a sensitized mother may cross the placenta and cause hemolysis of the fetal red blood cells, also known as *erythroblastosis fetalis*.

Autoimmune reactions in which the body produces antibody against self are also included in this type of immune reaction. Some examples include acute hemolytic anemia, myasthenia gravis, Graves' disease, and Hashimoto's thyroiditis, to name a few.

Immune Complex-Mediated Hypersensitivity

The diseases caused by this type of hypersensitivity are based on deposition of the antigen–antibody complex in various anatomic sites. The ratio of antigen and antibody determines the amount of deposition. The deposition of antigen–antibody complex can occur in the presence of excess antigen (Fig. 1.5c).

The prototype of this category is "serum sickness" (see Chap. 22). The term *serum sickness* originated from the initial observation of diphtheria treatment. Antibody against diphtheria toxin was historically prepared in horses; thus subsequent administration of such horse serum containing antitoxin was noted to cause fever, rash, arthritis, vasculitis, and glomerulonephritis after 10–14 days. The depositions of antigen–antibody complexes activate complement and eventually cause tissue injury.

Type IV: Cell-Mediated Hypersensitivity

Type IV hypersensitivity includes diseases that are caused by T-cell-mediated reactions. In delayed-type hypersensitivity, CD4+ T cells or CD8+ cells secrete cytokines that activate macrophages and result in inflammation and tissue injury. At times, CD8+ T cells directly kill the affected cells. The best known example is *Mantoux reaction*, which appears as an induration and erythema and is a result of the injection of tuberculin to a sensitized individual. The reaction appears in several hours and reaches a maximum in 24–48 h. In this type of reaction, histological examination of the lesions reveals mononuclear phagocytes and lymphocytes (Fig. 1.5d).

Allergic contact dermatitis is another example of this type of hypersensitivity. This type of reaction occurs as a result of contact with various allergens. Some common examples include reactions caused by contact with plants such as poison oak or poison ivy or with metals such as nickel sulfate found in jewelry. Chemicals used in various detergents, perfumes, hair dyes, and cosmetics may also cause this type of delayed hypersensitivity reaction. Delayed reaction may occur as early as 48 h after initial contact and as late as 4 days or longer (see Chap. 13). Diagnosis of this type of allergy is by patch testing (see Chap. 31). Figure 1.5 summarizes the four types of hypersensitivity reactions.

Evidence-Based Medicine

The world of immunology is constantly changing. As we learn and explore the unknowns, our understanding of the complex immune system changes. Discovery of new receptors, enzymes, and cytokines helps us understand the once unexplainable immune puzzle. What we have learned about the human immune system in the last quarter of a century is astounding. A better understanding of the immune system helps us manage and treat allergic and immune diseases more effectively.

Thanks to continuous research in the field of allergy and immunology, we are learning more about our immune system. A combination of basic research, observational studies, and clinical trials helps us put together the pieces of the unknown.

As we learn about the immune system, we come up with newer and better explanations for the pathophysiology of allergic and immunologic diseases. For example, many studies have shed light on the pathophysiology of allergen recognition; each study adds to our knowledge of evidence-based medicine in understanding the complicated nature of the disease.

In their 2015 report, Resch et al. demonstrated the difference in IgE recognition of mite allergen components in asthmatic and nonasthmatic children. The authors investigated the IgE and IgG reactivity profiles to a panel of seven house dust mite allergens in children with allergic asthma and compared the group with those of nonasthmatic atopic children. The result of the study revealed that the asthmatic children with house dust mite allergy not only showed an IgE response to each of the house dust mite allergens more frequently but recognized more allergens than nonasthmatic children with house dust mite allergy. Although several possibilities for such a recognition were hypothesized, the exact mechanism(s) remains unknown. In another study by Pascal et al., molecular diagnosis of shrimp allergy was studied. The investigators recruited shrimp-sensitized subjects and grouped them based on the history of shrimp-allergic reactions and challenge outcome. Then they determine the IgE reactivity to recombinant crustacean allergens and IgE and IgG4 reactivity to peptides. The investigators noted that individuals with a positive challenge more frequently recognized tropomyosin and sarcoplasmic calcium-binding proteins than those found tolerant to by the challenge. The authors concluded that tropomyosin and sarcoplasmic-calcium-binding-protein sensitization is associated with clinical reactivity to shrimp. In addition they stated that myosin light chain testing may help in the diagnosis of clinical reactivity.

I refer you to the evidence-based medicine section of every chapter to learn more about the recent findings and investigations of the various topics.

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Chapter 2
The History and Physical Examination of the Allergic Patient

Sarah J. Kuhl

The history and physical (H&P) examination remain the basis for diagnosis and treatment in allergy and immunology, and the myriad of presentations help to distinguish diseases that with allergic and immunologic etiology from others may present in a similar way. The history and physical structures the physician's thinking, so that the presenting problem yields itself to a treatable diagnosis. It may involve considerable detective work.

The allergy history and physical examination are typically focused on the particular presentation that appears to be allergic or immunodeficient.

History

The history is often focused toward one of the syndromes: rhinitis, sinusitis, asthma, and major allergic reactions such as anaphylaxis, angioedema, systemic mastocytosis, and stinging insect allergy. Most allergic and immunologic diseases were described and diagnosed in the era prior to the availability of extensive testing or laboratory results and thus can still be diagnosed by history and physical, with diagnosis subsequently confirmed by laboratory testing.

The allergy-immunology history can range from extremely thorough to very brief, for example, in the case of acute asthma or anaphylaxis, where emergent treatment is needed.

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Chief Complaint

The chief complaint typically guides the history, although occasionally a thorough history will reveal another allergic or immunologic problem that may need to be addressed. Many allergists use a form to elicit the initial history and physical, to expedite care particularly in the allergic rhinitis or asthma patient. In some patients with allergic rhinitis, the form may give adequate information, but in other cases, it will be the beginning of an investigation.

If the physician listens carefully, the patient will typically tell one the diagnosis.

Rhinitis and Sinusitis

While the H&P for rhinitis in the otherwise healthy patient appears to be straightforward, the absence of critical details such as seasonality may result in the less than optimal treatment for perennial allergy triggers such as dust mites. In older patients, ancillary diseases, habits, and medications may contribute or cause the presentation, so a history of smoking may have caused nonallergic rhinitis, which may be partially responsive to first-generation antihistamines, but not to second-generation antihistamines. Sometimes the correction of hyper- or hypothyroidism leads to improvement in rhinitis symptoms.

Sinusitis

A description of nasal secretions or change in secretions will sometimes help with a clinical diagnosis of sinusitis. Allergic rhinitis secretions are typically clear and watery, while thick green secretions that last for weeks can indicate sinusitis. Patients with sinusitis will sometimes experience a sensation of fever, particularly during hot weather, as well as pain over the maxillary sinuses or the osteomeatal complex. History of nasal or facial fracture may reveal a source of nasal obstruction. History of sinus surgery is typically an indication of serious problems with sinusitis or nasal obstruction in the past.

Asthma

In the case of acute asthma, the H&P is minimal, so that treatment may proceed simultaneously. Occasionally the patient may not be wheezing on presentation, but the respiratory rate, heart rate, accessory muscle use, oxygenation, and peak flow all point toward asthma, and the patient begins to wheeze with intensive beta-agonist treatment. Peak flow should always be checked in those with suspected asthma exacerbation.

It is also important to remember other causes of wheezing. Unilateral wheezing in an infant or toddler can indicate foreign body. A pneumothorax can be an occasional complication of asthma that may result in unilateral wheezing, and an obstruction such as a tumor can also cause a unilateral wheeze. Wheezing in an older person can be due to congestive heart failure or fluid overload.

In chronic asthma, the detailed history helps differentiate asthma from such diseases as vocal cord dysfunction, hyperventilation, restrictive lung disease, and bronchiectasis, although all of these diseases can coexist with asthma. Some patients with cough-variant asthma will never wheeze. There is increasing evidence that identification of the asthma phenotype can be helpful in recommending personalized treatment. The major asthma phenotypes are allergic, nonallergic, infection related, aspirin-associated respiratory disease (AERD), and childhood preasthma phenotype. In recent years, these have been further classified into (1) trigger induced (including occupational, cigarette smoke induced, air pollution induced, and exercise induced), (2) symptom based (including exacerbation prone, asthma with persistent airflow limitation, cough variant, adult onset, obese), and (3) biomarker based (including eosinophilic and neutrophilic). There can be an overlap of phenotypes in the same individual. Diagnosing and treating conditions that exacerbate asthma, such as rhinitis, sinusitis, gastroesophageal reflux disease, sleep apnea, and obesity, often result in great improvement of asthma.

Dyspnea

Dyspnea can be caused by heart failure, mitral stenosis, COPD, asthma, diffuse interstitial lung disease, pneumonia, spontaneous pneumothorax, acute pulmonary embolism, and hyperventilation caused by anxiety.

Sputum production often occurs in poorly controlled asthma, but may indicate pneumonia or even lung abscess, which may be foul smelling if anaerobic. Patients with immunodeficiency may develop bronchiectasis, with chronic or recurrent sputum production. Cystic fibrosis may also cause sputum production and should be considered in the differential diagnosis.

In asthma and other allergic diseases, a history of hospitalizations, intubations, emergency department visits, and courses and duration of prednisone as well as other asthma medications is part of a thorough history.

A dry cough can be caused by an acute viral laryngitis or tracheobronchitis, by mycoplasma or viral and bacterial pneumonias, as well as gastroesophageal reflux, left ventricular failure, and asthma. A cough productive of sputum can be associated with bacterial pneumonia, chronic bronchitis, bronchiectasis, tuberculosis, lung abscess, and sometimes asthma.

Pulmonary embolus and lung cancer may have either dry or productive cough. Allergic rhinitis and/or sinusitis with post nasal drainage can cause cough or repeated throat clearing. Cough-variant asthma presents with cough rather than wheeze, but can typically be confirmed by PFTs.

A history of smoking increases the likelihood of COPD or asthma-COPD overlap syndrome, or lung cancer.

Skin Rash

Certain rashes help diagnose the likely etiology of a reaction. In drug allergy, the description often helps to verify the allergy and may help determine the etiology. Generalized erythema is common in an acute nonallergic vancomycin reaction, commonly known as red man's syndrome, which typically occurs within hours of infusion, and may often be avoided by simply decreasing the rate of infusion. Maculopapular rashes are common reactions to penicillins and cephalosporins, but can occur with measles. Bullous lesions can denote toxic epidermal necrolysis or Stevens-Johnson syndrome in drug allergy.

Urticarial lesions typically disappear within 24 h, but urticarial lesions that last longer, or are painful or pigmented, should be biopsied for possible urticarial vasculitis.

Allergic shiners or dark areas under the eyes are often present in patients with chronic allergic rhinitis. Erythema surrounding the nose and eyes is often present during uncontrolled episodes of allergic rhinoconjunctivitis.

Atopic dermatitis in flexor surfaces such as the antecubital fossa, behind the knees, and on the neck, while the nonallergic disease, psoriasis, occurs mostly on the knees and elbows and behind the ears. Dermatographism is often present.

Contact dermatitis occurs in location of contact with the allergen and is most often associated with nickel in inexpensive jewelry or "German silver" or "new silver" belt buckles. Lotions, cosmetics, and plant exposures can all cause localized contact dermatitis.

Skin hyper- or hypopigmentation may be the residual of a rash or caused by a superficial fungal infection, tinea versicolor, which can also cause pruritus in some patients.

Cutaneous or systemic mastocytosis may present with urticarial pigmentosa or other collections of mast cells. Urticaria or edema may be elicited by rubbing. Fixed drug eruption typically presents as a single oval or round macule or plague, although more than one may appear.

Stinging Insect Allergy If possible, the type of hymenoptera should be determined, so that testing can be detected, and cross-reactivity can be determined. Whether the patient had large local reaction, urticaria or anaphylaxis is important to determine.

Anaphylaxis Attempts should be made to determine the etiology particularly if related to food (and sometimes exercise), drugs, stinging insects, etc.

Food Allergy or Intolerance *Food allergy or intolerance* can be assessed by history of food ingestion, timing of the reaction, and symptoms. The specific foods are important for patient education of possible cross-reacting foods.

Itching of the throat or mouth can occur in food allergy or pollen food allergy syndrome. Atopic dermatitis can be a manifestation of food allergy. Eosinophilic esophagitis is increasingly recognized as an important factor in many cases of GERD.

Recurrent Infection

In recurrent infection, important elements of the history include age at onset, site and type of infection, GI symptoms, autoimmune diseases, family history, a history of day care, passive smoking, atopy, and anatomic defects.

Patients with antibody deficiency disorders are usually well until 6–9 months of age because maternal immunoglobulin G is transferred during the third trimester. After birth, levels of maternally derived IgG rapidly decline, reaching a nadir at approximately 3–6 months, and the infant begins to produce IgG, but experiences a normal transient hypogammaglobulinemia. An occasional infant will experience infections consistent with antibody deficiency during this period, but subsequently have no problems with infection. Premature infants are more likely to experience infection during this time, due to decreased time for transfer of maternal antibody, and a lag in the development of production of IgG.

Patients with severe combined immunodeficiency typically present earlier, at 4–5 months or earlier, and may present with diseases associated with cell-mediated immune deficiency.

The type or site of infection, frequency, duration, and severity are important.

Otitis, mastoiditis, sinusitis, pneumonia, bronchiectasis, and meningitis can be associated with B cell deficiencies.

Recurrent skin infections are typically associated with phagocytic defects such as those associated with chronic granulomatous disease and hyper-IgE (formerly Job's) syndrome.

Normal young children may have four to six upper respiratory tract infections per year for the first 3–5 years of life. Children in day care, or with school-age siblings, can have more due to increased exposure. Normal children handle these infections well. Children with allergic rhinitis tend to have increased numbers of episodes of sinusitis and otitis media, so an allergy evaluation is typically indicated. In normal children, bacterial infection typically resolves rapidly with antibiotics.

The microbiology of the infection often lends a clue. *Mycobacterium avium-intracellulare* and herpesviruses including CMV and varicella are associated with T cell deficiency, NK cell defects, and IL-12/interferon-gamma deficiencies. Patients with T cell deficiency can also present with *Candida*, *Aspergillus*, *Toxoplasma*, *Pneumocystis*, *Cryptosporidium*, or *Cryptococcus* infection. Enteric bacterial infections with *Campylobacter*, *Salmonella*, or *Clostridium difficile* can be associated with B cell immunodeficiency, as can enterovirus or rotavirus infection or *Giardia* infection. Encapsulated organisms such as *Streptococcus pneumoniae*, *Hemophilus influenza*, or *Neisseri*a species can indicate a B cell or complement deficiency, while catalase-positive organisms such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Klebsiella*, and *Serratia* are often present in neutrophil or phagocyte defects. Patients with X-linked lymphoproliferative deficiency can present with fulminant EBV infection.

Review of Records

Review of records may be very helpful, especially for the patient with a history of recurrent infection or drug allergy. Sometimes the history of recurrent infection in a child taken to day care may in fact be normal (one URI per month or 12 per year) and more diagnostic of overly anxious parents. Other patients with self-reported recurrent pneumonia or bronchitis may in the absence of abnormal chest x-rays or documented infections have asthma. Other patients may only have recurrent upper respiratory infections with overwork, lack of sleep, or excessive exercise and have no immune deficiency.

In the case of drug allergy, the patient may not remember many of the details of a hospitalization, so a review of records is very helpful. In some cases, an allergy has been entered erroneously or has been entered for all medications administered at the time of a reaction.

Patients with a history of maculopapular rash during amoxicillin or ampicillin treatment of a sore throat later found to have mononucleosis typically tolerate subsequent treatment with the same antibiotic and so are not thought to be antibiotic allergic.

The Physical Exam in Allergy-Immunology

Although the physical exam is again tailored to the chief complaints, it is important that it is complete enough to allow the clinician to evaluate the possible contribution of other diagnoses.

Vital signs are part of any complete physical, but typically normal except in asthma or severe allergic reactions where there can be increased respiratory rate, tachycardia, and hypotension. Fever often signifies infection rather than allergy.

General Appearance Acute anaphylaxis often presents with an uncomfortable, flushed patient. Asthma presents with shortness of breath, wheezing except in severe asthma, and sometimes the use of accessory muscles in severe asthma. Patients with chronic nasal obstruction are often mouth breathers.

Skin Certain rashes help diagnose the likely etiology of a reaction, so that it is important to describe the rash as generalized or localized (with location), macular, popular, erythematous, vesicular, bullous, etc. Dermatographism may be present. In some cases, timing or duration of the rash helps determine the etiology.

HEENT: Head, Eyes, Ears, Nose, and Throat

Head

Paranasal Sinuses

Percussion over the maxillary and frontal paranasal sinuses may elicit a painful response that correlates with sinusitis.

Eyes

Allergic conjunctivitis often causes watery discharge and hyperemia or conjunctival injection and is most often associated with allergic rhinitis.

Conjunctival injection or erythema may indicate an allergic conjunctivitis which is typically bilateral. Occasionally, unilateral viral infection or pinkeye is mistaken for allergy. Conjunctivitis medicamentosa may result from the chronic use of vasoconstrictive eye drops. Conjunctiva may also be injected due to autoimmune disease causing uveitis or a number of other conjunctival inflammatory disorders (see chapter on eye allergy).

Thick mucus discharge may be indicative of infection or other pathologies. There are a number of allergic disorders of the eye that can cause papillae and cobblestoning and are described in detail in the chapter on eye allergy.

Ears

Occasionally the ears itch in allergic rhinoconjunctivitis, and evidence of scratching the canal is evident. Tympanic membranes can be scarred or perforated from otitis media associated with allergy or immunodeficiency.

Nose

The nose is typically examined with the largest ear speculum. Pale conjunctiva is often associated with an allergic nose, while erythema is associated with sinusitis. Enlarged or engorged turbinates can be due to rhinitis or sinusitis. A watery discharge is typically allergic in etiology, while a thick purulent discharge often indicates acute sinusitis (infection). The posterior ethmoids and sphenoids typically drain posteriorly, so an absence of nasal drainage does not rule out sinusitis. Polyps are glistening enlargements protruding from the turbinates. Septal deviation will sometimes explain obstruction. Septal perforation may cause symptoms. Irritation or bleeding of the nasal septum can indicate incorrect application of nasal steroid or sinusitis. Sinusitis is sometimes associated with an odor of infection from the mouth and nose. If the allergist is trained in endoscopy, further evaluation of the sinuses and larynx may be possible, or the patient may be referred to an otolaryngologist.

Throat

Tonsils can be enlarged due to chronic sinus drainage, can have white spots indicative of chronic infection or tonsiloliths, or may have been surgically removed. Although tonsils are now typically removed only for airway obstruction,

tonsillectomies were often performed routinely through the 1970s, so the absence of tonsils due to past tonsillectomy in a middle-aged or elderly patient may have no significance, in the absence of further history of infection. Tonsils and other lymphatic tissues are typically absent in patients with X-linked agammaglobulinemia.

The posterior pharynx can be inflamed by chronic sinus drainage or acute viral infection. An irregular appearance known as cobblestoning may result. Sometimes thick mucus or inflammation can be seen either unilaterally or bilaterally.

Extremely poor dentition can sometimes be the cause of maxillary sinusitis, which can only be improved by extraction of a severely infected tooth, so dentition should be assessed. Infected teeth can also cause a foul odor.

Neck

The neck should be palpated for lymphadenopathy, which can be associated with acute or chronic sinusitis, mastoiditis, otitis, and tonsillitis. Chronic lymphadenopathy is also associated with HIV and some immunodeficiency diseases.

Chest

Increased diameter or barrel chest can be seen due to chronic hyperinflation in chronic asthma or COPD. Percussion of the chest is typically resonant to hyperresonant in asthma and COPD. Pneumonia, pleural effusion, and atelectasis (which can occur with mucous plugging in asthma) cause an area of dullness to percussion.

Rhonchi or Rales

Wheezing in asthma may be heard only on expiration or on both inspiration and expiration, but is not always present in severe acute asthma or cough-variant asthma. In addition, all wheezing is not caused by asthma, so particularly in an elderly patient or chronically ill child, evaluation of the cardiovascular system is necessary. Localized wheezing suggests partial obstruction of a bronchus due to tumor or foreign body in an infant. An inspiratory wheeze or stridor suggests a partial obstruction of the trachea or larynx that merits immediate attention. Late inspiratory crackles are heard in heart failure and pneumonia. Faint crackles are heard in interstitial lung disease.

Heart

The heart exam should include murmurs, rubs, and gallops. The presence of a new murmur can indicate such things as pulmonary hypertension or congestive heart failure, which can cause dyspnea.

Extremities

Cyanosis is a bluish color in toes and fingertips; clubbing can occur with chronic lung disease. Heart failure can cause edema.

Abdomen

An abdominal exam may reveal an enlarged spleen or absence of spleen in certain immunodeficiency states. An enlarged liver or a shrunken cirrhotic liver may be present in alcoholism or chronic hepatitis that can be associated with increased susceptibility to infection.

Evidence-Based Medicine

The history is extremely important in allergy, as skin and in vitro testing can be falsely positive or negative. The recent "Choosing Wisely" campaign of the American Academy of Allergy Asthma and Immunology and the current literature recommend not performing unproven diagnostic tests, such as an indiscriminate battery of IgE tests (either skin or blood tests) in the evaluation of allergy. Any extensive panel of inhalant tests may yield a number of false-positive tests, so extensive panels should be avoided. Food IgE testing should not be done in the absence of a history consistent with potential IgE-mediated food allergy, as "False or clinically irrelevant positive allergy tests to foods are frequent" (Choosing Wisely Campaign). Conversely, serological testing for IgE antibody in drug allergy has low diagnostic sensitivity, so do not rule out drug allergy such as penicillin allergy. Intradermal skin testing to drugs such as penicillin continues to be the diagnostic test of choice. In addition, a positive serological or skin test for hymenoptera allergy cannot be ignored in the setting of a positive history. It is helpful to remember to always interpret allergy tests in the context of the history. Allergy cannot be diagnosed solely on the basis of skin or lab tests.

Conclusion

Often the allergic person will figure out the offending allergen with the help of the allergist, so even the most thorough H&P will result in the patient later remembering other details, or the patient will over the course of time with the help of the clinician figure out the offending allergen or syndrome. There are, of course, idiopathic causes of allergic reactions such as anaphylaxis, but these will also be diagnosed over time through history and physical and the exclusion of other possible diagnoses.

In the era of personalized medicine, the allergy H&P must continue to be tailored to the individual patient. Tests for all possible allergens do not exist, so in some cases, the history and physical is the only means of diagnosis and avoidance of the offending allergen leads to dramatic improvement. A thorough H&P typically leads to a reliable diagnosis and treatment and patient satisfaction.

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Chapter 3
Prevalence of Allergic Diseases in Children, Adults, and Elderly

Massoud Mahmoudi

Introduction

Allergic diseases affect individuals of all ages from infancy to the old age.

The incidence and prevalence of the specific disease, however, change as the allergic individual marches toward the late adulthood. Factors affecting natural history of allergic diseases include genetic predisposition, environmental exposure, occupational exposure, climate, infection, socioeconomic status, and most importantly physiological changes during aging (Table 3.1).

Theoretically, the same allergic disease may present in different age groups; yet, the prevalence of a specific allergic disease may be higher in one age group and not the other. An allergic disease in adults or elderly is either an extension of childhood disease or, less commonly, a new incidence. The prevalence of common allergies and correlated age groups are summarized in Table 3.2.

Allergic Rhinitis

Every year in the USA, 40 million people are affected by allergic rhinitis; this is 10–30% of adults and up to 40% of children population (see Chap. 6). According to the 2012

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Table 3.1 Various factors affecting prevalence of allergic diseases

Factors	Examples
Genetic predisposition	Family history of allergic disease (e.g., allergic rhinitis)
Environmental exposure	Dust mites, molds, pollens, bee stings
Infection	Viruses: upper respiratory infections (asthma exacerbations)
Physiologic changes	Atopic dermatitis (less common in the elderly)
	Food allergy (more common in children)
Occupational exposure	Latex allergy (e.g., in health-care professionals)
Climate	Cool, dry, and humid climate affects growth of certain organisms (e.g., humidity and dust mites)
Socioeconomic status	Asthma more prevalent in people with low socioeconomic status

Table 3.2 Prevalence of allergic diseases in various age groups

Allergic disease	Infancy–5 years	5–20 years	20–65 years	≥65 years
Atopic dermatitis	+++	++	+	±
Allergic rhinitis	++	++	++	+
Allergic asthma	±	+	++	++
Food allergy	++	+	±	±
Occupational allergy	–	±	++	+

– none, +–+++ increase of prevalence, ± rare occurrence

report of National Center for Health Statistics, 6–1 % of adults in 18–44, 9.7 % of 45–64, 7.9 % of 65–74, and 5.4 % of 75 and over age groups are affected in the USA.

In early childhood, i.e., less than 5 years of age, allergic rhinitis symptoms are mainly due to indoor allergens such as pet danders, dust mites, molds, and cockroaches. Seasonal allergies start at 3–4 years of age; this is due to the time, usually two to three seasonal exposures, needed from sensitization to expression of the symptoms. As one reaches the late adulthood, allergic rhinitis becomes a less common problem.

The incidence and remission of self-reported allergic rhinitis symptoms in an adult Swedish population were subjects of an investigation. The researchers mailed two sets of questionnaires, one in 1992 and the other in 2000. Responders, 4,280 individuals, were in 20–59 age group. Analysis of the responses indicated the increase in prevalence of allergic rhinitis from 12.4 % in 1992 to 15 % in 2000. The incidence of allergic rhinitis from 1992 to 2000 was 4.8 %. In 2000, 23.1 % had remission. The highest incidence was in 20–29 age group and the highest remission was in 50–59 age group.

Respiratory Allergy/Allergic Asthma

Asthma affects ten million adults and approximately five millions of children in the USA alone. Only a portion of wheezers in early life becomes asthmatics as adults. In a 2002 report by Behavioral Risk Factor Surveillance (BRFSS), lifetime asthma

prevalence and prevalence of current asthma within 50 states (USA) and District of Columbia were 11.8 % and 7.5 %, respectively. Current prevalence of asthma in the same report, using analysis of data regarding racial/ethnic population in selected areas (19 states of the USA), was highest in non-Hispanic multiracial population (15.6 %), followed by non-Hispanic American Indian/Alaska native (11.6 %), non-Hispanic blacks (9.3 %), non-Hispanic Whites (7.6 %), non-Hispanic persons of "other" race/ethnicity (7.2 %), Hispanics (5.0 %), non-Hispanic Asians (2.9 %), and non-Hispanic native Hawaiian/Pacific Islander (1.3 %).

According to early release of selected estimates based on data from the January to June 2014 (USA), National Health Interview Survey of National Center for Health Statistics, the prevalence of current asthma among person of all ages was 8.1 % (age adjusted). This number for persons under 15 years old was 9.2 %, for 15–34 years old was 8.8 %, and for 35 years old and over was 7.3 %. For both sexes combined, those who were 35 years old and over less likely had current asthma compared to persons under age 15 and 15–34. As far as ethnicity, the sex-adjusted prevalence of current asthma for children under 15 years old was higher among non-Hispanic black children (14.4 %) than among Hispanic children (8.9 %) and non-Hispanic white children (7.8 %). The sex-adjusted prevalence of current asthma for persons 15 years old and over was 6.5 % for Hispanics, 7.7 % for non-Hispanic white persons, and 8.9 % for non-Hispanic black persons.

In order to understand the natural history of asthma, one needs to follow patients over a long period of time. In a study reported by Lombardi and colleagues, 99 patients (mean age 31 years) with allergic rhinitis alone (44), allergic asthma alone (12), and allergic asthma and allergic rhinitis (43) were followed for a period of 10 years. The report found that after 10 years of follow-up, 31.8 % of allergic rhinitis patients had developed allergic asthma, and 50 % of patients with allergic asthma had developed allergic rhinitis. The study showed that the outcome of the disease progression was not the same for all the individuals.

Uncontrolled asthma in young adults leads to future airway remodeling later in adulthood. In addition, often elderly asthmatics present with picture of asthma/chronic obstructive pulmonary disease (COPD); such patients have poorer prognosis and are more difficult to manage and treat than those with asthma alone (see Chap. 30).

Food Allergy

Food allergy is the most common in infants and children. By 2–3 years of age, most food allergies resolve while some extend to adulthood.

Cow's milk allergy is the most common food allergy in infancy with incidence of 2–3 % in the first year of life. Fortunately, there is a approximately 40–50 % remission at 1 year of age and the number increases to 60–75 % at 2 years and to 85–90 % at 3 years of age. In some children, complete remission may take 8–10 years.

Allergies to certain food groups such as tree nuts, peanuts, fish, and shellfish usually persist for life. While 20 % of children outgrow peanut allergy by 5 years of age, tree nut allergy in one study was reported to have remission in 9 % of patients.

In adults and elderly, food allergy is usually an extension of childhood allergy and a new food reaction is mostly a result of food adverse reaction and intolerance.

Atopic Dermatitis

Atopic dermatitis is a common form of allergy in children. In the first few months of life, the motor skills of infants are not fully developed, and as a result, they are unable to scratch themselves and cause eczematous lesions. Williams and Strachan, using the National Child Developmental Study (NCDS), a data base of 6877 children born in England, Wales, and Scotland during the March 3–9, 1958, analyzed the age of onset and clearance rate for examined and/or reported eczema at ages 7, 11, 16, and 23 patients. Of the 571 children with reported or examined eczema, 65 % had clearance at the age of 11 years and 74 % at the age of 16 years.

In adults, atopic dermatitis is usually an extension of childhood onset, but adult onset atopic dermatitis has also been reported. In a report by Ozkaya, the files of 376 patients with atopic dermatitis between period of June 1996 and June 2003 were analyzed. Of the patients studied, 16.8 % (63 patients) had adult onset at age range of 18–71 years. Of the affected patients who developed atopic dermatitis, majority (73 %) were 18–29 years, followed by 30–39 years (14.3 %), 50–59 years (6.3 %), 40–49 years (4.8 %), and 70–79 years (1.6 %). In the study, flexural involvement was the main involved sites (88.9 %), whereas the trunk and extremities were the main nonflexural involved areas. For the complete discussion of atopic dermatitis, see Chap. 12.

Occupational Allergy

As individual ages, occupational allergy becomes prevalent. This is because younger adults may occupy their time with school and part-time jobs. Older adults, however, choose to participate in various jobs in industry, manufacturing plants, and office settings; this increases the chance of developing sensitivity and finally allergy, due to day-to-day exposure to occupational allergens. One example is latex allergy in those with frequent exposure to latex products. This is seen in health-care providers, workers of toy manufacturing plants, and others who are in frequent contacts with latex products.

Older adults retire and stop the contact with potential occupational allergens. Occupational allergy during the active employment would likely subside after retirement.

Evidence-Based Medicine

As a result of finding a better habitat, the human population is constantly immigrating to a place with higher socioeconomic status. The question is whether immigrants have different prevalence of allergic diseases from the native population. In a recent study, the investigators surveyed 13–14-year-old adolescent and parents/guardians of 6–7-year-old children on prevalence of asthma, rhinoconjunctivitis, and eczema and other information such as birth in or out of the country and age of immigration. The survey comprised of 326,691 adolescents from 48 countries and 208,523 children from 31 countries. The investigator found out that immigration was associated with a lower prevalence of asthma, rhinoconjunctivitis, and eczema in both ager groups in comparison with those who were born in the country studied. They also noted that such association was limited in high prevalence/affluent countries. In addition, as the time of stay in the host country increased, there was rapid decrease in protective premigration environment.

In another study, the investigators studied the incidence of respiratory and allergic symptoms in Italian and immigrant children. Parental questionnaire was sent to all children of 3–14 years old (3854) who lived in the Viadana district with high 99 % response rate. The investigators noted that parental asthma, allergic rhinitis, and eczema were less frequent in immigrant children than in Italian children. In addition, the children born to foreign parents especially if born abroad had lower incidence of wheezing and eczema with respect to Italian children.

The above studies shed light in factors involved in prevalence of the allergic diseases.

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Chapter 4
Allergic Diseases of the Eye

Brett Bielory and Leonard Bielory

Physicians in all specialties frequently encounter various forms of inflammatory diseases of the eye that present as red eyes in their general practice. However, the eye is rarely the only target for an immediate allergic-type response (less than 5 % of allergic patients). Typically, patients have other atopic manifestations that affect the nose (rhinitis), sinuses (sinusitis), lungs (asthma), and skin (urticaria or eczema). However, ocular signs and symptoms may be the initial and the most prominent feature of the entire allergic response that patients present to their physician as reported in 2014 in the AIRS study.

The prevalence of allergies ranges as high as 30–50 % of the US population. Industrialized countries report greater allergy prevalence, starting with the original reports of vernal catarrh in Great Britain after the Industrial Revolution. Many theories abound about the increasing prevalence of allergies in the United States, such as climate change, increased industrialization, pollution, urbanization, and the hygiene theory. The combination of allergic nasal and ocular symptoms (rhinoconjunctivitis) is extremely common, but it is not clear whether the two are equal (i.e., whether rhinitis is more common than conjunctivitis or vice versa). In studies of allergic rhinitis, allergic conjunctivitis is reported in more than 75 % of patients and in more recent studies to be equal as a primary complaint to nasal symptoms, whereas asthma is reported in the range of 10–20 %.

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The eye is probably the most common site for the development of allergic inflammation because it has no mechanical barrier to prevent the impact of airborne allergens on its surface. The nasal and ocular symptoms more appropriately called *conjunctivorhinitis* or *rhinoconjunctivitis* depending on which target organ symptom predominates may be perceived as a mere nuisance; their consequences can profoundly affect the patient's quality of life. Seasonal allergic rhinitis and conjunctivitis have been associated with headache and fatigue, impaired concentration and learning, loss of sleep, reduced productivity, somnolence, functional impairment, and increased occupational risks for accidents or injuries secondary to sedating oral antihistamine therapy, especially those sold over the counter. Patients with seasonal allergies appear to suffer equally from conjunctivitis symptoms as rhinitis symptoms. However, over 50% of patients with rhinoconjunctivitis never appreciate the impact of their ocular symptoms until they receive specific targeted treatment to the ocular surface.

The Ocular Surface

The surface of the eye easily attracts many deposits such as allergens and other ocular irritants. These agents are concentrated in tears and can cause allergic conjunctivitis as well as toxic/irritant conjunctivitis. Overuse of vasoconstrictive agents used to alleviate allergic conjunctivitis can cause *conjunctivitis medicamentosa*. Uveitis, scleritis, or other systemic autoimmune disorders may also be a cause of red eye, but are also more commonly associated with complaints of pain. The effects of the allergic inflammatory response are mediated by the release of an array of mediators including histamine, leukotrienes, and neuropeptides.

Clinical Examination

The history and clinical examination provide clues for the clinician to refine their differential diagnoses for the patient suffering from chronic conjunctivitis commonly referred to as the "pinkeye" (Fig. 4.1). The clinical examination of the eyes for ocular allergy should include an examination of the periorbital tissue followed by the ocular surface. The eyelids and eyelashes are examined for the presence of erythema on the lid margin, telangiectasias, scaling, thickening, swelling, collarettes of debris at the base of the eyelashes, periorbital discoloration, blepharospasm, and ptosis that are seen in blepharoconjunctivitis and dermatoconjunctivitis. Next, the conjunctivae are examined for hyperemia (injection), cicatrization (scarring), and chemosis (clear swelling). The presence or absence of discharge from the eye is noted, as are its amount, duration, location, and color. Differentiation between scleral and conjunctival injection must be made in the clinical examination that can be established upon instillation of phenylephrine 2% drop to monitor presence of arterial blanching. Scleral injection (scleritis) tends to develop over several days and is associated with severe intraorbital ocular pain on motion. Conjunctivitis is

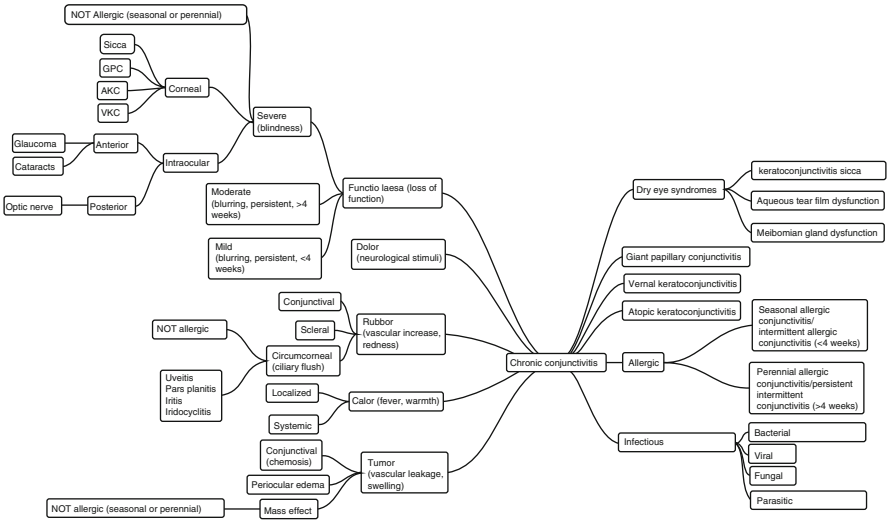

Fig. 4.1 The differential diagnosis of conjunctivitis is based on etiology of the underlying inflammatory response (i.e., infectious, allergic, or autoimmune); the signs and symptoms of inflammation (rubor, calor, dolor, tumor, functio laesa) can assist in honing of the etiology and provide a more focus approach to treatment

associated with discomfort, but not *pain*. Scleritis commonly develops in patients with systemic autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and Wegener's granulomatosis, but it has been known to occur in the absence of any other obvious clinical disorders. Ciliary flush is another form of ocular injection described as a ring of erythema around the limbal junction of the cornea that is a clinical sign for intraocular inflammation and uveitis. The bulbar and tarsal conjunctival surface should also be closely examined for the presence of inflammatory follicles or papillae. Follicles may be distinguished as grayish, clear, or yellow bumps, varying in size from pinpoint to 2 mm in diameter with conjunctival vessels on their surface, whereas papillae contain a centrally located tuft of blood vessels. The cornea is rarely involved in acute forms of allergic conjunctivitis, whereas in the chronic forms of ocular allergy, such as vernal keratoconjunctivitis and atopic keratoconjunctivitis, the prefix kerato- reflects the common involvement of the cornea.

The optimum examination of the cornea is with the slit-lamp biomicroscope. However, many important clinical features may be seen with the naked eye or a handheld direct ophthalmoscope. The direct ophthalmoscope can provide the desired magnification by "plus" (convex) and "minus" (concave) lenses. The cobalt blue filter on the new handheld ophthalmoscopic heads assists in highlighting anatomic anomalies affecting the cornea or the conjunctiva, which has been stained with fluorescein. The cornea should be perfectly smooth and transparent. Mucus adhering to the corneal or conjunctival surfaces is considered pathologic. Dusting of the cornea may indicate punctate epithelial keratitis. A localized corneal defect may develop into erosion or a larger ulcer. A corneal plaque may be present if the surface

appears dry and white or yellow. The limbus is the zone immediately surrounding the cornea and normally invisible to the naked eye, but when inflamed this area becomes visible as a pale or pink swelling. Some case reports of limbal allergy exist. Conjunctival erythema can be measured objectively with a spectroradiometer, which measures the chromaticity of reflected light. Erythema, edema, and itching can be graded on a Likert scale, e.g., 0–4 scale. Edema can be measured objectively by using a fractional millimeter reticule in the eyepiece of a slit-lamp microscope. Discrete swellings with small white eosinophilic collections at the limbal border (Horner-Trantas dots) are indicative of degenerating cellular debris, which are commonly seen in chronic forms of conjunctivitis. In addition, because the eye has thin layers of tissue surrounding it, there is an increased tendency to develop secondary infections that can further complicate the clinical presentation. Direct signs of inflammation such as conjunctival injection and edema significantly correlate with the severity of corneal complications. The height of papillae and the amount of mucous discharge do not necessarily correlate with the severity of corneal complications, but appear to be associated with location of corneal changes.

Immunopathophysiology of Ocular Allergy

Allergic diseases affecting the eyes constitute a heterogeneous group of clinicopathologic conditions with a vast array of clinical manifestations that range from simple intermittent symptoms of itching, tearing, or redness to severe sight-threatening corneal impairment. Inflammation of the conjunctiva rather than mechanical factors plays a greater role in the formation of corneal damage in chronic allergic eye disease. These conditions may be considered part of an immunologic spectrum that affects the anterior surface of the eye with a variety of disorders that may overlap and include seasonal and perennial allergic conjunctivitis, vernal and atopic keratoconjunctivitis (VKC, AKC), and giant papillary conjunctivitis (GPC). In addition, tear film dysfunction, also known as dry eye syndrome, commonly complicates ocular allergy and its treatments, especially as the age of the patient increases. Tear film dysfunction is also included in the spectrum of IgE-mast cell hypersensitivity conditions as it commonly overlaps with mast cell and cell-mediated disorders, but involve different mechanisms, cytokines, and cellular population. For example, mast cell degranulation, histamine release, and eosinophils play key roles in the common forms of seasonal and perennial conjunctivitis associated with a TH2 lymphocyte cell population. By contrast, AKC and VKC are characterized by more chronic, inflammatory cellular infiltrates, primarily composed of CD8+ lymphocytes with minimal interplay with mast cells and note changes in cytokine production such as TH1 lymphocyte cytokine, gamma-interferon (IFN). Tear film dysfunction, which is a CD4+-mediated disorder, commonly complicates ocular allergy syndromes.

Mast cell mediators, such as histamine, tryptase, leukotrienes, prostaglandins, and cytokines in the tear fluid, have diverse and overlapping biologic effects, all of

which contribute to the characteristic itching, redness, watering, and mucous discharge associated with both acute and chronic allergic eye disease. Histamine alone is involved in regulation of vascular permeability, smooth muscle contraction, mucus secretion, inflammatory cell migration, cellular activation, and modulation of T-cell function. Histamine is a principal mediator involved in ocular allergy and inflammation that is derived from the human conjunctival tissue that contains approximately 10,000 mast cells per cubic millimeter. Large amounts of histamine are present in several mammalian ocular structures, including the retina, choroid, and optic nerve. Histamine receptors have been found on the conjunctiva, cornea, and ophthalmic arteries. Most ocular allergic reactions appear to be mediated through the effects on a combination of histamine receptors (H1, H2, and potentially H4) as it can induce changes in the eye similar to those seen in other parts of the body. These include capillary dilation leading to conjunctival redness, increased vascular permeability leading to chemosis, and smooth muscle contraction.

In more severe chronic allergy-related conditions, T cells are the key cellular players in ocular surface impairment. Two predominant inflammatory pathways are differentiated by the CD4+ and CD8+ cell markers, which involve different cytokines and are crudely considered as antagonistic of each other when activated. In previous reports based on conjunctival biopsies in allergic patients, cytokine profiling displayed that Th2 activation occurred in VKC, whereas both CD4+ and CD8+ activations were found in AKC. However, evidence for Th1 involvement has been noted in the more severe form with expression of gamma-IFN. Historically, studies using conjunctival biopsies or brush cytology specimens have demonstrated increased CD8+ cytokines in SAC: IL-4 and IL-13 and an increasing awareness for the potential involvement of IL-9. In addition, it is not rare for a patient treated for typical seasonal allergic conjunctivitis also to develop dry eye, tear film disturbance, Meibomian dysfunction, tear film hyperosmolarity, adverse effects from the repeated use of toxic preservative-containing topical drugs, or contact cell-mediated conjunctival or eyelid hypersensitivity, conditions linked to the CD4+ cascade.

The four major ocular allergies, SAC/PAC, AKC, VKC, and GPC, exhibit increased levels of conjunctival cell adhesion molecules (CAMs) and eosinophils in conjunctival scrapings. The tears of patients challenged with high-dose allergens have been found to exhibit eosinophil cationic protein (ECP), which correlates with their symptomatology. Eosinophils found in the conjunctiva of patients with VKC are considered to be the “histologic hallmark” of the disease. It has been suggested that because the quantity of eosinophils correlates highly with the allergic signs and symptoms of VKC patients, their clinical status could be represented by tear ECP levels, which also correlate highly with the number of eosinophils. A large amount of major basic protein (MBP) has also been found in the tears of patients with VKC associated with the corneal ulcerations. In vitro experiments have shown that MBP exhibits corneal toxicity and retards wound repair in corneal epithelial cells. The number of eosinophils has also correlated with the severity of AKC with higher levels in patients with corneal erosions and ulcers compared to those with superficial keratopathy, which suggests that eotaxin causes corneal damage in AKC. Interestingly, patients with GPC have higher levels of eosinophilic infiltrate

than both VKC and AKC; however, tear ECP levels in these patients are significantly lower than tears from patients with VKC and AKC. Neutrophils and neutrophil-derived mediators (neutrophil myeloperoxidase, elastase) are also increased in the tears of both AKC and VKC. However, IL-8, which is a neutrophil chemoattractant, is increased in tears from AKC but not in tears from VKC. IL-8 still plays a role in the pathogenesis of VKC, but the response of IL-8 is enhanced in AKC. Colonization of *Staphylococcus aureus* is a possible explanation for the enhancement of IL-8 in AKC. Peptidoglycan from *S. aureus* has been shown to stimulate IL-8 release from conjunctival epithelial cells and is enhanced in the presence of gamma-IFN. AKC is a manifestation of atopic dermatitis, and 67 % of atopic dermatitis patients have colonization with *S. aureus* within conjunctival sacs and eyelid margins.

Acute Allergic Conjunctivitis

Allergic conjunctivitis (AC) is a bilateral, self-limiting conjunctival inflammatory process. AC occurs in sensitized patients with no sex difference. The most common target organ for the mast cell IgE hypersensitivity-mediated reaction may actually be the eye. The allergic reaction in allergic conjunctivitis is caused by direct exposure of the ocular mucosal surfaces to environmental allergens such as pollens from trees, grasses, and weeds. These allergens interact with the pollen-specific IgE found on the mast cells of the eye. Of all the various pollens, ragweed has been identified as the most common cause of "conjunctivorhinitis" in the United States. With the recent increase of ragweed growth in Europe and the Middle East, ragweed appears to contribute to approximately 75 % of all cases of hay fever with prevalence varying among different age groups in various regions of the world. Early allergy testing revealed Timothy grass as one of the most potent ocular allergy-inducing allergens. There are two forms of AC seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), which are defined by whether the inflammation is associated with seasonal change (spring, fall) or perennially. Both entities share the same inflammatory symptoms. However, seasonal allergic conjunctivitis is related to atmospheric pollens such as grass, trees, and ragweed that appear during specific seasons, whereas perennial allergic conjunctivitis is related to animal dander, dust mites, or other allergens that are present in the environment continuously. A major distinguishing feature between AC and VKC/AKC is that AC is self-limited, not causing ocular or visual damage, while VKC and AKC can involve the cornea causing visual damage. Common conjunctival symptoms in AC include itching, tearing, and often burning. Although involvement of the cornea is rare; blurring of vision can occur. Clinical signs include a milky or pale pink conjunctiva with vascular congestion that may progress to conjunctival swelling (chemosis). A white exudate may form during the acute state, becoming stringy in the chronic form. Ocular signs are typically mild; the conjunctiva frequently takes on a pale, boggy appearance that evolves into diffuse areas of papillae (small vascularized nodules), which tend to be most prominent on the superior palpebral conjunctiva. Occasionally, dark circles

beneath the eyes (allergic shiners) are present, which are formed as a result of localized venous congestion. The ocular reaction seen in both seasonal AC and perennial AC often resolves quickly when the offending allergen is removed. A detailed history from the patient or family members can expedite the diagnosis of AC. A family history of atopy or hay fever is often elicited. Both SAC and PAC are treated with agents that combine both antihistamines and mast cell stabilizers. The rationale for the dual treatment is rapid symptomatic relief with the antihistamine and long-term disease-modifying benefits with mast cell stabilization.

Vernal Keratoconjunctivitis

VKC is defined as a chronic allergic disorder of the conjunctiva mediated by mast cells and lymphocytes. There are three major forms of the disease: palpebral, limbal, and mixed. VKC is most prevalent in the spring (vernal). Symptoms include intense bilateral ocular pruritus, which is often induced by nonallergic stimuli: dust, wind, bright light, hot weather, or physical exertion. VKC is more common in prepubescent boys; however, after puberty, the sexes are equally afflicted with progressive dissipation of symptoms through the third decade of life. The most remarkable physical finding in VKC is giant papillae present on the tarsal conjunctiva, measuring 7–8 mm in diameter of the upper tarsal plate, which result in the cobblestone appearance seen on examination. Horner points and Horner-Trantas dots, thin, copious, mild-white fibrinous secretions or yellowish-white points, may be present. Other physical findings include an extra eyelid crease (Dennie's line), corneal shield ulcers, or a pseudomembrane formation of the upper lid when everted and exposed to heat (Maxwell-Lyon sign). VKC is most often bilateral; however, 5 % of patients are affected more in one eye with severe cases causing blindness. The use of a cobalt blue light with the application of topical fluorescein dye can reveal diffuse areas of punctate corneal epithelial defects. These defects may progress into shield ulcers, which are areas of desquamation of epithelial cells caused by the release of major basic protein from eosinophilic infiltrate. More than 50 % of patients with VKC do not report a history of atopic disease and do not show IgE sensitization, which proposes that VKC is not entirely mediated by IgE, but recent studies suggest increased local ocular sensitization to aeroallergens. VKC is characterized by infiltration of the conjunctiva by eosinophils, basophils, mast cells, CD4+ Th2, monocytes, macrophages, dendritic cells, plasma cells, and B lymphocytes organized as small lymphoid follicles. It is these infiltrates that cause the corneal involvement, photophobia, foreign body sensation, and lacrimation that are present in VKC. They serve not only as an anatomic barrier, but they are also capable of synthesizing chemokines, most notably eotaxin, a potent CC chemokine, and RANTES (Regulated on activation, normal T cell expressed and secreted) that can modulate inflammation. It has been noted that tarsal and bulbar conjunctival biopsy specimens with VKC have stained positive for estrogen and progesterone receptors, thus implicating that eosinophilic infiltrate in VKC may be influenced by these hormones.

The treatment of VKC includes cold compress, natural tears, avoidance of any known triggers, topical antihistamines, topical mast cell stabilizers, and periodic use of corticosteroids for acute exacerbations. The use of FK-506 has also shown favorable responses in VKC. In comparison to 2 % cyclosporine, FK-506 was shown to decrease symptoms of VKC up to 26 % from baseline, and FK-506 was not associated with the persistent burning sensation described with 2 % cyclosporine. Montelukast treatment of asthma patients with coexisting VKC resulted in decreased hyperemia, secretion, chemosis, burning, tearing, and photophobia. The benefits persisted 15 days after discontinuation of treatment, thus suggesting a role for leukotrienes in VKC with coexisting asthma. The plaques associated with VKC that can be caused by eosinophilic infiltrate may be removed by superficial keratectomy with possible reepithelialization of the cornea. Potential future treatments for VKC are targeting immunobiologicals targeting cytokine receptor antagonists to inhibit inflammation of the conjunctiva.

Atopic Keratoconjunctivitis

AKC is a bilateral, chronic mast cell and lymphocyte-mediated allergic disorder involving the conjunctiva, eyelids, and periorbital tissue often associated with a family history of atopy, eczema, and asthma. Approximately 15–40 % of patients with atopic dermatitis also have ocular involvement due to AKC. Patients often have atopic dermatitis and/or eczema from childhood and develop the ocular symptoms of AKC later in life, but pediatric and adolescent cases do occur. Primary care physicians should expect to see approximately 25 % of their elderly patients who have eczema to develop some components of AKC. It more commonly presents in individuals older than 50 years. There is no racial or geographical preference. AKC can cause disabling symptoms including blindness when the cornea is involved. Ocular symptoms of AKC are similar to the cutaneous symptoms of eczema, including intense pruritus and edematous, coarse, and thickened eyelids. Severe AKC is associated with complications such as blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex, ropelike mucus discharge, tylosis, and Meibomian gland dysfunction. The symptoms of AKC commonly include itching, burning, and tearing that are more severe than those seen in allergic conjunctivitis or perennial allergic conjunctivitis. The symptoms of AKC also tend to be present throughout the year and are associated with seasonal exacerbations, especially in the winter and summer months. AKC can be exacerbated by other allergic triggers, e.g., animal dander, dust, and certain foods. The chronicity of AKC and corneal infiltration are due to T-cell involvement. However, unlike vernal keratoconjunctivitis, which has a T helper cell type 2 profile, AKC is associated with a mixture of both T helper cell type 1 and 2. Of note, mast cells and eosinophils are found in conjunctival epithelium of AKC patients but not in patients not afflicted with AKC. Ocular disease activity in AKC correlates with exacerbations and remissions of the dermatitis. AKC-associated cataracts occur in approximately 10 % of patients with the severe forms of atopic dermatitis but are especially prone to

occur in young adults approximately 10 years after the onset of the atopic dermatitis. A unique feature of AKC cataracts is that they predominantly involve the anterior portion of the lens and may evolve rapidly into complete opacification within 6 months. AKC patients may also develop posterior polar-type cataracts due to the prolonged use of topical or oral corticosteroid therapy. A small percentage of patients with atopic dermatitis also develop keratoconus, a conical protrusion of the cornea caused by thinning of the stroma. Retinal detachment is increased in patients with AKC; however, it is also increased in patients with atopic dermatitis in general. An association has been found between exacerbations and specific microorganisms such as *S. aureus* and keratoconjunctivitis with specific IgE antibody to staphylococcal enterotoxin in tears of patients with VKC and AKC. Treatment for AKC involves corticosteroids, antihistamines, and mast cell stabilizers as well as treatment of any features of atopic dermatitis. The clinician should use antihistamines with caution in elderly patients because they cause increase drying of the conjunctival surface.

Giant Papillary Conjunctivitis

GPC is not a true ocular allergy, but rather the result of chronic mechanical irritation. Many of the features of GPC mimic other ocular hypersensitivity syndromes. GPC is even noted to have an increase in symptoms during the spring pollen season. Therefore, it is included in the differential diagnosis of ocular allergy. GPC has an association with extended-wear soft contact lenses and other foreign bodies, such as suture materials and ocular prosthetics. Lens-induced papillary conjunctivitis may develop 3 weeks after using soft contact lenses. Patients who wear rigid or hard contacts may develop symptoms of GPC within 14 months from the onset of wear. The pathogenesis of GPC is due to mechanical trauma followed by repeat immunologic presentation of foreign antigens, most often surface deposits or environmental agents. The signs of GPC include a white or clear exudate on awakening, which chronically becomes thick and stringy. The patient may develop papillary hypertrophy (cobblestoning), especially in the tarsal conjunctiva of the upper lid, which is more common in patients that wear soft contact lenses than hard contact lenses, 5–10 % versus 4 %, respectively. The contact lens polymer preservatives, such as thimerosal, and proteinaceous deposits on the surface of the lens have all been implicated in the cause of GPC. Common symptoms include intense itching, decreased tolerance to contact lens wear, blurred vision, conjunctival injection, and increased mucus production. Patients wearing contact lenses produce local antigenic factors that can trigger eotaxin production, which acts as a chemoattractant for eosinophils. The eosinophils then release major basic protein and toxic mediators causing the papilla formation. The treatment for GPC involves corticosteroids, antihistamines, mast cell stabilizers, and frequent enzymatic cleaning of the lenses or changing of the lens polymers. Disposable contact lenses have been proposed as an alternative treatment. GPC usually resolves when the patient stops wearing contact lenses or when the foreign body is removed from the eye.

Dry Eye Syndrome (Tear Film Dysfunction)

Dry eye syndrome (DES), also known as tear film dysfunction, develops from decreased tear production, increased tear evaporation, increased tear osmolarity, or an abnormality in specific components of the aqueous, lipid, or mucin layers that compose the tear film. DES is associated with atopy, female gender, and chronic medication use, including hormone replacement therapy. DES affects over 14 million people in the United States. Symptoms of DES are typically vague and include foreign body sensation, easily fatigued eyes, dryness, burning, itching, ocular pain photophobia, and blurry vision. Many symptoms overlap other forms of ocular allergy. Upon the onset of DES, patients complain of a mildly injected eye with excessive mucus production and gritty sensation, as compared with the itching and burning feeling that many patients report with allergy-associated histamine release onto the conjunctiva. Symptoms tend to be worse late in the day, after prolonged use of the eyes or exposure to adverse environmental conditions. DES has significant economic implications, including costs associated with increased health-care utilization, missed school and work, and leisure and quality-of-life issues. Although dry eye may occur as a distinct disorder resulting from intrinsic tear pathology, it is more frequently associated with other ocular and systemic disorders, including ocular allergy, chronic blepharitis, fifth or seventh nerve palsies, vitamin A deficiency, pemphigoid, and trauma. DES is a frequent confounding disorder that may complicate ocular allergic disease with several overlapping signs and symptoms, such as tearing, injection, and exacerbation. As the cornea becomes involved, the symptom progress to include photophobia as well as more scratchy and painful sensations. DES and ocular allergy conditions are not exclusive; as patients age, the likelihood of tear film dysfunction complicating ocular allergy increases. A more systemic form of DES, associated with systemic immune diseases such as Sjögren's syndrome, rheumatoid arthritis, and HIV infection, is commonly known as keratoconjunctivitis sicca and can be a symptom in postmenopausal women. The most common cause of DES is associated with the use of anticholinergic medications, which decrease lacrimation. Drugs with antimuscarinic properties include the first-generation antihistamines, phenothiazines, tricyclic antidepressants, atropine, and scopolamine and even newer antihistamine agents, such as loratadine and cetirizine. Other agents associated with a sicca syndrome include the retinoids, β-blockers, and chemotherapeutic agents. Tear film dysfunction is also associated with several pharmacologic agents, including antihistamines, anticholinergics, and certain psychotropic agents. Patients often note that their symptoms are exacerbated in the winter when heating systems decrease the relative humidity in the household to less than 25 %. The Schirmer test is used to diagnose DES. The test demonstrates decreased tearing (0–1 mm of wetting at 1 min and 2–3 mm at 5 min). Normal values for the Schirmer test are more than 4 mm at 1 min and 10 mm at 5 min. Tear osmolarity measurements also provide a qualitative assessment of tears as increased salt concentrations (increased osmolarity) correspond with severity of DES. Treatments for DES include addressing the underlying pathology, discontinuing the offending drug

(if possible), and making generous use of artificial tears or ocular lubricants. Topical cyclosporine (Restasis™) has been approved by the US Food and Drug Administration for the treatment of DES. For severe symptoms, insertion of punctual plugs may be indicated.

Contact Dermatitis of the Eyelids

Contact dermatoconjunctivitis is a delayed type of lymphocytic hypersensitivity reaction involving the eyelids and the conjunctiva as opposed to an ocular allergy, which activates the IgE mast cell. The eyelid skin is extremely thin, soft, and pliable and is capable of developing significant swelling and redness with minor degrees of inflammation or irritation. As a result, the patient frequently seeks medical attention for a cutaneous reaction that elsewhere on the skin would normally be less of a concern. Two predominant forms of contact dermatitis are attributed to cosmetics of the eye. These include contact dermatoconjunctivitis and irritant (toxic) contact dermatitis. Contact dermatoconjunctivitis is commonly associated with cosmetics to the hair, face, or fingernails (e.g., hair dye, nail polish) or with topical ocular medications (e.g., neomycin). Certain preservatives, such as thimerosal, which is in contact lens cleaning solutions, and benzalkonium chloride, which is in many topical ocular therapeutic agents, have both been shown by patch testing to be causes of contact dermatitis. The most common complaints associated with contact dermatitis are stinging, burning, and itching of the eyes and lids. The symptoms are subjective and are usually transitory if there is no evidence of objective signs of irritation. The patch test can assist in pinpointing the causative antigen, but interpretation of patch test results may be difficult. Patch testing is also associated with high false-positive reactions when associated with irritants. Patch tests performed with patients' own topical ophthalmic products are often negative. However, pretreatment with sodium lauryl sulfate increases patch test sensitivity.

Blepharoconjunctivitis

Blepharitis is a primary inflammation of the eyelid margins that is most often misdiagnosed as an ocular allergy because it commonly causes conjunctivitis secondary to a blepharitis. The most common causes are seborrhea and infection; the most common organism is *S. aureus*. The signs of staphylococcal blepharitis are dilated blood vessels, erythema, scales, collarettes of exudative material around the eyelash bases, and foamy exudates in the tear film. Antigenic products play the primary role in the induction of chronic eczema of the eyelid margins. Certain lipophilic organisms such as *Malassezia* yeast may be highly antigenic and induce chronic inflammatory reactions. Even a form of mite (Demodex) has been associated with refractory cases of blepharoconjunctivitis where the mite burrows into the rim of the

eyelid. Symptoms include persistent burning, itching, tearing, and a feeling of dryness. Blepharitis differs from dry eye syndrome in that the symptoms of blepharitis are more persistent in the morning than the evening and the symptoms of dry eye syndrome are more persistent in the evening. Crusted exudate develops with blepharitis that may prevent the eye from opening when the patient awakens in the morning. Blepharitis may be controlled with proper eyelid hygiene: using detergents (e.g., nonstinging baby shampoos) and steroid ointments applied to the lid margin with a cotton tip applicator that is used to loosen scales and exudate. Tea tree oil has been used in the treatment of Demodex infestation.

Ocular Allergy Treatment

A variety of treatment approaches have been used to manage allergic symptoms, foremost among them the avoidance of triggering allergens. In addition, pharmacotherapies with antihistamines, decongestants, nasal corticosteroids, mast cell stabilizers, and anticholinergics have all proven effective, as has immunotherapy. Ocular allergy treatment should be considered in a stepwise approach (Fig. 4.2). Primary treatment of any allergy, including ocular allergy, focuses on the avoidance of allergens. This strategy primarily involves the use of environmental interventions, from removal of the offending allergen source to a change of occupational venue. However, this is not often practical because it could mean attempting to avoid the outdoors or family pets. Lubrication is a form of avoidance, in that it has a dilutional effect on allergens and released mediators that interact with the conjunctival surface. Cold compresses provide considerable symptomatic relief, especially from ocular pruritus. All ocular medications should be refrigerated to provide additional subjective relief when applied to the conjunctival surface. Systemic agents can cause ocular drying that can alter the ocular tear film's ability to act as a protective barrier against external matter such as airborne allergens. This decreased tear production may decrease the eye's ability to wash allergens from the ocular surface, allowing them to remain there longer and possibly worsen allergic signs and symptoms. Secondary treatment regimens include the symptomatic use of topical agents, as well as oral decongestants, antihistamines, mast cell-stabilizing agents, and antiinflammatory agents. Topical decongestants primarily act as vasoconstrictors, which are highly effective in reducing the erythema and are widely used in combination with topical antihistamines. Adverse effects of topical vasoconstrictors include burning and stinging on instillation, mydriasis, especially in patients with lighter irises, and rebound hyperemia or conjunctivitis medicamentosa with chronic use. In the conjunctiva, H1 stimulation principally mediates the symptom of pruritus, as seen in various binding studies, whereas the H2 receptor has been inferred to be clinically involved in the vasodilation of the ocular allergic response. Although topical antihistamines may be used alone to treat AC, combined use of an antihistamine and a vasoconstricting agent is more effective than either agent alone.

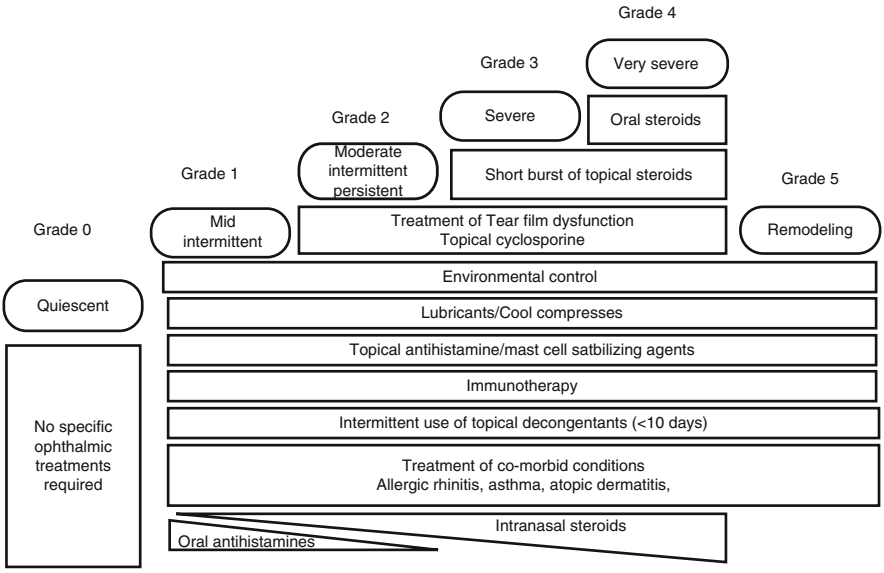

Fig. 4.2 The treatment of ocular allergy should proceed in a stepwise approach in concert of the treatment of other comorbid allergic disorders (e.g., allergic rhinitis, allergic urticaria, atopic dermatitis, tear film abnormalities/dry eye syndromes). Environmental control remains an important underpinning of all treatments of ocular that is complemented with nonpharmacologic treatments such as lubricants and cold compresses. Topical pharmacotherapy becomes the primary treatment when ocular symptoms predominate. The use of oral antihistamines should be limited to initial treatments as they may cause increased drying of the ocular surface in those that suffer from tear film insufficiency. Intranasal steroids improve mild symptoms of ocular allergy, but to be used when the patient has both nasal and ocular symptoms. Immunotherapy should be considered for those refractory to pharmacotherapy treatment

As monotherapy, oral or systemic antihistamines are an excellent choice when attempting to control multiple early-phase and some late-phase allergic symptoms in the eyes, nose, and pharynx. Despite their efficacy in relief of allergic symptoms, systemic antihistamines may result in unwanted side effects, such as drowsiness and dry mouth. Newer, second-generation antihistamines are preferred to avoid the sedative and anticholinergic effects associated with first-generation agents. SAC and PAC are ideally treated with a combination of antihistamine and mast cell stabilizers. These combination therapies have the advantage of giving immediate symptomatic relief via the antihistamine effect as well as having long-term modifying effects on the disease with mast cell stabilization.

When the allergic symptom or complaint is isolated, such as ocular pruritus, focused therapy with topical antihistaminic agents is often efficacious and clearly superior, either as monotherapy or in conjunction with an oral or nasal agent. Topical antihistaminic agents provide faster and better relief than systemic antihistamines. Topical antihistaminic agents also have a longer duration of action than other classes. However, their duration of action may not be as long as that of systemic

agents. Some of these agents have been found to have merits as topical multiple action agents possessing unique properties, including HI-receptor antagonism, low antimuscarinic properties, and H2-receptor antagonism; these maximize the symptomatic treatment of seasonal AC and are now widely used as first-line pharmacotherapy for ocular allergy. Many of the selective Hl-receptor antagonists have also demonstrated impact on cytokines that have an impact on the ocular late-phase reaction seen in more than 50 % of patients and may explain the persistent qualities of the acute allergic ocular reaction. For example, some of these newer antihistamines can block intercellular adhesion molecule-1 (ICAM-1) expression in epithelial cells, effectively reducing inflammatory cell mucosal infiltration and cytokines including IL-4, IL-10, and IL-17.

The use of mast cell stabilizers such as cromolyn was originally approved for more severe forms of conjunctivitis (i.e., GPC, AKC, VKC), but many physicians have used it for the treatment of acute seasonal and perennial AC with an excellent safety record. Mast cell stabilizers inhibit degranulation and block the release of preformed mediators within the mast cell. For mast cell stabilizers to be effective, the mast cell has to be deactivated before the allergic reaction is triggered. However, mast cell stabilizers require a loading period and must be applied for several weeks before antigen exposure to fully decrease the allergic response. Compliance is important with the use of mast cell stabilizers because they require frequent, regular dosing. Some of the studies reflecting their clinical efficacy for seasonal and perennial AC found marginal efficacy when compared with placebo in clinical settings and some animal models. After many years of clinical use, the mechanisms of cromolyn are still unclear.

Ketorolac is a nonsteroidal antiinflammatory drug (NSAID) that inhibits the prostaglandin production involved in mediating ocular allergy. Ketorolac is indicated for itchiness associated with AC. Clinical studies have shown that topical NSAIDs significantly diminish the ocular itching and conjunctival hyperemia associated with seasonal antigen-induced AC and VKC. These agents, unlike topical corticosteroids, do not mask ocular infections, affect wound healing, increase intraocular pressure, or contribute to cataract formation. Some of the studies reflecting their clinical efficacy for seasonal and perennial AC showed marginal efficacy when compared with placebo in clinical settings and in some animal models. Ketorolac is associated with stinging on application that quickly dissipates.

Tertiary treatment of ocular allergy using more potent immunomodulatory properties such as steroids may be considered when topically administered medications, such as antihistamines, vasoconstrictors, or cromolyn sodium, are ineffective. However, the local administration of topical steroids may be associated with localized ocular complications, including increased intraocular pressure, viral infections, and cataract formation. Two modified steroids that are topically applied, rimexolone and loteprednol, have recently been investigated for their efficacy in AC. Rimexolone is a derivative of prednisolone that is quickly inactivated in the anterior chamber. Loteprednol is another modified corticosteroid that is highly effective in the acute and prophylactic treatment of AC.

Immunotherapy has been used for the primary treatment of allergies, once known as spring catarrh before the discovery of antihistamines and other pharma-

cologic agents. In fact, in the original report on allergy immunotherapy in the early 1900s, it was used to "measure the patient's resistance during experiments of pollen extracts to excite a *conjunctival* reaction." Immunotherapy primarily involves the subcutaneous immunotherapy (SCIT) application of the suspected proteins in various formulations, but recently has expanded into sublingual immunotherapy (SLIT) administration to a limited array of specific allergens.

Although initial SCIT studies did not specifically address ocular symptoms, more recent clinical studies have started to identify improvement in ocular signs and symptoms in a separate domain of assessment outcomes. Additional physiologic studies involving SCIT have demonstrated a logarithmic increase (10- to 100-fold) in the tolerance to the allergen in the conjunctival provocation test or improvement of ocular symptoms. Interestingly, when specific allergen immunotherapy was instituted in adults and children with multiple allergies, the treatment was both effective and specific to the allergens in their season. When increasing doses of specific allergen or allergoid immunotherapy are used, there is progressive control of allergic inflammation. Allergoid immunotherapy induces immunomodulation with fewer doses of treatment (e.g., four allergoid doses versus weekly or monthly allergen doses over the course of a year). Subcutaneous administrations of allergen solutions are not convenient for all patients. SLIT has also been attempted in the treatment of seasonal and perennial rhinitis with a statistical decrease in ocular symptoms. Some produce no changes in the rhinitis symptoms, suggesting that ocular symptoms may be more sensitive to treatment with allergen immunotherapy. SLIT requires daily administration months in advance of the patient's specific allergy season.

Experimentally, AC has been suppressed by the oral administration of the offending allergen in animal models, with the concomitant decrease in the development of allergen-specific IgE. Recent experimental studies on the use of sublingual immunotherapy have also shown statistical improvement in the nasal and ocular symptom scores, which are also associated with an increase in the threshold dose for the conjunctival allergen provocation tests. Experimental topical application of allergen or immunostimulatory sequence oligodeoxynucleotides has predominantly shown a decrease in the late-phase response. Future treatments for ocular allergy may concentrate on various immunobiologicals that interfere with the ongoing allergic inflammation response as well as targeting specific targets such as eosinophils with inhibition of IL-5, CCR-3, and other cytokines.

Vasomotor Conjunctivitis or Perennial Chronic Conjunctivitis

The identification of vasomotor conjunctivitis (VMC) or perennial chronic conjunctivitis (PerCC) is not commonly included in the differential diagnosis of allergic conjunctivitis, although it may occur in as many as 25 % of patients complaining of ocular symptoms that are commonly confused with allergy. These patients are by definition skin test negative, but they react to

environmental stimulants such as weather, pollution, and/or wind. These disorders need to be better defined, categorized, and classified to determine the best treatment modalities as it may represent a form of tear film dysfunction and may benefit by the treatment trial of DES.

Conclusion

The prevalence of ocular allergy continues to be clearly underappreciated; it has been an underdiagnosed and undertreated area in primary care medicine. The ocular symptoms associated with the most common ocular allergy conditions, such as SAC and PAC, are intricately linked to allergic rhinitis in more than 90 % of cases. The emergence of new medications and forms of immunotherapy (e.g., subcutaneous allergoid, sublingual immunotherapy) for the specific treatment of ocular symptoms offers a new field for improved patient care by the primary and subspecialty healthcare providers and with further research into the immunobiologicals may offer sight-saving treatments for patient suffering from the more chronic forms of ocular allergy that have corneal involvement.

Evidence-Based Medicine

One of new areas of research in allergy is the examination of epithelial integrity in the promotion of the ongoing allergic inflammation. In one of few head to head studies of topical agents comparing topical antihistamines that are commonly prescribed in the stepwise approach in the treatment of ocular allergy, two antihistamines, olopatadine and alcaftadine, were compared for their ability to modify epithelial cell changes associated with allergic conjunctivitis at time points selected to reflect acute (15 min) and late-phase (24 h) reactions. Using an animal with similar conjunctival allergen challenge for eosinophil numbers and for tight junctional protein expression, Dr. Ono reported that the two agents were similarly equivalent for control of the acute phase, but alcaftadine-treated animals had significantly lower conjunctival eosinophil infiltration than either controls or olopatadine-treated animals. Allergen challenge caused a significant decrease in expression of the junctional protein, ZO-1, and this decrease was prevented by alcaftadine but not by olopatadine, suggesting that alcaftadine may have therapeutic properties beyond its antihistamine action in its ability to reduce conjunctival eosinophil recruitment and a protective effect on epithelial tight junction protein expression.

One also needs to maintain perspective of the emerging pipeline for the treatment of anterior inflammatory disorders that are related including allergic conjunctivitis (AC) and dry eye syndrome (DES) of the novel techniques and molecular entities. Nye et al. reported on the potential use of intralymphatic immunotherapy, CpG

oligonucleotides, N-acetylaspartylglutamate, resolvins (omega-3 fatty acids), lymphocyte function-associated antigen-1 (LFA-1) antagonist, chlorogenic acid, and other potential agents as well as updated various agents undergoing trials.

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Chapter 5
Prevalence of Pollens in the United States and Elsewhere

Massoud Mahmoudi

Understanding the distribution and prevalence of pollens is an important step in strategizing the management of allergic rhinitis and allergic asthma. Whether we move from one region of the country to the other or traveling abroad, such information is crucial in implementing steps for prevention and management of daily symptoms.

Pollen grains are male gametophytes of gymnosperms and angiosperms or higher plants. Most pollens range in size from 10 to 60 μm in diameter, the small size allowing exposure through wind carriage and contact with the respiratory mucosa and conjunctiva.

Pollens are composed of an outer wall with an external layer (exine) and internal layer (intine) that enclose cytoplasm. Immediate hypersensitivity reactions can occur when pollen contacts mucosal surfaces, triggering proteins stored in the exine and intine to be released through apertures (pores or furrows) of the outer wall. Most clinically relevant pollens are wind-borne, or anemophilous, rather than being from entomophilous plants, which pollinate via insect carriers.

Pollens vary in morphologic structure by size, number and form of pores, thickness of the exine, and other features of the cell wall. For example, ragweed pollen is about 20 μm in diameter and has characteristic short spines, whereas grass pollens range from 30 to 40 μm, have a smooth surface, and are monoporate.

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Tree Pollen

Tree pollen allergens range from 20 to 60 μm in diameter. Prevalence of different types of tree pollens mainly depends on geography. The pollen from each tree genus is morphologically distinct and shows marked variation in terms of allergenicity, duration, and seasonal pattern of pollination. Cross-reactivity among species is uncommon. Thus there is higher specificity to skin testing with individual tree pollen extracts compared with grass pollens, which do have significant cross-reactivity.

Tree pollination season varies significantly between different regions but usually occurs during the springtime. The tree season is generally brief and rather distinct because pollination occurs before, during, or shortly after leaves develop in deciduous trees.

Most tree pollen characterization has been studied using birch, hazel, alder, white oak, olive, and Japanese cedar allergens. Bet v 1, a birch pollen allergen, has been studied closely; it is a commonly known allergen in the oral allergy syndrome, which is due to cross-sensitizations between food proteins and certain pollens.

Grass Pollen

Worldwide, grass pollen sensitivity is the most common cause of allergic disease, due to the wide distribution of wind-pollinated grasses. Grass pollen is the second most common cause of allergic rhinitis and seasonal asthma in the United States, following ragweed. The season generally occurs in the spring and summer. Grass pollen is typically released in the afternoon. Concentrations of grass pollen are generally low at high altitudes.

Grasses are of the family Poaceae. Most grass pollens range from 30 to 40 μm in diameter, each grain having one pore or furrow and a thick intine. Currently, immunochemical methods have identified between 20 and 40 different grass pollen antigens.

It is difficult to distinguish different types of grass pollen from each other by morphology. There is also significant cross-reactivity among the grass species, with the exception of Bermuda grass. Therefore, the relative importance of a grass species in a given region is usually determined by its regional presence.

Weed Pollen

Weeds are small annual plants that grow without cultivation and tend to have relatively inconspicuous flowers. Weed pollens range from 20 to 40 μm in diameter. Release of weed pollen depends on seasonal daylight variation and is released typically in the morning.

The most important allergenic weed group is the Compositae family, which includes the ragweed tribe (tribe Ambrosieae). Ragweed is the single most important cause of seasonal allergic rhinitis and asthma in North America. In the United States, the highest concentrations of ragweed are found in the central plains and eastern agricultural regions.

Ragweed pollen season occurs in the fall, generally between late August and early October. Ragweed is a prodigious plant, with a single plant being able to release one million pollen grains in a single day. It also has a long travel range, having been detected even 400 miles out at sea.

The first studies of ragweed pollen revealed two major allergens, Amb a 1 (antigen E) and Amb a 2 (antigen K). Now, eight other intermediate or minor allergens of ragweed have also been identified.

Methods of Pollen Collection

Various methods exist for quantifying pollen grains. There are three main types of air samplers: passive samplers, rotary-impact samplers, and slit-type volumetric spore traps.

Passive/gravitational samplers are placed in an exposed environment, where particles are allowed to collect on the surface, which can be a microscope slide or plate. These samplers tend to overestimate larger particles, which fall more rapidly. An example of this device is the Durham sampler.

Rotary-impact samplers are made of a collection surface that collects particles as it spins through ambient air. These devices are efficient for trapping larger particles but less efficient for particles less than 5 μm in diameter. Rotorod samplers that employ plastic rods as a collection surface are a common example of a rotary-impact device.

Slit-lamp samplers contain a vacuum pump that draws air in to a chamber in which a collection surface sits. This type of device can also convert observed pollen counts to actual volumetric counts in the ambient air. It has greater efficiency in collection compared to rotary devices. An example of a slit-lamp sampler is the Burkhard trap.

Worldwide Prevalence of Pollens

Clinically relevant pollens vary from region to region. Several factors may influence the pollen count in a particular region. For example, preseasonal rainfall influences vegetative growth, which then determines abundance of pollen. Also, the release of pollen from anthers is promoted by low humidity and increased winds.

The collection of dependable pollen count data is slowly being accomplished worldwide (Fig. 5.1).

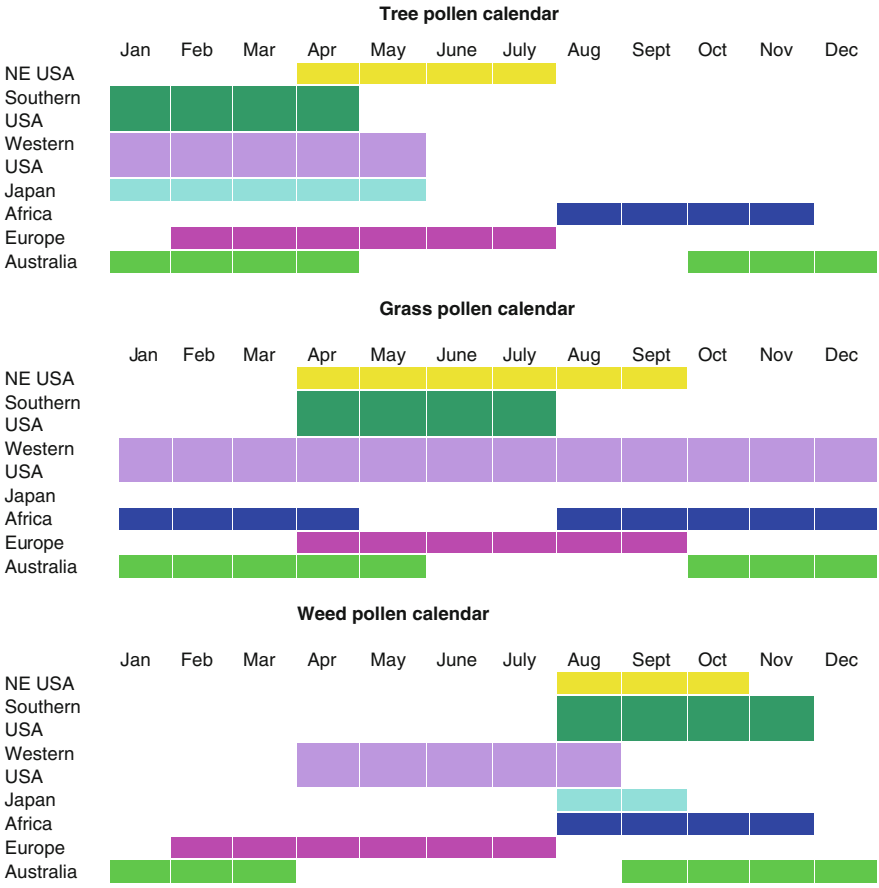

Fig. 5.1 World pollen calendar

North America

In most climates in North America, the allergy season begins with tree pollination. This usually occurs during late February through April but may start as early as December in regions with cedar trees. The main tree pollens present in North America include oak, alder, cedar, elm, birch, ash, hickory, poplar, sycamore, cypress, and walnut (Table 5.1).

Grass pollen season overlaps with the end of tree pollen season, starting approximately in May and lasting through July. The main North American grass pollens include timothy, Bermuda, orchard, sweet vernal, and red top and blue grasses.

In the late summer through October, weed pollination occurs. The most prominent weed causing allergic symptoms is ragweed, which is the single most important cause of seasonal allergic rhinitis in the United States. Other weeds include pigweed, marsh elder, dock/sorrel, plantain, Lamb's quarters, and Russian thistle.

Table 5.1 US regional pollens

Type of pollen	Genus and species
Northeast region of the United States	
Trees	
Oak (white, red)	*Quercus alba*, *Q. rubra*
Birch (yellow)	*Betula alleghaniensis*
Elm (white)	*Ulmus americana*
Cottonwood	*Populus deltoides*
Beech	*Fagus grandifolia*
Ash (white)	*Fraxinus americana*
Juniper	*Juniperus* spp.
Alder	*Alnus* spp.
Maple (sugar, red)	*Acer saccharum*, *A. rubrum*
Hickory	*Carya ovata*
Mulberry (red, black)	*Morus rubrum*, *M. nigra*
Red cedar	*Juniperus virginiana*
Sycamore	*Platanus* spp.
Walnut (black)	*Juniperus nigra*
Sweet gum	*Liquidambar styraciflua*
Grasses	
June/blue	*Poa pratensis*
Orchard	*Dactylis glomerata*
Timothy	*Phleum pratense*
Sweet vernal	*Anthoxanthum odoratum*
Red top	*Agrostis alba*
Rye	*Lolium* spp.
Weeds	
Ragweed	*Ambrosia* spp.
Lambs quarters	*Chenopodium album*
Sorrel	*Rumex* sp.
Plantain	*Plantago lanceolata*
Pigweed	*Amaranthus* spp.
Mugwort	*Artemisia vulgaris*
Cocklebur	*Xanthium strumarium*
Southeast region of United States	
Trees	
Oak (red, white)	*Quercus* spp.
Hickory (pecan)	*Carya* spp.
Maple (red)	*Acer rubrum*
Juniper/cedar	*Juniperus* spp.
Ash (white, green)	*Fraxinus americana*
Cottonwood	*Populus deltoids*
Sugar (hack) berry	*Celtis occidentalis*
Australian pine	*Casuarina* spp.

(continued)

Table 5.1 (continued)

Type of pollen	Genus and species
Mulberry (red, white)	*Morus* spp.
Sweet gum	*Liquidambar styraciflua*
Elm	*Ulmus* spp.
River birch	*Betula nigra*
Grasses	
June/blue	*Poa pratensis*
Timothy	*Phleum pretense*
Bermuda	*Cynodon dactylon*
Orchard	*Dactylis glomerata*
Johnson	*Sorghum halepense*
Red top	*Agrostis alba*
Rye	*Lolium* spp.
Bahia	*Paspalum notatum*
Weeds	
Ragweed	*Ambrosia* spp.
Sorrel	*Rumex* sp
Plantain	*Plantago lanceolata*
Pigweed	*Amaranthus* spp.
Burning bush	*Kochia scoparia*
Marsh elder	*Iva* spp.
Western water hemp	*Acnida tamariscina*
Russian thistle	*Salsola pestifer*
Midwest region of the United States	
Trees	
Oak (red, white, bur)	*Quercus* spp.
Elm (white, slippery)	*Ulmus* spp.
Box elder	*Acer negundo*
Hickory (pecan)	*Carya* spp.
Juniper/cedar	*Juniperus* spp.
Maple	*Acer* spp.
Birch	*Betula* spp.
Ash	*Fraxinus* spp.
Walnut	*Juglans* spp.
Cottonwood	*Populus* spp.
Willow	*Salix* spp.
Sycamore (eastern)	*Platanus occidentalis*
Grasses	
June/blue	*Poa* spp.
Orchard	*Dactylis glomerata*
Bermuda	*Cynodon dactylon*
Timothy	*Phleum pretense*
Rye	*Lolium* spp.

(continued)

Table 5.1 (continued)

Type of pollen	Genus and species
Red top	*Agrostis alba*
Weeds	
Ragweed	*Ambrosia* spp.
Russian thistle	*Salsola pestifer*
Burning bush	*Kochia scoparia*
Burweed marsh elder	*Iva xanthifolia*
Plantain	*Plantago lanceolata*
Pigweed	*Amaranthus* spp.
Pacific Northwest region of the United States	
Trees	
Alder	*Alnus* spp.
Juniper/cedar	*Juniperus* spp.
Birch	*Betula* spp.
Cottonwood	*Populus* spp.
Walnut	*Juglans* spp.
Ash	*Fraxinus* spp.
Willow	*Salix* spp.
Elm	*Ulmus* spp.
Oak	*Quercus* spp.
Grasses	
June/blue	*Poa pratensis*
Timothy	*Phleum pretense*
Rye	*Lolium* spp.
Brome	*Bromus* spp.
Red top	*Agrostis alba*
Weeds	
Sage	*Artemisia* spp.
Sorrel	*Rumex* spp.
Nettle	*Urticaceae* spp.
Pigweed	*Amaranthus* spp.
Southwest region of the United States	
Trees	
Juniper/cedar	*Juniperus* spp.
Elm	*Ulmus* spp.
Olive	*Olea europaea*
Ash	*Fraxinus* spp.
Mulberry	*Morus* spp.
Oak	*Quercus* spp.
Cottonwood	*Populus* spp.
Mesquite	*Prosopis* spp.
Box elder	*Acer negundo*
Grasses	

(continued)

Table 5.1 (continued)

Type of pollen	Genus and species
Bermuda	*Cynodon dactylon*
Johnson	*Sorghum halepense*
June/blue	*Poa* spp.
Weeds	
Ragweed	Ambrosia spp.
Sage	Artemisia spp.
Russian thistle	*Salsola kali*
Scales	*Atriplex* spp.

Africa

The most common pollens in Africa are grass pollens. South Africa, for example, has a very extensive grassland comprising more than 957 (10%) of the known grass species worldwide. African grasses belong largely to the subfamilies Chloridoideae and Panicoideae; Northern Hemisphere grasses are predominantly members of the Pooideae (Potter). There are an estimated 947 indigenous and 115 naturalized grass species. Common grass pollens include rye grass, Bermuda grass, kikuyu grass, and eragrostis. The grass season lasts through a majority of the year, stretching from August through April.

The tree season is comparatively shorter than the grass season, ranging from August through November. Common tree pollens include acacia, willow, cypress, oak, eucalyptus, plane, and poplar.

Weeds are not a highly prevalent source of pollen in Africa. However, plantain is a common weed.

Asia

Japan

The pollen responsible for a majority of seasonal allergic disease in Japan is Japanese cedar (*Cryptomeria japonica*). The Japanese cedar pollen is present from January through May. Another significant tree pollen is cypress. Weeds play a lesser role than tree pollens in Japan. Ragweed pollen is present in August and September.

India

Pollen counts vary in the different regions of India. In Northern India, tree pollens including Holoptelea, Eucalyptus, and Casuarina are highly prevalent, as well as Cassia grass. In Central India, dominant pollen types include Parthenium and Cheno/Amaranth weeds. Trees include Casuarina and Spathodia.

Australia

The most prevalent pollens in Australia are grass species, including rye, Bermuda, annual and Kentucky blue grass, Paspalum, and prairie grass. The southeastern area is the worst affected area because of its widespread grasslands and north winds. The grass season occurs during October through June.

The dominant tree pollens include the indigenous wattle and ti-tree, as well as birch, maple, olive, poplar, ash, and oak. Plantain is the most prevalent type of weed pollen.

Europe

Europe is a geographically complex continent with a diverse climate and wide spectrum of vegetation, resulting in much variation in the types of pollens found in different areas.

By far, the most prevalent allergen in Europe is grass. Timothy, orchard, meadow foxtail, and rye grasses are highly prevalent. The grass season occurs during May through July in Northern, Central, and Eastern Europe. In Mediterranean regions, grass begins and ends a month earlier. In general, grass flowering notoriously peaks in June.

Going northward, the tree season starts from April to late May and lasts generally through July. Pollens include birch, olive, hazel, alder, ash, and cypress. In Northern Europe, birch is a major cause of pollinosis, having the greatest allergenic potency. In Europe, the percentage of positive skin prick test to birch ranges from 5 % in the Netherlands to 54 % in Zurich, Switzerland. In Spain, Southern Italy, and Greece, olive pollen is one of the main causes of pollinosis, with its pollination season occurring from April to June.

Weed season occurs during February through October, and pollens include ragweed, mugwort, pellitory, nettles, and less commonly ragweed.

Evidence-Based Medicine

As discussed, several different methods for identification of pollen have been developed. Traditional measurements of exposure to pollen grains involve collection of an air sample and identification of the pollen sources on the basis of the morphologic characteristics of the particles viewed under a microscope. Durham and Burkhard methods are commonly used worldwide.

However, newer methods are being developed in hopes of obtaining more accurate pollen count readings. For example, under certain circumstances, a significant amount of airborne allergen is not associated with intact pollen grains because some are carried on paucimicronic particles.

In recent study, Benitez et al. used a flow cytometry technique to determine *Cupressus arizonica* pollen count and allergenic load (a particle that can be recognized by a specific antibody) using Cup a1 polyclonal rabbit antibody. In addition to the pollens, the investigators were able to identify a population of smaller incomplete pollens that were not defined by the light microscopy. They showed that the whole pollen and the smaller particles could induce allergic sensitizations.

In another development, the investigators studied the influence of meteorological parameters and air pollution on hourly fluctuation of birch (*Betula L.*) and ash (*Fraxinus L.*) airborne pollens. The importance of the study was based on the fact that the information obtained could help treatment and prevention of pollen allergies.

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Chapter 6
Allergic Rhinitis: Diagnosis and Treatment

Amber N. Pepper and Dennis K. Ledford

Introduction

Rhinitis is a syndrome defined by the symptoms of nasal congestion, postnasal drip, rhinorrhea, sneezing, and nasal itching, usually with physical findings of turbinate edema and increased secretions. The term implies inflammation as an essential component of the pathophysiology, but inflammation may not always be evident or confirmed in the pathophysiology of all rhinitis syndromes. Nevertheless, rhinitis, rather than rhinopathy or another term, is generally used to describe the constellation of symptoms listed. Classification of severity is generally based on symptom intensity and duration rather than physical examination or laboratory findings. Rhinitis may be subdivided into more than nine groups based on probable etiology or associations. These include allergic, idiopathic perennial nonallergic (sometimes referred to as vasomotor rhinitis), infectious, medication related (rhinitis medicamentosa), hormonal, atrophic, polypoid or hyperplastic, and rhinitis associated with systemic diseases. Some authorities divide nonallergic rhinitis into subgroups based on triggers (e.g., weather, odor, alcohol ingestion, or irritants among others), but the symptoms and physical findings of these rhinitis subgroups tend to be more alike than dissimilar, prompting others to classify all into one category, perennial nonallergic rhinitis (PNAR). Occupational rhinitis is a classification sometimes used, referring to irritant, nonallergic rhinitis or allergic rhinitis related to work environments. This chapter focuses on allergic rhinitis and includes the differential diagnosis of other rhinitis syndromes (Table 6.1)

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Table 6.1 Differential diagnosis of rhinitis

Allergic rhinitis
Seasonal/intermittent
Perennial/persistent
Local allergic rhinitis[a]
Perennial nonallergic rhinitis (PNAR or vasomotor rhinitis)
Gustatory rhinitis
Irritant/occupational rhinitis
Mixed rhinitis (concomitant allergic and nonallergic rhinitis)
Atrophic rhinitis
Nonallergic rhinitis with eosinophilia syndrome (NARES)
With or without polyps
Infectious rhinitis
Viral
Adenovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, rhinovirus
Bacterial
Haemophilus, Klebsiella, Mycobacterium, Staphylococcus, Streptococcus, Treponema
Allergic fungal rhinosinusitis
Rhinitis medicamentosa
Topical therapies
Cocaine, oxymetazoline, phenylephrine
Systemic therapies
α-Antagonists, β-blockers, estrogen or oral contraceptives, NSAIDS
Systemic diseases
Endocrine/hormonal
Diabetes mellitus, hypothyroidism, pregnancy/breast-feeding
Inflammatory/autoimmune
Cicatricial pemphigoid, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, relapsing polychondritis, reticular histiocytosis, sarcoidosis, Sjögren disease
Infiltrative
Amyloidosis
Structural disorders
Adenoid hyperplasia/cyst
Choanal atresia
Concha bullosa
Nasal polyps
Nasal septal deviation
Neoplasm
Angiofibroma (adolescent boys)
Esthesioneuroblastoma
Lymphoma
Sarcoma
Squamous cell carcinoma (smokers)
Ciliary defects

Table 6.1 (continued)

Foreign body
Cerebrospinal fluid rhinorrhea
Gastroesophageal reflux
Cystic fibrosis

NSAID nonsteroidal anti-inflammatory drugs
[a]Allergic rhinitis pathogenesis with eosinophilia but the absence of detectable systemic specific IgE and evidence of locally produced specific IgE

Table 6.2 Mediators and allergy symptoms

Mediators	Symptoms
Histamine	Itching
Prostaglandins	
Histamine	Sneezing
Prostaglandins	
Histamine	Nasal congestion/swelling (due to microvascular leakage)
Prostaglandins	
Leukotrienes	
Platelet-activating factor (PAF)	
Kinins	
Substance P	
Histamine	Mucous production
Leukotrienes	
Platelet-activating factor (PAF)	
Kinins	

Pathophysiology and Specific IgE

The pathophysiology of rhinitis is well defined for allergic, infectious, some medication related, and select systemic disease-associated rhinitis syndromes. The pathophysiology of allergic rhinitis stems from the degranulation of mast cells and the subsequent mucosal recruitment of inflammatory cells, particularly eosinophils. The role of mast cell degranulation has been confirmed by nasal allergen challenge, nasal lavage with analysis of mediators, nasal cytology, and nasal biopsy. Inflammation, characterized by recruitment of eosinophils into the nasal mucosa, is an essential component of the pathology of allergic rhinitis.

The symptoms of allergic rhinitis result from the combined effects of inflammatory cell recruitment and of the actions of mediators on receptors, for example, histamine 1 (H1) receptor or leukotrienes (LT), specifically LTD4, with the cysteinyl LT receptor 1. The mediators released from mast cells are responsible for the acute symptoms of allergic rhinitis, primarily itching and sneezing (Table 6.2 and Fig. 6.1). The mucosal inflammation is primarily a result of eosinophil immigration, activation, and persistence, due largely to factors released by the mast cell. The mast

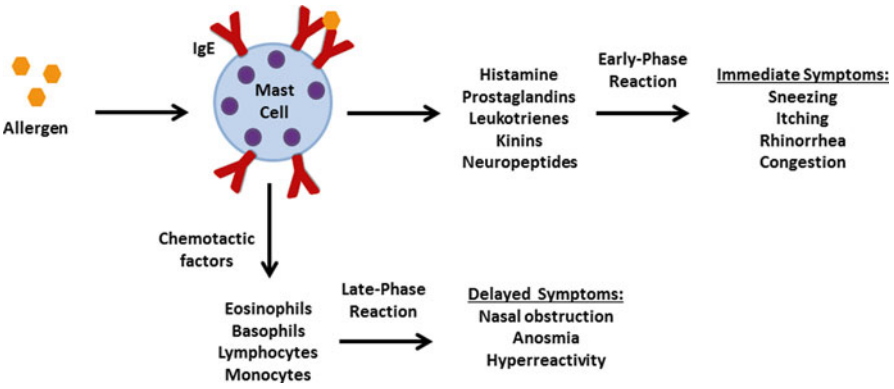

Fig. 6.1 Pathogenesis of allergic rhinitis

cell degranulates when high-affinity IgE receptors are cross-linked by antigen (allergen). IgE specific for a causal allergen is bound to the mast cell via the high-affinity IgE receptor, enabling the triggering of degranulation on exposure to specific allergen. The production of specific IgE is a result of the complex interaction of genetic predisposition and the environment. Exposure to environmental allergens, which is a risk factor for sensitization, does not result in uniform immune responses, even in subjects with similar, or even identical, genetic backgrounds. Modulation of the IgE response depends on variables such as the type of allergen, the route and dose of exposure, the timing of exposure (e.g., childhood versus adulthood), and concomitant or preceding exposure to infectious organisms or adjuvants, such as endotoxin. Genetic factors affect the epitope or specific portion of the antigen to which the individual responds (some epitopes are more likely to evoke an IgE response) as well as the immunologic regulation that modulates the tendency to produce IgE. Interactions between antigen-presenting cells, such as dendritic cells and B lymphocytes, T-regulatory cells (T_{reg}), group 2 innate lymphoid cells (ILC2), epithelial cells, and T helper 1- (Th1-) and Th2-like cells, determine the probability of specific IgG antibody formation versus IgE antibody formation versus tolerance to a specific allergen. To further complicate the understanding of this process, individuals may simultaneously be sensitized and tolerant to different allergens, for example, dust mite and cat, emphasizing that antigen properties, variation in exposure characteristics, and genetic factors regulate individual antigen responses. Finally, the blood concentration of specific IgE for a selected allergen or the magnitude of a skin test response with allergen does not generally correlate with the severity of symptoms on exposure to that allergen but rather the likelihood that the allergen is contributing to symptoms. Thus, a simple, unifying explanation of the allergic response or a measurable parameter that will consistently predict symptoms is not available.

The importance of specific IgE in the development of allergic rhinitis is confirmed by nasal challenge with allergen in subjects with specific IgE, correlation of symptoms with the level of allergen exposure, the predictive value of specific IgE in

determining response to specific allergen immunotherapy, evidence of mast cell degranulation with allergen contact, and the improvement of allergic rhinitis with anti-IgE monoclonal therapy. Local production of IgE, which would not be recognized by blood or skin tests, and non-IgE mechanisms of mast cell degranulation are hypotheses offered to explain allergic-like rhinitis in subjects without measurable, systemic specific IgE. Local allergic rhinitis is a distinct entity that presents with eosinophilia with evidence of locally produced specific IgE, but the absence of detectable systemic specific IgE.

Epidemiology

The prevalence of atopic disease in general and of allergic rhinitis in particular has increased during the past century. Currently, the prevalence of allergic rhinitis worldwide is between 20 and 30 %, increased from approximately 10–15 % at the midpoint of the twentieth century. The increase is more apparent in affluent socioeconomic circumstances, particularly Western Europe, North America, Australia, and New Zealand. Explanation for this increase remains elusive, with a variety of hypotheses summarized in Table 6.3. The hygiene hypothesis, as first suggested by Salzman and colleagues in 1979, is probably the most widely accepted explanation. This hypothesis proposes that reduced infections and endotoxin exposure in infancy diminish the stimuli to convert the Th2-like immune response (allergic-like with a predominance of interleukin 4 [IL-4] and IgE production) present at birth to a Th1-like response (nonallergic with gamma interferon production and reduced IgE). The endotoxin association suggests that the innate immune system and Toll-like receptors (TLRs) are important in the conversion of Th-2 to Th-1-like immune responses. The data supporting this is found both in epidemiologic studies as well as experimental work. For example, urban children with similar ethnic and genetic backgrounds to those in rural farming areas have a higher occurrence of allergic rhinitis.

Table 6.3 Theories for the increase of atopic diseases in the past century

Hygienic changes leading to decreased exposure to infections
Clean water
Introduction of broad-spectrum antibiotics
Use of vaccinations
Decrease in parasitic infections
Improved food preparation
Lifestyle changes
Increased time indoors with more exposure to indoor allergens
Urbanization with decreased exposure to farm animals
Increase in obesity and more sedentary way of life
Dietary changes (high in calories, low in nutrients)
Reduction in family size with fewer older siblings
Reduced breast-feeding

Furthermore, the occurrence of allergic rhinitis correlates inversely with exposure to farm animals and to endotoxin in early childhood. Conflicting data are a reminder that the hygiene hypothesis is not proven, and additional explanations for the increased prevalence of allergic rhinitis are likely.

There is a bimodal age variation in the prevalence of allergic rhinitis: one peak occurring in either the mid to late teenage years or late childhood and the second peak occurring in the mid-1920s. Most affected subjects initially develop symptoms prior to adulthood. However, a notable proportion of people with allergic rhinitis report symptom onset after the age of 30 years. The prevalence of allergic rhinitis diminishes progressively as the population ages, but an individual may develop allergic rhinitis at any age.

The importance of allergic rhinitis is its prevalence and impact on the quality of life of affected subjects. Individuals with symptomatic allergic rhinitis do not learn or process information as well as those unaffected. Sleep quality and sense of vitality are also commonly diminished. The treatments used, particularly sedating or first-generation antihistamines, may compound these problems. Allergic rhinitis is also associated with a variety of other airway diseases or symptoms, including otitis media, sinusitis, cough, and asthma, and with other allergic conditions, including atopic dermatitis and food allergy. Treatment of allergic rhinitis improves asthma and may reduce the development of asthma in those predisposed. Treatment of rhinitis may also decrease other associated conditions, including sinusitis, otitis media, and sleep disturbance. Thus, the importance of diagnosing and treating allergic rhinitis extends beyond the simple relief of nasal complaints.

Classification of Allergic Rhinitis

Traditionally, allergic rhinitis has been separated into perennial allergic rhinitis (responsible allergens found indoors, such as dust mites, cockroach, mouse, dogs, and cats) with year-round symptoms or seasonal allergic rhinitis (responsible pollen allergens found seasonally outdoors, such as trees in the spring, grass in the summer, and weeds in the fall in temperate climates in the Northern Hemisphere). The Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop, in collaboration with the World Health Organization, recommended a different classification in 2001, using the terms intermittent and persistence and the severity classifications of mild and moderate/severe. Intermittent is defined as having symptoms for less than 4 days a week or less than four consecutive weeks of the year. Mild is defined as not affecting quality of life or normal daily activities. Most subjects who seek medical care are expected to be in the moderate/severe, persistent category because over-the-counter products are available for treatment of less severe disease. Published studies report that the ARIA classification is more useful in clinical assessments than the seasonal and perennial terminology, suggesting that persistent rhinitis as defined is not equivalent to perennial rhinitis and intermittent is not equivalent to seasonal. Both classifications are used clinically and in the medical literature.

Differential Diagnosis of Allergic Rhinitis

Allergic rhinitis is the most prevalent form of rhinitis and should be considered in any individual presenting with nasal complaints. Other possible diagnoses are listed in Table 6.1. The principal factors used in distinguishing allergic rhinitis from nonallergic rhinitis are summarized in Table 6.4, with history being the most important. The diagnosis of allergic rhinitis is presumptive until specific allergic sensitivity is identified by epicutaneous or percutaneous testing or in vitro-specific IgE testing. Immediate wheal and flare skin tests remain the most cost-effective means of identifying specific IgE. The value of intradermal allergy testing is primarily to exclude the diagnosis with negative results, with positive intradermal results providing only tenuous support for a diagnosis of allergic rhinitis. The evidence of specific IgE should be correlated with exposure and symptoms to support the diagnosis. Identifying environmental factors that trigger nasal symptoms is important in distinguishing allergic rhinitis from nonallergic or mixed rhinitis (components of both allergic and nonallergic rhinitis). For example, worsening symptoms from odor

Table 6.4 Diagnosis of allergic versus nonallergic rhinitis

	Allergic rhinitis	**Nonallergic rhinitis**
Age of onset	Usually <20 years of age	Usually >30 years of age
Triggers	Allergen exposure	Odor, irritants, temperature/weather changes, alcohol, food (gustatory)
Symptoms	Sneezing (>4 in succession) Pruritus Rhinorrhea (watery) Nasal congestion	Nasal congestion Rhinorrhea (clear or mucoid) Postnasal drip Sinus pressure Sneezing (<4 in succession)
Seasonal variation	Usually seasonal (if sensitized to outdoor allergens) May be perennial (if sensitized to indoor allergens)	Usually no seasonal association, although changes in symptoms with weather/temperature variation may be confused for seasonality
Family history of atopy/allergies	Presence of atopic disease	Absence of atopic disease
Associated atopic features	Allergic conjunctivitis Atopic dermatitis (eczema)	None
Physical exam findings	Transverse nasal crease Variable nasal mucosa but classically described as pale and boggy	Erythematous nasal mucosa with edema of turbinates Watery or mucoid secretions
Confirmatory tests	Nasal eosinophilia Positive specific IgE testing	Nasal eosinophilia only present in NARES, otherwise absent Negative specific IgE testing

NARES nonallergic rhinitis with eosinophilia syndrome

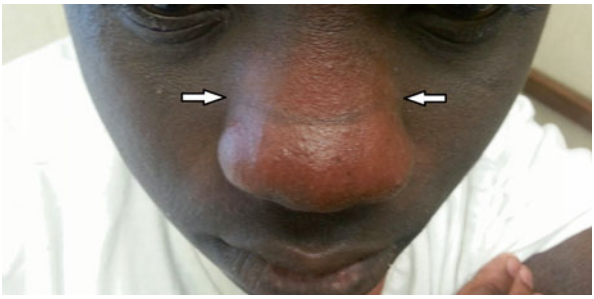

Fig. 6.2 Transverse nasal crease. Transverse nasal crease of allergic rhinitis. This photograph shows the transverse nasal crease (*arrows*) that is characteristic of allergic rhinitis. This linear change occurs from repetitive rubbing of the nose vertically, pushing the tip of the nose cephalad

would be attributed to nonallergic rhinitis, rather than allergic. If odor affects symptoms in a subject with allergic rhinitis, the individual has mixed rhinitis (i.e., coexistence of two rhinitis syndromes).

Congestion is the most common symptom prompting physician evaluation of nasal complaints but is nonspecific (Tables 6.2 and 6.4). Itching, particularly with rubbing of the nose vertically, is typical of allergic disease. The repetitive rubbing results in the characteristic "nasal crease" of allergic rhinitis (Fig. 6.2). Additional supportive historical features for allergic rhinitis include rubbing the tongue on the roof of the mouth, producing a "clucking" sound, and paroxysmal or episodic sneezing, particularly four or more in succession. Itching and sneezing are more common with intermittent or seasonal than persistent or perennial allergic rhinitis. The less frequent symptoms of itching and sneezing in persistent or perennial allergic rhinitis make it more challenging to diagnose.

The secretions in allergic disease typically are clear or white, but severe disease may result in cloudy mucus. Allergic rhinitis symptoms should be bilateral, with lateralizing complaints or findings suggesting an alternative diagnosis or a complication. The presence of other allergic diseases, particularly allergic conjunctivitis or atopic dermatitis, would also be strong support for the diagnosis of allergic rhinitis. Finally, family history is important because one immediate family member increases the likelihood of allergic rhinitis to approximately 40–50 %. Having two affected immediate family members makes the probability of having allergic rhinitis greater than 60 %.

Treatment of allergic rhinitis is reviewed in the next section.

Chronic or Perennial Nonallergic Rhinitis (Vasomotor Rhinitis)

Chronic or perennial nonallergic rhinitis (PNAR) is a term used to designate a heterogeneous group of disorders that share clinical features. The pathophysiology is not completely defined, and nasal histology does not correlate with symptoms.

PNAR is common, representing 30–60 % of subjects referred to an allergy/immunology or otolaryngology clinic for evaluation. PNAR coexists with allergic rhinitis in more than 50 % of adults with allergic rhinitis, a condition referred to as mixed rhinitis. Mucosal inflammation is less evident in PNAR than allergic rhinitis, making the term rhinitis sometimes a misnomer. However, the symptoms are consistent with other inflammatory nasal diseases, and inflammation may be present in a subset of PNAR.

The typical presentation of PNAR is complaints of nasal obstruction, with or without rhinorrhea or postnasal drip, exacerbated by physical stimuli such as odor (particularly floral smells), air temperature changes, air movement, body position change, food, beverage (particularly alcoholic drinks such as wine), or exposure to airborne irritants such as cigarette smoke. Paroxysmal sneezing and itching are less common in PNAR than allergic rhinitis. A variant of PNAR, with copious rhinorrhea associated with eating or meal preparation, is termed gustatory rhinitis. Exercise often improves the symptoms of PNAR, contrasting with allergic rhinitis.

Non-IgE degranulation of nasal mast cells, by physical stimuli such as cold, dry air, and hyperosmolar mucosal fluid, is not likely a critical part of the pathophysiology of PNAR because the symptoms of nasal itching, sneezing paroxysms, and mucosal eosinophilia are typically absent. However, mast cell degranulation has been demonstrated with cold air challenge of the nose in PNAR. Neurogenic mechanisms may play a pathophysiologic role in PNAR because some affected subjects hyperrespond with nasal congestion following challenge with cholinergic agents, suggesting a type of nasal hyperreactivity similar to that occurring in the bronchial airway with asthma.

The diagnosis of PNAR is suggested by the symptom history, the nature of provoking stimuli, adult onset, and the absence of a family history of allergy. The nasal mucosa is variable in appearance but generally is congested with normal to erythematous color. The secretions are usually clear and do not contain a significant number of eosinophils or neutrophils. Other causes of nasal symptoms should be excluded because of the lack of a confirmatory diagnostic test for PNAR. The exclusion of perennial allergic rhinitis is particularly important because the symptoms of the two are similar, and some subjects have both conditions. Sinusitis should also be considered because many symptoms are common to both.

The treatment of PNAR is symptomatic because the pathophysiology is unknown. The physician should focus the therapy on the primary symptom. Decongestants, nasal saline to lavage irritants from the mucosa or to dilute secretions, and topical ipratropium bromide 0.03 % (Atrovent Nasal) for rhinorrhea are often helpful. Oral antihistamine therapy offers limited benefits, although the anticholinergic effects of first-generation, sedating antihistamines may be helpful for rhinorrhea. Topical antihistamine therapy with azelastine is efficacious and approved for treatment of PNAR, contrasting with the lack of approval for any oral antihistamine. Topical nasal corticosteroid therapy relieves symptoms of PNAR, probably by reducing glandular secretion and blood flow to the nose. An anti-inflammatory effect of corticosteroid is not likely important in PNAR since mucosal inflammation is not consistently present. The response to topical nasal corticosteroids is variable and not as

predictable as with allergic rhinitis. Although only select nasal corticosteroids have a US Food and Drug Administration (FDA) indication for PNAR, most likely all work and all are generally used. Nasal corticosteroids with a detectable odor, for example, fluticasone (Flonase), may aggravate symptoms, suggesting a preference for sprays without smell. Intranasal capsaicin, a substance which depletes the neurokinin substance P and the active component of Sinus Buster, significantly improves symptoms in patients with PNAR as demonstrated by a placebo-controlled, clinical trial. Regular aerobic exercise, 20–30 min two to three times a week, may help reduce PNAR symptoms, at least temporarily, and is good for general health. Nasal congestion and sinus pressure are often the most bothersome symptoms, so emphasis on avoidance of regular topical decongestants is important because this may lead to rhinitis medicamentosa or rebound worsening of congestion. Oral lozenges containing menthol may affect the perception of nasal congestion but have no measurable effect on congestion. Finally, affected subjects need reassurance and empathetic care to reduce "doctor shopping," unnecessary surgery, overuse of antibiotics, and overinterpretation of allergy tests.

Nonallergic Rhinitis with Eosinophilia

Nonallergic rhinitis with eosinophilia (NARES) is a syndrome generally distinguished from PNAR by the presence of eosinophils in the nasal secretions or mucosa. The symptoms cannot be distinguished readily from PNAR, and the family history is generally negative for atopy, increasing the clinical confusion between NARES and PNAR. Affected subjects suffer from perennial nasal congestion, rhinorrhea, sneezing, and pruritus, but do not have specific IgE for allergens, an increase in total IgE, or a personal or family history of atopy. The nasal secretions contain eosinophils, which distinguishes this condition from other forms of PNAR. The lack of an atopic personal and family history in NARES makes an undefined allergy unlikely as the cause. The condition may be part of the spectrum of eosinophilic rhinitis and nasal polyposis. Subjects with the aspirin triad or aspirin-exacerbated respiratory disease (AERD; nasal polyps with eosinophils, asthma, and aspirin sensitivity) experience eosinophilic rhinorrhea and nasal congestion prior to the development of nasal polyps, suggesting a spectrum of eosinophilic nasal disease (Fig. 6.3). However, most subjects with NARES do not develop AERD.

Allergic rhinitis and nasal polyposis are the principal diagnoses to be excluded when assessing a subject with NARES. Treatment is symptomatic with topical nasal corticosteroid therapy, generally the most effective pharmacologic agent. Symptom relief may require a higher dosage of nasal corticosteroid than generally required for allergic rhinitis. Titrating the dose of nasal corticosteroid against the presence of nasal eosinophils may be of clinical value in determining the appropriate dose. Azelastine reduces eosinophil chemotaxis in vitro, but has not been studied in NARES.

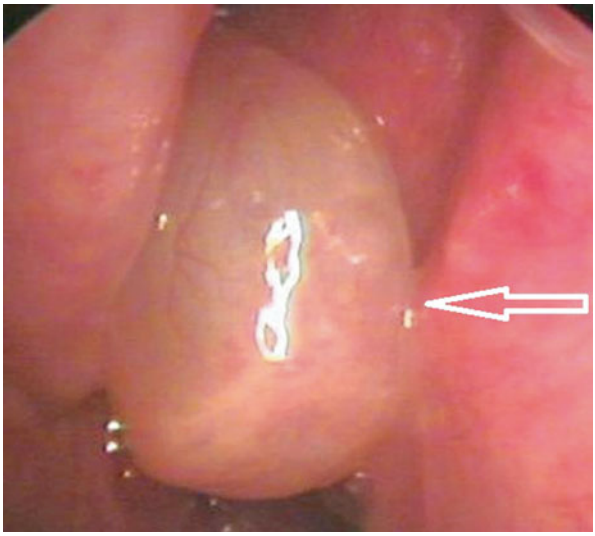

Fig. 6.3 Nasal polyp. This is a view from the rhinoscope in the left nostril. The septum is on the left, and the polyp is the pale soft tissue between the middle and inferior turbinate (*arrow*). Nasal polyps are associated with chronic inflammatory sinus disease, usually eosinophilic. Nasal polyps are not consistently found in subjects with allergic rhinitis but could explain persistent congestion. Cystic fibrosis is also associated with nasal polyps although not generally with eosinophilic inflammation

Rhinitis Induced by Drugs or Hormones (Rhinitis Medicamentosa)

Topical use of α-adrenergic decongestant sprays for more than 5–7 days in succession may result in a rebound nasal congestion following discontinuation of treatment or after the immediate effects have waned. Continued use of the decongestant to control withdrawal congestion can lead to an erythematous, congested nasal mucosa termed rhinitis medicamentosa. Regular intranasal cocaine use will have an even greater effect and should be considered in the differential diagnosis. Other systemic medications or hormone changes may also be associated with nasal symptoms, although the nasal mucosa may not always appear the same with each medication.

The mechanisms responsible for nasal symptoms associated with medications or hormones are variable. Antihypertensive therapies with β-blockers and α-adrenergic antagonists, less commonly calcium channel blockers and angiotensin-converting enzyme inhibitors, probably affect nasal blood flow. Oral α-adrenergic antagonists are also commonly used for symptom relief of prostate enlargement. Topical ophthalmic β-blocker therapy may also result in nasal congestion by the same mechanism. Oral phosphodiesterase inhibitors used for treatment of erectile dysfunction also are associated with nasal congestion, likely due to the enhancement of vasodilation from locally produced nitric oxide. Nasal congestion and/or rhinorrhea may

also result from changes in estrogen, and possibly progesterone, either from exogenous administration, pregnancy, or menstrual cycle variations. Hypothyroidism is associated with nasal congestion, rhinorrhea, and a pale, allergic-like nasal mucosa. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may result in congestion and rhinorrhea, primarily in subjects with AERD. Subjects with intermittent symptoms associated with aspirin or NSAIDs may be part of the evolving spectrum of chronic eosinophilic rhinosinusitis with nasal polyps (see section "Nonallergic Rhinitis with Eosinophilia").

The primary treatment of rhinitis medicamentosa is discontinuation of the offending agent or correction of the hormonal imbalance, if possible. Symptomatic treatment may be helpful. Treatment of rebound nasal congestion associated with topical decongestant use may require 5–7 days of oral prednisone or equivalent, 20–30 mg per day, followed by high-dose, topical, intranasal corticosteroid therapy. Reassurance that the nasal symptoms are the result of the medications or hormonal changes may be sufficient to discourage other unnecessary investigations if the medical treatments causing the rhinitis are essential.

Atrophic Rhinitis

Atrophic rhinitis usually occurs in late middle-aged to elderly patients. The cause of atrophic rhinitis is unknown with the leading theory being age-related mucosal atrophy, sometimes complicated by secondary bacterial infection. Primary atrophic rhinitis resembles the rhinitis associated with Sjögren syndrome or previous nasal surgery, particularly extensive turbinectomy. Examination generally reveals a patent nasal airway with atrophic erythematous turbinates, despite the symptoms of congestion.

Some subjects with atrophic rhinitis report crusting of the nasal airway and a bad smell (ozena). Ozena is associated with bacterial overgrowth of the mucosa, particularly by *Klebsiella ozaenae* or *Pseudomonas aeruginosa*. The appearance of ozena may resemble chronic granulomatous disease, such as granulomatosis with polyangiitis (Wegener granulomatosis) or sarcoidosis, or the effects of previous local irradiation. The prevalence of ozena is variable with a greater occurrence in select geographic areas, such as southeastern Europe, China, Egypt, and India, and a lower prevalence in northern Europe and the United States.

Symptomatic treatment of atrophic rhinitis with low-dose decongestants and nasal saline lavage is minimally effective. Individuals with confirmed sicca complex or Sjögren syndrome (Table 6.5) may benefit from oral cevimeline, 30 mg three times daily, keeping in mind that bronchospasm and arrhythmias are potential side effects. Oral antibiotic therapy is necessary for ozena. Topical antibiotic therapy, such as gentamicin or tobramycin, 15 mg/mL, or ciprofloxacin, 0.15 mg/mL in saline, may offer some benefit for subjects with atrophic rhinitis and recurrent mucosal infections or sinusitis, although no well-designed clinical studies are

Table 6.5 Potentially helpful tests in the diagnosis of systemic diseases with nasal symptoms

Disease	Laboratory tests and imaging studies
Common variable immunodeficiency	Quantitative immunoglobulins
Cystic fibrosis	Sweat chloride test CFTR genotyping
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)	ANCA (specifically p-ANCA)
Granulomatosis with polyangiitis (Wegener granulomatosis)	ESR ANCA (specifically c-ANCA)
Hypothyroidism	TSH
Immotile cilia syndrome	Saccharine taste test[a] Nasal fractional exhaled nitric oxide
Relapsing polychondritis	ESR CRP
Sarcoidosis	ESR Angiotensin-converting enzyme level Chest radiograph
Selective IgA deficiency	Quantitative immunoglobulins
Sjögren syndrome	ANA Anti-Ro (SSA), anti-La (SSB) Schirmer tear test[b]
Syphilis	RPR VDRL
Tuberculosis	Tuberculin skin testing Interferon-gamma release assays Chest radiograph

ANA antinuclear antibody, *ANCA* antineutrophil cytoplasmic antibody, *CFTR* cystic fibrosis transmembrane conductance register, *CRP* c-reactive protein, *ESR* erythrocyte sedimentation rate, *RPR* rapid plasma reagin, *TSH* thyroid-stimulating hormone, *VDRL* Venereal Disease Research Laboratory (test)

[a]Saccharine is placed with a cotton swab on the inferior turbinate, at the junction of the anterior and middle thirds of the turbinate. The time required for tasting is recorded, with normal usually less than 20 min. Greater than 30 min before tasting is considered indicative of dysfunction of ciliary motility. The patient must be instructed not to sniff, blow the nose, or use any topical nasal therapies during the test (Stanley et al., Corbo et al.).

[b]A 5 × 35 mm piece of sterile filter paper is folded 5 mm from the end and inserted over the inferior eyelid at the junction of the middle and lateral third. The eye is gently closed for 5 min, and the length of wetting is measured after removal. Less than 5 mm indicates significant dryness; normal is more than 15 mm (Available from Alcon Laboratories, Fort Worth, TX)

available to validate this treatment. The addition of propylene glycol, 3–15 %, or glycerin to nasal saline may prolong the benefits of topical moisturization by reducing the water's surface tension or reducing the irritation from irrigation. Application of petrolatum or petrolatum with eucalyptus/menthol (Vicks ointment) to the nasal mucosa at night may help reduce nasal bleeding. Topical shea butter (Butter Bar Moisture Therapy), an over-the-counter herbal therapy, also may be of some benefit but likewise is unproven.

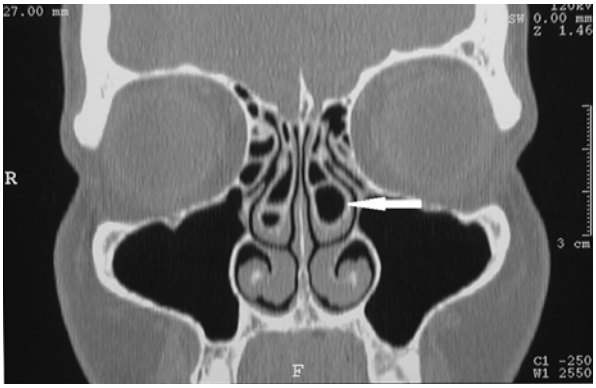

Fig. 6.4 Concha bullosa. This figure shows a coronal computed tomography scan image of the paranasal sinuses. The *arrows* point to the concha bullosa in each middle turbinate. In this case, septae divide the concha bullosa into more than one air space. The usual result of the concha bullosa is enlargement of the turbinate, usually resulting in chronic nasal congestion. Infection may occur in the concha bullosa. Frequently, the septum is deviated away from a unilateral concha bullosa. Therefore, this entity should be considered in a patient complaining of chronic congestion

Rhinitis Associated with Systemic Diseases or Anatomic Defects

The presence of systemic findings or the persistence of nasal symptoms despite treatment should prompt consideration of systemic diseases or anatomic problems resulting in nasal symptoms. Structural problems typically present with a predominance of unilateral symptoms or initially unilateral symptoms. Nasopharyngoscopy, paranasal computed tomography, and/or otolaryngologic consultation is an essential consideration with lateralizing nasal complaints, bleeding noted from one nasal airway, or unremitting congestion. Nasal septal deviations are the most common anatomic nasal variants noted, but often septal deviation is not primarily responsible for the symptoms, unless the deviation is very severe or coupled with mucosal disease such as allergic rhinitis or PNAR. A concha bullosa is an anatomic variant in which an air cell or cells occur within a nasal turbinate, often resulting in enlargement of the turbinate with congestion (Fig. 6.4). Profuse rhinorrhea should prompt testing of the secretions for glucose or for β-2 transferrin (β-trace protein) to exclude cerebral spinal fluid rhinorrhea.

Granulomatosis with polyangiitis (GPA or Wegener granulomatosis) may present initially with upper airway complaints, particularly hearing loss, intractable sinusitis, and persistent nasal congestion associated with purulent or bloody nasal discharge. Sarcoidosis of the nasal airway may appear similarly, although not usually as necrotizing. Persistent sinusitis or recurring infectious complications should prompt consideration of cystic fibrosis, partially cleft or submucosal cleft palate, humoral immunodeficiency, or ciliary dysfunction. Table 6.5 lists potentially useful tests to discriminate among the systemic possibilities.

Treatment of Allergic Rhinitis

The treatment of allergic rhinitis is three pronged—allergen exposure modification or avoidance, allergen immunotherapy (allergy shots or sublingual treatment), and pharmacotherapy. A stepwise approach to the treatment of allergic rhinitis is shown in Fig. 6.5. Clinical studies confirming efficacy of various therapies use symptoms as primary outcome variables. More objective means of assessing allergic rhinitis would be desirable, but such measures have not supplanted symptom scores in clinical trials or clinical care. Potential objective assessments include acoustic rhinometry, rhinomanometry, nasal peak flow, nitric oxide levels in exhaled air, concentration of mediators in nasal lavage, nasal cytology, and nasal histology. These assessments show promise, but difficulties with reproducibility, necessity of patient cooperation or mastering the technique, sampling error, and cost combine to reduce their utility. Using symptom scores as the primary outcome variable limits the ability to compare treatments, because the magnitude of response is not always consistent from study to study.

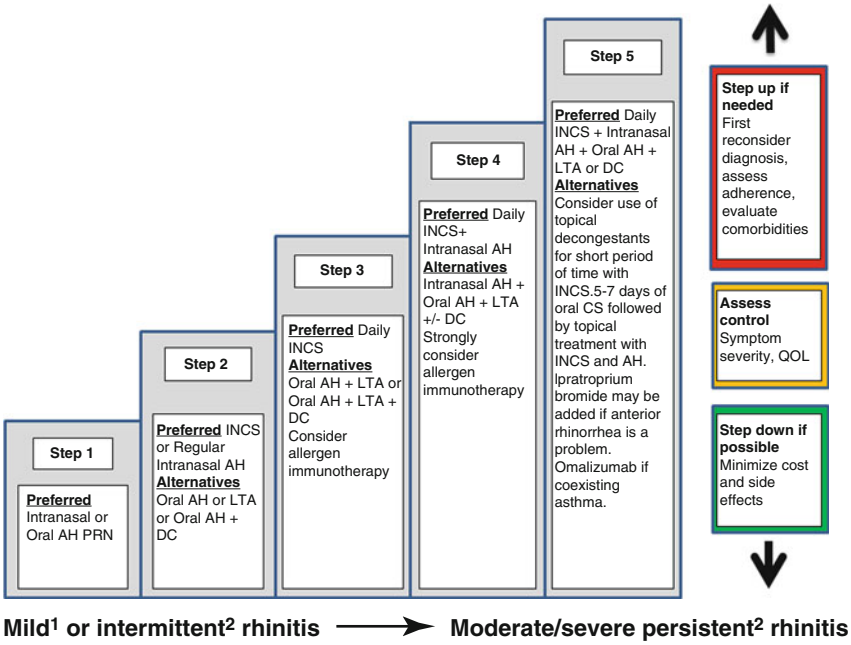

Fig. 6.5 Stepwise approach to the treatment of rhinitis (Adapted from Reference). *Legend*: *AH* antihistamines, *PRN* as needed, *LTA* leukotriene antagonists, *INCS* intranasal topical corticosteroid, *DC* oral decongestant, *CS* corticosteroid, *QOL* quality of life. [1]Mild indicates the absence of sleep disturbance, impairment of daily activities, impairment of school or work productivity. Symptoms are noted but not troublesome. [2]Intermittent is defined by ARIA as symptoms for 4 days or less a week or less than 4 consecutive weeks; persistent is greater than 4 days a week or 4 weeks

Allergen Avoidance

Avoidance is primarily helpful for indoor, domestic allergens, although occasionally modifiable occupational exposures, such as animal contact or colophony fumes during soldering, may be effective. Indoor avoidance focuses primarily on dust mite allergen reduction (encasing the pillow, mattress, and box springs with a material that does not allow dust mite movement) and washing all bedding in water at a temperature greater than 130 °F. Washing removes the allergen, which is primarily digestive enzymes present in dust mite excrement. The hot water is essential to control dust mite populations, the source of the allergen. Studies to show benefit of dust avoidance have failed when hot water washing was not assured. Air filter systems probably do not have a significant role in allergen avoidance, although high-efficiency particulate air (HEPA) filters may be helpful for homes with animals and possibly help with indoor mold spore reduction. Very little data support the use of filtration.

Allergen Immunotherapy

Specific allergen immunotherapy can be administered subcutaneously or sublingually. Indications include severe or persistent symptoms, poor response to medications, intolerance to or side effects from medications, or reluctance to take medications (Fig. 6.5). The main advantage of allergen immunotherapy, in addition to symptom improvement, is that the treatment alters the immune response. Immunotherapy shifts the immune response from Th2-like (pro-allergic) to Th1-like (nonallergic) upon exposure to an allergen, resulting in an increase in specific IgG, with some studies showing a switch from specific IgG1 to IgG4. This immunomodulation may reduce the development of additional sensitivities and minimize the occurrence of asthma in subjects with allergic rhinitis. Pharmacotherapy, aimed solely at symptom improvement, does not achieve these goals. Finally, immunotherapy offers the potential of treating allergic airway disease beyond the nose with improvement in allergic conjunctivitis and/or asthma.

Subcutaneous Immunotherapy (SCIT)

Traditionally, specific allergen immunotherapy has been administered subcutaneously. Subcutaneous immunotherapy (SCIT) is used for the treatment of seasonal and perennial allergic rhinitis, allergic asthma, and venom sensitivity with systemic reactions. SCIT provides a 50 % reduction in medication and symptoms if sufficient doses of the major allergens are administered to significantly (epicutaneous or percutaneous positive skin tests) allergic subjects. This improvement is confirmed by the majority of controlled trials with SCIT in both seasonal and perennial allergic

rhinitis. Duration of SCIT is based on clinical experience and limited evidence. In general, 3–5 years of maintenance treatment, usually administered every 3–4 weeks, is necessary to minimize reoccurrence of symptoms after discontinuation. Optimal duration minimum is likely longer for indoor, perennial allergens, suggested minimum of 4 years, compared to outdoor, seasonal allergic sensitivity, suggested minimum of 3 years.

The major impediments to SCIT are the inconvenience and cost of the therapy as well as the risk of anaphylaxis. Analyses have shown that high-dose allergen immunotherapy is cost-effective because of the reduction of regular medication use. Anaphylaxis following SCIT occurs in 0.1–3 % of treated subjects. This risk, which is minimized by identification and treatment of anaphylaxis, requires that SCIT be administered under the immediate supervision of a physician or health professional trained in the treatment of anaphylaxis. Treated subjects should remain under observation for 30 min after receiving SCIT to minimize risk of reaction after departure. Relative contraindications to SCIT include uncontrolled asthma, β-blocker therapy, and possibly angiotensin-converting enzyme inhibitor therapy. Some clinicians are less inclined to suggest SCIT in a subject with unstable autoimmune disease because of the theoretical, unproven possibility that autoimmune disease could be aggravated by the SCIT. SCIT should be initiated and supervised by a trained specialist but can be administered by any physician who is prepared to treat anaphylaxis, the most serious adverse effect of the treatment.

Sublingual Allergen Immunotherapy (SLIT)

In 2014, three sublingual tablets gained FDA approval in the United States for the treatment of allergic rhinitis, with or without allergic conjunctivitis, due to specific outdoor allergens. Two of the tablets are directed against grass pollens and the other against short ragweed. Oralair (Stallergenes) contains five northern grass pollens (Kentucky bluegrass, orchard, perennial rye, sweet vernal, and Timothy). Grastek (Merck) contains Timothy grass pollen. The third approved product, Ragwitek (Merck), contains short ragweed. A sublingual liquid containing short ragweed extract has also been studied. Appropriate candidates for sublingual immunotherapy (SLIT) must have documented positive epicutaneous or percutaneous skin test or in vitro-specific IgE testing to the allergen contained in the tablet. The first dose of each of these tablets must be administered under the supervision of a healthcare professional to monitor for anaphylaxis, but if tolerated, subsequent doses can be given at home. Given the inconvenience of recurrent office or clinic visits required with SCIT, the home administration of SLIT is attractive to patients. Grastek has the youngest approved age indication of 5 years. Oralair is approved for children and adults aged 10 through 65 years, and Ragwitek is approved for adults aged 18 through 65 years. Oralair and Grastek have an FDA Class B rating in pregnancy, while Ragwitek is Class C. SLIT can be given co-seasonally (initiated before the season and continued throughout the season) or year-round. If used co-seasonally,

Oralair should be started 4 months before grass pollen season. Grastek and Ragwitek should be started 12 weeks before the start of grass pollen season and ragweed pollen season, respectively.

Side effects of SLIT are generally localized to the mouth and gastrointestinal tract. Pruritus of the mouth and ears and throat irritation are the most common adverse reactions, but cases of eosinophilic esophagitis are reported. Sublingual immunotherapy may cause anaphylaxis, less than 1 case per million doses, and patients should be prescribed auto-injectable epinephrine during home administration. All of the tablets are contraindicated in patients with a history of severe uncontrolled asthma, anaphylaxis, or eosinophilic esophagitis.

In terms of efficacy, further evidence is needed to definitively compare SCIT and SLIT. However, some evidence suggests SCIT is superior to SLIT in the treatment of allergic rhinitis. Also, SCIT offers the advantage of treating multiple allergen sensitivities with a single injection, while SLIT is likely more effective for treatment of a limited number of allergens. Currently, there is no approved SLIT product in the United States which can be used in combination or contains multiple, non-cross-reacting allergens. The advantages and disadvantages of each administration modality should be discussed in order to choose the most appropriate immunotherapy for each individual patient.

Pharmacotherapy

Pharmacotherapy may be divided into two broad classes—topical or oral (Fig. 6.5). Advantages of topical therapy are greater efficacy for nasal complaints and limited adverse effects. Patient acceptance due to nasal irritation or taste is the major objection. Advantages of oral therapy include the potential to address the systemic nature of the allergic response and greater patient acceptance compared to sprays.

Topical Therapy of Allergic Rhinitis

Topical corticosteroids offer 70% improvement in approximately three-fourths of treated subjects, with the greatest response generally in allergic rhinitis. In addition, topical nasal corticosteroids improve symptoms in nonallergic rhinitis and subjects with nasal polyps, conditions that typically do not respond to oral therapy, other than corticosteroids and decongestants. Response with topical corticosteroids may occur within 7–12 h, but maximum effect requires days to weeks. Differences among the various products are minimal, although some agents (ciclesonide, fluticasone, mometasone) have a greater first-pass clearance of swallowed drug with less oral bioavailability. Almost 80% of a nasally administered drug is swallowed, but the relatively low dosage used in nasal therapy limits potential systemic side effects. However, studies with triamcinolone (Nasacort AQ) and beclomethasone dipropionate (Beconase or Vancenase) at recommended dosage demonstrated a significant, but small, reduction in growth of children. This is a reminder that systemic side

effects may occur with topically applied medications. Mometasone (Nasonex), triamcinolone (Nasacort AQ), and fluticasone furoate (Veramyst) have the youngest, approved age indication, 2 years of age, and budesonide (Rhinocort) has the safest Food and Drug Administration (FDA) classification for pregnancy, Class B, with other agents Class C. The most common side effect with nasal corticosteroid therapy is nasal bleeding. Bleeding is minimized by instructing the patient to administer the spray in a lateral direction or toward the ipsilateral ear, to minimize septal deposition. Mucosal atrophy does not occur with topical corticosteroids, but the anterior nasal septum and anterior inferior turbinate have a squamous epithelium, with a possibility of irritation, ischemia, and very rarely septal perforation with topical corticosteroid application.

Other topical nasal treatments include antihistamines (azelastine and olopatadine), ipratropium, and cromolyn sodium. Olopatadine reduces mast cell degranulation and is approved for seasonal allergic rhinitis. Azelastine seems to have anti-inflammatory properties when applied topically. These effects include inhibition of mast cell degranulation and inflammatory cell recruitment and reduction of adhesion receptors necessary for cell trafficking. Azelastine nasal spray is approved for both seasonal allergic rhinitis and nonallergic rhinitis. Presumably, the anti-inflammatory effects, rather than antihistamine properties, are important in the improvement of nonallergic disease because histamine does not seem to be an important mediator in nonallergic rhinitis. Thus, oral antihistamine therapy is ineffective for nonallergic rhinitis. Topical azelastine may provide symptom improvement within 30 min to an hour in allergic rhinitis, making this an ideal therapy for intermittent or as-needed use. A combination nasal spray containing both azelastine and fluticasone (Dymista) is approved for the treatment of seasonal allergic rhinitis in patients greater than 6 years of age. This combination therapy improves nasal symptoms significantly more than either treatment alone. Ipratropium nasal spray minimizes rhinorrhea by inhibiting muscarinic receptors. The indication is for both allergic and nonallergic rhinitis, but the treatment is not as effective for mucoid secretions as for watery secretions. Nasal sodium cromolyn is available over the counter. This product must be used every 4–6 h to be significantly effective because sodium cromolyn does not treat existing symptoms but rather reduces subsequent symptoms from mast cell mediator release. Nasal sodium cromolyn is likely to be useful in circumstances in which the affected subject can predict exposure to a known allergen and use the product before exposure. For example, an animal-allergic individual could use topical sodium cromolyn to suppress allergic rhinitis if the medications were applied prior to visitation of the home with the animal and if the sodium cromolyn is reapplied every 4–6 h. The requirement for regular administration makes sodium cromolyn relatively ineffective for chronic disease.

Oral Therapy of Allergic Rhinitis

Oral antihistamines, with or without decongestants, are the most commonly utilized approach in allergic rhinitis (Table 6.6). The second- and third-generation antihistamines offer excellent relief of itching and sneezing without the side effects of

Table 6.6 Oral antihistamines used in the treatment of rhinitis

Antihistamine	Generation	Availability[a,b]
Cetirizine (Zyrtec)	Second	OTC
Chlorpheniramine (Aller-Chlor; Chlor-Trimeton)	First	OTC
Clemastine (Tavist Allergy)	First	OTC
Cyproheptadine (Periactin)	First	Prescription only
Desloratadine (Clarinex)	Third	Prescription only
Diphenhydramine (Benadryl)	First	OTC
Fexofenadine (Allegra)	Third	OTC
Hydroxyzine (Atarax, Vistaril)	First	Prescription only
Levocetirizine (Xyzal)	Third	Prescription only
Loratadine (Claritin)	Second	OTC

OTC over the counter; trade name in parentheses
[a]Availability information for the United States of America
[b]Antihistamines listed are all available as generic

excessive sedation, dryness, constipation, or bladder dysfunction. Thirty percent improvement in 50 % of treated subjects is the approximate expected clinical response. The explanation for the reduced magnitude of response with oral antihistamine therapy, compared to topical nasal corticosteroids, is the general lack of improvement in congestion and inflammation and limited, if any, effect on nonallergic rhinitis. Nonallergic rhinitis may coexist with allergic rhinitis in up to 50 % of affected adults. In addition, symptoms of allergic rhinitis are the result of multiple mediators, limiting the benefits of a single inhibitor (Table 6.2 and Fig. 6.1).

Selecting an oral antihistamine therapy is often predicated on formulary coverage, cost, prior therapeutic trials, tolerance, degree of functional impairment, and personal bias. Sedating oral antihistamines, such as hydroxyzine or diphenhydramine, are very effective H1 inhibitors but are limited by anticholinergic side effects and sedation. Second- and third-generation antihistamines cause less anticholinergic side effects and sedation. Cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine are the second- and third-generation oral antihistamines available in the United States. Distinguishing these agents is a challenge and subject to individual opinion more than evidence. Several antihistamines are available over the counter, including diphenhydramine, cetirizine, loratadine, and fexofenadine. Others, including hydroxyzine, levocetirizine, and desloratadine, are available by prescription only. A complete list is shown in Table 6.6. Cetirizine, desloratadine, levocetirizine, and loratadine have the youngest approved age indication, 6 months. One study shows some benefit in 50 % of subjects after changing oral antihistamine therapy in individuals who have noted declining benefit with chronic antihistamine treatment. This supports the commonly reported phenomenon of “resistance” or tolerance to oral antihistamine therapy, without evidence of measurable change in the histamine receptor. Adding an oral decongestant to an antihistamine may improve the clinical response, particularly by reducing nasal congestion, but also may result in side effects of nervousness, sleep disturbance, increase in blood

pressure, tremor, and bladder dysfunction. This is a popular alternative due to the primal importance of nasal congestion among affected subjects.

Oral montelukast is also effective for seasonal and perennial allergic rhinitis and associated with minimal side effects. The degree of improvement is difficult to compare to oral antihistamine therapy but is probably equivalent to slightly less effective. An advantage of oral montelukast is a greater effect on asthma than oral antihistamines at approved doses. Montelukast may be particularly useful in a subject with cough, attributed to upper airway disease, but who may have a component of asthma as well.

Oral corticosteroid therapy of relatively short duration is effective for severe rhinitis associated with congestion such that topical therapy is limited by the inability to deliver the treatment to the affected mucosa. Oral corticosteroid therapy is also helpful for nasal polyps and rhinitis medicamentosa. Treatment is generally limited to 5–7 days to minimize side effects, and the dose is generally 0.5 mg/kg/day of prednisone or equivalent.

Future Therapeutic Options for Allergic Rhinitis

Future therapies for allergic rhinitis may include immunomodulators such as monoclonal anti-IgE (omalizumab), inhibitors of inflammatory cell immigration into the nasal mucosa, and anti-inflammatory therapies. Omalizumab binds to soluble IgE and also results in a reduction in the high-affinity receptor for IgE on mast cells and basophils and probably on select dendritic cells and B lymphocytes. Omalizumab is currently FDA approved for the treatment of moderate to severe, persistent asthma and chronic idiopathic urticaria unresponsive to oral antihistamine therapy. It is not approved for allergic rhinitis. Despite lacking FDA approval, omalizumab significantly improves symptoms and quality of life in patients with poorly controlled allergic rhinitis. Histamine 3 (H3) and histamine 4 (H4) receptor antagonists are considerations for the treatment of allergic rhinitis. H3 receptors modulate vascular patency in the nasal mucosa, and H4 receptors are expressed on mast cells, basophils, and eosinophils, making these receptors attractive targets for allergic rhinitis therapy. Modulation of TLRs is under investigation for the treatment of allergic rhinitis. Other potential therapies include cytokine inhibitors and phosphodiesterase 4 inhibitors. The potential of more rapid application of this cutting-edge science to allergic rhinitis is greater than other diseases due to the relative ease of applying these therapeutics to the nasal mucosa.

Conclusion

Allergic rhinitis is a common condition that significantly impacts the quality of life of affected subjects and occurs coincidentally with a variety of other airway, systemic, or allergic conditions. The application of an appropriate differential diagnosis and targeting therapy to the predominant symptom of the patient will allow the

physician to make a major difference in the lives of affected subjects. Nasal disease is complex in scope, but the two most common conditions, allergic rhinitis and perennial nonallergic rhinitis, can be assessed with a modest degree of investigation. As with most medical conditions, the history is paramount because the physical findings in rhinitis are somewhat limited or nonspecific. Consideration should always be given to systemic diseases other than allergy, particularly if the clinical data are inconsistent or initial response to therapy is disappointing. Appropriate allergy testing is essential to confirm the diagnosis of allergic rhinitis. Knowledge of the environment and the important allergens in a particular area are critical to understanding the results of allergy testing. Many of the "panels" offered by commercial laboratories are not targeted to specific environments. Allergists/immunologists have a unique advantage in the assessment of affected subjects because their training encompasses both the immunologic and environmental factors that affect the upper airway.

Evidence-Based Medicine

Tsabouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. J Allergy Clin Immunol Pract. 2014;2(3):332–40.e1.

Omalizumab, a monoclonal antibody which binds and neutralizes IgE, shows promise in the treatment of poorly controlled seasonal and perennial allergic rhinitis. This systematic review examines 11 randomized controlled trials including 2,870 subjects. Omalizumab significantly improved nasal symptoms and quality of life and reduced the use rescue medications. However, the magnitude of reduction in nasal symptoms was somewhat modest, especially when considering the substantial cost of this therapy.

Chelladurai Y, Suarez-Cuervo C, Erekosima N, Kim JM, Ramanathan M, Segal JB, Lin SY. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. J Allergy Clin Immunol Pract. 2013;1(4):361–9.

Dretzke J, Meadows A, Novielli N, Huissoon A, Fry-Smith A, Meads C. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. J Allergy Clin Immunol. 2013;131(5):1361–6.

Although both subcutaneous and sublingual immunotherapy are useful in the treatment of allergic rhinitis, the superiority of one mode of administration over the other is an area of active debate. Two systematic reviews attempted to assess if SCIT or SLIT is more effective. Dretzke et al. stated more head-to-head trials are needed to make a conclusion about the relative effectiveness of SCIT versus SLIT. However, Chellandurai et al. concluded there is moderate-grade evidence that SCIT is superior to SLIT in reducing allergic rhinitis and rhinoconjunctivitis symptoms. Continued research is needed to elucidate the comparative effectiveness of SCIT versus SLIT.

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Chapter 7
The Effect of Rhinitis on Sleep, Quality of Life, Daytime Somnolence, and Fatigue

Geetika Sabharwal and Timothy J. Craig

Introduction

Patients with allergic rhinitis, one of several inflammatory disorders of the upper respiratory tract, often suffer from impaired sleep. A recent survey of allergic rhinitis patients revealed that 68 % of respondents with perennial allergic rhinitis (PAR) and 48 % with seasonal allergic rhinitis (SAR) reported that their condition caused significant sleep disturbances. The major symptoms of the disorder, nasal congestion, mediators of the underlying inflammatory reaction, and other allergic symptoms such as ocular pruritus, can cause the sleep impairment associated with allergic rhinitis, daytime somnolence, and fatigue.

The symptoms of allergic rhinitis include rhinorrhea; sneezing; pruritus of the eyes, nose, and throat; and nasal congestion. Nasal congestion stands as one of the most prominent and bothersome symptoms of the disorder, especially since it is linked to sleep-related problems associated with allergic rhinitis, such as sleep-disordered breathing, including snoring and sleep apnea.

The prevalence of inflammatory disorders of the upper respiratory tract makes the sleep impairment associated with many of these disorders a common problem. Allergic rhinitis alone reportedly affects approximately 25 % of the world's population, and its prevalence has continued to climb. It has been estimated that the disorder affects 20–40 million people in the United States, which includes approximately 40 % of the nation's children. In Europe, the prevalence of allergic rhinitis is estimated as 23 % of the population.

Those who suffer from allergic rhinitis often cannot escape the socioeconomic burdens associated with living with the disorder. In 2000, patients spent over six

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billion dollars on prescription medications for allergic rhinitis. Along with this overwhelming cost of treatment, patients also experience the secondary cost of poor productivity, which stems from the negative impact of the disorder's symptoms on patients lives. Also, the use of therapies can induce daytime somnolence and other factors can impinge upon quality of sleep. The detrimental effect of allergic rhinitis on patient's quality of life has been demonstrated by generic health-related quality of life questionnaires, such as the Medical Outcomes Study Short Form Health Survey (SF-36), and disease-specific measures, such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). This adverse impact on patient's quality of life may result from the sleep impairment associated with the disorder.

Though studies have shown that treatments for allergic rhinitis, particularly those that improve symptoms of nasal congestion, can improve patient's sleep and quality of life, further research is needed to elaborate these limited existing data. This chapter explores the sleep impairment associated with allergic rhinitis and the adverse effects of disturbed sleep on patient's quality of life. This chapter will also examine how these effects are impacted by therapies that target the disorder's underlying problems influencing sleep.

Evidence for Sleep Impairment in Allergic Rhinitis

Allergic rhinitis and other inflammatory disorders of the upper respiratory tract are generally associated with sleep impairment, daytime somnolence, and fatigue. All of the multiple symptoms of allergic rhinitis, nasal congestion in particular, can detrimentally affect sleep. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (Table 7.1) serve to classify allergic rhinitis severity and provide a measure for this degree of sleep impairment. The sleep disturbances allergic rhinitis patients suffer from include microarousals and sleep-disordered breathing, which includes snoring to obstructive sleep apnea and/or hypopnea. Chronic excessive daytime sleepiness or fatigue has been demonstrated as a more likely disturbance in patients with frequent nighttime symptoms than in those with rare or no such symptoms. Further examples illustrating that sleep impairment is a major concern for

Table 7.1 ARIA guidelines for the classification of allergic rhinitis

I. Classified into intermittent and persistent based on symptoms	
Intermittent	**Persistent**
Symptoms present less than 4 days per week or less than 4 consecutive weeks	Symptoms present more than 4 days per week or more than 4 consecutive weeks
II. Classified into mild and moderate to severe based on severity	
Mild	**Moderate to severe**
Symptoms present but are not troublesome	Symptoms are troublesome
No sleep impairment or impairment in school or work or of daily activities, leisure, or sport	Associated with impairment of sleep and impairment of school or work and of daily activities, leisure, or sport

allergic rhinitis patients include studies showing that allergic rhinitis leads to snoring and that concomitant allergic rhinitis independently relates to difficulty sleeping and daytime sleepiness in bronchial asthma patients.

Mechanisms of Sleep Impairment

To alleviate the symptom of sleep impairment in patients with allergic rhinitis, the mechanisms involved in this problematic issue must first be identified. Recent studies have proposed that the reduced sleep quality and daytime fatigue characteristic in allergic rhinitis patients may consequently arise from sleep impairment secondary to symptoms of the disorder, particularly nasal congestion. Or, indeed sleep impairment may be due to the effects of the disorder itself, such as the underlying pathophysiological changes associated with allergic rhinitis leading to the release of cytokines and other inflammatory mediators.

Nasal Congestion

Nasal congestion, which results when the cavernous tissues of the nasal turbinates swell following dilation of the capacitance vessels, is a common and bothersome symptom that affects numerous allergic rhinitis patients. Its mechanism involves the reduction in the internal nasal diameter and the increase in airway resistance to nasal airflow. The symptom can also cause nasal obstruction. Subjective, clinical assessments of nasal congestion severity exist, as well as objective measures of nasal airflow, such as peak nasal inspiratory flow (PNIF), assessments of airway resistance and conductance (rhinomanometry), and acoustic rhinometry, which assess the volume and area of the nasal cavity by analyzing reflected sound waves.

The symptom of nasal congestion worsens at night and first thing in the morning, peaking at 6 AM, presumptively due to the posture change when an individual first lays down and to the normal decrease in serum cortisol levels overnight. The lower cortisol levels lead to greater nocturnal airway obstruction and may partially explain the large-amplitude circadian variation (Fig. 7.1). These changes and others noted in Table 7.2 may serve to explain why patients with inflammatory nasal conditions and nasal congestion often suffer from sleep impairment and daytime fatigue (Table 7.2).

Results from an Internet survey of 2355 individuals with allergic rhinitis or the parents of children with allergic rhinitis further reinforced the complaints of those suffering from the disorder. Eighty five percent of the respondents or their children reported experiencing nasal congestion, and 40 % of all respondents, the greatest proportion of participants who rated the severity of various symptoms, considered their nasal congestion severe (Fig. 7.2). Approximately 50 % of the respondents reported that nasal congestion was their most bothersome symptom and that it woke

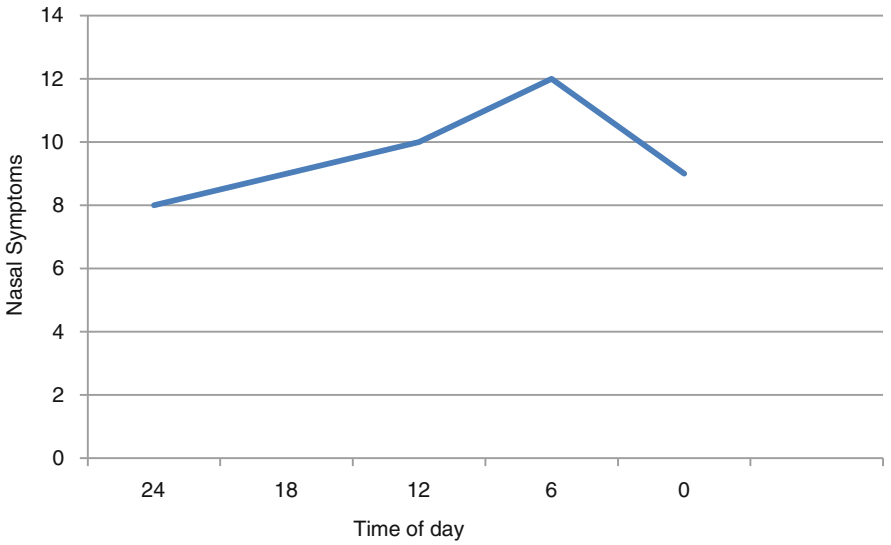

Fig. 7.1 Circadian rhythms in nasal congestion

Table 7.2 Factors causing circadian variation in allergic rhinitis

Specific reactions to allergens and histamines
Release of histamine mediators
Catecholamine secretion
Cell-mediated immunity
Increase vagal tone
Accumulation of secretions overnight
Mite and indoor allergen exposure is high

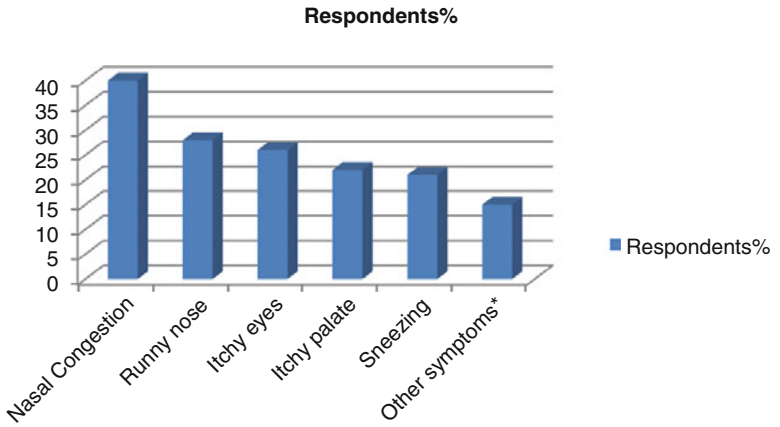

Fig. 7.2 Severity of symptoms in individuals with allergic rhinitis. *Other symptoms include watery eyes, itchy ears, and itchy nose

them during the night and made it difficult to fall asleep. Twenty percent of adult respondents claimed that their partner's or spouse's sleep was adversely affected by their nasal congestion, and the degree of sleep impairment correlated with the severity of their congestion. Moreover, the survey revealed that nasal congestion negatively impacted the individual's or their children's emotions and ability to perform daily activities, all of which may result from the detrimental effects of nasal congestion on sleep.

Studies on treatments for nasal congestion associated with allergic rhinitis, such as one by Craig et al. on treatment with topical nasal corticosteroids, propose that the poor sleep and daytime somnolence characteristic of the disorder is predominantly attributed to the symptom of nasal congestion. Increased sleep apnea and transient arousals even occur when subjecting healthy individuals to nasal occlusion with a noseclip. Previous studies that objectively assessed the sleep patterns of allergic rhinitis patients demonstrated that their symptoms of nasal congestion led to increased microarousals and episodes of apnea at night. Subjective instruments, such as Juniper's Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ), correlate with the objective findings noted on polysomnography. Allergic rhinoconjunctivitis patients who complained of impaired sleep due to nighttime symptoms found nasal and sinus congestion to be among their most bothersome and troublesome symptoms.

A population-based study on the role of acute and chronic nasal congestion in sleep-disordered breathing, which used 4927 subjects with a history of nasal congestion and impaired sleep, showed that patients with frequent nocturnal rhinitis symptoms, compared to those with rare or no symptoms, were more likely to complain of habitual snoring, chronic nonrestorative sleep, and excessive daytime fatigue. Additionally, the study illustrated that subjects with allergic rhinitis-associated nasal congestion were 1.8 times more likely to suffer from moderate to severe sleep-disordered breathing, compared to subjects with allergic rhinitis and no reported nasal congestion. Rhinitis and other forms of nasal obstruction must be considered and treated in patients with primary sleep-associated breathing disorders as an adjunct to surgical and nonsurgical treatment. Topical nasal steroids may enhance compliance and effectiveness of continuous positive airway pressure (CPAP) especially in patients, but not limited to those, with allergic rhinitis.

Immune Response Mediators

Histamine and cytokines are examples of inflammatory mediators released in the process of an allergic reaction, and such mediators, or the inhibition of, may directly influence the central nervous system and result in the disturbed sleep and daytime somnolence characteristic of allergic rhinitis. Histamine helps regulate the sleep-wake cycle and arousal, while the higher levels of the cytokines interleukin (IL)-1β, IL-4, and IL-10 seen in patients with allergies, compared with healthy individuals, correlate with increased latency to rapid eye movement (REM) sleep, decreased time

Table 7.3 Comparison of cytokines associated with rhinitis and sleep disturbance in patients with allergy, nonallergic patients, and patients with obstructive sleep apnea

Allergic individuals	Nonallergic individuals	Individuals with obstructive sleep apnea
Elevated IL-1β, IL-4, IL-10, and histamine	Elevated IL-1ra, IL-2, IL-12	Elevated IL-1, IL-6, TNFα, T-helper 2 lymphocytes, and bradykinin

Table 7.4 Assessment of sleep quality and quality of life based on questionnaires

Disease-specific questionnaires
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)
Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ)
Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)
General measures questionnaires
Epworth Sleepiness Scale (ESS)
Stanford Sleepiness Scale (SSS)
Pittsburgh Sleep Quality Index
Calgary Sleep Apnea Quality of Life Index
University of Pennsylvania Functional Outcomes of Sleep Questionnaire
Summary diary
Medical Outcomes Study Sleep Module (MOSSM)
Medical Outcomes Study Short Form 36 (SF-36)

in REM sleep, and decreased latency to sleep onset. It is postulated that any such disruptions in REM sleep may cause daytime fatigue, difficulty concentrating, and poor performance in allergic rhinitis patients. Inflammatory cells and mediators exhibit evident circadian variation, with its highest levels in the early morning hours, thus possibly explaining why the peak of allergic rhinitis symptoms frequently occurs upon waking and why nighttime sleep is detrimentally affected in the disorder. In addition, TNF, IL-1, and IL-6 are cytokines increased in allergic rhinitis and may cause daytime fatigue and other nonspecific generalized symptoms typical of a "flu-like condition." A list of inflammatory mediators in rhinitis that can account for the symptoms of daytime somnolence and fatigue is outlined in Tables 7.3.

Sleep Impairment and Quality of Life

The Effects of Sleep Impairment

Patients with allergic rhinitis often face adverse consequences of sleep disturbances, such as impaired cognitive function, decreased productivity, and poor performance. In children with allergic rhinitis, learning ability and school performance are

afflicted. While symptoms of the disorder may lead to these consequences, the sleep impairment caused by allergic rhinitis is the most likely cause of poor productivity. Sleep-disordered breathing and sleep impairment have been known to correlate with decreased quality of life in the general population. Specifically, it has been shown that experimentally induced sleep fragmentation in healthy subjects leads to impaired mental flexibility and attention, increased daytime fatigue, and impaired mood. Children and adolescents with allergic rhinitis also suffer from impaired sleep, which has been shown to result in problems doing schoolwork and poor school performance, compared to controls.

A survey across five European countries using patients suffering from allergic rhinitis or urticaria showed that a considerable proportion of respondents reported snoring or poor sleep and not feeling rested in the morning. Of these respondents, 29–79 % and 28–56 %, respectively, depending on the country, considered these problems either disruptive and extremely disruptive. Results from an Internet survey of 1322 individuals with rhinitis showed that both perennial and seasonal rhinitis interfered with sleep (68 % and 51 % of respondents, respectively) and daily routine (58 % and 48 %, respectively). Additionally, the sleep impairment suffered by allergic rhinitis patients has been linked to reduce psychological well-being, daytime fatigue, difficulty concentrating, and impaired psychomotor performance.

Measuring Sleep Impairment and Impact on Quality of Life

Studies on the subjective and objective measurements of sleep impairment and its influence on patients' quality of life particularly emphasize the major impact of this problem in patients with such inflammatory nasal conditions as allergic rhinitis. In patients with this disorder, the majority of studies have utilized subjective measures, such as questionnaires (Table 7.4) or daily scoring of symptoms, sleep problems, daytime somnolence, and fatigue. Juniper's Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) uses quality of life measures that are disease specific and includes a domain that assesses the effects of disease and/or treatment on patients' sleep. Such questionnaires emphasize the problems and symptoms patients commonly complain of and seek help for and are thus more sensitive to alterations in patients' quality of life than generic health status questionnaires. The Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ) focuses on the functional impairments of patients with nighttime symptoms and assesses problems and symptoms during sleep time, as well as upon waking hours. The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) focuses on similar symptoms but is designed for children. The Epworth Sleepiness Scale, Stanford Sleepiness Scale (SSS), Pittsburgh Sleep Quality Index, Calgary Sleep Apnea Quality of Life Index, and the University of Pennsylvania Functional Outcomes of Sleep Questionnaire, summary diary, Medical Outcomes Study Sleep Module, and Medical Outcomes Study Short Form 36 serve as general questionnaires that examine quality of sleep and daytime somnolence. However, the latter questionnaires

may be inadequate in their analysis of the mild-to-moderate sleep impairment characteristic of allergic rhinitis since they have less sensitivity.

Studies on allergic rhinitis that objectively assess sleep by using polysomnography are small in number. One such study observed 25 patients with SAR and 25 healthy volunteers, all of whom underwent two consecutive nights of polysomnography before and during the pollen season. The results showed statistically significant differences between the two groups in sleep parameters, which included increases in the apnea index (number of apneas per hour), hypopnea index (number of hypopneas per hour), apnea-hypopnea index (AHI), snoring time, amount of REM sleep, and sleep latency. However, the AHI was within normal limits (below 5 AHI per hour) both during and out of the allergy season, suggesting that rhinitis does not predispose to sleep apnea; however, the subjects did experience significant changes in some of the other outcomes of the study. Most importantly, statistical significance was also reported in daytime sleepiness, which was subjectively measured using the Epworth Sleepiness Scale, in SAR patients, compared to healthy subjects. These results suggest a correlation between subjective and objective measures of sleep impairment and worsening of sleep quality when allergy symptoms are active.

Effects of Therapy

Treatments aimed at reducing nasal congestion may alleviate sleep disturbances and daytime somnolence and consequently improve the quality of life in those who suffer from allergic rhinitis. However, the multiple treatments for the disorder vary in their efficacies.

Sedating antihistamines are no longer recommended in allergic rhinitis and are especially contraindicated in patients who complain of daytime sedation, fatigue, and functional impairment. Common treatment for allergic rhinitis includes nonsedating oral antihistamines, which alleviate nasal symptoms such as rhinorrhea, sneezing, and pruritus, but may be less effective in reducing nasal congestion. Studies by *Murray* et al., *Golden* et al., and others suggest that treatment using oral or topical antihistamines results in improved sleep and quality of life, but less so than topical nasal corticosteroids.

Oral decongestants are successful in improving nasal congestion but may detrimentally impact sleep due to their stimulatory effects and, additionally, may result in systemic side effects, such as tachycardia, urinary retention, and decreased sexuality. For these reasons the benefits of oral decongestants often outweigh the benefits. Topical decongestants improve sleep in patients with nasal obstruction but should not be used for more than a few days, due to the risk of rhinitis medicamentosa or "rebound" congestion. Minimal data are available suggesting that nasal corticosteroids and topical decongestants can be used together safely for prolonged periods, but more data are needed before suggesting this treatment.

Data, though very limited, shows that the anticholinergic agent, ipratropium bromide, may improve sleep and quality of life. However, ipratropium bromide appears to be unsuccessful in the relief of nasal congestion. Studies have shown that either leukotriene receptor antagonists as monotherapy or in combination with an antihistamine effectively improve sleep and quality of life in allergic rhinitis patients and in those who suffer from sleep-disordered breathing, but less so than topical nasal corticosteroids. Unfortunately, data addressing the benefits of immunotherapy (allergy vaccine) on sleep and daytime somnolence associated with allergic rhinitis are limited. Intranasal corticosteroids alleviate congestion and other nasal symptoms of allergic rhinitis and are used as first-line therapy when nasal obstruction is a predominant symptom in patients.

The Role of Intranasal Corticosteroids

Intranasal corticosteroids have been shown to effectively relieve all the nasal symptoms of allergic rhinitis including congestion. The effectiveness of intranasal corticosteroids in relieving nasal congestion may have a positive impact on sleep, daytime somnolence, and quality of life in patients who suffer from allergic rhinitis. Studies on adults and children with PAR support the hypothesis that intranasal corticosteroids decrease nasal congestion and subjective daytime sleepiness and fatigue and improve sleep and quality of life. Further studies displayed efficacy in the improvement of nasal symptoms and quality of life, as well as verbal memory. Treatment was also proven to alleviate allergic rhinitis associated with OSAS and to consequently lead to both significantly lower frequencies of apnea-hypopnea episodes and subjective improvements in nasal congestion and daytime alertness, though snoring noise was unchanged.

Studies in allergic rhinitis patients using the RQLQ, NRQLQ, and the Pittsburgh Sleep Quality Index revealed that intranasal corticosteroid improves both nasal congestion and health-related quality of life, including sleep. These studies therefore support the notion that treatments focusing on the nasal symptoms of allergic rhinitis may reduce sleep impairment and improve patients' quality of life.

Conclusions

The quality of life in patients with allergic rhinitis is detrimentally impacted by the sleep impairment associated with the disorder. One of the key causes leading to sleep disruptions and sleep-disordered breathing is nasal congestion, which is one of the most common and bothersome symptoms of allergic rhinitis. Recent research has led to the use of therapeutic agents that specifically target nasal congestion associated with sleep impairment.

Intranasal corticosteroids stand as effective treatment that significantly reduces nasal congestion in allergic rhinitis. Clinical trials using this treatment suggest that this reduction in nasal congestion correlates with decreased sleep impairment, reduced daytime somnolence, and improved quality of life.

Further research is necessary to definitively conclude with objective instruments that intranasal corticosteroids hold the ability to improve sleep and quality of life in patients with allergic rhinitis. In addition, studies with immunotherapy are needed since few have addressed sleep or daytime somnolence. These studies should utilize sleep-related measures as primary end points and assess sleep parameters both subjectively and objectively, thus serving to identify the most effective therapies for alleviating the detrimental effects of sleep impairment associated with allergic rhinitis.

Evidence-Based Medicine

The hypothesis of sleep and the consequences of poor sleep from allergic rhinitis has been primarily supported by controlled subjective assessments, but controlled objective studies have also shown that allergic rhinitis can interfere with sleep and that the reduction of nasal congestion correlates with improvement in daytime somnolence and fatigue. Nonetheless, better research studies are necessary with immunotherapy, allergen avoidance, and traditional medications, using objective measures and demonstrating a direct correlation between improvements of congestion, sleep quality, daytime somnolence, and fatigue and reduction in inflammatory mediators. In a recent study by Trikojat et al., seasonal allergic rhinitis patients had a slower processing speed during both symptomatic and non-symptomatic allergy periods. They showed a more flexible adjustment in attention control, which may serve as a compensatory strategy. Reduction in processing speed was positively associated with total IgE levels, whereas flexible adjustment of attention was linked with anxious mood. No association was found between seasonal allergic rhinitis-related attention deficits and allergy characteristics or sleep. These cognitive alterations are more likely to be influenced by mood and basal inflammatory processes than sleep impairments or subjective symptom severity.

In another study by Ridolo et al., parents of children suffering from allergic diseases were recruited from the Pediatric Allergy Units of Parma University. Evaluation of sleep in parents was based on the Pittsburg Sleep Quality Index (PSQI), while in children it was based on the Sleep Disturbance Scale for Children (SDSC). 75.6 % of them had a PSQI $\geq$5, indicating that most parents had a sleep quality perceived as bad. The PSQI $\geq$5 was more common in parents of children with asthma and rhinitis. In children, 62.3 % had a total score $\geq$39 on the SDSC. The quality of sleep in parents and children was significantly correlated ($p < 0.001$). These findings make it apparent that an alteration of sleep in children can also affect the parents. Such effect further weighs the burden of respiratory allergy and needs to be considered in future studies.

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Chapter 8
Sinusitis

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General Considerations

Inflammation or infection of the paranasal sinuses is termed *sinusitis.* Because sinusitis as a clinical entity rarely exists without associated rhinitis, the use of the term *rhinosinusitis* when referring to this disease entity is preferred. Acute and chronic rhinosinusitis affect approximately 12 % of the US population annually. The impact of rhinosinusitis results in nearly 25 million visits to physicians annually with direct and indirect health-care expenditures exceeding $11 billion. In addition to the financial implications, rhinosinusitis results in significantly reduced health-related quality of life with patients reporting worse scores than patients with other chronic medical conditions including congestive heart failure and chronic obstructive pulmonary disease. For these reasons, rhinosinusitis remains a subject of active research in both the medical and pharmaceutical communities.

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Classification of Rhinosinusitis

In the clinical setting, virtually all episodes of acute bacterial rhinosinusitis (ABRS) are preceded by viral rhinosinusitis (VRS) or the common cold. Studies consistently show that distinguishing VRS from ABRS is often difficult because the two conditions possess similar symptom profiles, and the available imaging modalities have failed to reliably distinguish between the two disease entities. VRS is also very common with adults averaging two to five episodes per year. This results in frequent inappropriate treatment of VRS with antibiotics and the potential development of antibiotic resistance. In fact, a recent randomized double-blinded placebo-controlled trial demonstrated that amoxicillin was no better than placebo in treating symptoms and duration of acute rhinosinusitis. Nevertheless, as the duration of the illness increases, the likelihood of a bacterial suprainfection increases. Therefore, the clinical diagnosis of ABRS may be made after 10 days of purulent nasal drainage with nasal obstruction and/or facial pain/pressure/fullness without improvement or an initial improvement in symptoms followed by worsening within 10 days from the onset of the upper respiratory infection (double worsening). Bacterial rhinosinusitis is arbitrarily categorized in terms of the duration of symptoms. Acute bacterial rhinosinusitis is diagnosed when signs and symptoms have been present for less than 4 weeks. Recurrent acute rhinosinusitis (RARS) is diagnosed in patients who have >3–4 episodes of ABRS/year. Subacute bacterial rhinosinusitis is diagnosed when signs and symptoms have been present for 4–12 weeks. Chronic rhinosinusitis (CRS) is diagnosed in patients with 12 weeks of two to four subjective symptoms and at least one objective finding of paranasal sinus inflammation (Table 8.1). Based on the presence of polyps on endoscopic examination, patients with CRS are broadly divided into two phenotypes: CRS without nasal polyposis (CRSsNP) and CRS with nasal polyposis (CRSwNP), although many feel that this does not adequately characterize patients with CRS given variance in histopathology. Patients diagnosed with CRSwNP may also have additional clinical characteristics that allow further subclassification such as cystic fibrosis, aspirin sensitivity and asthma (Samter's triad), or allergic fungal sinusitis which may alter treatment recommendations and outcomes.

Table 8.1 Diagnostic criteria for chronic rhinosinusitis (CRS)

Twelve weeks of symptoms including two or more of the following:
Mucopurulent drainage (anterior or posterior)
Nasal obstruction/congestion
Facial pain/pressure/fullness
Decreased sense of smell
AND one or more of the following objective findings:
Purulent sections or edema of the middle meatus or ethmoid region on endoscopy
Polyps in the nasal cavity or middle meatus on endoscopy
Radiographic imaging (CT preferred over MRI) demonstrating inflammation of the paranasal sinuses

Adapted from Rosenfeld et al. and Fokkens et al.

Anatomy

The anatomy of the nose and paranasal sinuses is highly variable and often complex. Knowledge of the anatomy and relationships (Figs. 8.1 and 8.2) of the paranasal sinus structures to each other and to other vital organs (orbit, optic nerve, and carotid artery) permits an understanding of the pathophysiology of rhinosinusitis as well as the factors that impede treatment and lead to recurrent disease. Each sinus is lined with mucosa consisting of ciliated pseudostratified columnar epithelium. The cilia propel mucus and debris toward the natural ostium of each sinus in a predictable fashion (Fig. 8.3).

The Septum and Turbinates

The septum anatomically divides the nasal cavity into two halves. It is composed of four bony and cartilaginous elements: the quadrilateral cartilage (anterior), the perpendicular plate of the ethmoid bone (superior and posterior), the vomer bone (inferior and posterior), and the maxillary crest (along the floor of the nasal cavity). It is lined with ciliated pseudostratified columnar epithelium. It is estimated that as many as 80 % of septa are deviated in some fashion; however, these deviations are often asymptomatic and infrequently the cause of disease. Significant septal deviations may cause nasal obstruction or compress the middle turbinate, thus obstructing the ostiomeatal complex and preventing sinus outflow.

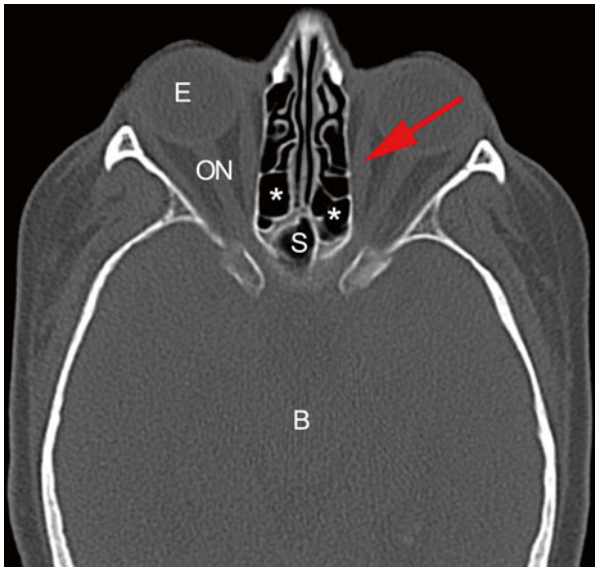

Fig. 8.1 Axial anatomy of the nasal cavity and the paranasal sinuses. Important anatomic landmarks and relevant sinuses are detailed. *E* eye, *ON* optic nerve, *S* sphenoid sinus, *B* brain, * ethmoid sinuses; *red arrow* points to medial rectus muscle, which is susceptible to injury during endoscopic sinus surgery given its proximity to the ethmoid sinuses

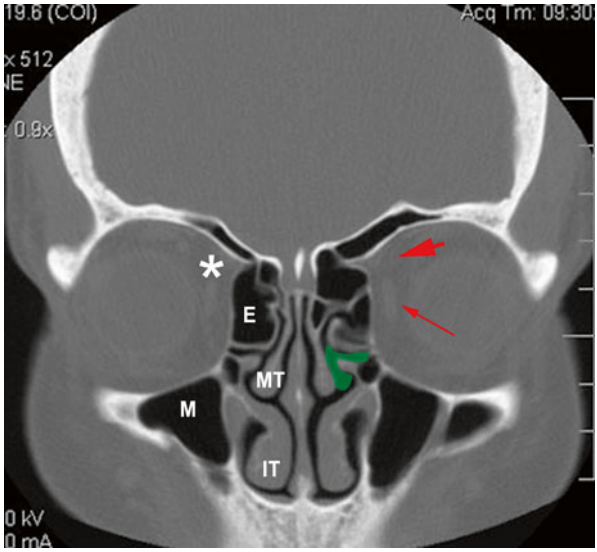

Fig. 8.2 Coronal anatomy of the nasal cavity and the paranasal sinuses. Important anatomic landmarks and relevant sinuses are detailed. *M* maxillary sinus, *E* ethmoid sinus, *F* frontal sinus, *IT* inferior turbinate, *MT* middle turbinate, * anterior ethmoidal artery; *long arrow* medial rectus muscle; *short arrow* superior oblique muscle. The area shaded in *green* is the middle meatus and ostiomeatal complex

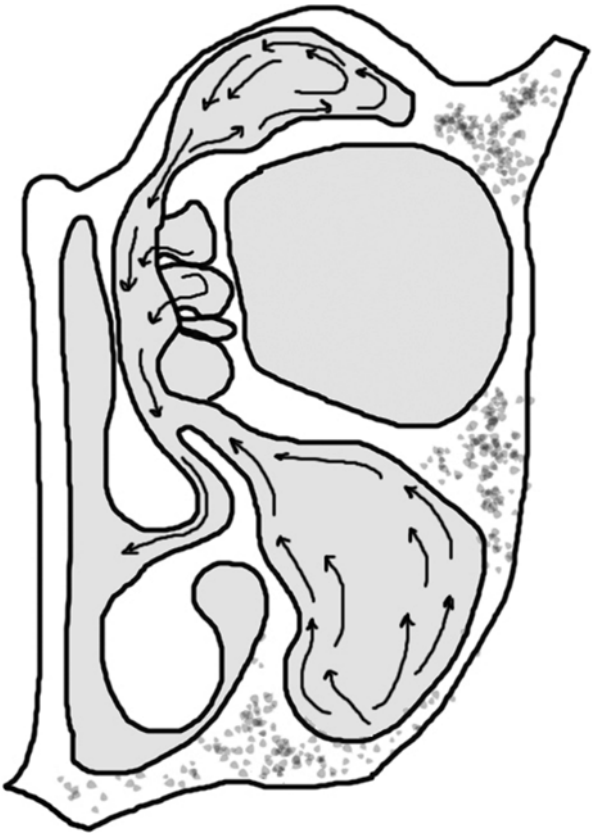

Fig. 8.3 The pathway of mucociliary clearance cilia beat in a predictable fashion such that mucus and debris are propelled toward the natural ostium of the sinus. Disrupting this flow can lead to stasis or recirculation (if an iatrogenic ostium is created)

The turbinates are mucosa-lined structures that arise from the cartilaginous nasal capsule during the eighth week of embryological development. Typically, three turbinates on each side (superior, middle, and inferior turbinates) persist into adulthood. The majority of each turbinate is lined with ciliated pseudostratified columnar epithelium, and olfactory tissue can be found on the middle and superior turbinates. The inferior and middle turbinates contain numerous venous plexuses that under parasympathetic stimulation dilate in a cyclic fashion to alter the patency of the nasal cavity. This natural phenomenon is known as the nasal cycle. Additionally, the mucosa lining these turbinates is particularly responsive to external irritants and allergens that can lead to nasal obstruction and rhinorrhea.

The Ostiomeatal Complex

The confluence of drainage pathways from the maxillary sinus, frontal sinus, and anterior ethmoid sinuses forms the ostiomeatal complex (OMC) (Fig. 8.4). The OMC is not an anatomic structure per se, but rather a pathway that when obstructed by inflamed mucosa or a mass may cause subsequent sinus obstruction and ultimately infection. Familiarity with the OMC is particularly important in understanding the pathophysiology of acute and chronic rhinosinusitis, and this outflow pathway should be examined in great detail when reviewing computed tomography scans in patients (discussed later). Obstruction of the ostiomeatal complex helps one understand how disease in this region can lead to secondary obstruction of the maxillary and frontal sinuses.

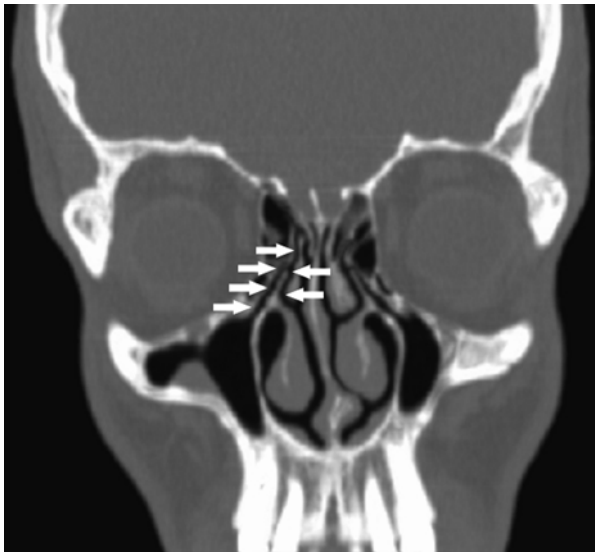

Fig. 8.4 A coronal computed tomography image of a patient demonstrating the ostiomeatal complex (*arrows* defining black space). It should be evident that obstruction of this small region can lead to obstruction in the maxillary or ethmoid sinuses

The Paranasal Sinuses

Maxillary Sinus

The maxillary sinus represents an expansion of the lateral nasal wall (infundibulum) into the maxillary bone that occurs around the eighth week of gestation. Subsequent pneumatization is biphasic: the first phase in early childhood and the second phase in adolescence. Through most of its expansion, the floor of the maxillary sinus remains at the same level as the floor of the nasal cavity; however, during its final growth, the floor of the maxillary sinus may pneumatize the maxillary alveolar process and rest 5–10 mm below the floor of the nasal cavity. The ostium of the maxillary sinus is located on the medial wall of the sinus and is approximately 2–3 mm in diameter. An accessory ostium located posterior to the natural ostium is identified in 15–20 % of cases. The cilia of the maxillary sinus direct mucus and debris through the natural ostium and into the middle meatus.

Ethmoid Sinuses

The ethmoid sinuses develop from a series of lamellae and grooves that suspend from the cribriform plate and along the lateral nasal wall around the eighth week of gestation. The first lamella typically forms the agger nasi cell superiorly and the uncinate process inferiorly. The second lamella forms the *bulla ethmoidalis*, an anterior ethmoid cell. The third lamella forms the middle turbinate, the medial boundary of the middle meatus. The remainder of the lamellae forms the posterior ethmoid cells and the superior turbinate. Several other ethmoid cells that may develop are of clinical importance. An infraorbital ethmoid or Haller cell may project into the maxillary sinus near the maxillary sinus ostium, which may impede maxillary sinus outflow. A sphenoethmoid or Onodi cell may pneumatize around the optic nerve, posing a surgical risk.

Sphenoid Sinus

The sphenoid sinus develops in early adolescence as epithelium invaginates into the sphenoid bone where pneumatization occurs. The sphenoid sinus is divided by a septum, which typically divides the sinus asymmetrically. The sphenoid possesses two ostia through which the sinus ventilates and drains mucus. These ostia are 2–3 mm in diameter and sit superiorly on the anterior face of the sinus near the base of the skull. The sphenoid sinus is clinically significant in that several critical structures surround it. The optic nerve usually indents the lateral wall of the sphenoid, and approximately 5–7 % of patients have no intervening bone between the optic nerve and the sphenoid sinus. The carotid artery also indents the lateral sphenoid sinus wall with 7 % of these being dehiscent, that is, with no bone separating the artery and the sphenoid sinus. Posterior and lateral to the sphenoid sinus

is the cavernous sinus, a venous plexus structure through which the carotid artery, the oculomotor (CN III) nerve, trochlear (CN IV) nerve, trigeminal (CN V) nerve, and abducens (CN VI) nerve pass. Additionally, the pituitary gland rests superior and posterior to the sinus and can typically be identified as an indentation in the sinus.

Frontal Sinus

The frontal sinus represents the superior pneumatization of the frontal bone by anterior ethmoid cells starting around the second year of life. Pneumatization of the frontal bone is occasionally incomplete, with 5 % of the population having only a unilateral frontal sinus and 5 % of the population having no frontal sinus cells. To complicate matters, ethmoid cells may expand into the frontal sinus causing unique patterns of obstruction. The frontal sinus drains through the frontal recess, which, unlike the other sinuses, is not an ostium or duct, but rather a pathway of drainage formed by the walls of specific ethmoid sinuses, chiefly the agger nasi and the *bulla ethmoidalis*.

Pathophysiology

Acute and chronic rhinosinusitis are different in many respects. The most significant is that ABRS is an exudative process that involves purulence and local neutrophilic infiltration of the sinuses. Chronic rhinosinusitis, however, appears to have multiple etiologies.

Acute Bacterial Rhinosinusitis

The insults that lead to rhinosinusitis have been well characterized. As previously stated, ABRS is usually preceded by VRS. Whether by local destruction of mucosal epithelium or by upregulation of cytokines and infiltration by host immune cells, viral infections result in inflammation and edema of the nasal and sinus mucosa. Mucosal edema, when in the proper location, can cause ostial obstruction, leading to both stasis of secretions within the sinuses and relative hypoxia. The edema, inflammation, and stasis impair ciliary function, and patients may be susceptible to infection by bacteria colonizing the nasal cavity and nasopharynx. The subsequent bacterial infection leads to more inflammation, edema, and the influx of neutrophils. Therefore, ABRS can be viewed as an exudative and suppurative process. Several risk factors for ABRS have been proposed including exposure to cigarette smoke, allergic inflammation, odontogenic infections, and potentially anatomic factors (e.g., Haller or infraorbital ethmoid cells).

Chronic Rhinosinusitis

The pathophysiology of CRS is complex and the subject of active research. Chronic rhinosinusitis is now believed to be a multifactorial inflammatory disease rather than a solely pathogen-driven disease. The current literature leads to the hypothesis that CRS is caused by a dysfunctional host-environment relationship and may be further modified by certain genetic, epigenetic, and environmental factors.

Intrinsic causes may be subdivided into genetic and acquired causes. The genetic causes include primary ciliary dyskinesia, cystic fibrosis, or any other condition with ultrastructural abnormality of the cilia. Each sinus is lined with a thin layer of mucosa populated by ciliated pseudostratified columnar epithelium. The cilia beat rhythmically and in a coordinated fashion to propel a mucous layer (and debris) in a genetically programmed manner through the sinus toward its natural ostium. In many instances, such as in the maxillary sinus and sphenoid sinus, this is often against the force of gravity. (This brings to light the physiological reasons why dependent drainage sinus surgery or improperly placed openings into the sinuses often fail to resolve chronic inflammatory diseases within the sinuses.) Ciliary function is easily impaired by many insults, including bacterial, fungal, or viral damage, exaggerated host inflammatory changes, changes in temperature, changes in pH, the effects of cigarette smoke, and changes in the consistency of the gel and sol layers of the mucous blanket. Genetic conditions such as primary ciliary dyskinesia or cystic fibrosis can either directly or indirectly impair the ability of the cilia to function effectively. Recent associations of sinusitis with genetic variants of the bitter taste receptor highlight the numerous possible genetic influences on sinusitis that will continue to be discovered as our ability to evaluate subtle genetic variations improves. Acquired causes include aspirin sensitivity (i.e., aspirin-exacerbated respiratory disease or Samter's triad with concomitant asthma and nasal polyposis), hormonal rhinitis, and systemic causes, which are chiefly rheumatologic or autoimmune (e.g., Wegener granulomatosis, sarcoidosis, polyarteritis, and systemic lupus erythematosus).

Extrinsic causes are the subject of intense research. This category is subdivided into allergic, bacterial, fungal, and immunologic.

Allergic

Allergic rhinitis (AR) is discussed extensively throughout this book. Briefly, it is characterized by an abnormal hypersensitivity to extrinsic inhalant allergens that manifest in an IgE-mediated acute-phase response and an eosinophilic delayed-phase response. No causal relationship between AR and CRS has been consistently demonstrated; nevertheless, the association between the two is widely recognized. Studies demonstrate that in the presence of AR, patients with symptoms of CRS demonstrate computed tomography (CT) or endoscopic evidence of CRS approximately 50 % of the time. Furthermore, AR is present in 41–84 % of patients with

CRS who need surgery. In patients with CRS, the scoring of severity based on CT exams correlates with the severity of AR in those patients. Moreover, some studies reveal that in patients with concomitant CRS and AR, the benefits of surgery are more lasting when allergic therapy is administered following surgery. In any event, the correlation between AR and CRS is such that concomitant treatment of AR and CRS is appropriate, particularly in the patient who is undergoing surgery.

Bacterial

Unlike ABRS, a causal relationship between bacteria and CRS is not as obvious. Determining whether bacterial isolates are infectious causes of CRS, initiate or perpetuate inflammation, or are merely contaminants of the paranasal sinuses in patients with CRS, especially those who have undergone surgery, can be difficult. One significant drawback to the bacterial hypothesis for CRS is that bacterial infections usually incite a Th17 inflammatory response, but CRS, particularly recalcitrant CRS, tends toward a Th2 inflammatory response. It may be more appropriate to regard the role of bacteria in CRS as a modifying agent rather than an etiologic agent. Regardless, several hypotheses implicating bacteria as the etiologic agent for CRS have been proposed.

One proposed theory of how bacteria may contribute to CRS is through the *Staphylococcus aureus* "superantigen hypothesis." As opposed to the typical method of antigen presentation to T-cell receptors, superantigens bypass antigen-presenting cells to superstimulate T-cell receptors inappropriately. This leads to activation of large numbers of T cells and the overproduction of cytokines that result in inflammation and the histologic response seen in patients with CRSwNP. The "superantigen hypothesis" is supported by the fact that about 50 % of patients with CRSwNP exhibit evidence of B- and T-cell responses to superantigens. However, many control patients, patients with CRSsNP, and patients with cystic fibrosis have evidence of *S. aureus* colonization without the superantigen response. For this reason, it seems more likely that superantigens are a modifying factor for CRSwNP and enhance an underlying inflammatory condition.

The discovery of biofilms in 42–75 % of patients with CRS undergoing sinus surgery has given rise to the biofilm hypothesis. Biofilms represent the aggregation of bacterial organisms that are protected by a membrane consisting of extracellular matrix. Biofilms are significant in that they provide sufficient shielding of bacteria from antimicrobial agents and may contribute to the survivability of bacteria following antimicrobial administration and the development of resistant organisms. *S. aureus* biofilms are associated with recalcitrant sinusitis and could potentially enhance inflammation through a superantigen response, but there is a known pathway through which biofilms could independently cause CRS.

The description of complex microbial communities in normal and diseased sinuses has been made possible by the use of genetic techniques such as gene chip analysis and pyrosequencing. Dysbiosis of the microbial community has been described in patients with sinusitis. Diseased sinuses have significantly reduced

diversity relative to normals, a finding which has been seen in other disease processes as well. This theory contends that patients with sinusitis have developed a stable but unhealthy microbial community that propagates chronicity and demonstrates colonization resistance or stability in the face of perturbing forces.

It is important to recognize that the bacteria in CRS are different from those in ABRS. Their role in the pathogenesis of CRS is unclear and may be only one of several factors required in the development and treatment of CRS.

Fungal

Colonization of the nasal cavity is frequently found in healthy volunteers and in patients with CRS. As with bacteria, finding a causal relationship between isolated fungal species and CRS is difficult. For many years, the *Alternaria* "fungal hypothesis" was a leading hypothesis to explain the pathophysiology of CRS. It was believed that a dysfunctional host response to *Alternaria* was the trigger for CRS. However, there has been little evidence in the basic science literature or clinical trials using antifungals to support fungal etiology as a sole cause for CRS.

Although fungi are not responsible for the global etiology of CRS, dysfunctional immune response to fungus may be a disease modifier and certainly appears to play a significant role in patients with allergic fungal sinusitis (AFS). These patients are considered a subset of CRSwNP and have documented IgE-mediated responses to the isolated fungal species, nasal polyposis, CT findings that are characteristic of the disease (heterogeneous opacification of involved sinuses), and a distinct lack of bone invasion.

Immunologic

The lack of substantial evidence clearly implicating an environmental or microbial factor in the development of CRS has led investigators to consider that CRS may arise from a dysfunctional relationship between the host and environment. This immune dysfunction may occur within the innate or adaptive immune system resulting in chronic inflammation.

Several primary defenses of the sinonasal cavities are derived from the innate immune system including mucociliary clearance, epithelial barrier, secreted antimicrobials, and pattern recognition receptors such as toll-like receptors (TLR). There is a growing body of literature to suggest that alterations in the innate immune system may play a role in the chronic inflammatory state found in CRS. In particular, decreases in S100 proteins, derangements in TLR signaling, and IL-22 cytokine expression may be potential mechanisms for the development of CRS.

The adaptive immune system may also play a role in the inflammatory response of CRS. There is evidence of increased total and activated T cells particularly in the inflammatory infiltrate of patients with CRSwNP. In addition, the epithelium may also play a direct role in activating the adaptive immune system through engaging T cells and secreting cytokines and chemokines to activate and attract dendritic

cells, B cells, and T cells. The exact mechanisms of these interactions are not yet elucidated and represent an active area of research.

Bacteriology

The paranasal sinuses were once thought to be sterile environments as many previous studies performed to assess for colonization proved to demonstrate sterile cultures or cultures with no growth. There is newer evidence to suggest that the sinuses are rife with bacterial colonization, giving rise to a recent explosion of research into the microbiome of the sinuses. Nevertheless, when applying conventional culture techniques, it is known that the nasal cavity and nasopharynx are environments frequently colonized by flora that have been implicated in both acute and chronic rhinosinusitis.

Acute Bacterial Rhinosinusitis

Community Acquired

The maxillary sinus has been frequently studied given the relative ease with which an aspiration of contents can be performed in patients who have signs and symptoms consistent with ABRS.

The most common bacterial isolate in community-acquired ABRS in children and in adults is *Streptococcus pneumoniae* (20–45 % of isolates), an encapsulated Gram-positive facultative anaerobe usually occurring in chains or pairs. By age 2, approximately 60 % of children are nasopharyngeal carriers of *S. pneumoniae*, and by age 3, almost all children carry this species. These species come in several serotypes, and they are frequently undergoing recombination, which results in a change in serotype or serogroup. The relative hypoxia of an inflamed sinus provides the ideal grounds for replication and growth. Pneumolysin, a soluble 53 kDa monomer, is the primary factor in virulent strains of pneumococcus. Pneumolysin binds to cell membrane cholesterol molecules and cross-links them, creating large transmembrane pores that result in cell lysis and death. *S. pneumoniae* resists antibiotic therapy through several mechanisms: efflux of antibiotic molecules, mutations in penicillin-binding proteins, and mutations in the encoding of ribosomal proteins.

Haemophilus influenzae, a Gram-negative facultative anaerobe, is isolated in 20–35 % of cases of ABRS in children and in adults. Nearly half of all children are colonized with *H. influenzae*. With the regular administration of the *H. influenzae* type b vaccine, *H. influenzae* type b strains are found infrequently. However, types a, c, d, e, and f and nontypable (unencapsulated) species are frequently recovered from nasopharyngeal and lateral nasal wall culture swabs. *H. influenzae* also thrive in the hypoxic environment of the inflamed paranasal sinuses. The incidence of resistance to β-lactams in this group is rising with the production of β-lactamase, a family of enzymes that catalyze the hydrolysis of the β-lactam ring that forms the

basis of penicillins and cephalosporins. To combat this enzyme, various β-lactamase inhibitors (sulbactam, tazobactam, clavulanic acid) have been manufactured to increase the concentration of the delivered β-lactam. However, strains of *Haemophilus* that are inherently resistant to penicillins through mutations in penicillin-binding proteins are on the rise and effectively nullify the advantage of adding a β-lactamase inhibitor to a penicillin.

The frequency of other species isolated in ABRS varies from study to study and in the age of the patient. In children, the third most common isolate (15–20 %) is *Moraxella catarrhalis*; however, in adults, this organism is isolated in only about 5–7 % of cases of ABRS. *Moraxella catarrhalis* is a Gram-negative aerobe that, like *H. influenzae*, produces β-lactamases as its primary defense against antibiotic agents. More than 90 % of isolates are known to produce three closely related β-lactamases, making them virtually resistant to penicillins not containing a β-lactamase inhibitor. Cephalosporins still show good activity against this organism, however.

Various streptococcal species and anaerobes also occur as pathogens in about equal frequencies (5–7 %) in cases of pediatric and adult ABRS. Interestingly, approximately 20–35 % of isolates in the pediatric population may be sterile.

Nosocomial Acquired

Nosocomial ABRS often occurs in the setting of a prolonged hospital stay or in patients suffering from maxillofacial trauma or head trauma, nasotracheal intubation, and nasogastric intubation or patients with burn injuries. These organisms are generally Gram-negative organisms: *Pseudomonas aeruginosa, Serratia marcescens, Klebsiella pneumoniae,* and *Proteus* species. Additionally, *S. aureus* is also frequently isolated. These organisms may be responsible for the development of ABRS, or they may be the consequence of impaired mucociliary clearance and simply colonizing agents.

Chronic Rhinosinusitis

As previously stated, the role of bacteria in CRS is not clear. Directed cultures of patients with CRS have demonstrated a wide variety of bacterial pathogens that are often quite different from those isolated in ABRS. The most common isolates are coagulase-negative staphylococci, *S. aureus*, and *P. aeruginosa*. The latter two bacteria are also known for their biofilm production, and *S. aureus* is particularly known for its superantigenicity. Coagulase-negative staphylococci are frequently found in healthy subjects, and their role in infection of other areas of the body is often called into question; therefore, one must ask the question of whether coagulase-negative staphylococci are simply contaminates, infectious causes, or inflammatory "mediators" in CRS. Gram-negative species commonly isolated in CRS include *P. aeruginosa*, *Escherichia coli*, and *Enterobacter* species. Other organisms isolated include

viridans streptococci, *Prevotella*, *Peptostreptococcus*, and *Fusobacterium*. Finally, like ABRS, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are also isolated; however, these three agents are not found as frequently as *S. aureus* and coagulase-negative staphylococci.

Proper identification of the involved bacterial agents in CRS involves a directed culture of the involved sinus. Maxillary puncture was once considered the gold standard for the diagnosis of maxillary sinus disease; however, puncture techniques could not be performed for any other sinus. Nasal cultures correlate poorly with antral puncture isolates and are not clinically helpful. Current techniques that show efficacious results include cultures that are obtained via endoscopic placement of culture media (swabs, aspiration traps); cultures derived endoscopically from the middle meatus have been shown to correlate nicely with antral puncture and are commonly used to determine the bacteriology of sinusitis. Trephination of the frontal sinus can be carried out, although this typically requires a procedure in the operating room and is seldom used outside of the context of urgent treatment of a complicated acute frontal sinusitis. Identification of any offending organisms should begin with Gram stain quantification as well as aerobic and anaerobic culture. Fungal cultures are commonly used in the clinical setting, although the significance of a positive culture for fungus is unclear. Pathologic examination of debris from the sinuses can confirm fungal involvement and suggest speciation, although this method is typically reserved for tissue obtained during surgery for sinusitis. As previously discussed, the overlapping etiologies in CRS lead one to question whether isolated organisms simply represent colonization or are causative of sinus inflammation.

Diagnosis

The symptoms of ABRS and CRS are often nonspecific, and although there are established criteria for making the diagnosis, they should be made within the context of the duration of symptoms, physical examination findings, adjunctive measures, and, in the case of CRS, imaging or endoscopy.

History and Physical Examination

The diagnosis of ABRS or CRS begins with a thorough history of the illness. As stated before, the duration of illness is important in making the distinction between viral rhinosinusitis and acute bacterial rhinosinusitis. Patients with symptoms persisting beyond 10 days or initial improvement followed by worsening (double worsening) within 10 days have a history more consistent with acute bacterial rhinosinusitis. The previous or current usage of antibiotics by the patient for the present illness or past illnesses should be noted.

Pattern of illness is important to characterize. Acute bacterial rhinosinusitis or acute exacerbations of CRS are typically preceded by a viral upper respiratory infection. Nasal congestion and obstruction with discolored nasal drainage also accompanies these episodes. Facial pressure, although not headache, is common, and care should be taken to distinguish rhinosinusitis from other causes of headache. Pain in the temporal area, a band-like sensation around the head, and pain in the occipital area are not generally seen in sinusitis. Pain characterized as constant, cyclic, or occurring daily is also atypical and should prompt additional questions to determine migraine (which can present with throbbing facial pain, congestion, and nasal discharge if in the trigeminal distribution), tension headache, cluster headache, or headaches associated with hormonal changes.

Comorbid illnesses such as allergic rhinitis, asthma, and autoimmune diseases or causes of ciliary dysfunction (e.g., cystic fibrosis or primary ciliary dyskinesia) should be ascertained because they may be misinterpreted as rhinosinusitis or complicate treatment of rhinosinusitis. Additionally, a history of smoking tobacco or inhalation of environmental irritants should also be noted.

The physical examination of the patient should be carried out systematically for all patients. The general appearance of the patient should be assessed to identify patients who appear ill or in distress. The ears should be examined for signs of otitis media (serous or purulent effusions), which can occasionally be seen in children and adults related to upper airway respiratory illnesses or obstruction of the eustachian tube orifices due to mucosal edema or a mass. The eyes should be carefully observed for evidence of lid edema, erythema, chemosis, enophthalmos, and proptosis and for any restriction of movement, all of which may suggest an orbital complication. Additionally, periorbital "allergic shiners" (venous engorgement of the skin around the eyes) and Dennie-Morgan lines (folds beneath the lid) may provide evidence of atopic disease. The external nose should be examined for signs of deviation or trauma as well as for a transverse nasal crease (which occurs as a result of rubbing the nose, "the allergic salute") signifying atopic disease. The nasal cavity should be examined with a speculum and a light source prior to and following decongestion. The examination should make note of any septal deviation, the size of the inferior turbinates, the quality of the nasal mucosa (e.g., erythematous, boggy, or atrophic), the quality of any nasal discharge (e.g., clear, mucoid, or purulent), or the presence of polyps, masses, or any other lesions.

Although transillumination of the sinuses can be performed for the frontal and maxillary sinuses, it is neither sensitive nor specific for maxillary or frontal sinusitis. Transillumination cannot be used to identify disease in the ethmoid sinuses or the sphenoid sinus.

Whenever possible, an endoscope, either flexible or rigid, should be used to examine beyond the anterior nasal cavity. The endoscope provides a superior and detailed view of the relevant anatomic structures in the nasal cavity when compared to visualization with the headlight and speculum (Fig. 8.5). The first inspection with endoscope should involve inspection of the inferior meatus, nasal floor, and nasopharynx. Next, the endoscope should be used to inspect the middle meatus and middle turbinate. Finally, the

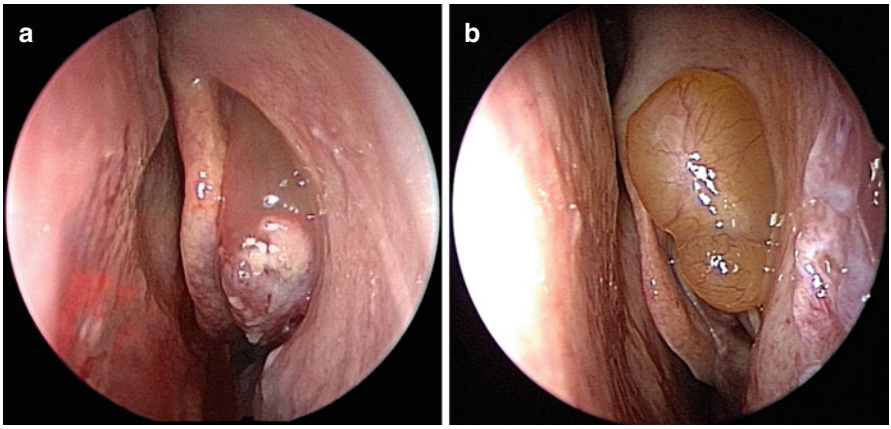

Fig. 8.5 Endoscopic view of the nasal cavity. The endoscope provides superior detailed examination of the nasal cavity and sinuses when compared to anterior rhinoscopy, which is done with a headlight and speculum or handheld otoscope. In Frame (**a**), polyps with fibrous transformation can be seen. In Frame (**b**), watery inflammatory polyps are seen

endoscope should be used to inspect the middle meatus complex. The examiner should make note of any masses, polyps, or exudates and from where they arise.

The oral cavity should be examined for the presence of any abnormality that may be related to rhinosinusitis (maxillary alveolar dental infection or polyp within the posterior oropharynx) or paranasal sinus neoplasm that has invaded the oral cavity. The neck should be examined for signs of lymphadenopathy.

Diagnostic Imaging

A direct coronal CT scan with 1–2 mm cuts is considered the most appropriate scan to characterize the radiographic findings in rhinosinusitis. An alternative at some institutions uses fine-cut axial scans 1 mm or less in slice thickness that can be reformatted to display images in the coronal plane. Although CT scanning is not recommended in the routine imaging of ABRS, patients who are unresponsive to appropriate medical therapy, patients who present a diagnostic dilemma, and patients who are concerning about a complication of rhinosinusitis should undergo radiographic evaluation with CT scanning.

CT findings in patients with VRS may be indistinguishable from those with ABRS; therefore, these imaging modalities do not aid in the differentiation of the two diseases or change the management of either. This is an important notion because patients presenting with complaints of rhinosinusitis can display radiographic abnormalities of the paranasal sinuses within 72–96 h of symptom onset, and the vast majority of the patients will show resolution of their radiographic abnormalities without the use of antibiotics. Clinical history plays a very important role in the

timing and interpretation of the CT images. Patients are not generally imaged during an exacerbation of rhinosinusitis because scans will virtually always demonstrate mucosal thickening and are better imaged after resolution to characterize residual disease. However, patients being evaluated for complications of rhinosinusitis should obtain a coronal and axial CT scan with bone and soft tissue windows with intravenous contrast material immediately to aid in evaluation and management.

Magnetic resonance imaging (MRI) should be employed whenever a neoplasm of the sinuses is suspected. Use of MRI for evaluation of intracranial complications can also be helpful. Plain radiographs are neither sensitive nor specific for rhinosinusitis and are not recommended to evaluate the sinuses.

Culture

For patients who have failed standard medical therapy, a culture should be obtained. As previously stated, in the setting of community-acquired ABRS in adults, an endoscopic-directed culture of the middle meatus correlates well with cultures obtained through a maxillary "sinus tap" (the gold standard) performed with a needle through the canine fossa. Cultures of the nasal cavity are not recommended. In children, the carriage rates for the organisms responsible for ABRS are much higher than in adults, and endoscopic-directed cultures do not correlate well with maxillary sinus taps. However, consideration to developing maxillary dentition should be given before performing a puncture through the canine fossa, and an alternative puncture site in the inferior meatus in the nasal cavity can be used.

Because the organisms are different in nosocomial-acquired ABRS, a maxillary sinus tap or endoscopically directed culture may be beneficial for culture information.

Treatment

Medical Therapy

The primary end points in the treatment of rhinosinusitis are the eradication of disease, the improvement in symptoms, and the reestablishment of normal paranasal sinus function.

Adjunctive Topical and Systemic Therapy

Acute VRS is treated with conservative measures: nasal saline irrigation, topical or systemic decongestants, mucolytics, and analgesics. Of note, topical decongestants should not be used for more than 3–5 days due to the risk of rhinitis medicamentosa.

Unfortunately, there is no cure for the common cold. It is inappropriate to treat VRS with antibiotics. When VRS has persisted for more than 10 days or improves and then worsens within 10 days, it is reasonable to presume that suprainfection with bacteria has occurred and ABRS is present. As with VRS, the administration of topical or systemic decongestants, nasal saline irrigations, and mucolytics is appropriate in ABRS. Topical intranasal steroids may also provide a modest benefit and may be used per patient and physician preference.

Antibiotic Therapy

Per the American Academy of Otolaryngology-Head and Neck Surgery, uncomplicated ABRS may be treated with antibiotics or watchful waiting provided that close patient follow-up is possible. The period of watchful waiting should extend no more than 7 days from the diagnosis of ABRS, and antibiotics should be prescribed if symptoms worsen or there is no improvement in this window.

The selection of the proper antibiotic depends on the patient's history of antibiotic use and the probability of any one or more of the well-established bacterial causes of ABRS to be present.

Acute Bacterial Rhinosinusitis-Mild Disease

For patients with mild ABRS (Table 8.2) who have not taken antibiotics in the past 4–6 weeks, an appropriate first-line antimicrobial agent is amoxicillin (1.5–4 g/day), amoxicillin/clavulanate (1.75–4 g/day), cefpodoxime, cefuroxime, or cefdinir. Patients not improving within 72 h of administration are presumed to have resistant organisms and should be switched to fluoroquinolone or a combination of

Table 8.2 Antibiotic treatment guidelines for mild acute bacterial rhinosinusitis with no recent antibiotic use

Starting therapy	Efficacy	Failed therapy (after 72 h)
Amoxicillin/clavulanate	91 %	
Amoxicillin	88 %	Fluoroquinolone
Cefpodoxime	87 %	Amoxicillin/clavulanate
Cefuroxime	85 %	Ceftriaxone
Cefdinir	83 %	Amoxicillin/clavulanate or clindamycin and cefixime
Penicillin-sensitive patients		
Trimethoprim-sulfamethoxazole (TMP/SMX)	83 %	
Doxycycline	81 %	Fluoroquinolone
Azithromycin, clarithromycin	77 %	Rifampin and clindamycin

Adapted from Sinus and Allergy Health Partnership

Table 8.3 Antibiotic treatment guidelines for mild acute bacterial rhinosinusitis with recent antibiotic use or moderate acute bacterial rhinosinusitis

Initial therapy	Efficacy	Second therapy for medical failures
Fluoroquinolone	92 %	Reexamine/culture
Amoxicillin/clavulanate	91 %	Reexamine/culture
Penicillin sensitive		
Fluoroquinolone	92 %	Reexamine/culture
Clindamycin and rifampin	92 %	Reexamine/culture

Adapted from Sinus and Allergy Health Partnership

antibiotics. For those that are allergic to penicillin derivatives, trimethoprim/sulfamethoxazole, doxycycline, or a macrolide may be prescribed.

Acute Bacterial Rhinosinusitis-Moderate Disease or Prior Antibiotic Use

Patients who have moderate ABRS or have used antibiotics in the past 4–6 weeks (Table 8.3) should be administered a fluoroquinolone, gatifloxacin, levofloxacin, or moxifloxacin or high-dose amoxicillin/clavulanate (4 g/250 mg). Patients allergic to penicillin and/or cephalosporins should be administered a fluoroquinolone or rifampin/clindamycin. Patients who do not improve within 72 h should be reevaluated and consideration be given to obtaining a culture either endoscopically or via transantral puncture.

Chronic Rhinosinusitis

For patients with CRS, some of the same adjunctive measures (e.g., nasal saline irrigations) should be deployed. Antimicrobial therapy for CRS is controversial. There is no evidence to support the use of topical antibiotics and topical or oral antifungals in CRS, but there is some evidence to support the use or oral antibiotics particularly in patients with CRSsNP. The evidence for oral steroid use is stronger for patients with CRSwNP, but oral steroids are often used in the management of both phenotypes. Several retrospective and prospective studies have shown subjective improvement in patients with CRS who have been treated with 4–6 weeks of antibiotics, topical or systemic corticosteroids, and adjunctive measures. These subjective results have been correlated with improvements in CT and endoscopic grading. These studies, however, have been confounded by the coadministration of topical or systemic corticosteroids. Nevertheless, it is reasonable to treat patients with chronic sinusitis with 3–6 weeks of antibiotics, topical corticosteroids, a short course of systemic corticosteroids, and a brief period (3–5 days) of topical decongestants. Oral corticosteroid dose commonly employs a taper of prednisone from approximately 60 mg to 10 mg over a 2- to 3-week period.

Patients with refractory disease may be candidates for additional treatment and evaluation. The American Academy of Allergy, Asthma, and Immunology advocates

an evaluation for immunodeficiency in patients refractory to surgery and medical therapy. This consists of quantitative immunoglobulins (IgA, IgG, and IgM), specific antibody responses, and if necessary complement function and T-cell evaluation.

Consideration has been given to the use of long-term macrolide antibiotics for treatment of CRS due to their known anti-inflammatory effects. Several studies have demonstrated that prolonged therapy (3 months) results in subjective (quality-of-life survey results) and objective (endoscopic grading) improvement as well as decreased circulating IL-8 in patients with CRSsNP treated with macrolide antibiotics versus placebo. Long-term macrolide therapy appears to be more effective in patients when IgE levels are not elevated. This treatment option should be reserved for patients with refractory disease, and more effective in patients when IgE levels are not elevated.

Finally, there is some evidence to support the use of biologics in the treatment of CRSwNP. In particular, anti-IgE (omalizumab) has been shown to improve both symptoms and disease severity measures and may be considered in patients who have failed both medical and surgical therapy. In addition, anti-IL-5 (reslizumab, mepolizumab) has been investigated for CRSwNP though it is not commercially available for this purpose.

Surgical Therapy

Surgical treatment of ABRS is rarely indicated; however, it may need to be performed in patients who suffer from recurrent acute infection, are refractory to medical management, or develop complications. Functional endoscopic sinus surgery (FESS) is employed as surgical therapy for these patients and in patients who are refractory to medical management with CRS. This procedure is considered functional because it is a mucosal-sparing operation that maintains the physiology of the sinuses by widening the natural ostia of the sinuses, preserving the natural mucociliary clearance. All sinuses may also be surgically drained from either an external, an intranasal, or combination of the two approaches when necessary. External approaches to the sinuses are uncommon for routine nonemergent treatment of sinusitis because less invasive endoscopic approaches can virtually always be employed. The frontal sinus and ethmoid sinuses may be drained by making an incision in the skin along the medial and superior aspect of the orbital rim and entering into the sinus with a drill or osteotome. The maxillary sinus may be drained by making an incision in the gingivolabial sulcus (intraorally) and entering the sinus through the anterior maxillary sinus wall (i.e., the canine fossa). Alternately, the maxillary sinus may be entered intranasally, beneath the inferior turbinate by creating a nasoantral window. These procedures are not functional because they disrupt the natural flow of cilia within the affected sinuses and may contribute to stasis and recirculation.

The most common complications related to sinus surgery include bleeding and postoperative scarring or synechiae. For those patients with an intact sense of smell,

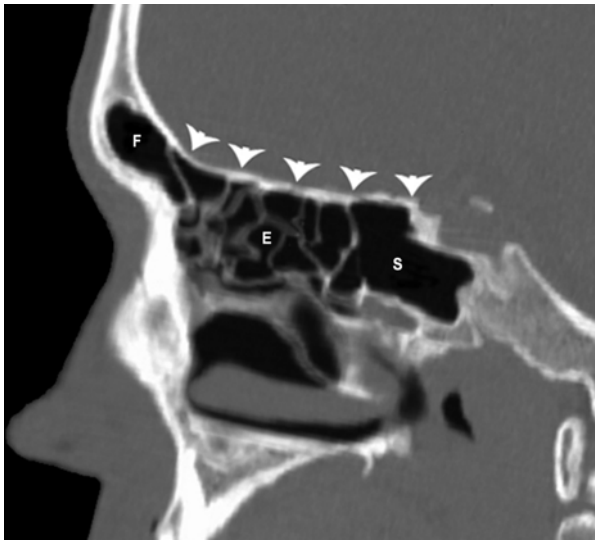

Fig. 8.6 Parasagittal anatomy of the frontal (*F*), ethmoid (*E*), and sphenoid (*S*) sinuses in relationship to the skull base (*arrowheads*)

there is a small risk of postoperative anosmia. Given the proximity of the sinuses to the skull base (Fig. 8.6), the risk of a cerebrospinal fluid leak is present if aggressive dissection of the sinuses is undertaken. Other rare complications include injury to the orbit (e.g., globe, extraocular muscles, and hematoma) or injury to the carotid artery and optic nerve. Recently, FESS has been augmented with intraoperative image guidance. Using a patient's CT or MRI scan, a probe or instrument can be used to help the surgeon confirm anatomy and is particularly useful in difficult or revision cases.

It is important that patients be informed that surgery is not a cure for CRS, rather an adjunct to the proper – and often indefinite – medical management of chronic rhinosinusitis. Unless anatomic obstruction is the sole cause of rhinosinusitis, it is likely that the underlying pathophysiology (e.g., allergic rhinitis, mucosal hyperreactivity, ciliary dysfunction, etc.) will persist after surgery unless managed with the appropriate medical therapy. Nevertheless, when appropriately employed, medical and surgical therapy can help obtain long-term relief of signs and symptoms of chronic rhinosinusitis. Several studies show that symptomatic improvement can be sustained in 85–92 % of patients over 8 years, and improvement in objectively measured outcomes such as olfaction, ciliary beat frequency, and olfactory threshold can be accomplished as well.

Complications

Untreated ABRS resolves spontaneously in approximately nearly all cases without evidence of sequelae. However, infectious complications do occur, and these typically result from the direct extension of disease into neighboring structures or hematogenous spread of infection via thrombophlebitis and bacteremia.

Orbital Complications

The orbit is lateral to the ethmoid sinuses and superior to the maxillary sinus. Directly overlying the orbit are supraorbital ethmoid air cells and the frontal sinus. Direct extension of bacteria into the orbit can occur from any of these sinuses. Chandler's classification divides orbital complications into five groups. Group 1 is preseptal cellulitis, which becomes manifest with eyelid edema and erythema. Group 2 is orbital cellulitis, which is marked by proptosis and potentially decreased ocular movement (due to edema) and vision. A group 3 complication arises when a subperiosteal orbital abscess is found. Group 4 complications involve the formation of an orbital abscess. Group 5, the most severe, is cavernous sinus thrombosis, which occurs via direct extension or retrograde movement through a plexus of valveless veins into the cavernous sinus. Cavernous sinus thrombosis is typically evident with proptosis, ophthalmoplegia, and loss of vision. Wide-spectrum antibiotics and a sinusotomy of the responsible sinus are indicated. The use of anticoagulation is controversial. Despite aggressive treatment, mortality is high (approximately 50–80 %).

Approximately two-thirds of orbital complications require surgery. Indications for surgery include abscess formation, progressive loss of visual acuity, or lack of improvement in 48–72 h. Surgery may be carried out with the endoscope; however, external approaches are often employed because the nasal mucosa is edematous and friable and the patient is at higher risk for postoperative synechiae in an endoscopic approach.

Intracranial Complications

Intracranial complications usually arise from the frontal sinus and its valveless venous communications with central blood drainage patterns. Frontal bone osteomyelitis may occur with or without a frontal subperiosteal abscess (also known as Pott's puffy tumor). Intracranial extension may lead to meningitis, epidural abscess formation, or a brain abscess. Sagittal sinus thrombosis is particularly worrisome and has a high morbidity and mortality. Consultation with a neurosurgeon is recommended.

Fungal Rhinosinusitis

Fungal colonization of the nasal cavity and nasopharynx is common in healthy volunteers and patients with CRS. Fungal elements may proliferate to cause local forms of disease within the nasal cavity or paranasal sinuses. When circumstances (allergy or immunocompromised state) permit, the fungal elements may proliferate to cause more significant disease or fungal rhinosinusitis. Fungal rhinosinusitis occurs in several forms; however, it can be simplified into allergic fungal sinusitis (AFS) and invasive fungal sinusitis.

Allergic Fungal Sinusitis

Allergic fungal sinusitis is documented in a patient with CRS who demonstrates evidence of fungal elements on nasal smears or cultures, documented IgE-mediated allergy to the isolated fungal organism, allergic mucin (dense eosinophilic-rich secretion), nasal polyposis, and a required lack of invasion of the paranasal sinus bone. Erosion or expansion of the paranasal sinus bone is frequently found; however, invasion cannot. Typical isolates include *Bipolaris*, *Alternaria*, and *Curvularia* species.

Management of allergic fungal sinusitis is frequently frustrating. However, the mainstays of treatment include debridement of nasal polyps, conservative functional endoscopic sinus surgery, and extirpation of allergic mucin. Postoperative medical management involves topical and systemic corticosteroids and, in some cases, administration of antifungal therapy (e.g., itraconazole). There currently is no consensus, however, regarding the proper dose or length of corticosteroids and the effectiveness of systemic or topical antifungal medications.

Invasive Fungal Sinusitis

Invasive fungal sinusitis comes in acute (fulminant) and chronic forms. As the name implies, the hallmark of invasive fungal sinusitis is invasion of soft tissue and bone. The most common agents causing acute invasive fungal sinusitis include *Aspergillus*, *Rhizopus*, *Mucor*, and *Candida*. Risk factors for invasive forms of fungal sinusitis include patients with diabetes (especially ketoacidosis), immunocompromised states (bone marrow transplantation, chronic immunosuppression), or leukemia.

Fungal elements invade local tissues to cause tissue necrosis, which is manifest as necrotic-appearing or dark insensate tissue within the nasal cavity seen on endoscopy. Manipulated tissue typically does not bleed. Because fungal elements persist in this environment, delivery of systemic antifungal agents is impaired. The cornerstones of therapy include reversal of the underlying medical condition, aggressive surgical debridement of the infected region, and prolonged administration of systemic antifungal agents (typically amphotericin B or voriconazole). The prognosis for patients with invasive fungal sinusitis is poor, especially when there is intracranial extension or systemic spread. Treatment of rhinocerebral fungal sinusitis involves a multidisciplinary approach and requires aggressive debridement of all infected tissue, control of the underlying medical condition, and prolonged administration of antifungal antibiotics.

Evidence-Based Medicine

CRS can be treated both medically and surgically with the choice of therapy determined through shared decision-making between the patient and physician. Clinical practice guidelines as well as practice parameter updates offer insight into this

decision-making process. Additionally, a recent prospective, multi-institutional, non-randomized trial demonstrated significantly higher levels of quality-of-life improvement in patients undergoing surgery compared to patients undergoing medical management. In addition, approximately one-third of patients who elected medical management crossed over into the surgical cohort and noted statistically significant improvements. Although this study is limited by the lack of randomization and a tertiary care population, it provides strong evidence for surgery in the treatment of CRS.

Although endoscopic sinus surgery is highly successful for the treatment of CRS, it often needs to be followed with continued medical management given chronic ongoing inflammation. Recent literature has suggested that topical intranasal steroids delivered via nasal saline irrigations are effective at improving postoperative symptoms, quality-of-life measures, and endoscopy scores. Adjuvant topical intranasal steroid therapy is now a widely used postoperative treatment regimen.

Conclusion

Rhinosinusitis is common and has a tremendous impact on society in terms of productivity and health-care expenditures. The most common form is VRS, which should be treated conservatively. When ABRS results, the use of antibiotics directed toward the most likely causative agents is typically indicated. Treatment should be modified depending on the efficacy of the primary therapy and whether antibiotics have been used within 4–6 weeks of initiating therapy. Chronic rhinosinusitis is a complex syndrome that has no clear etiology at this time. Active research into the pathophysiology may ultimately lead to effective preventative measures and medical therapies for this disease entity. Oral antibiotics, oral and topical corticosteroid therapy, and adjunctive measures appear to improve patient quality of life and reduce disease burden. When surgery is indicated, functional endoscopic sinus surgery can be carried out with significant improvement in quality-of-life measures when appropriate follow-up and medical management are employed after surgery. With this understanding, rhinosinusitis can be effectively managed.

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Chapter 9
Allergic Diseases of the Ear

Doris Lin and Steven W. Cheung

General Considerations

The ear has multiple targets for allergic diseases (Table 9.1). The external ear may be afflicted with contact dermatitis to earrings or hearing aid molds, eczema, or sensitization to eardrops or fungus. The middle ear may be plagued with persistent effusion secondary to eustachian tube dysfunction or chronic inflammatory response to allergens. The inner ear may be troubled by Ménière's disease and cochlear hydrops, both disorders with possible allergic bases.

Allergic Diseases of the External Ear

Chronic Otitis Externa

The skin of the pinna and external ear may be afflicted in two major ways. Eczema of the auricle or external auditory canal (EAC) may manifest as erythematous, scaling, and pruritic dermatitis. Atopic eczema is the most common type of eczema and closely associated with asthma and allergic rhinitis. The usual treatments are with emollients that maintain skin hydration and topical steroids to reduce inflammation. Another type of eczema seen is seborrheic eczema, which is most commonly seen on the scalp as dandruff but can spread to the face and ears. The condition is thought to be caused by yeast and can be treated with an antifungal cream if necessary.

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Table 9.1 Otologic manifestations of allergy

External ear
Chronic external otitis
Sensitization to eardrops
Contact sensitivity (hearing aid ear molds, earrings)
Dermatophytid reaction
Eczema
Middle ear
Eustachian tube dysfunction
Patulous eustachian tube
Otitis media with effusion
Chronic otitis media
Inner ear
Ménière's disease
Vestibular hydrops
Cochlear hydrops
Dizziness
Tinnitus

Chronic otitis externa that follows the use of topical antimicrobial drops, particularly those containing neomycin, can actually be a hypersensitivity reaction. Symptoms generally resolve with discontinuation of the offending agent; however, occasionally topical steroid drops may be needed to accelerate recovery.

Contact Sensitivity

Some patients may develop contact sensitivity to certain plastic molds attached to hearing aids. The problem manifests as a localized skin reaction. Boiling the hearing aid mold in water for 30 s, substituting a different material for the mold, and plating a thin film of gold onto the mold may reduce symptoms. Along this vein, patients may develop contact sensitivity to nickel and chromium in earrings. Treatment often involves use of earring posts of surgical stainless steel or 14-karat gold or titanium.

Dermatophytid Reaction

The auricle or EAC can be the site of a dermatophytid reaction in a sensitized individual. Usually there is a primary site of fungal infection. The fungus or their allergenic products spread hematogenously to a secondary site, causing an allergic skin eruption. Resolution requires treatment of the primary fungal infection, desensitization with an allergenic extract of the infecting fungus, and control of any secondary bacterial infections. The most common fungus involved is *Trichophyton*, although Candida (*Oidiomycetes*) and *Epidermophyton* have also been described. Common

sites for the primary fungal infection include the nails (onychomycoses), skin, and vagina (monilial vaginitis).

Allergic Diseases of the Middle Ear

Otitis media with effusion (OME) can impair hearing significantly, cause profound mucosal changes, delay speech development, and result in permanent middle ear damage. OME is the most common cause of hearing loss in children today and causes a conductive hearing loss with a flat tympanogram (Fig. 9.1). Of particular interest is OME refractory to conventional antibiotic treatment and surgical therapy

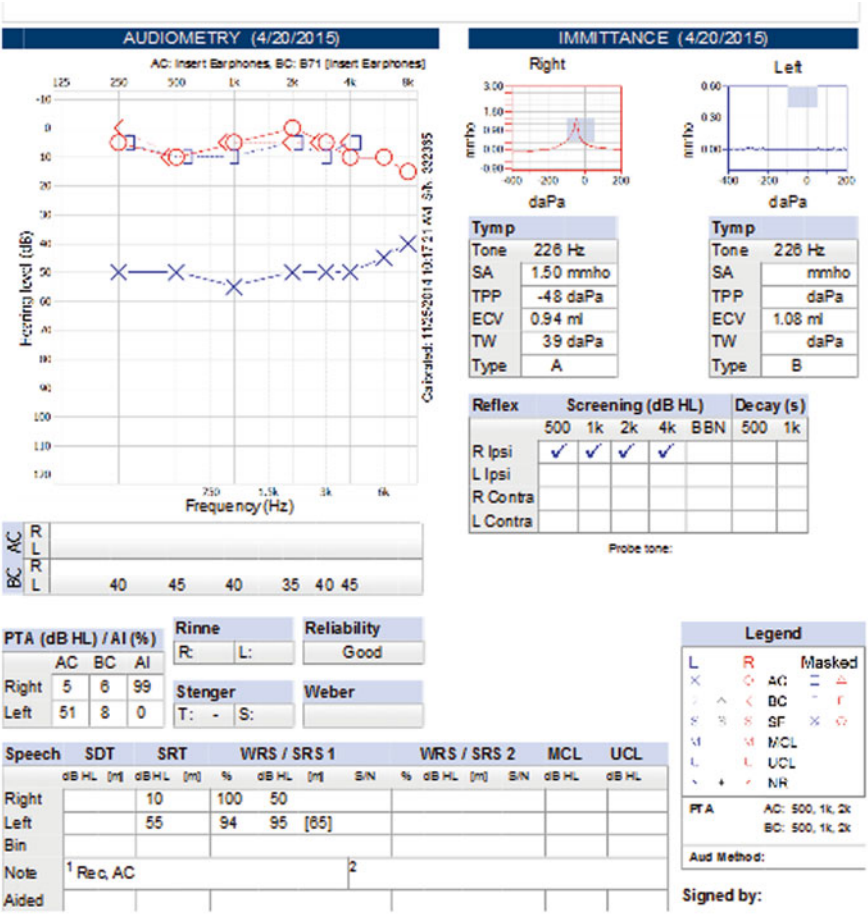

Fig. 9.1 Example of an audiogram from a patient with a left otitis media and resultant conductive hearing loss. This patient also has a flattened left tympanogram resulting from a tympanic membrane stiffened by fluid in the middle ear. The normal right ear is shown for comparison

such as myringotomy, tonsillectomy, adenoidectomy, tympanostomy tube placement, and even radical mastoidectomy. Chronic mucosal inflammation is a major finding in these cases. The role of allergy in these cases is under active investigation and is discussed in the following sections.

Eustachian Tube Dysfunction

Eustachian tube dysfunction (ETD) is a major factor in the development of OME. Upper respiratory infections and allergies contribute to ETD and, in some cases, contribute to a patulous eustachian tube. Patients with patulous eustachian tube may complain of autophony (abnormal awareness of their own voice), reverberation, or tinnitus resembling the sound of an ocean roar. Provocative intranasal challenges of pollen, house dust mites, and histamine worsen ETD. Allergic rhinitis results in a significantly higher rate of ETD, particularly during childhood, as demonstrated by nasal turbinate changes (Fig. 9.2). Bernstein proposes that ETD in the setting of allergy may be a result of retrograde spread of edema and congestion of nasal mucosa, decreased mucociliary function that permits secretions to cover the ostium and subsequent intraluminal inflammation, or obstruction of the eustachian tube orifice from hypersecretion by seromucous glands. Those symptoms can be alleviated with specific allergy therapy, including immunotherapy and elimination diets depending on the offending agent.

Otitis Media with Effusion

OME often results from ETD or can be the result of chronic inflammation or microbial infection. The causative contribution of allergy to OME is unknown, with a broad range of attribution (0–100 %) reported in the literature. The controversy regarding the role of allergy in OME is reflected in different types of skin and

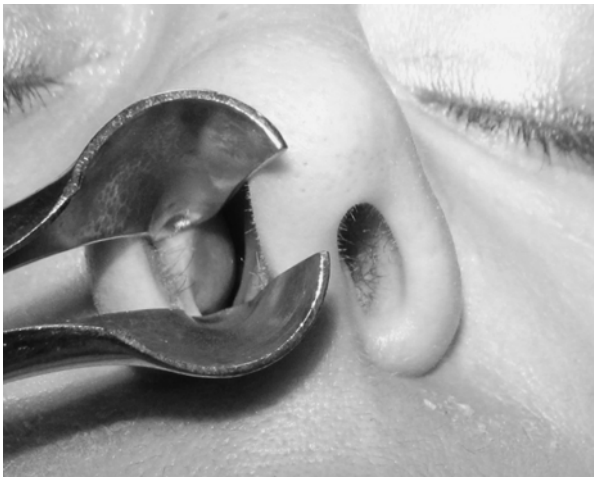

Fig. 9.2 An enlarged and boggy right inferior turbinate from a patient with allergic rhinitis

in vitro testing, and heterogeneous types of allergens included in each study. Many would agree that OME caused by allergy is most likely from ETD secondary to an allergic reaction in the proximal eustachian tube or nasopharynx. However, some studies have demonstrated the presence of histamine and other biologic mediators of inflammation in the middle ear fluid of patients with OME, suggesting that the middle ear is also a primary target of allergic reactions. The middle ear mucosa responds the same way as other mucosae in the respiratory tract to allergens regardless of location. Middle ear mucosa has been found in animal studies to respond to allergens in the same way as the lung and nasal mucosa.

An argument against a significant role of allergy in the pathogenesis of OME is that although allergy is typically considered seasonal with regional variation, OME has its highest incidence in the winter, regardless of region. In addition, an IgE-mediated reaction is brief and not typically long enough to cause significant ETD. Also, there is no clear evidence for an intranasal challenge directly producing a middle ear effusion. Although intranasal challenges have resulted in ETD, the duration of dysfunction is insufficient to result in OME. Even complete eustachian tube obstruction produced by sectioning the tensor veli palatini muscle in an animal model takes 1–4 weeks to result in a middle ear effusion. Intranasal provocative challenge persists for only several hours to a few days.

Counter-arguments contend that winter is the time of year when dust and mold counts tend to be highest. Intranasal challenges of histamine, pollen, and house dust mites result in ETD, albeit of unclear sufficient duration to cause OME. Epidemiologic studies have shown that patients with OME have an increased prevalence of atopic conditions, such as allergic rhinitis, eczema, and asthma. More than 50 % of patients with OME have allergic rhinitis, whereas 21 % of patients with allergic rhinitis have OME.

One study of 20 patients with OME refractory to medical and surgical management showed that allergy immunotherapy in patients tested with the radioallergosorbent test (RAST) resulted in preservation of hearing and elimination of recurrent infections for 3 years when compared with controls. Although small, this study encourages consideration of allergic factors in patients with refractory OME to conventional treatments. For OME refractory to conventional treatments, allergy testing is recommended, especially for children requiring multiple sets of tubes, as immunotherapy has been shown to resolve OME in atopic patients.

Food Allergy in Otitis Media with Effusion

Few studies address the role of food antigens in OME. One study of 56 children found food allergies in children with OME (45 %) were significantly higher than in children without complaints of food allergy or OME (18 %). Another study of 104 children with recurrent OM found that 78 % had food allergy diagnosed by skin prick or IgE tests and food challenge. They reported that 86 % of the children with food allergy who were treated with food elimination had significant amelioration of OME, as documented by clinical examination and tympanometry. Food challenge resulted in recurrence of OME in 94 % of the children with food allergies who underwent challenge. A few studies have suggested that cow's milk allergy in

infancy, even when treated properly, is associated with significantly higher rates of recurrent OME. A few of these studies address possible mechanisms for this association. These include nasal congestion induced by food allergy, direct middle ear mucosal damage by food immune complexes, and other hypersensitivity responses. One study demonstrated elevated serum IgG response, but a lack of IgE response, to foods in otitis-prone children compared with controls. More definitive studies are needed in this area. Nevertheless, current results encourage consideration of a food elimination diet in select patients before surgical intervention.

Allergic Diseases of the Inner Ear

Ménière's Disease

Ménière's disease is characterized by aural fullness, tinnitus, vertigo, and fluctuating sensorineural hearing loss (SNHL). Two related variants are cochlear hydrops (fluctuating SNHL without vertigo) and vestibular hydrops (imbalance without fluctuating SNHL). The etiology of Ménière's disease is unclear and has been attributed to anatomic, infectious, immunologic, and allergic factors. The target organ appears to be the endolymphatic sac. The mainstays of medical therapy have included diuretics (particularly thiazide), carbonic anhydrase inhibitors, oral and intratympanic steroids, salt reduction (<1.5 g/day), and dietary restrictions. Recently, long-acting hydrogel delivered to the middle ear to modulate labyrinthine function has shown vertigo control promise. Surgical therapy is reserved for cases refractory to medical management. These include chemical labyrinthectomy (intratympanic aminoglycoside), surgical labyrinthectomy, endolymphatic shunt, and vestibular nerve section.

Both inhalant and food allergies have been linked with symptoms of Ménière's disease and cochlear hydrops. Patients with Ménière's disease have a 40 % rate of allergy, as measured by skin or in vitro testing, which is twice as high as that reported for the general population. The success of sedating antihistamines in the treatment of Ménière's disease is usually attributed to vestibular suppressant effects, but allergic reaction-suppressant properties may also contribute to clinical improvement. Dietary restrictions on sodium, caffeine, nicotine, alcohol, and foods containing theophylline (e.g., chocolate) improve symptoms in patients with Ménière's disease, although the mechanism has usually been attributed to fluid regulation of the endolymphatic sac. Regardless, immunotherapy and food elimination diets have mitigated both allergic and labyrinthine symptoms in Ménière's disease.

Evidence-Based Medicine

Studies over the last few years have focused on the possible roles of allergy in OME. Allergic rhinitis and nasal/nasopharyngeal inflammation resulting in ETD are associated with increased rates of OME. Allergy-related mediators (IL-4, IL-5, IL-6,

regulated on activation, normal T cell expressed and secreted [RANTES], eosinophil cationic protein [ECP], tryptase, IgE) isolated from middle ear effusions have been shown to be elevated. In a prospective cohort study, Hurst has shown that 85 % of atopic patients ($n=89$) with OME had complete resolution of their fluid after treatment with specific allergy immunotherapy, whereas none of the controls (patients with OME who were not treated with immunotherapy) improved spontaneously ($p<0.001$). This study lends support to the role of allergy in the pathogenesis of OME as aggressive treatment of the allergy did improve the OME in a significant portion of the atopic patients. In a randomized, double-blind placebo-controlled trial of a new delivery system for treatment of Ménière's disease, Lambert et al. showed a meaningful reduction in vertigo frequency compared to placebo at 3 months of treatment. This clinical study of 44 patients used a steroid-infused hydrogel to deliver sustained glucocorticoid to the inner ear. In the future, hydrogels could be used to deliver other medications directly to the middle and inner ear in a sustained fashion.

The role of food allergy in OME and in other allergic diseases of the ear is under active investigation. For OME and Ménière's disease, an allergic basis of disease and treatment should be considered in cases refractory to conventional medical and/or surgical management.

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Chapter 10
Cough and Allergic Diseases

Shanti K. Shenoy and Michael Schivo

Introduction

Cough is an essential mechanism for airway clearance and protection, but it is also a troublesome symptom and one of the most commonly encountered in the outpatient setting across a variety of disciplines. Cough represents a challenge for primary care and specialty physicians alike given its pathophysiologic complexity, broad differential, and sometimes elusive nature. The global impact of cough on healthcare cost is substantial, and it is responsible for more than 30 million outpatient visits per year in the United States alone. This has prompted the development of national guidelines surrounding the diagnosis and management of cough.

The duration of symptoms classifies cough as acute, subacute, or chronic. Acute cough lasts up to 3 weeks, while subacute cough lasts 3–8 weeks. If symptoms persist beyond 8 weeks, it is termed chronic cough. The etiologies vary according to chronicity and patient comorbidities and will be discussed here.

Definition and Physiology

Cough is a highly coordinated reflex designed to protect the airway. It is composed of a series of four maneuvers that generate the distinctive cough sound. A deep inspiration is followed by a forceful exhalation against a closed glottis. The glottis opens with an expulsive flow of air, giving the cough sound. The final recovery phase is marked by a restorative inspiration.

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Involuntary coughing is entirely mediated by the vagus nerve and its branches, which receive chemical and mechanical inputs primarily from the larynx and proximal tracheobronchial tree. Irritation at other sites such as the pharynx, tympanic membrane, and external auditory canals can also induce cough. Direct stimulation of nerve receptors or "sensors" termed rapidly acting receptors (RARs), located in the tracheobronchial tree, causes the cough reflex. RARs respond primarily to changes in airway mechanics and indirectly to chemical stimuli (i.e., substance P, histamine, and bradykinin). Additionally, intrapulmonary slowly adapting stretch receptors (SARs) and C-fibers have been implicated in modulating the cough reflex.

Recent advances in the field have described suprapontine control networks that influence the basic cough reflex and may be responsible for the perception of cough and the related cognitive and emotional responses.

Causes of Cough

The causes of cough are broad and varied. The first step in narrowing the differential is assessing the duration of cough and classifying it as acute, subacute, or chronic. Within each is a list of etiologies ranging from infectious to inflammatory and/or hypersensitivity reactions involving the airway and/or lung parenchyma (Table 10.1). A thorough history and physical examination are essential, and institution of empiric therapy may be sufficient. Persistent or deteriorating symptoms should prompt additional workup with a chest radiograph, pulmonary function testing, and other relevant diagnostic testing.

Upper Airway Cough Syndrome (Postnasal Drip Cough)

Upper airway cough syndrome (UACS) describes what was previously referred to as the postnasal drip syndrome and characterizes any condition that irritates the structures of the upper airway and stimulates cough, including postnasal drip. A number of etiologies may lead to a final pathway of postnasal drip, including allergic rhinitis, nonallergic rhinitis, infectious rhinitis, nonallergic rhinopathy, and drug-related rhinitis. Therefore, UACS is a more comprehensive term and includes the possibility that the mucoid secretions of postnasal drip may not be the sole trigger of cough, but rather the conditions listed above directly stimulate upper airway cough receptors and elicit cough.

Patients may describe hoarseness, a "tickling" sensation, and frequent throat-clearing in conjunction with chronic nasal drainage. The absence of these symptoms does not preclude the diagnosis of UACS, as they may be clinically unapparent and only manifest as chronic cough.

Table 10.1 Causes of cough

Infectious
Rhinosinusitis
Tracheobronchitis
Bronchopneumonia
Pertussis
Noninfectious
Upper airway cough syndrome
Allergic rhinitis
Nonallergic rhinitis
Rhinitis medicamentosa and drug-induced rhinitis
Vasomotor rhinitis
Gustatory rhinitis
Airway disease
Asthma (including cough-variant asthma)
Chronic obstructive pulmonary disease
Bronchiectasis
Cystic fibrosis
Tracheomalacia
Tracheal diverticulum
Subglottic masses and stenoses
Nasal polyps
Laryngeal polyps
Parenchymal lung disease
Interstitial lung disease
Sarcoidosis
Vasculitis
Tumors
Benign and malignant tumors of the airway and/or mediastinum
Middle ear pathology
Cardiovascular disease
Congestive heart failure
Aortic aneurysm
Other diseases
Gastroesophageal reflux disease
Laryngopharyngeal reflux
Chronic aspiration
Psychogenic cough
Foreign bodies
Drugs
Angiotensin-converting enzyme inhibitors
Others

Allergic Rhinitis and Cough

Allergic rhinitis is an IgE-mediated inflammatory response of the nasal mucosa to inhaled allergens. Symptoms include rhinorrhea, airflow obstruction, inflamed nasal passages, itching of the hard palate, and allergic conjunctivitis. As the sensitization to aeroallergens is becoming increasingly recognized, the prevalence of allergic rhinitis is rising and likely affects up to 15–30 % of the US population. Patients may report postnasal drip, which irritates the larynx and trachea and triggers the cough reflex. Allergic rhinitis is also closely linked to asthma; therefore the cough may arise from within the tracheobronchial tree. Clinicians should have a heightened suspicion for allergic rhinitis in patients with systemic atopy.

Allergic rhinitis is a heterogeneous disorder that includes seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). SAR occurs in response to tree, grass, and weed pollens, and the disease activity is often episodic and follows a seasonal variation. In contrast, PAR is a result of sensitization to indoor allergens, such as dust mites, cockroaches, and animal dander, and patients report symptoms year-round. Diagnosis is often made from clinical evaluation alone; however, allergen-specific testing can be of some utility. These include immediate hypersensitivity skin testing (skin prick testing) and/or serum tests for allergic-specific IgE antibodies, which can identify particular inhalant allergens that should be avoided. A thorough physical exam with special attention to the nose, oropharynx, and ears is essential. Infraorbital edema and a transverse nasal crease may be identified by simply inspecting the patient's face. The nasal mucosa often assumes a pale, bluish hue. The posterior oropharynx may have bands of lymphoid tissue, giving it a "cobblestoned" appearance. Additionally, otoscopic evaluation may reveal tympanic membrane retraction from serous fluid accumulation.

Pharmacotherapy is centered on intranasal glucocorticoids, antihistamines, and leukotriene-receptor antagonists. Intranasal glucocorticoids have the most benefit in SAR as maintenance therapy, while the efficacy in PAR is less clear. They are often used as first-line agents, and while the onset of action takes just hours, patients may not report symptomatic benefit for several days to weeks. Step-up therapy with the addition of antihistamines and leukotriene-receptor antagonists should be considered. Allergen immunotherapy may be beneficial if suboptimal response is obtained with traditional pharmacologic therapy, and this involves administering subcutaneously or sublingually the known allergen(s) in serial aliquots in efforts to lessen the allergic response.

Nonallergic Rhinitis and Cough

Nonallergic rhinitis is characterized by nasal congestion and clear mucous discharge, and less often by sneezing and itching. The true prevalence is uncertain as it frequently coexists with allergic rhinitis. It differs from allergic rhinitis in that it is not an IgE-mediated event, and therefore serum IgE and allergen-specific testing are often unremarkable. Identifiable triggers are perennial upper airway irritants such

as strong odors and perfumes, tobacco smoke, pollution, and temperature variations. Nonallergic rhinitis comprises several clinical entities, including vasomotor rhinitis, nonallergic rhinitis with eosinophilia syndrome, rhinitis medicamentosa, and gustatory rhinitis, which will be discussed here.

Nonallergic Rhinopathy

Patients with nonallergic rhinopathy (NAR, formerly called vasomotor rhinitis) experience symptoms related to chronic mucous hypersecretion causing nasal congestion and rhinorrhea in the absence of immunologic or infectious etiologies. The precise mechanisms are unknown but are thought to involve some degree of nociceptive and autonomic dysfunction, producing an exaggerated response to environmental triggers such as smoke, odors, and, in particular, cold air. It can present a challenge to distinguish NAR from other forms of rhinitis, especially since the diagnosis is made clinically. Patients may report increased mucous production, postnasal drip, and cough after exposure to the offending agent. Nasal and palatal itch, ocular symptoms, and sneezing are not customary, but the presentation can vary. Avoidance of known triggers is the first step in treatment. The efficacy of pharmacologic therapy in NAR is less clear but usually involves intranasal corticosteroids and topical histamine antagonists such as azelastine. Ipratropium bromide, an anticholinergic, is also approved to treat rhinorrhea.

Nonallergic Rhinitis with Eosinophilia Syndrome

Nonallergic rhinitis with eosinophilia syndrome (NARES) is a clinical syndrome that presents similarly to nonallergic rhinitis with the exception that nasal cytology analysis demonstrates greater than 20 % eosinophils. NARES lacks an allergic component, as patients have negative serum IgE and allergen-specific testing. In addition to chronic rhinorrhea, nasal obstruction, nasal pruritis, and sneezing, these individuals may complain of anosmia, which is unique to this syndrome. NARES has some overlapping features with nasal polyposis and often precedes its development. The pathophysiology is thought to involve the activation of eosinophils and mast cells in the formation of a chronic eosinophilic infiltrate, followed by a disrupted nasal mucosa and nasal hyperresponsiveness. Intranasal corticosteroids are the cornerstone of treatment and are also beneficial if nasal polyps are present.

Rhinitis Medicamentosa

Rhinitis medicamentosa describes a rebound phenomenon of nasal congestion and rhinorrhea owing to the overuse of topical nasal decongestants. This is observed with sympathomimetic amines and imidazolines, such as oxymetazoline, which

initially works well to control the nasal blockage. However, persistent use leads to an earlier return of symptoms, and patients begin to increase the frequency of administration and soon become reliant on the agent. Immediate discontinuation of the nasal decongestant is recommended but may transiently worsen the congestion and induce more mucous production. In some cases, intranasal glucocorticoids and, rarely, oral corticosteroids are needed to abate symptoms. When patients report disabling nasal obstruction, we recommend no more than 3 days of the topical decongestant.

A separate clinical entity is drug-induced rhinitis, which is seen with a variety of medications. This differs from rhinitis medicamentosa in that symptoms occur almost immediately after onset of use and terminate with drug withdrawal. Table 10.2 lists some of the medications that cause drug-induced rhinitis.

Gustatory Rhinitis

Gustatory rhinitis is a nonallergic and noninflammatory form of rhinitis that occurs after the ingestion of solid and liquid foods (often hot and spicy). Patients report watery rhinorrhea within several seconds to minutes after consuming the food. Nasal obstruction, pruritis, or sneezing is typically not observed. It is believed to be related to an increased parasympathetic response and stimulation of trigeminal sensory nerve endings. Avoidance of culprit foods is recommended. Intranasal application of ipratropium bromide has demonstrated efficacy in relieving symptoms.

Table 10.2 Common medications associated with drug-induced rhinitis (partial list)

Aspirin
NSAIDs
Clonidine
Prazosin
Doxazosin
Phentolamine
Phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, vardenafil)
Angiotensin-converting enzyme inhibitors
β-Blockers
Calcium channel blockers
Hydralazine
Hydrochlorothiazide
Estrogens and oral contraceptives
Risperidone

Infectious Rhinitis and Cough

Infectious rhinitis is the most frequent acute illness managed in the outpatient setting. Patients may present with an acute or subacute cough in the setting of recent nasal congestion, rhinorrhea, and a sore or scratchy throat. This is routinely due to viral infections as bacterial and fungal pathogens rarely cause acute rhinosinusitis. Cough typically begins 1–5 days after the onset of the upper respiratory tract infection (URI) symptoms. Postnasal drip can elicit the cough, but there is also a heightened cough reflex during an acute viral URI via inflammatory effects on the airway epithelium and stimulation of cholinergic pathways causing bronchial hyperreactivity. As such, the URI itself resolves within 3–7 days, but a post-URI cough can linger for up to 8 weeks. This post-viral tussive syndrome may persist longer in patients with known underlying airway disorders such as asthma or bronchiectasis. Patients may present later in the course of their illness with unremitting cough and can often trace it back to the onset of the URI.

Diagnosis is made with clinical history alone, as there are rarely suggestive physical exam findings. Treatment is supportive. The American College of Chest Physicians (ACCP) evidence-based guidelines recommend an antihistamine/decongestant preparation to treat cough related to URI. Other remedies include saline nasal irrigation, inhaled anticholinergics, antitussives, and expectorants.

Viral rhinitis can progress to sinusitis. Occasionally, a viral rhinitis can be complicated by an acute bacterial sinusitis in which the majority of cases are due to infection with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Purulent nasal discharge, maxillofacial tenderness, and fever are typically associated with a bacterial etiology, but these are not always reliable making it challenging for the clinician when deciding on antimicrobial therapy. Guidelines from the Infectious Diseases Society of America indicate the following three ways to identify an acute bacterial sinusitis:

1. Symptoms persisting for ≥10 days without evidence of clinical improvement
2. High fever (≥39 °C [102 °F]) and purulent nasal discharge or facial pain lasting at least three to four consecutive days
3. Worsening symptoms, such as fever and purulent nasal discharge, that develop several days after the onset of illness that was initially improving

Empiric antibiotic therapy is often instituted since cultures are not routinely obtained. Amoxicillin-clavulanate is first line; doxycycline or a respiratory fluoroquinolone can be used in penicillin-allergic patients. Urgent referral to a specialist is indicated if orbital swelling, visual disturbances, or concerns of intracranial infection arise.

Angiotensin-Converting Enzyme Inhibitor Cough

Angiotensin-converting enzyme (ACE) inhibitors are often an overlooked cause of dry cough. The widespread use of these agents has made this side effect more recognizable. It is believed to be related the accumulation of substance P and

bradykinin in the airways from the inhibition of ACE, which normally serves to degrade these mediators. Cough develops in as many as 35 % of patients treated with an ACE inhibitor and can occur immediately or have a delayed onset of weeks to months. Discontinuation of the drug typically leads to resolution of the cough within a few weeks. Angiotensin II receptor blockers (ARBs) are alternatives and are less associated with cough.

Asthma and Cough

Asthma is among the top three causes of chronic cough in adults. It is a chronic inflammatory disease of the lower airways, leading to bronchial hyperresponsiveness and variable airflow limitation. Recurrent episodes of cough, wheeze, breathlessness, and chest tightness occur in response to exposure to known aeroallergens, infection, or exercise. Asthma is really a syndrome and encompasses different subtypes, including cough-variant asthma and nonallergic forms of asthma. Asthma-associated cough can be a challenge to diagnose since symptoms overlap with other causes of chronic cough. The mechanism of cough in asthma is poorly understood. Bronchial hyperresponsiveness, mucous hypersecretion, and neurogenic inflammation caused by sensitized sensory nerve endings are thought to induce airway hyperalgesia and subsequent cough.

Pulmonary function testing is routinely performed to assess the degree of airflow obstruction and potential air trapping; however, this can be normal between exacerbations. In this case, bronchoprovocation testing can evaluate for bronchial hyperreactivity. Baseline spirometry is performed and then successive increasing doses of aerosolized methacholine or histamine are administered to the patient, followed by spirometry. A positive test is confirmed if the FEV_1 (forced expiratory volume in 1 s) drops by at least 20 % from baseline, and the dose at which this occurs is termed the provocation dose.

Home peak expiratory flow (PEF) monitoring with portable meters is an objective way of monitoring airway changes. Diurnal variation of at least 20 % is diagnostic of asthma, and the magnitude of variability between morning and evening measurements is proportional to the severity of disease.

Anti-inflammatory agents, such as inhaled corticosteroids (ICS), are first-line agents in maintenance asthma control. Oral preparations may be necessary in severe cases and exacerbations. Long-acting beta-agonists and leukotriene-receptor antagonists are used in conjunction with ICS. Individuals with severe, refractory atopic asthma may benefit from anti-IgE therapy.

Cough-Variant Asthma

When cough is the predominant symptom in asthma, it is termed cough-variant asthma (CVA). These individuals demonstrate an exaggerated cough reflex but less bronchial hyperreactivity compared to individuals with typical asthma who cough.

In fact, patients with CVA often do not experience typical asthma symptoms, such as wheeze or chest tightness. Spirometry may be normal. Standard anti-asthma therapy is employed in CVA, and symptom resolution is often diagnostic of the condition.

Nonasthmatic Eosinophilic Bronchitis

Nonasthmatic eosinophilic bronchitis (NAEB) is a form of airway inflammation marked by chronic cough and increased sputum eosinophils in the absence of variable airflow obstruction and airway hyperresponsiveness. It has been suggested that sensitization to specific aeroallergens or occupational chemical inhalants can induce NAEB. Mast cell localization plays a significant role in the pathophysiology of NAEB. In addition to avoidance of known offending agents, the cornerstone of pharmacologic treatment is inhaled corticosteroids.

Gastroesophageal Reflux Disease and Cough

Gastroesophageal reflux disease (GERD) is a frequent but under-recognized cause of chronic cough in adults. The median symptom duration is 48 months before a diagnosis is made, compared to less than 12 months for other causes of chronic cough. GERD involves irritation and stimulation of upper airway cough receptors and recurrent episodes of microaspiration from the esophagus into the lower respiratory tract. Recent studies suggest that the cough reflex also may be enhanced. Symptoms typical of GERD, such as heartburn or water brash, do not necessarily accompany the cough. Clinicians may elect a 6–8-week trial of acid suppression with proton pump inhibitors and/or H2-receptor antagonists. Ambulatory esophageal 24-h pH monitoring off acid-suppressive therapy is a confirmatory test, in which the percentage of time the pH of the esophagus measures below four is recorded.

Barium swallow can identify mucosal abnormalities related to acid irritation. Upper endoscopy should be considered if worrisome symptoms are present, empiric therapy fails to resolve the symptoms, and other tests are normal.

Laryngopharyngeal reflux (LPR) is an extra-esophageal variant of GERD in which gastric acid, enzymes, or gasses reflux through the upper esophageal sphincter to the larynx and pharynx. This leads to laryngeal irritation, inflammation, and chronic cough.

Symptomatic Treatment of Cough

A wide range of disease processes may present with cough and definitive treatment is contingent upon finding the underlying cause. In some cases, an etiology is not identified, has no specific treatment, or requires prolonged treatment;

management of symptoms is fundamental. The problem is complicated by the lack of effective antitussive therapies and an unpredictable response to therapy. Cough that does not respond to typical therapy should be investigated further with appropriate imaging and pulmonary function testing. Consideration of invasive procedures, such as laryngoscopy and/or flexible bronchoscopy, may be necessary.

Medications with antitussive effect are classified based on location of action, centrally versus peripherally-acting. Centrally-acting agents, which include narcotic opioids and dextromethorphan (a nonnarcotic opioid), influence brainstem circuitry in the basic cough reflex. Attendant intolerable side effects, such as sedation and GI upset, often limit their use. Older-generation antihistamines, dexbrompheniramine and diphenhydramine, exert their anticholinergic effects in UACS.

Benzonatate is a peripherally-acting agent that reduces cough by inhibiting pulmonary stretch receptors. Guaifenesin is an expectorant that enhances mucociliary clearance and decreases the viscosity of secretions to promote effective removal.

Studies suggest that the tricyclic antidepressant amitriptyline and gamma-aminobutyric receptor antagonist baclofen have off-label use in refractory cough. Caution is required when using these agents as they can have considerable side effects, especially in elderly patients.

Emerging Concepts

Neuropathic Cough

An emerging concept in the pathophysiology of chronic cough is the cough hypersensitivity syndrome (CHS). Defined by a Task Force of the European Respiratory Society in 2011 and ultimately published in 2014, CHS is “a clinical syndrome characterized by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure.”

Prior upper respiratory viral infections or exposure to inhaled irritants induces inflammatory changes leading to airway sensory neural dysfunction and upper airway paresthesia. This enhances the cough reflex, and low levels of tussive and nontussive stimuli are sufficient to trigger cough. A number of mechanisms have been proposed to underlie CHS, including amplified expression of the transient receptor potential vanilloid-1 (TRPV1) in afferent nerves. The TRPV1is a subtype of the transient receptor potential (TRP) family of ion channels and is expressed in several tissue types and disease states. Experimental studies suggest that various noxious stimuli not only activate but also sensitize this receptor to otherwise bland mediators, producing sustained damage of airway mucosa, which may be the basis for the hypertussive response in chronic cough (Fig. 10.1).

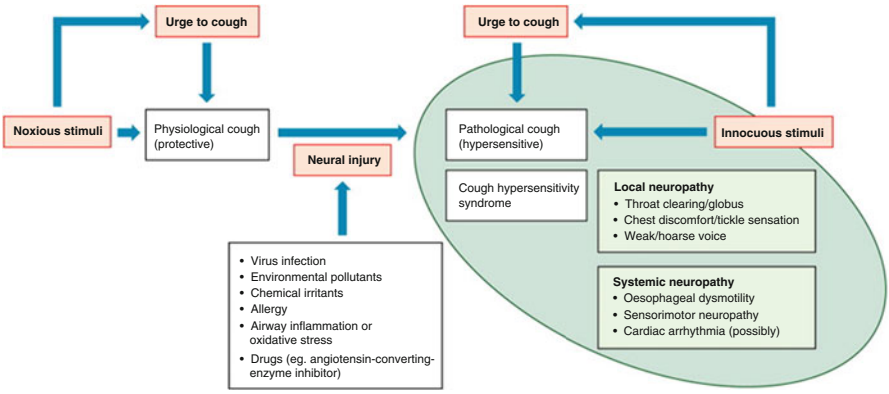

Fig. 10.1 The proposed mechanisms of cough hypersensitivity syndrome. In the healthy adult, cough begins as a protective defense mechanism in response to noxious stimuli. Prolonged or repeated insults generate afferent neural injury and remodeling, leading to local and systemic neuropathy, such that even benign stimuli trigger the cough reflex (Reprinted from Chung et al.)

Conclusion

Cough is one of the most frequently encountered problems in general practice, has a significant impact on quality of life, and contributes a substantial cost to the healthcare system.

More than of 90 % of cases of chronic cough in the adult are attributed to UACS, GERD, and airway inflammation (including asthma and NAEB). History and physical examination may be sufficient, and a trial of therapy can be both diagnostic and therapeutic, without the need for invasive tests. Progression of symptoms and the development of worrisome symptoms warrant further investigation. The etiology is not always discovered, leaving patients with idiopathic or unexplained cough and need for symptom management. Even in cases where a cause is identified, response to treatment is variable.

A novel paradigm termed "cough hypersensitivity" describes persistent upregulation of the cough reflex owing to dysfunction of vagal afferents and heightened stimulation of laryngeal and upper airway cough receptors. This is an evolving concept and believed to be a principal feature of chronic cough.

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Chapter 11
Urticaria and Angioedema

Bettina Wedi and Alexander Kapp

Urticaria, commonly known as hives, is a common dermatological condition. It is characterized by acute or chronic, superficial swelling of the skin that is almost invariably associated with itching. Lifetime incidence is higher than 20 %. The mechanism is local vasodilatation and increase in capillary permeability with plasma leakage and IgE-mediated or non-immunologic activation of mast cells causing mediator release, predominantly of histamine. The itching can be pricking or burning and is usually worse in the evening or nighttime. Typically the lesions are rubbed and not scratched; therefore, excoriated skin is usually not a consequence of urticaria.

Angioedema is caused by a similar mechanism but is localized deeper in the dermis, subcutaneous, and submucosal tissues. Urticaria and angioedema can occur anywhere on the body. Angioedema most often involves the eyelids, lips, and genitalia but sometimes also the tongue and laryngopharynx, which can be life threatening and causes anxiety (symptoms occur often at nighttime). Systemic symptoms such as fatigue and respiratory, gastrointestinal, and arthralgic symptoms are rare.

Urticaria is not a single disease but a reaction pattern. The clinical pictures are of heterogeneous etiology and therefore it is subclassified into distinct groups.

Classification of Urticaria

Spontaneous urticaria (about 80 %) that can be acute or chronic is separated from chronic inducible urticarial subtypes (about 20 %). The term chronic inducible urticaria summarizes physical urticaria (about 10 %) and special types of urticaria (<10 %) (see Table 11.1).

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Table 11.1 Classification of urticaria subtypes

Urticaria group	Subtype of urticaria	Definition
Acute	*Acute spontaneous*	*Spontaneous wheals, angioedema, or both for less than 6 weeks*
Chronic	*Chronic spontaneous*	*Spontaneous wheals, angioedema, or both for longer than 6 weeks*
	Chronic inducible:	*Reproducible eliciting factors*
	(Physical)	
	Cold	Cause: cold (air/water/wind)
	Delayed pressure	Cause: vertical pressure (latency of 3–8 h)
	Localized heat	Cause: local heat
	Solar	Cause: UV and/or visible light
	Dermographic	Cause: mechanical shear forces
	Vibratory	Cause: vibratory forces (pneumatic hammer)
	(Special type)	
	Aquagenous	Cause: water contact of any temperature
	Cholinergic	Cause: increased body temperature
	Contact	Cause: contact with urticariogenic substance

Two or rarely more subtypes of urticaria can occur in the same patient such as chronic spontaneous urticaria and dermographism or delayed pressure urticaria. In these cases urticaria is more often difficult to treat and is long persisting.

Other diseases such as urticaria vasculitis and urticaria pigmentosa although associated with the name urticaria for historical reasons are no longer grouped under the heading urticaria.

Spontaneous Urticaria

About two-thirds of spontaneous urticaria is acute (allergic or nonallergic), and about one-third is chronic spontaneous urticaria (nonallergic).

Acute Spontaneous Urticaria

Definition

Acute spontaneous urticaria is defined as spontaneous wheal and flare reaction of less than 6 weeks duration (Fig. 11.1). Most often it is a single episode lasting 1 or 2 weeks. Angioedema is associated in more than 50 % of cases. Acute spontaneous urticaria is a common skin disease in medical emergency service. There is no gender preference.

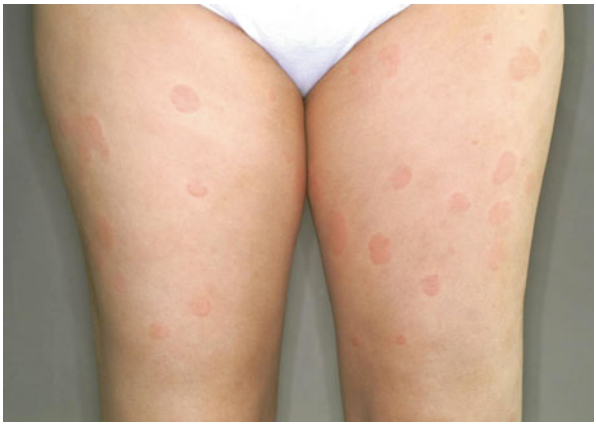

Fig. 11.1 Typical wheal and flare reaction in spontaneous urticaria

Table 11.2 Common causes of acute spontaneous allergic urticaria and/or angioedema

Foods (peanuts, shellfish, milk, eggs, tree nuts, soy, latex-associated fruits such as banana, kiwi, avocado, chestnut)
Drugs (beta-lactam antibiotics)
Insect venoms, fire ant

Clinical Symptoms

The size, number, and shape of wheals (elevated erythema) vary considerably and can develop anywhere on the body. Sometimes the lesions become annular, arcuate, or polycyclic when confluent. Urticarial wheals are always very itchy but are not scratched so that secondary skin lesions like erosions are rarely seen. General symptoms like fever, arthralgia, headaches, or cardiovascular disturbances may accompany an exacerbation. Involvement of the tongue and pharynx is often associated with hoarseness, difficulties to swallow, and dyspnea.

Pathogenesis and Diagnosis

The most common type of acute urticaria is *acute nonallergic urticaria* in which most cases are associated with an acute upper respiratory or genitourinary infection and/or a pseudoallergic reaction (particularly to cyclooxygenase I inhibitors such as aspirin and other NSAIDs). In contrast, in atopics *acute allergic urticaria* caused by IgE-mediated allergy (e.g., to food allergens, hymenoptera stings, and drugs such as penicillin) can be found more frequently (Table 11.2).

Diagnosis is based upon a careful history to identify potential triggering factors (ask for atopic diseases, known allergies, drug intake, signs of infections) and physical examination (blood pressure, pulse, lung auscultation). If a cause cannot be identified by history, no investigations are needed due to the self-limiting nature of acute spontaneous urticaria.

Management (Prognosis)

Medical supervision (inpatient care) is recommended in case of dyspnea, hypotension, and generalized severe urticaria. Causal treatment includes stopping of culprit drug intake, removing insect stinger, and prescription of antibiotics in bacterial infections. Symptomatic treatment consists of second-generation H1-antihistamines up to fourfold daily (consider potential side effects when increasing the dose!) and if favored, also local treatment with antipruritic and cooling lotions. In severe cases (associated severe angioedema) often additional administration of glucocorticosteroids up to 100–250 mg prednisolone (IV) and H1-antihistamine (IV) are needed, maybe repeatedly. In progressive cases, anaphylactic shock treatment including proper administration of epinephrine is mandatory. Most cases improve promptly after (IV) treatment with H1-antihistamines and glucocorticosteroids. However, symptoms may reoccur several hours later (in most patients total symptoms persist less than 2 weeks). Therefore, outpatients should take second-generation H1-antihistamines in adequate dose (up to fourfold) for 1–2 weeks and should be provided with a rescue medication, e.g., drinkable corticosteroid, for severe symptoms. There is no prognostic factor identifying patients at risk for progression to chronic spontaneous urticaria (less than 1 %). It is discussed that adequate treatment of acute spontaneous urticaria can inhibit the progression to chronic spontaneous urticaria.

Chronic Spontaneous Urticaria

Definition

Urticaria is chronic if it persists for more than 6 weeks with nearly daily whealing episodes. Urticaria with less frequently occurring bouts over a long period is called episodic and is more likely to have an identifiable environmental trigger. Chronic spontaneous urticaria usually persists on average for 3–5 years. In 40% of those who suffer from it for more than six months, it will be still present for 10 years. 20% have chronic urticaria for more than 20 years. Lifelong prevalence is about 0.5 % and as far as known does not vary greatly across the world. Chronic spontaneous urticaria is most common in middle-aged adults, particularly in women, but also occurs in infants and children (Fig. 11.2).

Clinical Symptoms

Clinical symptoms are similar to acute spontaneous urticaria but persist longer than 6 weeks. Like in acute spontaneous urticaria, at least half of the patients suffer from concomitant and sometimes life-threatening angioedema. Ten percent to 20 % of patients have recurrent angioedema without urticaria. In chronic spontaneous urticaria, systemic symptoms are possible.

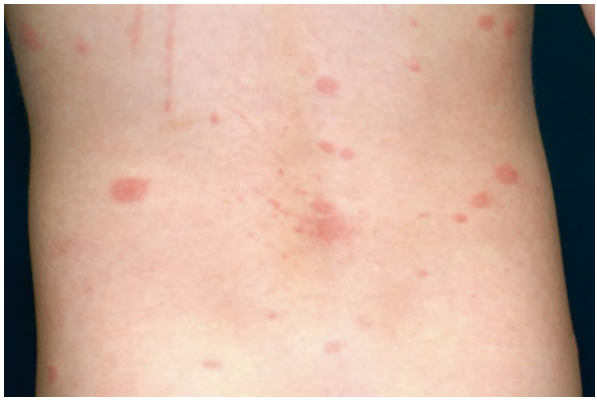

Fig. 11.2 Chronic spontaneous urticaria combined with dermographic urticaria in a child

Quality of life is significantly impaired equal to that experienced by patients with severe atopic dermatitis, psoriasis, or triple coronary arterial disease. The main reasons for decreased quality of life are intense pruritus, particularly in the evening and night, and sleep disturbances. Often secondary conditions such as psychosocial problems also develop.

Pathogenesis and Diagnosis

The diagnosis of chronic spontaneous urticaria is based upon a thorough history considering potential triggering factors, a physical examination including a test for dermographism, laboratory investigations, and if needed additional specific procedures. Patient diaries are very helpful to understand the fluctuating intensity of the disease.

Every attempt should be made to find an underlying etiology in each patient, because the identification and elimination of causal factors represent the best therapeutic approach. IgE-mediated hypersensitivity due to exogenous allergens is generally very rarely the cause of symptoms in chronic spontaneous urticaria, and there is no increased frequency of atopy. The implication of genuine food allergy is exceptional, in contrast to acute spontaneous urticaria. Thus, routine skin prick tests to inhalant and food allergens are of little value. However, many direct and indirect releasing factors may be involved. Possible mechanisms include autoimmune mechanisms, infectious diseases (viral, bacterial, fungal, parasites) particularly *Helicobacter pylori*-associated gastritis, pseudoallergic mechanisms, and others such as internal diseases and malignancies. It is often overlooked that several of these mechanisms may be active in a single patient. About one-third of patients show evidence for an autoimmune pathogenesis caused by functional mast cell stimulating IgG antibodies against the alpha subunit of the high-affinity IgE receptor and more rarely against IgE itself. Indicative is a positive autologous serum skin test (ASST) performed by a specialist although the clinical relevance is far from being clear (ASST can be still positive after resolution of urticaria). At present, there are no commercial sources of direct measurement of these autoanti-

bodies. In addition, about 30 % of chronic spontaneous urticaria cases are also associated with antithyroid antibodies. Aspirin and NSAIDs (Table 11.3) aggravate symptoms and evoke exacerbations by a non-IgE-mediated pseudoallergic mechanism in one-third of patients. Often regular intake of these drugs is not reported. Other mast cell-activating drugs are morphine, codeine, muscle relaxants, polymyxin, and dextran. Rarely, nonallergic hypersensitivity reactions to food additives play a role but generally have no role unless proven by a double-blind, placebo-controlled challenge.

A reliable diagnostic procedure is outlined in Fig. 11.3. With regard to the long duration of the annoying skin disease, a well-directed workup based upon a thorough history is indicated. An expert opinion should be sought in severe and unusual cases.

In case of prolonged duration of individual wheals (more than 24 h) and resolution with purpura and pigmentation, biopsies should be taken to exclude vasculitis by histology and immunofluorescence assay. This is important as systemic disease like lupus erythematosus is usually associated with extracutaneous manifestations.

Table 11.3 Common NSAIDs triggering urticaria and angioedema

Acetylsalicylic acid (aspirin)
Ibuprofen
Diclofenac
Naproxen
Metamizol

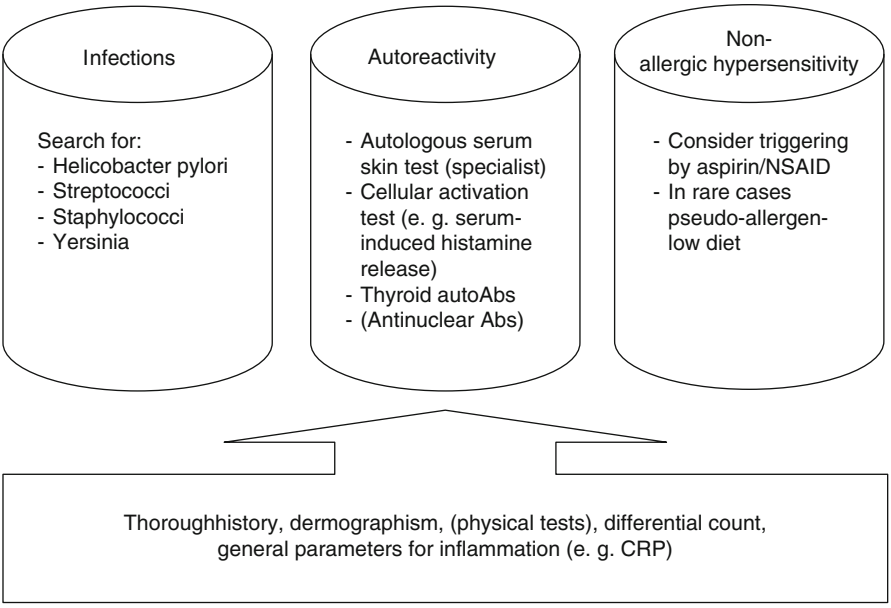

Fig. 11.3 Recommended diagnostic schedule in chronic spontaneous urticaria

Although very rare, chronic spontaneous urticaria can be associated with malignant diseases. Moreover, genetic syndromes (e.g., Muckle-Well's syndrome, hyper-IgD syndrome, chronic infantile neurological cutaneous and articular syndrome), hematologic (e.g., Schnitzler's syndrome), and immune disorders (e.g., systemic lupus erythematosus, hypocomplementemic urticaria vasculitis syndrome) may present with (often non-itching!) urticaria-like skin lesions. Other differentials include scabies, arthropod reactions, urticarial stages of autoimmune bullous skin diseases such as bullous pemphigoid, and early stages of vasculitis and erythema multiforme.

It has been shown that 20–30 % of *children* with acute spontaneous urticaria of which almost all were associated with acute infections progressed into chronic spontaneous urticaria. Accordingly, persistent chronic, often bacterial infections (e.g., with streptococci, staphylococci, but also with *Helicobacter pylori*) are common in childhood chronic spontaneous urticaria. Furthermore, like in adults, positive autologous serum skin test indicating autoreactivity can be found in one-third. In children and young adults, serology for Epstein-Barr virus and cytomegalovirus should also be included in the diagnostic workup.

Management (Prognosis)

According to current international urticaria guidelines, the aim of treatment of every urticaria subtype should be achievement of complete symptom control. Relevant outcomes of treatment trials include pruritus, wheal size, number and frequency of wheals and/or angioedema, loss of awakening, overall physician and patient assessment, and permanent remission of the disease. Modern treatment control strategies are using established instruments such as urticaria activity score (UAS, weekly: UAS7), angioedema activity score (AAS, weekly: AAS7), urticaria control test (UCT), and chronic urticaria questionnaire for quality of life (CUQ_2oL). The goal is to maximize quality of life and ability to work or to attend school and to minimize drug-related side effects such as sedation. Unspecific trigger factors such as intake of aspirin/other NSAIDs (in favor to acetaminophen), alcohol, and overheating, in case of angioedema ACE inhibitors (often also sartans) should be avoided. Specific and sufficient treatment of identified persistent bacterial and parasitic infections can result in complete remission. In single cases with challenge-proven nonallergic hypersensitivity reactions to food additives, dietary avoidance for 3–6 months may be helpful.

Long-acting second-generation H1-antihistamines are the mainstay of symptomatic treatment and can be given the highest grade of recommendation according to the criteria of evidence-based medicine (Table 11.4). They reduce itch, wheal duration, and numbers and increase quality of life. To administer an adequate dose in chronic spontaneous urticaria, it is common practice to exceed the licensed dose. The current international guideline recommends an increased dose of up to fourfold the normal dose while considering the side effects. Due to the long-term duration of the disease, second-generation H1-antihistamines are preferred, particularly when increased dosage is needed. H1-antihistamines demonstrating high-quality evidence

Table 11.4 Recommended treatment for chronic spontaneous urticaria

Line	Recommended treatment
First	A. Standard dose of second-generation H1-antihistamine daily
	B. Adequate treatment of identified triggering factors, e.g., triple therapy for *Helicobacter*, antibiotics for streptococci, or L-thyroxine in case of thyroid autoimmunity
	C. Avoid overheating, tight clothing, alcohol, aspirin/NSAID, ACE inhibitors, and ATII antagonists
	D. Reassure patient about the benign nature of the condition and the difficulties in treatment
	E. Optional topical treatment (2 % menthol or 2 % polidocanol in aqueous cream or lotion)
Second	A. Increased dose of second-generation H1-antihistamine daily (up to fourfold, off-label use)
	B. Try another second-generation H1-antihistamine (up to fourfold dose, off-label use)
Third	Add omalizumab 300 mg SC monthly or Add montelukast 10 mg daily or Add cyclosporine A 3 mg/kg daily

in chronic spontaneous urticaria treatment include azelastine, bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine (alphabetical order). Management is better achieved by taking daily H1-antihistamines, not just when the patient is symptomatic. Moreover, replacement of one H1-antihistamine with another should be tried because of individual differences in responsiveness.

As a general rule, H1-antihistamines are safe but potential side effects such as impairment of performance, sedation, interaction with CYP450 enzymes, liver and cardiac side effects, and nephrotoxicity should be considered for the respective choice. In pregnancy loratadine and cetirizine in standard dose are regarded as safe.

Systemic glucocorticosteroid treatment is included in the international guideline treatment algorithm at each step but only for acute exacerbations and short periods (maximum of 10 days, initial recommended dose 0.5–1 mg prednisolone equivalent per kg weight).

Complete symptom relief is rarely achieved with a standard dose of a second-generation H1antihistamine. If symptoms are not controlled at step 2, the dose is increased up to fourfold considering potential side effects (off-label use). If the symptoms persist, at step 3 add-on treatment with omalizumab (monoclonal anti-IgE antibody) or cyclosporine A (immunosuppressant) or montelukast (leukotriene receptor antagonist) are recommended in the guidelines. After the guidelines have been developed and published, omalizumab at a dose of 300 mg every fourth week subcutaneously has been approved for chronic spontaneous urticaria in adults and adolescents (>12 years old) that do not respond to H1-antihistamines. The exact working mechanism in urticaria has not been clarified in detail so far but may be dependent on deactivation of mast cells/basophils. In vitro and in vivo

omalizumab is building small complexes with IgE. Deposition of complexes or complexes with a molecular weight of more than one million Dalton has not been observed until now.

Approval is based upon randomized placebo-controlled clinical trials including more than 1000 patients with chronic spontaneous urticaria aged 12–75 years. Therefore, omalizumab is the treatment of choice with highest level of evidence. In many patients it is effective 1 or 2 weeks after the first injections. Nevertheless, treatment is symptomatic and after discontinuation, symptoms return in about 4 weeks. Complete symptom control has been demonstrated in 34–44 % of such patients compared to 5–9 % in the placebo control group. The clinical trials have not demonstrated other safety risks compared to the known risk in severe allergic asthma.

Short-term studies have demonstrated good evidence for treatment with cyclosporine A (2.5–5 mg per kg body weight). Such a treatment represents another off-label alternative at step 3 of the international guideline treatment algorithm. However, clinical response often does not occur before 4–6 weeks, and potential severe side effects (e.g., disturbances of kidney and liver function, arterial hypertension, immunosuppression, and cancer risk) have to be considered.

The leukotriene receptor antagonist montelukast (10 mg per day) is another choice included at step 3 of the international guideline algorithm, although efficacy data are sparse and contradictory. In single cases it may be worth trying; the side effects and costs are manageable and response is anticipated within 4 weeks of treatment.

Due to insufficient evidence, H2-antihistamines and dapsone are no longer included in the treatment algorithm.

Drugs that have demonstrated success in small trials, case series, or case reports are hydroxychloroquine, dapsone, sulfasalazine, tacrolimus, methotrexate, mycophenolate mofetil, cyclophosphamide, UVB phototherapy, autologous blood injections, intravenous immunoglobulins, and plasmapheresis. Not recommended are antidepressants (doxepin), mast cell stabilizers (oxatomide, ketotifen), calcium channel blockers (nifedipine), sympathomimetics (terbutaline), anticoagulants (warfarin), and stanozolol.

If chronic spontaneous urticaria persists for longer than 6 months, prognosis is increasingly bad. After 10 years, more than 40 % still suffer from the disease. Regarding chronicity and impairment of daily life and occupational disability, it is also reasonable to treat the psychological factors involved in chronic spontaneous urticaria.

Chronic Inducible Urticaria

Chronic inducible urticaria is a distinct group that is reproducibly caused by a certain stimulus and should be clearly differentiated from spontaneous urticaria although both can coexist. Chronic inducible urticaria summarizes physical urticarial and special urticarial subtypes. In chronic inducible urticarial subtypes,

usually the wheals resolve within 2 h except in delayed pressure urticaria and delayed dermographic urticaria. Although clinically impressive, to date, neither the pathomechanisms have been clarified nor are sufficient data available to recommend treatment schedules based upon an evidence-based view. Prognosis of physical urticaria is worse than chronic spontaneous urticaria.

Physical urticaria is diagnosed by thorough history, clinical examination, and provocation procedures using standardized physical tests. These tests are not without risk. Infection as an etiology of physical urticaria has been subject of controversy. Autoreactivity, i.e., positive autologous serum skin test, autoantibodies against IgE receptor/IgE, or against thyroid has not been described.

Dermographic Urticaria

Definition and Pathogenesis

Dermographic urticaria (synonyms: factitial urticaria, symptomatic dermographism) develops within a few minutes after mechanical shearing forces and presents with intensely itching wheals. It is possible to write on the skin (Fig. 11.4). In contrast, urticarial dermographism is asymptomatic. Dermographic urticaria is the most frequent subtype of physical urticaria with a mean duration of 6.5 years and is often combined with spontaneous chronic spontaneous urticaria. Dermographic urticaria can occur after infections or may be drug induced (e.g., penicillin).

Clinical Symptoms and Diagnosis

Rubbing and touching the skin and also wearing of clothes result in local itchy wheals which again are rubbed (vicious circle). Simply scratching the skin for a length of about 10 cm with a pen produces linear wheals beyond the area of contact. More standardized is the use of a dermographometer (spring-loaded stylus). Thorough history guides further investigations to exclude infections or drugs as causative agents.

Management (Prognosis)

Treatment is similar to chronic spontaneous urticaria and consists of second-generation H1-antihistamines given regularly and at adequate dose (up to fourfold the normal dose). Additional low evidence exists for ketotifen. The patient should be reassured about the benign nature of the disorder. Dermographic urticaria is distressing but not life threatening.

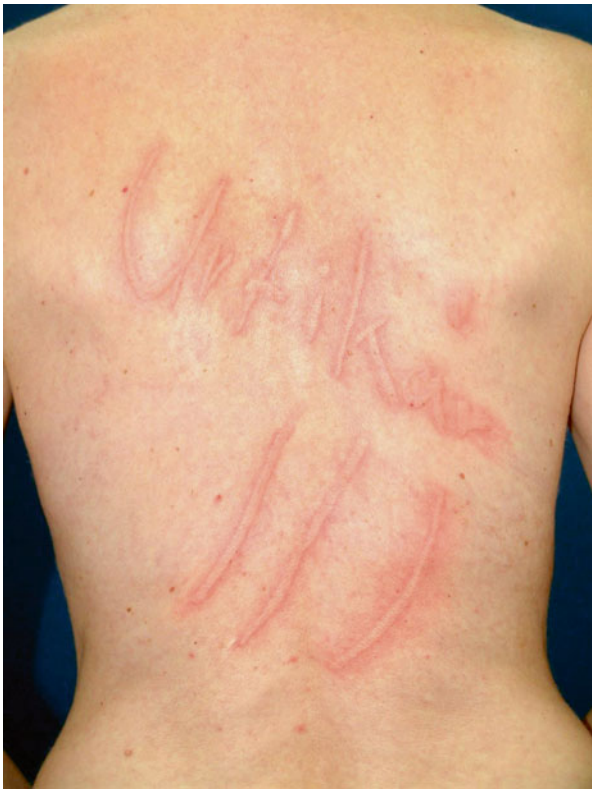

Fig. 11.4 Writing on the skin in dermographic urticaria

Delayed Pressure Urticaria

Definition and Pathogenesis

Sustained vertical pressure is the eliciting factor of delayed pressure urticaria. Delayed pressure urticaria is more common in middle-aged males and persists for an average of 6–9 years, often resulting in work disability. It may also be associated with chronic spontaneous urticaria.

Clinical Symptoms and Diagnosis

Deep, painful swellings develop 6–8 h after sustained pressure and persist for up to 2 days. Typical localizations are the palms and soles, buttocks, back, and skin under straps and belts. The condition may be accompanied by systemic symptoms of malaise, arthralgia, myalgia, and leukocytosis.

Standardized pressure test consists of applying weight in amount of 0.5–1.5 kg/cm^2 for 10 min in different areas (back, ventral, and dorsal thigh) (Fig. 11.5). Evaluation of the testing area should be done at least after 30 min, 3, 6, and 24 h intervals. Only definite raised wheals occurring after several hours indicate delayed pressure urticaria. Elicited wheals that persist for more than 24 h should be biopsied to exclude vasculitis.

Management (Prognosis)

Delayed pressure urticaria responds poorly to H1-antihistamines, even in increased doses. Nevertheless, they represent the mainstay of treatment. Some patients are well controlled by additional low-dose corticosteroids (e.g., 40–20 mg prednisone), others by treatment with dapsone (100–150 mg/day). Other low-evidence alternatives are omalizumab, methotrexate (15 mg/week), montelukast, ketotifen plus nimesulide, sulfasalazine, or topical clobetasol prop. 0.5 % ointment.

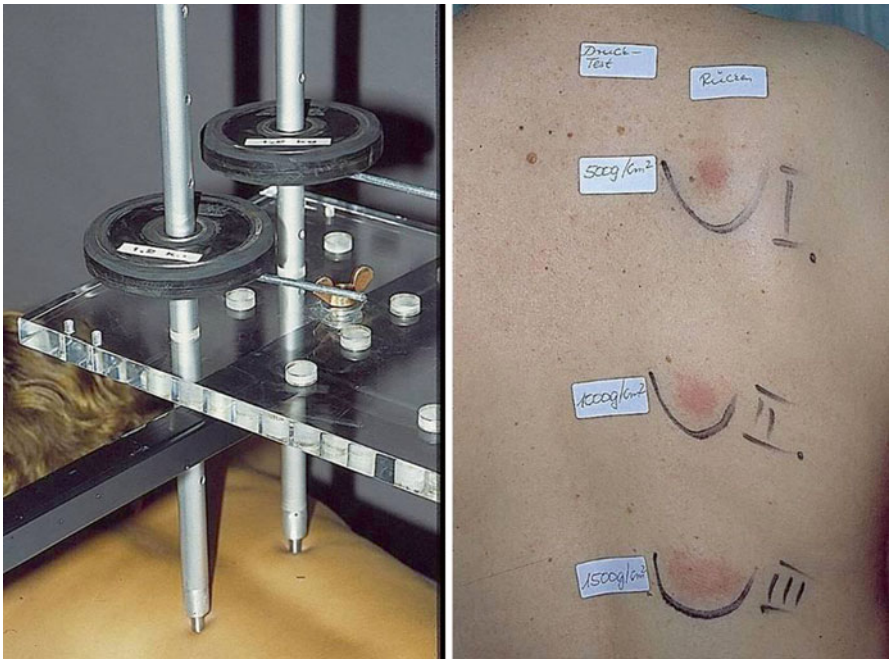

Fig. 11.5 *Left*: standardized pressure test applying 500, 1000, and 1500 g/cm^2 for 10 min. *Right* reading after 24 h revealed wheals of delayed pressure urticaria

Cold Urticaria

Definition and Pathogenesis

Cold bodies or cold water, also cold air and cold food/drinks, can provoke cold urticaria and angioedema within minutes. Mainly young adults are affected with an average duration of 5 years. It may coexist with cholinergic urticaria.

Clinical Symptoms and Diagnosis

Immediate but rarely delayed reactions occur after cold exposure at the size of localized cooling but may also be generalized following lowering of the body temperature. Infectious diseases such as syphilis, borreliosis, hepatitis, infectious mononucleosis, and HIV infections can induce cold urticaria but unrecognized bacterial infections are also reported. Cold provocation can be done by applying ice-filled metal cylinders, ice cube, and/or cold water for 1–10 min (Fig. 11.6). Ideally the threshold temperature is defined. Recently low-voltage Peltier thermoelectric elements have been used to standardize cold provocation. Depending on the history, cold ventilator wind provocation may also be used.

Management (Prognosis)

Identified infectious diseases should be treated adequately. Second-generation H1-antihistamines are the first line in treatment. In idiopathic cases, antibiotic treatment (e.g., with doxycycline or penicillin, IM or PO) is worthwhile trying. Several case reports demonstrated efficacy of omalizumab. Other low-evidence alternatives are cyproheptadine, ketotifen, and montelukast.

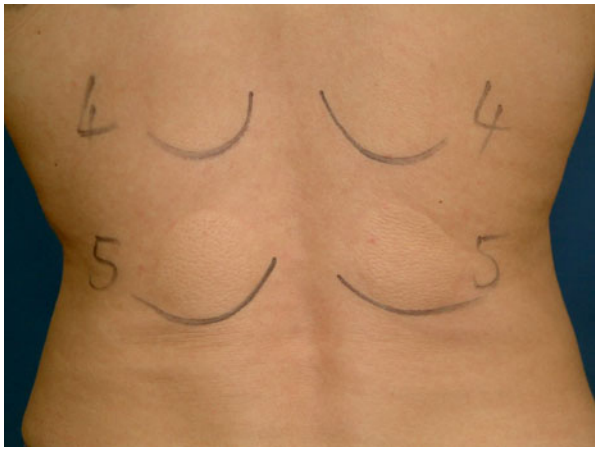

Fig. 11.6 Significant swelling of the skin ("peau d'orange") developing 5 min after a 5 min exposure to ice-filled copper cylinders to the back

Localized Heat Urticaria

Definition and Pathogenesis

Localized heat urticaria is a rare phenomenon that is developed by direct contact with a warm object such as air or water.

Clinical Symptoms and Diagnosis

The eliciting temperature ranges from 38 °C to more than 50 °C. Ideally the threshold temperature should be defined using a 38 °C warm arm bath for 10 min (if negative the temperature may be increased) or to apply a glass tube containing hot water (38–50 °C for 1–5 min). Wheals occur immediately and are often small sized and fleeting.

Management (Prognosis)

Evidence-based treatment is not available. Skin hardening to heat, omalizumab, or chloroquine may be tried.

Solar Urticaria

Definition and Pathogenesis

Solar urticaria is rare. It comprises only 4 % of all photosensitive skin disorders. Wavelengths ranging from 280 to 760 nm, mostly UV light are the eliciting physical stimuli. Women in their third or fourth decade of life are predominantly affected.

Clinical Symptoms and Diagnosis

Within minutes of light exposure, pruritic wheals develop although constantly exposed areas might be not involved. Provocation is done using specific wavelengths of a monochromator and, for example, a slide projector (visible light) for 10 min to determine the minimal urticarial dose (MUD). The lesions usually fade 15 min to 3 h after onset. When forming a differential list, in addition to systemic lupus erythematosus or erythropoietic protoporphyria, more common polymorphous light eruptions should be considered.

Management (Prognosis)

Treatment can be frustrating. Second-generation H1-antihistamines are the first line of treatment. Photohardening of the skin or omalizumab can be effective. Other low-evidence possibilities include plasmapheresis, cyclosporine A, photophoresis, plasma exchange, and intravenous immunoglobulins or hydroxychloroquine.

Vibratory Urticaria (Angioedema)

Definition and Pathogenesis

Very rarely strong vibrating forces (e.g., pneumatic hammer) result in vibratory urticaria and/or angioedema.

Clinical Symptoms and Diagnosis

The symptoms are reproduced by a vibrating machine.

Management (Prognosis)

Exposure to vibrating forces is the treatment of choice.

Cholinergic Urticaria

Definition and Pathogenesis

Cholinergic urticaria is subclassified as a special type of urticaria since it is rather caused by a short increase in body temperature and not by external physical stimuli. The rise in body temperature can be the result of physical exercise, passive warmth (hot bath), or emotional stress. Cholinergic urticaria is common in young adults lasting for an average of 5–6 years and it may coexist with cold urticaria.

Clinical Symptoms and Diagnosis

The wheals are fleeting, typically only of pinhead size and disappear within several minutes to 1 h. In severely affected patients, systemic symptoms such as nausea, headache, and dizziness may be observed. In exercise-induced urticaria/anaphylaxis

which is the main differential diagnosis, usually the wheals are larger than pinhead size and persist for a long period. For diagnostic purposes, usually cholinergic urticaria is provoked by ergometer exercise or by running in place for 5–15 min.

Management (Prognosis)

As in other urticaria subtypes, use of the second-generation H1-antihistamines (in increased dose) regularly and/or 60 min before characteristic triggering situations is the mainstay of treatment. Nevertheless, they often fail. It is difficult to achieve exercise tolerance. Omalizumab has been shown to be effective in several cases. Ketotifen may be an optional medication to use. Efficient treatment with danazol has been described, but adverse effects have to be considered when prescribing the medication.

Aquagenic Urticaria

Definition and Pathogenesis

Aquagenic urticaria is a very rare phenomenon. Contact to water of any temperature liberates a water-soluble allergen from the stratum corneum that diffuses into the dermis.

Clinical Symptoms and Diagnosis

After water contact small-sized wheals occur in the contact area. In contrast, in aquagenic pruritus itch develops without urticaria. Challenge test is performed by application of water compresses at approximate body temperature (37 °C) for 30 min.

Management (Prognosis)

In most cases, prophylactic treatment with second-generation H1-antihistamines is sufficient.

Contact Urticaria

Definition and Pathogenesis

Contact urticaria develops after contact to an urticant that may cause an immunologic (IgE dependent) or non-immunologic reaction (IgE independent). Examples of allergic contact urticants are food, latex, and animals; these mainly

play a role in atopic individuals (particularly in atopic dermatitis) whereas non-allergic contact urticants have a direct effect on blood vessels and include irritants such as balsam of Peru, benzoic acid, and cinnamic aldehyde in cosmetics. Contact to stinging nettles is the most common form of nonallergic contact urticaria.

Clinical Symptoms and Diagnosis

Contact urticaria is characterized by immediate whealing and itching at sites of penetration of substances through the skin or mucous membranes. In immunologic contact urticaria, the reaction may spread beyond the site of contact and progress to generalized urticaria/anaphylaxis. Most reactions occur at work therefore details of the patient's employment are essential. If IgE-mediated reactions are suspected, skin prick test and specific IgE measurements are indicated. Other commonly used tests are open application tests with readings at 20, 40, and 60 min intervals or chamber tests applied for 15 min with similar reading.

Management (Prognosis)

Several episodes of contact urticaria can result in protein contact dermatitis. Therefore, early diagnosis is critical to educate the patient to avoid the contact.

Angioedema Without Urticaria

Angioedema is defined as sudden, pronounced swelling of the lower dermis and subcutis and is often more painful than itching. Frequently the mucous membranes are involved and resolution can take up to 3 days.

Classification of Angioedema Without Urticaria

Recurrent angioedema without urticaria must be regarded as a separate entity. To diagnose, hereditary (only 5 % of all angioedema without urticaria) and acquired angioedema due to C1-inhibitor (C1 INH) deficiencies (very rare) must be excluded. Angioedema without urticaria and normal C1 INH may be of pharmacologic (ACE inhibitor induced), pseudoallergic (NSAID induced), allergic (IgE mediated), infectious (e.g., *Helicobacter pylori* induced), physical (e.g., in cold urticaria), or of unknown (idiopathic) nature (Table 11.5). ACE inhibitor angioedema is the most common cause of acute angioedema in accidents and emergency hospital departments, and up to 20 % may be life threatening.

Table 11.5 Classification of angioedema without urticaria

Angioedema	Subtype	Cause
Non-C1 INH deficient	Pharmacologic	ACE inhibitor induced (class effect)
	Pseudoallergic	NSAID-induced (usually with urticaria)
	Allergic	IgE-mediated (usually with urticaria)
	Infectious	For example, associated with *H. pylori* infection (80 % with urticaria)
	Physical	Exposure to vibration, cold, pressure
	Idiopathic	No identifiable cause
C1 INH deficient (ex. type III)	Hereditary, type I	C1 INH protein deficiency, low C4
	Hereditary, type II	C1 INH dysfunction, low C4
	Hereditary, type III	Normal C1 INH, normal C4, low C1q, exclusively in women
C1 INH deficient	Acquired, type I	Secondary to lymphoma, immune complex-mediated depletion of C1 INH
	Acquired, type II	Autoimmune, autoantibodies against C1 INH

Non-C1 INH-Deficient Angioedema Without Urticaria

Definition and Pathogenesis

Recurrent angioedema without urticaria occurs in 10–20 % of patients who present for urticaria consultation (Fig. 11.7). Particularly angioedema of the tongue and laryngopharynx (sometimes with serious breathing difficulties) can be triggered through a pharmacologic effect by angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (sartans), and particularly to omapatrilat (vasopeptidase inhibitor). These drugs cause decreased bradykinin degradation resulting in increased bradykinin levels. Angioedema occurs in about 0.6 % of patients receiving ACE inhibitor treatment and is more common in Afro-Americans. In most cases this side effect occurs within 3 months of starting the drug, but occurrence after several years is also possible. Angioedema in omapatrilat-treated patients are more frequent (1.2 %).

Other drug-related triggers include aspirin (usually a higher dose than 100 mg/day dose) and other NSAIDs. Sometimes persistent bacterial infections, such as those in chronic spontaneous urticaria, may be associated.

Clinical Symptoms and Diagnosis

Angioedema without urticaria like angioedema with urticaria most often involves the eyelids, lips, and genitalia but sometimes also the tongue and laryngopharynx which can be life threatening and causes anxiety (symptoms occur often at nighttime). ACE inhibitor angioedema may also present with sudden abdominal pain, diarrhea, and vomiting.

A search for a dysfunction or deficiency in the C1 INH is obligatory to exclude HAE.

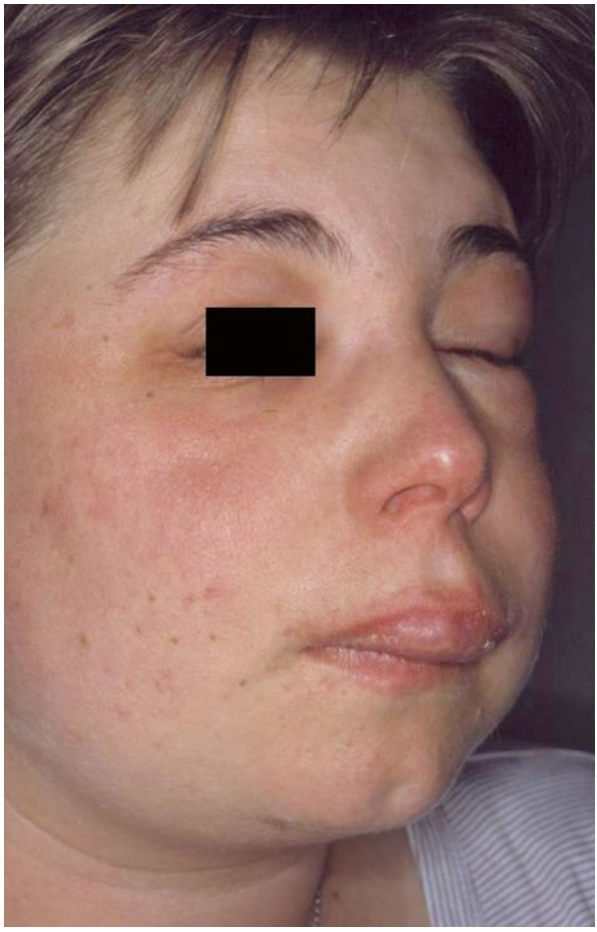

Fig. 11.7 Attack of recurrent idiopathic angioedema of the left eye and upper lip

Management (Prognosis)

In recurrent angioedema ACE inhibitors, sartans and NSAIDs should be avoided. Occasionally, angioedema may continue for some weeks or even months after the ACE inhibitor has been withdrawn. H1-antihistamines are of little value but may attenuate severity or frequency of angioedema. Randomized controlled trials focusing on recurrent non-C1 INH-associated angioedema without urticaria are not available. Treatment is similar to chronic spontaneous urticaria, but often emergency treatment is needed. Forty to 60 mg of prednisone can be used; if needed, the treatment may be extended by additional 1 or 2 days. For life-threatening episodes, parenteral corticosteroids, adrenaline, or even intubation or tracheotomy may be necessary. There is a recent evidence that the bradykinin-2 receptor antagonist icatibant is effective in bradykinin-mediated ACE inhibitor-induced angioedema.

Hereditary Angioedema

Definition and Pathogenesis

Hereditary angioedema (HAE) is a rare autosomal dominant condition with a prevalence of 1:50,000 in the general population. It is caused by a deficiency (type I, 85 %) or dysfunction (type II, 15 %) of C1 INH and there is no sex bias in these classic forms. A third (type III) form occurs exclusively in women with quantitatively and functionally normal C1 INH activity related to estrogens.

Clinical Symptoms and Diagnosis

HAE develops more slowly compared to ordinary angioedema, often beginning with prodromi and can be associated with colicky abdominal pain. Laryngeal involvement can be life threatening and treatment with corticosteroids/H1-antihistamines is ineffective. HAE may develop spontaneously or after trauma, particularly with dental maneuvers. Most cases are diagnosed in childhood and have a positive family history. The attacks become worse at puberty and usually decrease in frequency and severity after the age of 50. The main sites involved are face, hands, arms, legs, genitalia, and buttocks. Glossal, pharyngeal, or laryngeal involvement with sometimes fatal outcome is feared. In one large series, 10 % had at least one required intubation or tracheostomy.

Laboratory findings reveal decreased protein levels of C1 INH in 85 % of patients (in most cases 15–20 % of normal value) and dysfunctional inhibitor in 15 % of cases (in most cases 15–20 % of normal values). The level of complement C4 is decreased. The C1 esterase deficiency should be detected by both antigenic and functional assays.

Management (Prognosis)

Treatment of HAE is difficult. Three classes of medications have recently been approved by the US Food and Drug Administration (FDA). For acute attacks, C1 INH concentrate, ecallantide, or the bradykinin B2-receptor antagonist icatibant should be administered. Formerly given fresh frozen plasma is no longer recommended. However, intubation or tracheotomy may be necessary. Corticosteroids and H1-antihistamines are not helpful but subcutaneous adrenaline may be tried. Prophylactic treatment involves C1 esterase inhibitor concentrate or anabolic androgens (danazol and stanozolol) that increase the serum levels of C1 INH. Anabolic androgens should be prescribed in the lowest effective dosage (hepatotoxicity, liver tumors, hirsutism). In mild HAE, avoidance of provoking factors, ACE inhibitors, estrogens together with C1 INH, or fresh frozen plasma prophylactically before dental or surgical procedures may be sufficient.

Acquired C1 INH Deficiency Angioedema

Definition and Pathogenesis

Clinically this condition is similar to HAE, but the onset occurs in the fifth and six decades of life. Two types are differentiated. In type I, C1 INH depletion may be the result of circulating immune complexes secondary to malignancy (e.g., B-cell lymphoma, myeloma). In type II, autoantibodies directed against C1 INH itself are generated.

Clinical Symptoms and Diagnosis

Clinical symptoms are similar to that seen in HAE. Most acquired C1 INH deficiencies are found in the setting of lymphoproliferative disease in older patients with negative family history.

Laboratory assessment should include C1 INH protein level and function and levels of C4 and C1q. The laboratory findings in both types of acquired C1 INH-deficient angioedema are similar to that in HAE except that C1q levels are also decreased.

Evidence-Based Medicine

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Detailed method report describing all GRADE questions, the discussion, and the voting results.

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Chapter 12
Atopic Dermatitis

Satoshi Yoshida

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic skin lesions, disrupted skin barrier function, dysregulation of the immune system, and allergic reactions to food and environmental allergens. The first cases of AD in the United States were identified in 1947. AD generally presents in early childhood as often familial onset. Scratching at the area of pruritus leads to redness, cracking, scaling, and potential superinfection of the skin. Most patients with AD have a personal or family history of atopy (allergic rhinitis, allergic conjunctivitis, AD, or asthma). The word "atopy" can be defined as a hypersensitivity of skin and mucous membranes against environmental substances, associated with increased immunoglobulin E (IgE) production and/or altered nonspecific reactivity in different organ systems, for example, skin in the case of AD and lung in the case of asthma. It is a chronic, highly pruritic, inflammatory skin disease frequently seen in patients with a history of respiratory allergy and allergic rhinitis. The prevalence of AD in children has been steadily increasing since 1920s and that it now affects more than 10 % of children at some point during their childhood. The term atopic dermatitis was first introduced in 1933 in recognition of the close association between AD and respiratory allergy. However, there has been considerable debate over whether AD is primarily an allergen-induced disease or simply an inflammatory skin disorder found in association with respiratory allergy. Recent studies, however, suggest that the mechanisms underlying asthma and AD have greater similarities than differences. AD is a common, potentially debilitating condition that can compromise quality of life. Its most frequent symptom is pruritus. Attempts to relieve the itch by scratching simply worsen the rash, creating a vicious circle. Treatment should be directed at limiting itching, repairing the skin, and decreasing inflammation when necessary. Lubricants, antihistamines, and topical corticosteroids are the mainstays

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of therapy. When required, oral corticosteroids can be used. If pruritus does not respond to treatment, other diagnoses, such as bacterial overgrowth or viral infections, should be considered. Treatment options are available for refractory atopic dermatitis, but these measures should be reserved for use in unique situations and typically require consultation with a dermatologist or an allergist. Allergic reactions play a role in some patients but not necessarily in all. In many patients different factors such as a disturbance of skin function, infection, and mental and/or physical stresses are potentially more relevant. Immunologic disturbances are reflected in the elevated IgE production and T-cell dysregulation observed in AD. Nonspecific altered reactivity is reflected in increased releasability of chemical mediator secreting cells and bronchial, nasal, and skin hyperreactivity. Each disease that forms the atopic triad has important immunologic parallels. However, they involve a different regional sphere of immunologic influence, for example, the skin-associated lymphoid tissue in AD as opposed to bronchial-associated lymphoid tissue in asthma.

Pathogenesis

AD is a condition that requires interplay from several factors to explain its pathogenesis. Defects in epidermal barriers, dysregulation of various types of immune responses, genetic polymorphisms, and environmental factors have been implicated in the pathogenesis of the disease. The current review will examine the cellular and immunologic mechanisms underlying AD as well as the potential role of microbial superantigens in the pathogenesis of AD. An understanding of the relative contributions of allergens, IgE, T cells with skin-homing capability, Langerhans cells, keratinocytes, eosinophils, and mast cells to the inflammatory process in AD may lead to improved treatments for this potentially debilitating disease. The concept that AD has an immunologic basis is supported by the observation that patients with primary T-cell immunodeficiency disorders frequently have elevated serum IgE levels, eosinophilia, and eczematoid skin lesions indistinguishable from AD. Laboratory observations suggest an underlying immunoregulatory abnormality in AD (Table 12.1). IgE plays pivotal roles in pathogenesis of AD (Table 12.2). There have also been a number of studies demonstrating increased frequency of allergen-specific T cells producing increased IL-4 and IL-5 but little IFN-gamma in the peripheral blood and skin lesions of patients with AD. It should be pointed out, however, that the majority of allergen-specific T-cell clones are TH0-type cells with the potential for development into either TH1 or TH2 cells after they have infiltrated into the skin. The above data support an important role for TH2 cell development early in the atopic skin process. The ability of TH0 cells to develop into the TH1 or TH2 pathway is dependent on a number of determinants including the cytokine milieu in which T-cell development is taking place, the host's genetic background, the pharmacologic factors, and the costimulatory signals used during T-cell activation (Table 12.3). There is supportive data for each of these determinants in AD.

Table 12.1 Peripheral blood findings in atopic dermatitis

Increased IgE levels
Eosinophilia
Increased basophil spontaneous histamine release
Decreased CD8 suppressor/cytotoxic number and function
Increased expression of CD23 on mononuclear cells
Chronic macrophage activation with increased secretion of GM-CSF, prostaglandin E2, and IL-10
Expansion of IL-4 and IL-5 secreting TH2-type cells
Decreased numbers of IFN-gamma secreting TH1-type cells
Increased serum sIL-2 receptor levels
Increased serum eosinophil cationic protein levels
Increased soluble E-selectin levels
Increased soluble vascular cell adhesion molecule-1 levels
Increased soluble intercellular adhesion molecule-1 levels

Table 12.2 Multifunctional role for IgE in atopic dermatitis

IgE-dependent late-phase skin reaction
Allergen presentation by IgE-bearing Langerhans cells
Allergen-induced activation of IgE-bearing macrophages
IgG/IgM antibodies to IgE
IgE autoreactivity to human proteins

Table 12.3 Factors contributing to the development of TH2 cells

Genetic background (e.g., IL-4 promoter polymorphism)
Cytokine milieu in which antigen presentation takes place (i.e., IL-4)
Antigen-presenting cell (e.g., Langerhans cells)
Nature of antigen (e.g., allergens vs parasites)
T/B cell costimulatory signals (i.e., CD28/B7.2) (CD86) interactions
Pharmacologic factors (i.e., prostaglandin E2, cAMP phosphodiesterase activity)

Defective Epidermal Barrier

The epidermis has four layers. The outermost layer, called the stratum corneum, serves as a barrier to decrease water evaporation and penetration of exogenous allergens and microbes. The stratum corneum is composed of cells that have keratin proteins and structural components, such as ceramides, filaggrin, and lipids. Filaggrin protein (FLG) plays a crucial role in maintaining the structure of the epidermis by aggregating keratin filaments to form a cytoskeleton in epidermal cells. FLG is released from keratohyalin F granules as an inactive form and is converted to an active form by proteolysis and dephosphorylation. Studies have found that mutations in the FLG gene, specifically R501X and 2282del4, can induce a decrease

of natural moisturizing factors, including sodium pyrrolidone carboxylic acid, urocanic acid, and lipoprotein components, especially ceramides. A meta-analysis of these nonsense mutations has confirmed that these mutations represent the most compelling genetic risk for AD. The alteration of the epidermal structure from this protein mutation leads to transepidermal water loss and evaporation, resulting in dry skin and itching. Apart from FLG, a decrease of SPINK5 gene expression, which encodes Kazal-type 5 serine protease inhibitor, can increase cleavage of intercellular attachments in the stratum corneum and can compromise barrier function. In addition, De Benedetto et al. reported that decreased expression of epidermal claudin-1, a transmembrane protein component of tight junctions, can cause an impairment in tight junctions, which leads to skin barrier dysfunction in patients with AD.

Dysregulation of Cutaneous Immune Response

Thymic stromal lymphopoietin (TSLP) plays an important role in AD. TSLP expression in keratinocytes is induced by mechanical injury and stimulation of Toll-like receptors 2, 5, and 6. TSLP activates dendritic cells. This leads to proliferation of CD4 T cells, which then differentiate into T-helper cell type (TH) 2. Next, inflammatory cytokines, such as interleukin (IL)-4, IL-5, and IL-13, are produced and released. Furthermore, TSLP stimulates mast cells, basophils, and eosinophils, which play a crucial role in cutaneous inflammation. It has been shown that scratching can induce TSLP expression and aggravate the course of AD, resulting in a vicious cycle of itching, scratching, TSLP expression, and TH2 upregulation. Furthermore, TH2 cells produce IL-31, which provokes pruritus. TH17 cells, which can produce IL-17 and IL-22, also are involved in AD pathogenesis. TH17 cells are normally found in acutely inflamed skin lesions. An increase in the number of TH17 cells correlates with the severity of AD. In a mouse model, FLG deficiency led to TH17-dominated skin inflammation. In addition, IL-22 induces epidermal hyperplasia that can lead to epidermal acanthosis in the chronic stages of AD.

Immunohistology

The histologic features of AD depend on the acuity of the skin lesion. Uninvolved or clinically normal-appearing skin of patients with AD is histologically abnormal and demonstrates mild hyperkeratosis and a sparse perivascular cellular infiltrate consisting primarily of T lymphocytes. Acute lesions are characterized by marked intercellular edema (spongiosis) of the epidermis and a sparse epidermal infiltrate consisting primarily of T lymphocytes. In the dermis, there is a marked perivenular

inflammatory cell infiltrate consisting predominantly of T lymphocytes and occasional monocyte/macrophages. Essentially all T cells infiltrating into the skin lesion express high levels of cutaneous lymphocyte antigen (CLA), which functions as a skin-homing receptor for T lymphocytes. Eosinophils, basophils, and neutrophils are rarely present in the acute lesion. Mast cells, in various stages of degranulation, are present in normal numbers. In chronic lichenified lesions, the epidermis is hyperplastic with elongation of the rete ridges, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of IgE-bearing Langerhans cells in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. The number of mast cells are increased in number but are generally fully granulated. Increased numbers of eosinophils are observed in chronic AD skin lesions. Although the role of eosinophils in the pathogenesis of AD is not completely understood, it is thought to contribute to tissue injury in AD through the production of reactive oxygen intermediates and release of cytotoxic granules.

Cutaneous Infections: Role for Superantigens

Aside from food and inhalant allergens, fungal and bacterial skin infections exacerbate AD. Viral infections include herpes simplex, vaccinia, warts, molluscum contagiosum, and papilloma virus. The most common viral infection is herpes simplex, which tends to spread locally or can become generalized. Superficial fungal infections also appear to occur more frequently in atopic individuals. Recurrence of dermatophyte infections has occasionally been documented to coincide with flaring of AD. Recently there has been considerable interest in *Malassezia furfur*, also known as *Pityrosporum ovale* or *Pityrosporum orbiculare*, as a pathogen in AD. *M. furfur* is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* is commonly found in patients with AD and most frequently in patients with head and neck dermatitis but rarely outside of AD. The greatest attention has focused on the contribution of *Staphylococcus aureus* colonization and infection to the severity of AD. *S. aureus* is found in more than 90 % of AD skin lesions. In contrast, only 5 % of normal subjects harbor this organism and its localization is mainly in the nose and intertriginous areas. The importance of *S. aureus* in AD is supported by the observation that not only patients with impetiginized AD but also patients with AD without superinfection show clinical response to combined treatment with anti-staphylococcal antibiotics and topical corticosteroids. Recent studies suggest that one strategy by which *S. aureus* exacerbates or maintains skin inflammation in AD is by secreting a group of toxins known to act as superantigens, which stimulate marked activation of T cells and macrophages (Tables 12.4 and 12.5). Several lines of investigation concluded that superantigens may induce an atopic process in the skin. It is therefore of interest that superantigens have recently been demonstrated to induce T-cell expression of the skin-homing receptor through stimulation of IL-12 production. In the case of AD, it has been

Table 12.4 Evidence for role of staphylococcal superantigens in atopic dermatitis

Majority of *Staphylococcus aureus* isolates secrete superantigens
Majority of patients with AD produce IgE antibodies to superantigens
AD severity correlates with presence of IgE antibodies to superantigens
Superantigens augment allergen-induced skin inflammation
Superantigens induce dermatitis on application to skin by patch testing
Chronic eczema develops in patients recovering from toxic shock syndrome
Superantigens induce the cutaneous lymphocyte antigen skin-homing receptor on T cells
Peripheral blood mononuclear cell from AD, as compared with normal control subjects, have higher proliferative responses to superantigens
Superantigens induce corticosteroid resistance
Treatment with a combination of anti-staphylococcal antibiotics and topical corticosteroids is more effective than using either medication alone

Table 12.5 Optimal bathing and moisturizing for severe dermatitis or during flares

Bathing
Tub bath for severe flaring or for very dry skin; bathe twice daily for 20 min (until fingertips wrinkle), using lukewarm water only wet compresses if bathing is painful or for nighttime itch control shower, acceptable when skin is under good control or when flare is mild
Avoid washcloths, rubbing, scrubbing, or overuse of soap. After bathing, dry off only partially by patting with a towel—do not rub
While some water is still on the skin, within 3 min and before leaving the bathroom: apply steroid ointment/cream to red, itchy areas; apply moisturizer (not lotions) to other areas
Moisturizing should be repeated as often as necessary to keep skin soft throughout the day

proposed that staphylococcal superantigens secreted at the skin surface could penetrate inflamed skin and stimulate epidermal macrophages or Langerhans cells to produce IL-1, TNF, and IL-12. These mechanisms would tend to markedly amplify the initial cutaneous inflammation in AD and perhaps also create conditions favoring staphylococcal skin colonization. Peripheral blood mononuclear cell from children with AD have been reported to have a significantly higher proliferative responses to both *S. aureus* and *Staphylococcal enterotoxin* B as well as diminished production of IFN-gamma in response to *S. aureus* and *Staphylococcal enterotoxin* B. In contrast, peripheral blood mononuclear cell from children with AD were more likely to produce IL-4 in response to *S. aureus*. Impaired IFN-gamma production to *S. aureus* in vivo may result in failure to eradicate this organism from the skin. Persistence on the skin could contribute to inflammation by causing continued T-cell activation, release of proinflammatory mediators, and corticosteroid resistance. Furthermore, by eliciting an IgE response, staphylococcal toxins could exacerbate AD by activating mast cells, basophils, or other Fc receptor-bearing cells. It should be noted that other staphylococcal proteins/toxins such as protein A and alpha-toxin could also participate in the induction of skin inflammation by releasing TNF-alpha from epidermal keratinocytes or direct cytotoxic effects on skin keratinocytes.

The Diagnosis

Atopy is universally recognized as a complex genotypic diathesis that manifests a syndrome of immunologic aberrations. It would indeed be an oxymoron to make the diagnosis of AD without establishing atopy in the personal or family history and examination. A history of atopy is best obtained by specifically asking for the recognized clinical signs and symptoms of the atopic triad and not by the confusing question: "Are you allergic?" In 1980 Hanifin and Rajka published diagnostic criteria for AD that have become universally accepted as the standard for the diagnosis of that clinical entity. The diagnosis of AD can only be made by the presence of three essential criteria (each of which is included in the Hanifin and Rajka major and minor features of AD): personal or (first-degree) family history of atopy, pruritus, and eczema. Since then, significant progress in our understanding of AD, both on the clinical level and immunopathogenetic level, compels us to consider a reexamination of those original criteria. The discordance is often eloquently supported by the clinical observations of well-reputed "proallergic" investigators and skeptics. However, most of the controversy seems to be the result of one's interpretation of the indistinctive designation "allergy," which is defined as "an altered state of immune reactivity," but the term is still, almost exclusively, associated with what most physicians recognize as "immediate" or type I (IgE/mast cell) hypersensitivity instead of the full gamut of immunologic phenomena. As Leung so clearly reports, "an understanding of the immunologic basis of AD is likely to have important clinical implications in our approach to the diagnosis and management of AD" (see Table 12.1). Pruritus must be considered a quintessential feature of AD; pruritus is variable, fluctuating from mild to extremely intense. The itch of AD should be regarded as more than merely the result of a "lowered threshold." That common dermatologic dictum that "AD is an itch that erupts, rather than an eruption that itches" is not accurate. AD is an itch that when scratched erupts. If the atopic patient's itch is not rubbed or scratched, the skin (when provoked) may get red (vasodilate), but no eczema appears until it is traumatized. This can be described as an isomorphic response, or Koebner phenomenon, commonly noted in psoriasis and other skin conditions. An erythema caused by certain histamine-releasing or vasodilatory foods (i.e., alcohol, spices) is a more common trigger of pruritus than the IgE-mediated reaction. Because the former is nonimmunologic, it is dose related and is not dependent on prior sensitization. Many patients with AD benefit from avoiding the flushing foods that trigger rosacea (i.e., hot and spicy foods; hot drinks [including hot cider, hot chocolate, coffee, or tea]; soy and vinegars). The clinical implication of recognizing the many triggers of itch suggests that the pharmacologic mediator causing the pruritus may be different for each trigger. Despite the fact that histamine is the most abundant pruritogenic mediator in our body, its role as the major causation of itch in the patient with atopy remains questionable. Pruritus is the basic bane of atopic individuals. Although immunomodulators may offer symptomatic relief for some patients with AD, the ultimate goal of management for the patient with AD is the identification and avoidance of all the triggers of

the pruritus. Eczema is a nonspecific term often confounding the clinical and histopathologic description of various unrelated inflammatory diseases. The eczemas include such disparate diseases as allergic contact dermatitis, AD (which may include nummular eczema, dyshidrotic eczema, and eyelid dermatitis), pityriasis rosea, lichen simplex chronicus, and seborrheic dermatitis. These eczemas do not all have clinical and histologic features in common. What is more, the clinical morphologic condition of each entity can undergo evolutionary changes, proceeding through three distinct stages, namely, acute, subacute, and chronic. The eczema of AD, we must remember, is the isomorphic response of scratching the itchy, atopic skin, and the clinical morphologic condition (oozy and/or vesicular and/or scaly and/or crusted and/or lichenified) is inherently never stationery and is constantly undergoing an evolutionary process (i.e., acute, subacute, and chronic).

Differential Diagnosis

We have to rule out some kinds of skin diseases as follows: infant seborrheic eczema, infant xerantic eczema, congenital ichthyosis including sex-linked recessive ichthyosis caused by steroid sulfatase deficiency, bullous congenital ichthyosiform erythroderma, scabies, pediatric dermatomyositis, mycosis fungoides (skin malignant lymphoma), Pautrier's microabscess, photocontact dermatitis, contact dermatitis, chronic actinic dermatitis, and dermatitis due to *Cryptomeria* (cedar) pollen.

Complications

We have to pay attention to common complications as follows: Kaposi varicelliform, streptococcal impetigo, body trichophytosis, atopic alopecia, systemic lupus erythematosus, syphilis, and thyroid diseases.

The Treatment

Education of patients and families is one of the most effective treatments for AD. Information about avoidance of irritants and allergens is important in preventing AD exacerbations. In addition, written eczema action plans may be beneficial by enabling eczema self-management by reminding patients and caregivers of maintenance regimens and additional therapies to incorporate during flares. The American Academy of Dermatology and Joint Council of Allergy, Asthma, and Immunology (American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI)) published the guideline of care for AD. The treatment of AD consists of five pivotal structures. A 2012 updated

practice parameter discusses a stepwise approach based on severity, including allergen and irritant avoidance, skin barrier repair, and use of anti-inflammatory and antimicrobial agents. However, AD that is difficult to control can still be a therapeutic challenge. There are different proven AD therapies. Topical steroids and calcineurin inhibitors are preferred in the treatment of severe AD. In addition, systemic anti-inflammatory treatment, allergen-specific immunotherapy, and phototherapy are options for management of refractory AD cases. In rare cases, hospitalization might be needed to temporarily decrease exposure to environmental triggers while initiating intensive patient education, further diagnostic testing, and administration of antibiotics, among other aggressive treatments. Outpatient therapy also can include the use of bleach baths, vitamin D supplementation, and immunomodulatory and biologic therapies (see Tables 12.6 and 12.7):

- Avoidance of allergens
  That is, RAST. and/or skin test strongly positive of allergens should be avoided.
- Skin care
  That is, skin hydration, moisturizers, phototherapy, and others
- Avoidance of irritants/treatment for pruritus and deterrent to skin scratching
  That is, antihistaminic agents
- Antiallergic inflammation
  That is, topical corticosteroids, topical calcineurin inhibitors, and other antiallergic therapies
- Exclusion of exacerbation factors
  That is, appropriate skin care and avoidance of subclinical infections

Major impediments to effective management of AD are (1) ambivalence relating to skin care versus allergy as the management priority, (2) uncertainty about bathing and moisturizing, and (3) hesitation about adequate topical corticosteroid therapy. At the initial assessment, an atopic dermatitis evaluation form focuses on history and physical features essential to diagnosis and provides a review of trigger factors and past therapies:

1. Age of onset and clinical course of disease
2. Personal and family history of atopic conditions
3. Trigger factors
   (a) Infections
   (b) Bathing/moisturizing errors
   (c) Irritant exposure
   (d) Heat/sweating
   (e) Emotional stress
   (f) Allergic diseases
4. Review of past and current therapy
5. Physical features

Table 12.6 Potency chart of topical corticosteroids

Brand name (®)	Generic name
[Class 1 – superpotent]	
Clobex Lotion, 0.05 %	Clobetasol propionate
Cormax Cream/Solution, 0.05 %	Clobetasol propionate
Diprolene Gel/Ointment, 0.05 %	Betamethasone dipropionate
Olux Foam, 0.05 %	Clobetasol propionate
Psorcon Ointment, 0.05 %	Diflorasone diacetate
Temovate Cream/Ointment/Solution, 0.05 %	Clobetasol propionate
Ultravate Cream/Ointment, 0.05 %	Halobetasol propionate
[Class 2 – potent]	
Cyclocort Ointment, 0.1 %	Amcinonide
Diprolene Cream AF, 0.05 %	Betamethasone dipropionate
Diprosone Ointment, 0.05 %	Betamethasone dipropionate
Elocon Ointment, 0.1 %	Mometasone furoate
Florone Ointment, 0.05 %	Diflorasone diacetate
Halog Ointment/Cream, 0.1 %	Halcinonide
Lidex Cream/Gel/Ointment, 0.05 %	Fluocinonide
Maxiflor Ointment, 0.05 %	Diflorasone diacetate
Maxivate Ointment, 0.05 %	Betamethasone dipropionate
Psorcon Cream 0.05 %	Diflorasone diacetate
Topicort Cream/Ointment, 0.25 %	Desoximetasone
Topicort Gel, 0.05 %	Desoximetasone
[Class 3 – upper mid-strength]	
Aristocort A Ointment, 0.1 %	Triamcinolone acetonide
Cutivate Ointment, 0.005 %	Fluticasone propionate
Cyclocort Cream/Lotion, 0.1 %	Amcinonide
Diprosone Cream, 0.05 %	Betamethasone dipropionate
Florone Cream, 0.05 %	Diflorasone diacetate
Lidex-E Cream, 0.05 %	Fluocinonide
Luxiq Foam, 0.12 %	Betamethasone valerate
Maxiflor Cream, 0.05 %	Diflorasone diacetate
Maxivate Cream/Lotion, 0.05 %	Betamethasone dipropionate
Topicort Cream, 0.05 %	Desoximetasone
Valisone Ointment, 0.1 %	Betamethasone valerate
[Class 4 – mid-strength]	
Aristocort Cream, 0.1 %	Triamcinolone acetonide
Cordran Ointment, 0.05 %	Flurandrenolide
Derma-Smoothe/FS Oil, 0.01 %	Fluocinolone acetonide
Elocon Cream, 0.1 %	Mometasone furoate
Kenalog Cream/Ointment/Spray, 0.1 %	Triamcinolone acetonide
Synalar Ointment, 0.025 %	Fluocinolone acetonide
Uticort Gel, 0.025 %	Betamethasone benzoate
Westcort Ointment, 0.2 %	Hydrocortisone valerate

Table 12.6 (continued)

Brand name (®)	Generic name
[Class 5 – lower mid-strength]	
Cordran Cream/Lotion/Tape, 0.05 %	Flurandrenolide
Cutivate Cream, 0.05 %	Fluticasone propionate
Dermatop Cream, 0.1 %	Prednicarbate
DesOwen Ointment, 0.05 %	Desonide
Diprosone Lotion, 0.05 %	Betamethasone dipropionate
Kenalog Lotion, 0.1 %	Triamcinolone acetonide
Locoid Cream, 0.1 %	Hydrocortisone butyrate
Pandel Cream 0.1 %	Hydrocortisone probutate
Synalar Cream, 0.025 %	Fluocinolone acetonide
Uticort Cream/Lotion, 0.025 %	Betamethasone benzoate
Valisone Cream/Ointment, 0.1 %	Betamethasone valerate
Westcort Cream, 0.2 %	Hydrocortisone valerate
[Class 6 – mild]	
Aclovate Cream/Ointment, 0.05 %	Alclometasone dipropionate
DesOwen Cream, 0.05 %	Desonide
Synalar Cream/Solution, 0.01 %	Fluocinolone acetonide
Tridesilon Cream, 0.05 %	Desonide
Valisone Lotion, 0.1 %	Betamethasone valerate
[Class 7 – Least potent]	
Topicals with hydrocortisone, dexamethasone, methylprednisolone, and prednisolone	

The following potency chart categorizes brand-name topical steroid medications along with the name of the corresponding generic drug. The list positions these medications according to their potency. The list may not be comprehensive

During and after this assessment, we highlight with the patient/parent the steps needed for successful prevention, management, and therapy. Patients can quickly be taught increased awareness of (1) signs of infection with staphylococcal and herpes simplex infection along with the need to request antibiotic or antiviral medications; (2) irritating skin care products, clothing (such as wool or rough and occlusive fabrics), hobbies, habits (such as excessive handwashing), and job exposures; (3) the pruritus produced by overheating from excessive ambient temperatures and physical activity and clothing or bedding that are too warm; (4) stressful situations that cause anger and frustration that in turn cause increased pruritus; and (5) allergens that cause real symptoms (in contrast to the often myriad of positive skin tests and RAST reports), whether from foods, airborne sources, or chemicals that have contact with the skin.

Skin Hydration and Moisturizers

Atopic skin shows enhanced transepidermal water loss associated with impaired function of the water permeability barrier. The latter is formed by intercellular lipid lamellae found between the horny cells of stratum corneum. Both epidermal

Table 12.7 Treatments, actions, and adverse effects for atopic dermatitis

Treatment	Action	Common adverse effect
Emollient, moisturizers, and help repair defective skin barrier	Moisturizes dry skin	No significant side effect
Avoidance of triggers	Prevents known allergic reactions	–
Topical corticosteroids	Anti-inflammatory response	Striae and atrophy of the skin, rosacea, suppression of hypothalamic–pituitary–adrenal axis
Topical calcineurin inhibitors	Anti-inflammatory response, proactive treatment (tacrolimus)	Burning sensation of skin, facial flushing, itching
Vitamin D	Improves cathelicidin production	Hypercalcemia, nausea, vomiting
Antihistamines	Sedating effect aids in sleeping, decreases nighttime scratching, and skin excoriation	Drowsiness, dizziness
Bleach bath	Decreases microbial load on skin with atopic dermatitis, especially *Staphylococcus aureus*	No significant side effect
Topical or systemic antibiotic	Treats cutaneous bacterial, fungal, or viral infection	Depends on each drug's adverse effect
Immunomodulation agents		
Systemic corticosteroids	Anti-inflammatory response	Abdominal discomfort, increased risk of infection, suppression of hypothalamic–pituitary–adrenal axis
Azathioprine	Inhibits purine biosynthesis with anti-inflammatory activity	Myelosuppression, elevated liver enzyme
Cyclosporin A	Suppresses inflammatory cytokine gene transcription in T cells	Abdominal discomfort, hypertension, hyperbilirubinemia, renal impairment
Mycophenolate	Inhibits purine biosynthesis with immunosuppressive activity	Gastrointestinal symptoms (nausea, diarrhea), leukopenia, thrombopenia
Methotrexate	Inhibits purine and pyrimidine synthesis	Nausea, elevated liver enzyme level
Alitretinoin	Binds to retinoid and rexinoid receptors with anti-inflammatory activity	Headache, elevated TSH, and serum lipid level
Interferon-γ	Downregulates TH2 function	Influenza-like symptoms

Table 12.7 (continued)

Treatment	Action	Common adverse effect
Phototherapy	Anti-inflammatory response through inhibition of Langerhans cells of cytokine production; antimicrobial effects by decreasing colonization by *Staphylococcus aureus*	Short term, skin erythema, pain, pruritus, pigmentation; long term, premature skin aging and cutaneous malignancy
Narrow-band UV-B (peak 331–313 nm)		
Broadband UV-B (peak 280–320 nm)		
UVA1 (peak 340–400 nm)		
Allergen immunotherapy	Induces apoptosis/anergy of T cells and induces immune-regulatory responses and immune deviation toward TH1	Transient increase in serum IgE levels, transient eczema flares, increased risk for anaphylaxis reaction, or transient exacerbation of underlying atopic disease

TH T-helper cell type, *TSH* thyroid-stimulating hormone

hydration and skin surface lipids were reduced, referring to an abnormality of the hydrolipid film. Hydration of the skin is best accomplished through soaking baths. Bathing might also reduce colonization by *S. aureus*. To prevent evaporative effects, which are damaging to the skin barrier, patients need to apply medication or moisturizer immediately after bathing or wetting their skin. Use of moisturizers together with hydration might help reestablish and preserve the stratum corneum barrier. Daily moisturizer therapy can also increase high-frequency conductance, a parameter for the hydration state of the skin surface. This allows for ranking the efficacy of moisturizers according to the duration of effects or the magnitude of increase in the hydration level of the stratum corneum. The urea treatment significantly increased skin capacitance, indicating increased skin hydration. The water barrier function, reflected by transepidermal water loss values, improved, whereas skin susceptibility to sodium lauryl sulfate was significantly reduced. Thus, certain moisturizers could improve skin barrier function and reduce susceptibility to irritants. Adding a moisturizer to a low-potency topical corticosteroid has also been shown to improve clinical parameters in patients with AD. Moisturizers decrease the need for topical corticosteroids. Ceramide-dominant emollient is added to standard therapy in a group of children with "stubborn-to-recalcitrant" AD. Transepidermal water loss decreased concomitantly, whereas stratum corneum integrity and hydration status improved. In addition, ultrastructure of the stratum

corneum revealed extracellular lamellar membranes, which were largely absent in baseline samples. Errors in bathing and moisturizing are the major cause of persistent AD. Physicians and patients have too long been stymied in their therapeutic endeavors by two true but opposing facts about bathing. Bathing dries the skin: Wetting followed by evaporation causes stratum corneum contraction and fissures, impairing the epidermal barrier. On the other hand, bathing hydrates the skin: Moisturizer is applied within 3 min to retain hydration, keeping the barrier soft and flexible. Until this paradox is explained to the patient, there can be only confusion. Although an infrequent bathing regimen may work for some people, daily bathing is preferred because it cleanses and hydrates, it enhances penetration of corticosteroids, and people are more relaxed and comfortable when they bathe. A 20-min soaking bath is optimal for hydrating the stratum corneum, although even a brief shower helps. The choice of soap may not be very important, but, if patients are concerned, we note that Dove® (Lever Brothers Co, New York, NY) and Olay Sensitive Skin bars® (Procter & Gamble Co, Cincinnati, Ohio) have reduced irritancy. The important issues are the "3-minute rule" (i.e., application of moisturizer [or topical corticosteroid] within 3 min, before water evaporates) and the use of a proper, unfragranced moisturizer, either ointment (e.g., petrolatum, Neutrogena Hand Cream® [Neutrogena Corp, Los Angeles, Calif], Aquaphor® [Beiersdorf, Inc, Norwalk, Conn], Albolene [Menley & James Laboratories, Inc, Horsham, Pa], and Plastibase® [E.R. Squibb & Sons, Princeton, NJ]) or cream (e.g., Cetaphil [Galderma Laboratories, Inc, Fort Worth, Tex],Vanicream [Pharmaceutical Specialties, Inc, Rochester, NY], Acid Mantle® [Doak Dermatologics, Fairfield, NJ], DML® [Person & Covey, Inc, Glendale, Calif], and Aveeno Moisture Cream® [Rydelle Laboratories, Racine, Wis].

Avoidance of Irritancy

Patients with AD have a lowered threshold of irritant responsiveness and need to avoid irritancy. In addition, patients with AD have an abnormal stratum corneum, even in noninvolved skin, which contributes to diffusional water loss after application of a topical irritant, confirming a functional abnormality. In addition, inflammatory changes including spongiosis, perivenular mononuclear infiltrate, and activated eosinophils can be seen, suggesting that nonspecific triggers might contribute to chronic inflammation in AD. Because soaps and detergents are potential irritants, patients are often advised to completely avoid them. However, cleansers might be useful, especially in patients with frequent skin infections. In a double-blinded, placebo-controlled study, use of an antimicrobial soap containing 1.5 % triclocarban resulted in reduction in *S. aureus* colonization and significantly greater clinical improvement. In addition, patients are often counseled to avoid swimming in chemically treated pools, although such activity can in fact be beneficial to some patients. Patients should be instructed to use a gentle cleanser to remove chlorine or bromine and then apply a moisturizer. Environmental factors that can modulate the effect of

irritancy include temperature, humidity, and texture of fabrics. Temperature in home and work environments should be temperate with moderate humidity to minimize sweating. Occlusive clothing should be avoided, and loose-fitting cotton or cotton blend garments should be substituted to help with overheating. The most important quality of clothing fabrics might be nonabrasiveness and breathability. Texture or roughness, rather than whether a fabric was natural or synthetic, determined tolerability and skin irritancy.

Treatment for Pruritus and Deterrent to Skin Scratching

Appropriate use of antihistaminic agents is variable for the treatment of pruritus and deterrent to skin scratching. The second-generation antihistaminic agents, such as cetirizine, loratadine, and fexofenadine, are good to take daytime without their uncomfortable side effects (i.e., drowsiness, malaise, and hydrodipsia). However, they are not effective for the control of strong itching. In such cases, the first-generation antihistaminic agents, such as diphenhydramine, chlorpheniramine, and hydroxyzine, are effective. The strongest drug for the treatment of pruritus and deterrent to skin scratching is hydroxyzine. Despite that side effect of drowsiness, the efficacy of control pruritus in patients with AD and restrain their skin scratching is indispensable for the treatment of AD. Administration of 30–50 mg of diphenhydramine hydrochloride (Benadryl®, Belix®, or Banophen® in the USA, Restamine® in Japan) three times a day or 25–50 mg of hydroxyzine pamoate (Atarax-P®) before sleep for more than moderate AD patient is good to restrain involuntary scratching of their skin. Especially, control of pruritus and deterrent to skin scratching during sleep is so important for patients with AD because unconscious skin scratching should potent exacerbation factor of AD. As mentioned above, the first-generation antihistaminic agents have strong effect with strong side effects; on the other hand, the second-generation antihistaminic agents have mild effect with mild side effects. Olopatadine hydrochloride (Patanol® in the USA, Allelock® in Japan) places in the middle rank of antihistaminic agents. Also, topical diphenhydramine ointment (Dermarest® in the USA, Restamine® in Japan) is strongly effective for the control of pruritus without major side effects. This ointment is usually used with topical corticosteroids for the treatment of AD. Of course, we can use both drugs together. Some physicians use topical diphenhydramine ointment and topical corticosteroids in the daytime, whereas some administer 25–50 mg capsule of hydroxyzine before sleep for the control of pruritus in the patients with AD. You should recognize that deterrence of skin scratching is critical for the treatment of AD. We have to administer these different drugs with the accurate understanding each character of these drugs conform to each skin condition of patients with AD. Generally speaking, so-called antiallergic agents without antihistaminic effect are thought to be not effective neither for the control of pruritus nor for the deterrence of skin scratching.

Avoidance of Allergens

Food allergens have been shown to play a role in a subset of patients with AD, with milk, egg, peanut, soy, wheat, and fish accounting for approximately 90 % of the foods found to exacerbate AD. Removal of proven food allergens from the patient's diet can lead to significant clinical improvement. It is important for patients to avoid implicated foods completely, because even small amounts of the food allergen can contribute to food-specific IgE synthesis. Following the natural history of food-related AD is important because most patients will become tolerant to food allergens, even in the face of positive skin test results. Although food challenges have generally been performed to help define clinical allergy, more recently, specific IgE levels to several food allergens by the Pharmacia Immuno-CAP system® (Pharmacia, Uppsala, Sweden) have been shown to have predictive value in terms of clinical relevance. Serial measurements with this assay have proved to be of value in following the natural history of patients' food allergies to help determine when a food could be reintroduced or food challenge performed. The possibility of preventing AD through dietary manipulation has been considered. Restricting the mother's diet starting in the third trimester of pregnancy and during lactation and the child's diet during the first 2 years of life resulted in decreased prevalence of AD in the prophylaxis group compared with a control group at 12 months of age but not at 24 months. Follow-up at 7 years of age showed no difference between the prophylaxis and control groups for AD or respiratory allergy. Breast-feeding did not affect the lifetime prevalence of AD in a large ethnically and socially diverse group of children. In contrast, infants who were breast-feeding exclusively for more than 6 months had a significantly lower prevalence of eczema at 1 year and 3 years compared with infants who were breast-fed for less than 1 month or were intermittently breast-feeding. The benefits of breast-feeding infants with AD have been described, although sensitization to allergens in the mother's diet transferred through breast milk is a potential problem for at-risk infants. The degree of sensitization to aeroallergens has also been shown to be associated with the severity of AD. In addition, patients with dust mite sensitivity likely need to avoid other triggers that could contribute to chronic skin inflammation. The use of polyurethane-coated cotton encasings compared with cotton encasings resulted in clinical benefit even in patients not sensitized to house dust mite, suggesting that impermeable covers could reduce exposure to other allergens as well as irritants or possibly even superantigens. With respect to early dust mite allergen exposure, the authors of a placebo-controlled trial of mite-impermeable covers reported an inverse correlation between dust mite allergen exposure at 3 months of age and development of AD during the first year of life, even after adjusting for potential confounders.

Avoidance of Exacerbating Factors

Severe/persistent AD patients have been affected by the plural exacerbating factors. We have to identify those in each patient with AD; thereafter we have to try to remove/avoid each exacerbating factor in each patient to improve clinical condition.

Major exacerbating factors which are mentioned order the frequency by our investigation are as follows: shampoo or soap, hair treatment, inappropriate topical medicine, subclinical infection (e.g., chronic tonsillitis, pyorrhea, paranasal sinusitis, urinary tract infection), cosmetics, house dusts, ticks, folk remedies, pollens, bathing habit, psychosocial factors, occupation, 4-hydroxybenzoate (paraben), and other preservatives.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children beyond infancy. Some different studies showed that in not only infants but also children up to 13 years of age, treatment with lactobacillus was beneficial in patients with AD and allergies.

Topical Corticosteroids

Since their introduction approximately 50 years ago, topical corticosteroids have been the mainstay of treatment for AD, showing efficacy in both acute and chronic disease. By acting on multiple resident and infiltrating cells, primarily through suppression of inflammatory genes, they are effective in reducing inflammation and pruritus. In addition, topical corticosteroids might have an effect on bacterial colonization in AD, reducing the density of *S. aureus*. Topical corticosteroids are available in extremely high (class 1) to low (class 7) potencies (Table 12.6). Choice of which topical corticosteroid preparation to prescribe will depend in large part on the severity and distribution of eczematous lesions. Patients need to be informed about the potency and potential side effects of their prescribed topical corticosteroid. In general, using the least potent corticosteroid that is effective should be the rule. This approach needs to be balanced by the possibility that initiation of therapy with a topical corticosteroid that is too weak might result in persistence or worsening of AD, which in turn can lead to decreased adherence with the treatment regimen. In addition, patients might be prescribed a high-potency corticosteroid with instructions to discontinue it within 7–14 days without a plan to step down, resulting in rebound flaring of their AD, similar to what is frequently seen after oral corticosteroids. Therapy-resistant lesions have been treated with potent topical corticosteroids under occlusion, although this approach needs to be used cautiously, primarily for hand or foot eczema, to avoid systemic side effects. Prescribing topical corticosteroids in inadequate amounts can contribute to suboptimally controlled AD, especially in patients with widespread disease, because it takes approximately 30 g of medication to cover the entire body of an average adult. In children, the fingertip unit (FTU) is defined as the amount of topical medication extending from the tip to the first joint on the palmar aspect of the index finger as a measure for applying topical corticosteroids. Approximately 1 FTU is needed to cover the hand or groin, 2

FTUs for the face or foot, 3 FTUs for an arm, 6 FTUs for the leg, and 14 FTUs for the trunk. Topical corticosteroids have typically been applied twice daily and using them more frequently might increase side effects without significant clinical benefits. Fluticasone propionate cream has been shown to be safe and effective in children and infants with AD as young as 3 months of age even when applied on the face and over significant body surface for up to 1 month. In addition, once daily treatment has been shown to be effective for topical fluticasone propionate and mometasone furoate, which might improve adherence with the treatment regimen. In a different approach, a short course of a potent topical steroid applied for 3 days was found to be equal in clinical efficacy to chronic use of a low-potency corticosteroid. Given the concern over side effects associated with chronic use, topical corticosteroids have not been considered appropriate for maintenance therapy especially on normal-appearing skin in AD. However, several studies with fluticasone propionate in patients as young as 3 months of age have shown that once control is achieved with a once daily regimen, long-term control can be maintained with twice weekly therapy. Of note, during the maintenance phase of the study, the corticosteroid preparation was applied to areas that appeared to have healed, which resulted in delayed relapses compared with placebo therapy. Patients with AD might not respond appropriately to topical corticosteroid therapy. Reasons for this might include ongoing exposure to irritants or allergens, *S. aureus* superinfection, inadequate potency of the steroid preparation, or insufficient amount dispensed. Other causes for apparent treatment failure include steroid allergy and possibly corticosteroid insensitivity. However, a much more practical reason for therapeutic failure with topical corticosteroids is nonadherence with the treatment regimen. A significant number of patients or caregivers admit to nonadherence with topical corticosteroids because of fear of adverse effects.

Topical Calcineurin Inhibitors

Topical corticosteroids have been the traditional mainstay of topical drug therapy for AD because of broad immunosuppressant and anti-inflammatory effects. However, topical steroids have been associated with adverse local effects such as dermal atrophy, striae, telangiectasia, perioral dermatitis, acneiform eruptions, as well as a risk of systemic effects such as hypothalamic–pituitary–adrenal axis suppression. The development of nonsteroid topical immunosuppressants has been a historic development in therapy of AD. Topical calcineurin inhibitors are an important class of medications that have been shown to have clinical efficacy in AD, as displayed in a broad set of clinical trials and in extensive clinical use. Topical calcineurin inhibitors were developed after the utility of systemic cyclosporin A, a potent inhibitor of T cells, was noted in the treatment of eczematous dermatitis and psoriasis. Cyclosporin A had been used for prevention of organ transplant rejection after solid organ transplants and as a systemic immunosuppressive for a broad set of conditions. Cyclosporin A is not useful as a topical medication, presumably because

of its large molecular size, which impedes its ability to penetrate skin. Its use orally is associated with a risk of serious systemic effects, particularly renal toxicity. Tacrolimus (Protopic®) is another potent immunosuppressant used to prevent graft rejection. Tacrolimus, however, is active topically and has been shown to be effective for treatment of AD. It has been marketed by Asteras Inc. (Deerfield, Ill) as Protopic ointment (0.03 % and 0.1 % for children 2 years of age and older and adults, respectively). Pimecrolimus (Elidel®) is an ascomycin derivative with potent calcineurin inhibition developed specifically to treat inflammatory skin conditions, the result of a prospective screening of hundreds of compounds. Pimecrolimus is the active agent of Elidel cream 1 % (Novartis Pharmaceutical Corporation, East Hanover, NJ), a formulation approved by the Food and Drug Administration for use in patients 2 years of age or older with mild to moderate AD. Both tacrolimus and pimecrolimus work through inhibition of phosphorylase activity of the calcium-dependent serine/threonine phosphatase calcineurin and the dephosphorylation of the nuclear factor of activated T-cell protein (NF-ATp), a transcription factor necessary for the expression of inflammatory cytokines including IL-2, IL-4, and IL-5. Also, they might inhibit the transcription and release of other T-cell derived cytokines including IL-3, IFN-gamma, TNF-alpha, and GM-CSF, which can contribute to allergic inflammation. The majority of the studies of topical pimecrolimus and tacrolimus discussed above assessed efficacy of these medications as primary monotherapy of AD, with topical or systemic steroids used as "rescue" for disease flares. Clearly, new steroid-free topical agents might offer improved long-term management options for patients with AD. Evolution of topical therapy will likely include combinations of topical anti-inflammatory agents including calcineurin inhibitors and topical corticosteroids, although the optimal combination therapy has yet to be defined. With evolving therapeutic options, guidelines for care of AD, perhaps similar to those used for treatment of asthma, might prove useful and are being developed.

Tacrolimus

Tacrolimus (FK 506) is a macrolide lactone isolated from *Streptomyces tsukubaensis*. Tacrolimus-binding receptors (the major ligand is FKBP12, also known as macrophilin) have been found on a number of cells. Tacrolimus inhibits the activation of a number of key cells involved in AD including T cells, Langerhans' cells, mast cells, and keratinocytes. Tacrolimus 0.03 % and 0.1 % ointments have been shown to be safe and effective in the treatment of children (older than 2 years of age) and adults with AD. According to product labeling, less common adverse events (less than 5 %) of varicella zoster infections (mostly chicken pox) and vesiculobullous rashes were more common in patients treated with tacrolimus ointment 0.03 % compared with vehicle during clinical trials. An average of 2.2 g of tacrolimus was used per day. The outcome measure, a modified eczema and severity index score, showed 61 % improvement from baseline after 3 months of treatment and 71 % of baseline at 1 year. Pruritus decreased throughout the treatment course, and

application site burning diminished within the first few days of tacrolimus use. In other long-term studies, *S. aureus* colonization decreased during long-term therapy with tacrolimus ointment, and cutaneous infection rates decreased with extended use beyond 1 year.

Pimecrolimus

Unlike FK 506 and cyclosporin A, the ascomycin derivative pimecrolimus was developed specifically to treat inflammatory skin conditions. Pimecrolimus binds to FKBP/macrophilin and interferes with calcineurin action, apparently with preferential drug distribution to the skin. Topical pimecrolimus appears to be effective topically for AD with little systemic absorption in children and adults with AD. In one study the systemic availability of topical pimecrolimus was measured in 22 infants aged 3–23 months, with pimecrolimus 1 % cream applied twice daily for 3 weeks to all affected areas including the face and neck. There was a wide range in body surface area involvement, ranging from 10 % to 92 %. Pimecrolimus blood concentrations were consistently low, with approximately one-third of the samples below the assay limit of quantitation (0.1 ng/mL), 71 % were below 0.5 ng/mL, and fully 98 % of the samples were below 2 ng/mL. Long-term pharmacokinetic studies with repeated application of pimecrolimus did not significantly accumulate in the blood and appeared to have minimal adverse systemic risks. The poor absorption of pimecrolimus and absence of experience with the drug systemically have made it difficult to interpret the low serum levels seen in topical use studies. However, the pharmacokinetics of systemic pimecrolimus given orally have been studied in patients with moderate to severe chronic plaque psoriasis as well as in healthy subjects. In the psoriasis study, patients received pimecrolimus (5 mg every day to 30 mg twice a day) for 4 weeks. Blood concentrations reached steady state after 5–10 days, and drug exposure demonstrated linear dose dependency. No serious adverse events or clinically significant changes in physical examination or laboratory safety tests were reported in this study. Multiple clinical studies have demonstrated the efficacy and safety of pimecrolimus 1 % cream in AD. A low rate of burning and stinging was seen in pimecrolimus patients, lower, although not significantly, than with vehicle cream. Although not approved by the Food and Drug Administration for use in children younger than 2 years of age, multiple studies of pimecrolimus 1 % cream have been performed in this age group, showing excellent tolerance and effectiveness. Long-term therapy with pimecrolimus 1 % cream for 6 months and 1 year investigated whether the early treatment of the signs and symptoms of AD with pimecrolimus could influence long-term outcome by preventing disease progression. Patients received twice daily treatments of the study medication at the first signs of AD for up to 12 months. Emollients and moderately potent topical steroids were permitted for maintenance or if study medication was insufficient to treat flares. The primary efficacy was the incidence of flares, and the need for topical corticosteroid intervention was necessary. Eczema area and severity index and pruritus scores were used to assess the efficacy of pimecrolimus in AD maintenance.

Historically, combination therapies with different classes of drugs have been used to maximize efficacy while managing the risk of adverse events. Combining a calcineurin inhibitor and corticosteroids should be no different in this regard. Using a topical calcineurin inhibitor as a first-line pharmacologic agent for the treatment of early signs and symptoms of AD, as opposed to treating only more severe exacerbations, necessitates an excellent safety and tolerability profile to ensure practicability and compliance. In this respect, neither skin atrophy nor hypothalamic–pituitary–adrenal axis suppression has been observed with topical calcineurin inhibitors, making them more suitable than topical steroids for frequent or prolonged use, especially on larger body surfaces or on areas especially prone to atrophy with steroid use. Building on the positive experience of combining pimecrolimus with steroids sequentially and concomitantly once daily, an appealing treatment strategy would be to use a topical calcineurin inhibitor twice daily and add a mid-potency steroid such as fluticasone propionate or mometasone once daily. Data from several studies suggest that using pimecrolimus as a first-line pharmacologic agent to treat early signs and symptoms of AD prevents the progression to more severe exacerbations in approximately 50 % of the cases, reducing the need for topical steroids. If, despite such early intervention, the addition of a mid-potency steroid is warranted to treat breakthrough flaring of AD, it can be used in short pulses, maximizing the benefit–risk ratio and enhancing patient compliance.

Specialized Therapy

A broad array of therapies are used for AD. Although it is beyond the scope of this review to address all of them comprehensively, phototherapy and systemic immunomodulatory agents are briefly discussed below.

Phototherapy

Broadband UV-B, broadband UV-A, narrow-band UV-B (311 nm), UV-A-1 (340–400 nm), psoralen ultraviolet A-range (PUVA), and combined UV-A-B phototherapy are useful adjuncts in the treatment of AD. These therapies are well established, although relapse can occur after cessation of treatment. Most patients in a broad set of studies experienced improvement in symptoms as well as reduction in topical corticosteroid use. The photoimmunologic effects of UV-A phototherapy with and without psoralen are presumably mediated through Langerhans' cells and eosinophils, whereas UV-B's immunosuppressive effects occur through blocking of antigen-presenting Langerhans' cells and altered keratinocyte cytokine production. Photochemotherapy with PUVA might be indicated in patients with severe, widespread AD. Studies comparing the different modes of phototherapy are limited. Short-term adverse effects with phototherapy might include erythema, burns, pruritus, and pigmentation. Long-term adverse effects include premature skin aging and

cutaneous malignancies. Limited descriptive studies of extracorporeal phototherapy with UV-A and methoxypsoralen have been reported, and this method is not widely used.

Systemic Immunomodulatory Agents

A broad set of systemic immunomodulatory agents have been used for severe AD refractory to topical therapies. There are extensive clinical use and clinical experience with systemic corticosteroids and cyclosporin A. Systemic glucocorticoids such as oral prednisone are highly immunosuppressive but generally avoided in the treatment of chronic AD because of systemic toxicities. Rarely, short courses of oral glucocorticoids might be initiated for acute exacerbations of AD while other treatment measures are being introduced. If used, intensive topical therapy should be initiated during systemic treatment to prevent rebound flaring of AD. Cyclosporin A is a potent immunosuppressive that works by inhibiting calcineurin. Multiple studies have demonstrated that both children and adults with severe AD refractory to conventional treatment can benefit from short-term cyclosporine treatment. Various oral dosing regimens have been recommended; 5 mg/kg has generally been used with success in short-term and long-term (1 year) use, whereas some authorities have advocated body-weight independent daily dosing of adults with 150 mg (low dose) or 300 mg (high dose) daily of cyclosporine microemulsion. Treatment with cyclosporine has been associated with reduced skin disease and improved quality of life. Discontinuation of treatment, however, generally results in rapid relapse of skin disease. Possible side effects include elevated serum creatinine level, renal impairment, or hypertension. Other systemic therapies include recombinant human IFN-gamma, tacrolimus, and intravenous immunoglobulin. Antimetabolites have been used for AD including mycophenolate mofetil, a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation, methotrexate, and azathioprine. These systemic agents all have significant risks of systemic toxicities, requiring careful monitoring and restricting their use. Other systemic medications such as leukotriene receptor antagonists have been suggested as useful, but they have limited peer-reviewed evidence to support routine use. Oral pimecrolimus has been used in clinical trials with some efficacy, although published data are limited. Usefulness of new biologic agents such as infliximab and etanercept in AD is unknown at present.

To assess the severity and extent of AD, several parameters have been used, such as the eczema area and severity index, the Rajka–Langeland grading of severity of atopic dermatitis, and the scoring of atopic dermatitis (SCORAD) designed and produced by Pr J. F. Stalder, under the auspices of the European Task Force on Atopic Dermatitis. SCORAD is a parameter widely used to assess disease severity and determine whether treatment is effective. There are three major components in SCORAD: (1) percentage of affected surface area; (2) intensity of eczema at lesions, on a scale of 0–3, composed of erythema, edema, excoriations, oozing, lichenification, and skin dryness; and (3) functional impact evaluated by a visual

scale (0–10) composed of pruritus and sleep disturbance. The SCORAD is calculated using the formula A/5 + 7B/2 + C. SCORAD scores lower than 20, 20–40, and higher than 40 suggest mild, moderate, and severe AD, respectively. In details, see reference 15 and visit the website of the European Task Force on Atopic Dermatitis.

http://adserver.sante.univ-nantes.fr/Scorad.html

Future Perspective

Corticosteroids, calcineurin inhibitors, UV therapy, and the immunosuppressant macrolides are all therapeutic agents that are likely to be effective in controlling the complex inflammatory cascades of chronic AD. However, future studies are needed to focus on strategies preventing the initial development of AD. Given the central role of TH2 cytokines and chemokines in the development of allergic skin inflammation, strategies directed at reducing TH2 responses and blocking the action of chemokines by antagonists of CCR3 and CCR4 will be important. Further studies are also needed to examine the potential role of IFN-gamma, IL-12, and IL-18 in restoring the shift toward a more balanced TH0 response with equal production of TH1 and TH2 cytokines. There is also a strong rationale for examining the effect of therapeutic agents capable of blocking the actions of IL-4 and IL-5. Anti-IL-5 antibody has been shown to block eosinophil infiltration in sensitized animals whether administered before or after allergen challenge. It would be of interest to determine the clinical effects of blocking the action of IL-4 in patients with AD. Elimination of the IgE response may have less importance in patients with continuing TH2-mediated allergic inflammatory responses. Thus the combination of several approaches will be needed to effectively interrupt the complex inflammatory cascades associated with allergic diseases including AD.

Evidence-Based Medicine in AD

Diagnosis

To confirm the diagnosis of atopic dermatitis in a patient with dermatitis, allergist–immunologists are specifically trained to diagnose atopic dermatitis. Defining IgE-mediated sensitivity (by means of skin or in vitro testing) is useful in the differential diagnosis.

Joint Task Force on Practice Parameters. Disease management of atopic dermatitis: an updated practice parameter. American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2004;93(Suppl):S1–21. Evidence grade: IV.

Management

Recent studies have suggested that epidermal barrier dysfunction contributes to the development of AD and other allergic diseases. Approximately 32 % fewer neonates who received the moisturizer had AD/eczema by week 32 than control subjects ($P = 0.012$, log-rank test). No statistically significant effect of emollient on allergic sensitization based on the level of IgE antibody against egg white was shown. However, the sensitization rate was significantly higher in infants who had AD/eczema than in those who did not (odds ratio, 2.86; 95 % CI, 1.22–6.73). Daily application of moisturizer during the first 32 weeks of life reduces the risk of AD/eczema in infants. Allergic sensitization during this time period is associated with the presence of eczematous skin but not with moisturizer use.

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Chapter 13
Allergic Contact Dermatitis

Bettina Wedi

Definition, Classification and Epidemiology

Allergic contact dermatitis (ACD), a subtype of contact dermatitis, is a common inflammatory skin condition caused by direct contact with an allergy-causing substance. Over 3,000 contact allergens have been identified. ACD affects approximately 1 % of the general population, equally as likely in infancy as in adulthood (apparently increasing in children). Contact dermatitis occurs twice as frequently in women as in men and often starts at young age.

In affected individuals ACD has a serious impact on their quality of life. Moreover, in severe, persistent condition, the disease is sometimes job threatening or life threatening. Occupational contact dermatitis is the second cause of recognized occupational diseases with considerable economic impact. Occupational ACD is most common in hairdressers; printers; machine tool operators; chemical, gas and petroleum plant operatives; car assemblers; and machine tool setters. The prevalence of hand eczema in workers with wet work exposures is approximately 20 %. Irritant contact dermatitis (ICD) and ACD are more common in patients with filaggrin loss-of-function mutations.

Airborne contact dermatitis is caused by dust, pollen or volatile substances and is located on air-exposed areas, for example, to the preservative (MCI/MI) in paintings (Fig. 13.1). Passive exposure via social contacts termed "consort" or "connubial" dermatitis should also be considered (e.g. ACD of the face in a mother due to benzoyl peroxide acne treatment of her son). Several episodes of contact urticaria (e.g. to meat, vegetables or spices) may result in protein contact dermatitis (Fig. 13.2). Systemic ACD after systemic intake of the allergen (e.g. orally ingested nickel, balsam of Peru or spices) is a rare subtype of ACD although at least systemic

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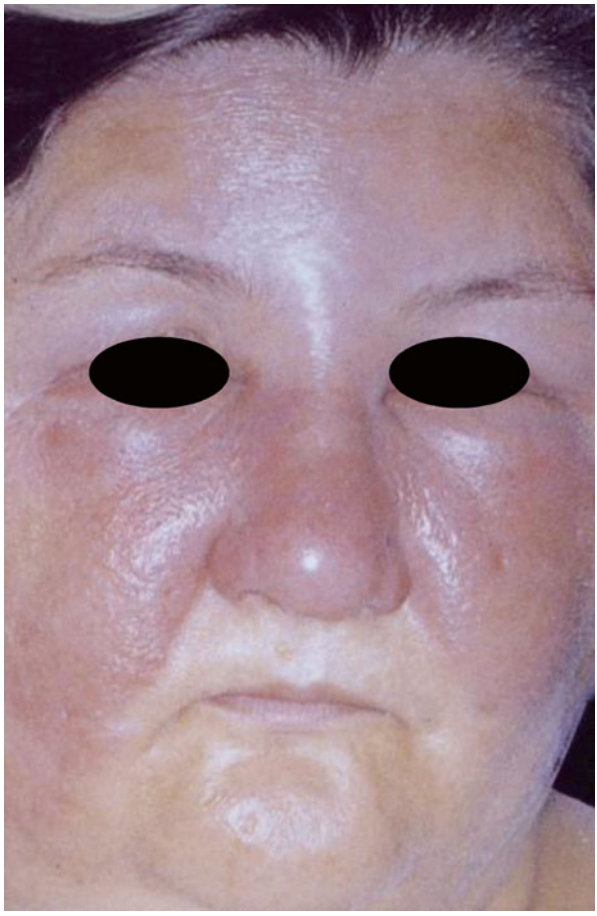

Fig. 13.1 Airborne contact dermatitis to the preservatives MCI/MI in paintings

ACD to nickel may be underdiagnosed because nickel represents the most common occupational as well as public contact allergen. Baboon syndrome (formerly called mercury exanthema) is a special type of systemic ACD, symmetrically involving the intertriginous areas (buttocks, axillae) and is most common after drug intake. ACD to food is uncommon but is more frequent in food handlers. It frequently involves the hands or fingertips (e.g. by diallyl disulphide in garlic) but can also be present around the mouth or on the face (e.g. by urushiol, the allergenic oleoresin of *Toxicodendron* plants, present in mango and cashew nuts).

In photoallergic contact dermatitis, additional exposure to ultraviolet light is needed.

ACD can occur at any time, after many years of contact with a substance or after a few exposures. Irritant contact dermatitis (common irritants: water, cleaning agents, acids, alkalis, oils, organic solvents) facilitates the development of sensitization and thus often precedes ACD (e.g. cleaners who perform wet work and develop ICD, prompting them to start wearing rubber gloves. They then become allergic to the rubber accelerators in the gloves).

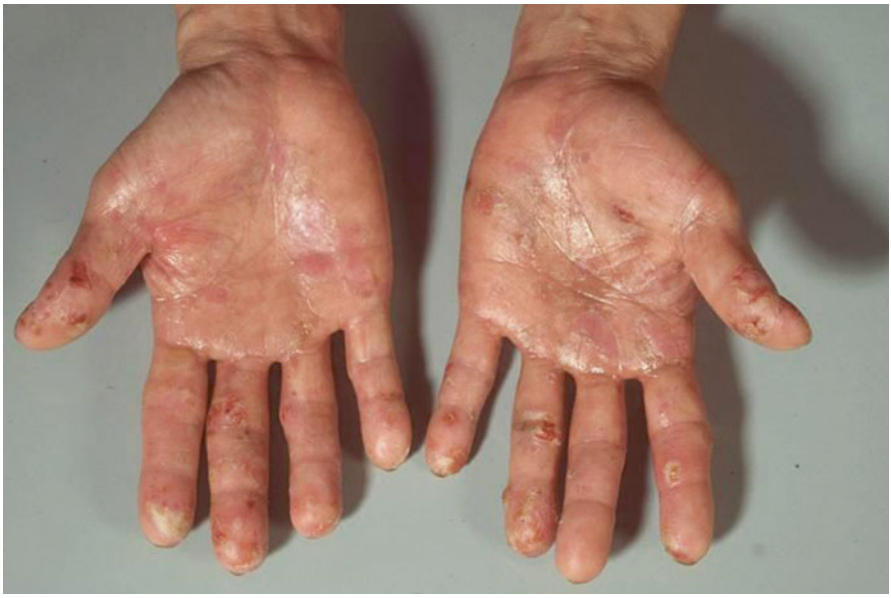

Fig. 13.2 Protein contact dermatitis to wheat flour in a baker

Recognizing Those at Risk

Acquired risk factors are generally inflammatory skin diseases such as ICD, stasis and possibly atopic dermatitis, while genetic variances might result in higher susceptibility.

Atopic dermatitis The pattern and the frequencies of observed sensitizations do not differ greatly between atopic dermatitis patients and nonatopic individuals (exception: bufexamac). No association exists between atopic dermatitis and reactions to nickel. However, atopy is a well-recognized risk factor for ICD and thus possibly also for ACD.

Stasis dermatitis There is higher risk for developing ACD to materials and agents applied to the areas of stasis dermatitis and leg ulcers (e.g. neomycin).

Otitis externa There is higher risk for ACD to topical neomycin and topical corticosteroids.

Regulatory Aspects

Regulatory aspects aim to reduce exposure to contact sensitizers, for example, the European Union regulated the content of chromium in cement in 2005, and since then sensitization to chromate in construction workers has declined.

The local lymph node assay in mice is used for regulatory risk assessment of potential allergens. Novel in vitro strategies have been developed to identify skin-sensitizing chemicals. Nevertheless, epidemiological and clinical data continue to represent a critical decision point in risk assessment and management. In several countries clinical epidemiological surveillance systems exist. For example, the Information Network of Departments of Dermatology in Germany is monitoring clinical epidemiology data, although at the moment their activity is significantly impaired. Actually, the European Union legislation labels patch test materials as drugs. Large epidemiological studies with putative novel contact allergens, which usually precede clinical registration trials, cannot be achieved under current legislation. This is unnecessary and harmful for management of patients with dermatitis, as it diminishes patch testing and correct diagnoses significantly. Important and emerging contact allergens will be detected later, if ever.

Pathogenesis

Molecular and Cellular Mechanisms

The immune response to contact allergens in the skin is a highly dynamic process. Cells are leaving the skin, some recirculate between the skin and lymph nodes and others are recruited to the skin.

ACD is caused by specific T-lymphocyte-mediated sensitization to low molecular weight substances (haptens). Protein haptenation is one of the key molecular events in skin sensitization. It is a rule without exception that ACD will only develop if molecules are able to penetrate the skin and behave as haptens, that is, bind to cell surfaces in the epidermis or dermis, modify self-skin protein(s) and thus induce immunization. For protein haptenation to occur, a chemical must be electrophilic, for example, must have a polarized bond such as halogenated compounds or be a cation such as Ni2+. Importantly, a chemical can also be converted to a protein-reactive species by air oxidation or cutaneous metabolism.

Very recent results showed that toll-like receptors, which recognize pathogen-associated molecular pattern (PAMPs) expressed by bacteria, parasites, viruses and fungi, are activated by haptens. Nickel, the most relevant contact allergen, directly activates TLR4. Therefore, recent models incorporate the danger theory in the pathomechanism of ACD. The hapten produces both an antigenic signal and a danger signal through the release of damage-associated molecular pattern (DAMP) molecules, ligand stimulation of toll-like receptor (TLR)-4 and TLR2 and release of proinflammatory cytokines. The cytokines induce expression of vascular adhesion molecules and chemokines, thereby recruiting Th1 and Th17 cells.

The initial sensitization typically takes 10–14 days from initial exposure to a strong contact allergen such as poison ivy. Once an individual is sensitized to a chemical, ACD develops within hours to several days of exposure. $CD4^+$ $CCR10^+$ memory T cells persist in the dermis after ACD clinically resolves.

It is widely accepted that sensitization is specific. However, recent data demonstrated that with an increasing strength of a positive reaction to nickel or to fragrance mix, the likelihood of further positive reactions to unrelated contact allergens increased significantly. This recent finding can raise new questions with regard to the conception that sensitization is in any case and throughout an exclusively allergen-specific process.

Histology

Histologically contact dermatitis is characterized by spongiosis (intraepidermal edema) and a mononuclear infiltrate. Thickening of the epidermis (acanthosis) with hyperkeratosis and parakeratosis may be seen in the epidermis and stratum corneum. Some dermatohistopathologist believe they can differentiate allergic from irritant contact dermatitis because ICD may show epidermal necrosis and less intercellular edema whereas ACD may be associated with the presence of eosinophils.

Clinical Symptoms

Acute ACD is characterized clinically by intense pruritus, erythema, vesiculation and weeping and crusty deposits, whereas in chronic ACD thickened skin and lichenification predominate in addition to erythema and pruritus. Quality of life is impaired similar to patients with psoriasis or hair loss.

Clinical symptoms vary at different areas of the body due to different thicknesses of the skin. For example, erythema and edema predominate in thin skin (the eye lids, penis, scrotum), whereas the scalp, palms and soles may exhibit few clinical signs of ACD. Location of the skin or mucosal lesions often points to the offending allergen(s) (Fig. 13.3), for example, nickel in a trouser button, chromate in leather shoes, metals in dental prosthesis (Fig. 13.4) or chemicals in ophthalmologic preparations causing dermatitis around the eyes. However, sometimes detective work is needed to uncover the allergen(s) (Fig. 13.5).

Diagnosis

Telling ACD apart from ICD can be very difficult because both cannot be easily differentiated by clinical, histological or electron microscopic examination. Differences in clinical distribution and morphology are useful guides but dangerous to rely on uncritically (undress the patient completely!). A detailed history is crucial in evaluating individuals with ACD to identify potential causes of ACD. Patients with ACD require a much more detailed history compared to those with most other

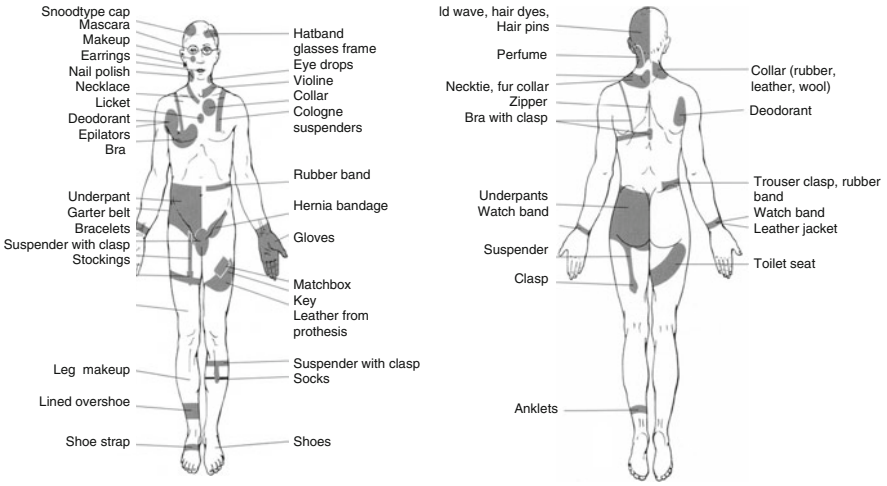

Fig. 13.3 Clues to distribution

dermatologic disorders. If occupational ACD is suspected, it should be considered that the material safety data sheets often provide incomplete data, and it is frequently necessary to contact the manufacturer.

The demonstration of a type IV immune reaction remains the specific point of difference, which is done by appropriate patch testing that requires at least three office visits and must be done by a clinician with detailed experience in the procedures and interpretation of results.

In protein contact dermatitis, patch testing and prick testing should be combined to test for type I and type IV immune reaction.

Some substances need additional exposure to sunlight to cause ACD. Thus, if photoallergic contact dermatitis is suspected, additional photopatch testing (irradiation with 10 J/cm^2 ultraviolet A) should be performed.

In systemic ACD (the most classic being a refractory vesicular hand dermatitis or acral or flexural erythema, occurring with ingestion of allergenic metals and usually associated with strong positive patch test, e.g. to nickel, cobalt, chromium or balsam of Peru) challenges might be considered (e.g. oral provocation with nickel (Fig. 13.6).

Patch Test Procedure

Potential causes of ACD and the materials to which individuals are exposed should be patch tested (sensitivity and specificity between 70 and 80 %). Approximately 25 chemicals appear to be responsible for as many as one-half of all cases of ACD. Based on the principles of evidence-based medicine, patch testing is cost effective only if patients are selected on the basis of a clear-cut clinical suspicion of contact allergy

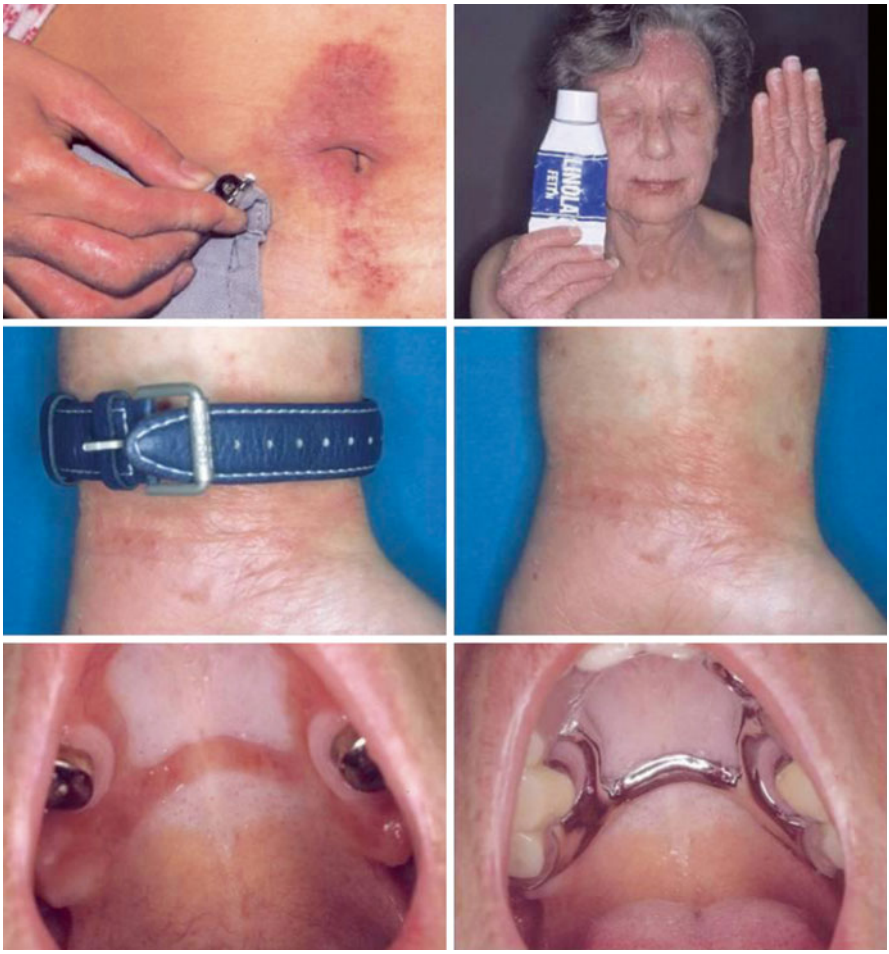

Fig. 13.4 Examples of allergic contact dermatitis in different areas of the body

and only if patients are tested with chemicals relevant to the problem. Frequent allergens in children and adolescents include nickel (and cobalt), fragrance mix, rubber chemicals, PPD (paraphenylenediamine) and thiomersal (due to presence in vaccines, usually irrelevant). Tables 13.1a and 13.1b presents the important contact and occupational contact allergens.

The Finn Chamber was designed in the 1970s; this is the standard method for patch testing individuals to chemicals (Fig. 13.7) not found in the thin-layer rapid use epicutaneous (TRUE) test, which became available in the US in the 1990s. Patch testing must be performed by healthcare providers trained in the proper technique. Patch test screening series, which will pick up approximately 80 % of allergens, varies from country to country.

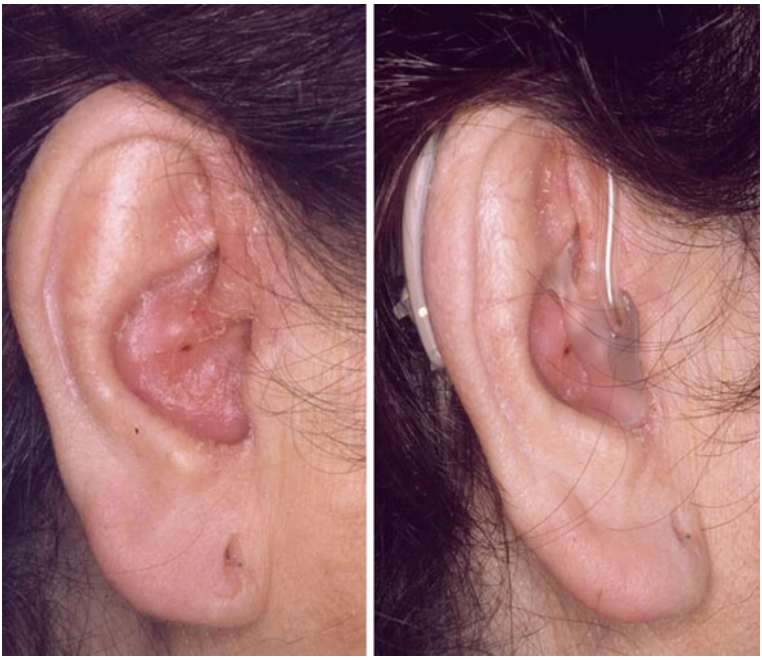

Fig. 13.5 Allergic contact dermatitis to acrylics in hearing aid

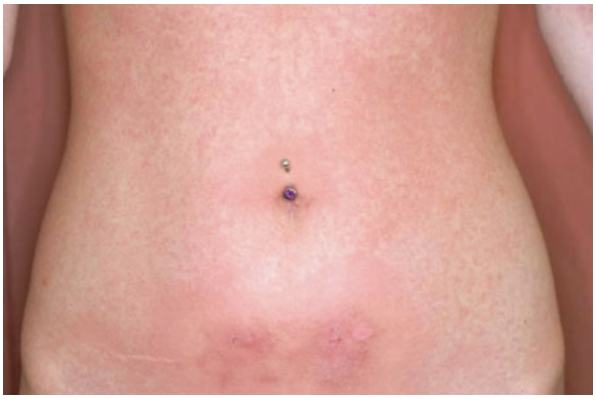

Fig. 13.6 Positive double-blind oral provocation test with nickel

The proper concentration of each chemical should be used. This usually means undiluted substances for leave-on products and dilutions for wash-off products. Hairy areas should be shaved and the areas should be cleaned with plain water. Occlusion of the patch tests is usually for 48 h and the reading after removing (according labelling) but again at least after 72 h. Additional reading after 96 h and sometimes also later (e.g. for corticosteroids, neomycin) may be recommended.

Table 13.1a Important contact allergens and some of their sources

Nickel sulphate (jewellery, zips, paper clips, coins, keys, metal industry, food)
Cobalt chloride (inks, varnishes, enamels, fertilizers, feed additives, humidity indicators)
Chromate (tanned leather, cement)
Rubber accelerators or antioxidants (gloves, shoes, waistband)
Cosmetic ingredients, preservatives, fragrances (make-up, perfume, soaps, shampoos, nail products, sunscreens, moisturizers, cleansers, hair dyes)
Colophony (coniferous tree resin, string wax, adhesives, mascara)
Plants, wood (families: *Toxicodendron*, Primulaceae, *Chrysanthemum*, *Liliaceae*)
Topical medications (iatrogen topical treatment: creams, adhesive patches, eye drops, suppositories)

Table 13.1b Important occupational contact allergens

Rubber chemicals in protective gloves
Epoxy resins in surface coatings or glues
Hair dressing chemicals
Chromate, nickel
Fragrances
Coconut diethanolamide
Colophony/rosin (adhesives)
Acrylates (denture making)
Preservatives (metal working fluids, glues)

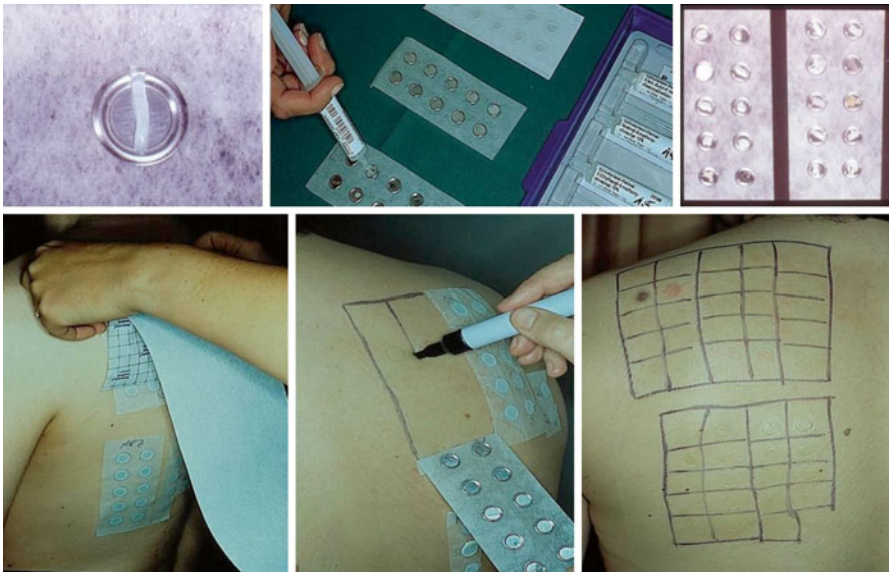

Fig. 13.7 Patch test procedure using Finn Chambers

A positive patch test shows up as a miniature eczema during the following few days. Interpretation should be performed according to standardized International Contact Dermatitis Research Group (ICDRG) criteria (Table 13.2). A "crescendo" or "plateau" reaction is more likely associated with an allergic reaction whereas a "decrescendo" reaction points to an irritant reaction. The relevance of each reaction should be assessed and recorded as present, past or unexplained.

The routine patch test was supplemented with a SLS (sodium lauryl sulphate) patch test to identify increased irritability. This allows interpretation of doubtful (erythematous) or even positive (erythematous and infiltrated) patch test reactions to certain allergens, which are at the same time marginal irritants when patch tested. Irritability might also imply increased susceptibility to contact allergy. Another possibility to clarify doubtful cases is a repeated open application test (ROAT).

Repeat Open Application Test

ROAT is most useful when a 1+ reaction to a chemical is found (e.g. in a leave-on product) to determine whether the reaction is significant. The chemical is applied twice a day for a week, for example, to the antecubital space of the upper arm. If the individual develops dermatitis following a few days of repeated application of the suspected product, the weak patch test reaction is relevant.

Angry Back or Excited Skin Syndrome

If a large number of positive patch test reactions to unrelated allergens (more than five) occur (Fig. 13.8), retesting the patient sequentially to a small series of these allergens may be necessary to exclude non-specific false-positive reactions. Angry back is most likely in individuals who have active dermatitis or who have a strong positive patch test reaction, both of which may induce local skin hyperreactivity.

Table 13.2 Interpretation of patch test results according to ICDRG criteria

–	Negative reaction
(+) or ?	Doubtful reaction (faint homogenous erythema, no infiltration)
+	Weak positive reaction (erythema, mild infiltration, papules)
++	Strong positive reaction (erythema, infiltration, papules, vesicles)
+++	Extreme positive reaction (coalescing vesicles, bullous reaction)
IR	Irritant reaction (discrete patchy erythema without infiltration)
NT	Not tested
Photopatch tests are graded similarly by just adding the prefix Ph	

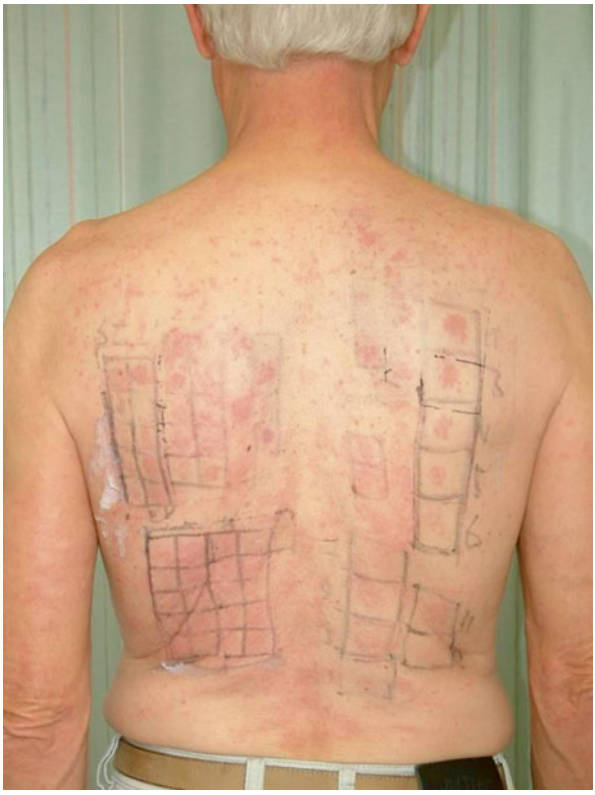

Fig. 13.8 Angry back syndrome

Pitfalls

False-positive reactions occur if irritant allergen concentrations are used or in angry back syndrome. Table 13.3 presents the causes for false-negative reactions. In ACD of the eyelid, tapping of the skin may be needed to get positive patch test reactions. Table 13.4 lists the adverse reactions of patch testing. Contact with allergens via the patch test rarely induces contact allergy, the risk depending on the type and dose of the allergen. Active sensitization is defined as a negative patch test followed by a flare-up of this initial negative test reaction after 10–20 days and then a positive patch test reaction when retested already observed after 2 or 3 days.

The patch test is not capable to predict the development of ACD and is not recommended in the diagnosis of unspecific symptoms that do not involve the skin. Unnecessary repetition of patch testing should be clearly avoided.

In contrast to Europe, in the USA sensitization to urushiol in poison ivy is very common (50–80 %). An individual who never has been sensitized to poison ivy may develop only a mild dermatitis 2 weeks following the initial exposure but typically develops severe dermatitis within 1–2 days of the second and subsequent exposures.

Table 13.3 Causes for false-negative patch test reactions

Low allergen concentration
Topical or systemic concomitant therapy: glucocorticoids, calcineurin inhibitors, immunosuppressives
Recent ultraviolet radiation
Immunocompromised patients
Inappropriate allergen choice
Testing with cosmetic products
Variability of individual threshold reactivity
Improper testing techniques: inappropriate vehicle, poor contact of the allergen to the skin, failure to perform delayed readings (important in elderly patients and in testing of neomycin, corticosteroids, PPD, cobalt)
Missing cofactors: sweating, disrupted skin, UVA

Table 13.4 Adverse reactions of patch tests

Irritation on the back from the presence of the patches
Hyper- or hypopigmentation
Excessive reaction
Persistence of reaction (e.g. to gold chloride)
Exacerbation of ACD in some cases (pointing to relevance)
Risk of sensitization (potent sensitizers: e.g. PPD, plant oleoresins)
Delayed reactions (after 2–3 weeks) point to the development of sensitization

The hallmark of the diagnosis of poison ivy is linear skin lesions. Patch testing is not recommended due to the strong sensitization potential. The presence of small amounts of urushiol in mango and cashew nut should be considered.

Management

Accurate diagnosis of the type of ACD and the eliciting factors are the key to proper management. Strict avoidance of the offending allergen(s) is the treatment of choice. However, detection and avoidance of the allergen is often easier said than done.

Evidence-based medicine data for treatment showed good- and fair-quality evidence for potent or moderately potent topical steroids. Other treatments are not evidence based but commonly used such as symptomatic treatment with cool compresses with saline. Tanning agents are helpful for acute vesicular dermatitis and emollients, in chronic lichenified dermatitis. Oral H1-antihistamines may help diminish pruritus. Patients should avoid using topical antihistamines, including topical doxepin, because of the apparently high risk of iatrogenic ACD to these agents.

Acute severe ACD (e.g. to poison ivy) often needs to be treated with a 2-week course of systemic corticosteroids. Most adults require an initial dose of 40–60 mg. The oral

corticosteroid is tapered over a 2-week period, but a complicated tapering regimen probably is not necessary given the short duration of systemic corticosteroids.

Topical calcineurin inhibitors/immunomodulators are approved for atopic dermatitis and may be prescribed for cases of ACD when they offer safety advantages over topical corticosteroids (e.g. avoidance of cutaneous atrophy). Pimecrolimus is a topical treatment often helpful for ACD of the face. Tacrolimus appears to be the most helpful topical immunomodulator for ACD of the hands.

Chronic ACD that is not controlled well by topical corticosteroids may benefit from psoralen plus ultraviolet A (PUVA) treatments.

Recent evidence-based medicine data regarding prevention of ACD demonstrated fair-quality evidence for the topical skin protectant and quaternium-18-bentonite to prevent rhus dermatitis and for diethylenetriaminepentaacetic acid to prevent nickel, chrome and copper dermatitis.

In occupational ACD, barrier creams use should not be overpromoted, because they may confer a false sense of security. After-work emollients should be encouraged and made readily available in the workplace.

In proven systemic ACD to food ingredients (e.g. to nickel or balsam of Peru), restricted diets are recommended.

Patch test results, their relevance and potential cross-reactive allergens should be explained in detail to the patient. An allergy pass and information sheet (e.g. lists of alternatives) should be given (see www.contactderm.org: contact allergen replacement database). Susceptible individuals prone to ICD need career advice.

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Chapter 14
Pediatric Asthma

Sixto F. Guiang

Introduction

Distinctive Features of Pediatric Asthma Not Seen in Adult Asthma

The pediatric patient is not a miniature adult, so goes the old teaching. The pediatric patient is a constantly changing patient. There are ever-changing landmarks of growth and development, all of which may be of minor significance in the adult patient, but significant in a growing patient. There is also the matter of medical intervention causing alterations in growth and development, altered in the course of treatment as a result of the effect of drugs used to control the patient's asthma or the effect of the disease itself. Then there is the involvement of a third party caretaker whose cooperation, training, and ability to understand the clinician's instructions may be pivotal in the success or failure of any therapeutic regimen no matter how well intentioned.

There are certain areas of uniqueness in pediatric asthma that makes it worthwhile to allocate a few pages in pediatric asthma.

First, the highest incidence of the disease occurs in children and the recently described rise in incidence has occurred in children. Second, a delay in the diagnosis and thus a delay in the initiation of treatment can have far-reaching consequences. Third, permanent changes of remodeling can occur even at an early age. There are also some unique albeit subtle characteristics in pediatric asthma hyperresponsiveness. These would be defined by the drug concentration needed to significantly decrease airway function, a hallmark of asthma in all age groups. This hyperresponsiveness seems heightened in infants and children, although it decreases

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with further maturation. In fact, a heightened degree of hyperresponsiveness has been described even in normal infants.

A question often asked is what is the link between pediatric asthma and adult asthma? What are the characteristics in the pediatric asthmatic that would alert one to monitor even more closely a pediatric asthma patient who is more likely to progress to persistent asthma in adulthood?

Several general observations can be made in this regard: First, severe asthma in early life is associated with significantly higher incidence of allergic rhinitis at age 35 years of age. Second, having a history of atopic dermatitis in early life is significantly associated with persistent wheezing at age 29–32 years old. Third, among children who wheezed during the first year of life, low lung function is a significant predictor of subsequent wheezing. Stated differently, children with moderate symptoms have moderate symptoms as adult. Children with severe symptoms have severe symptoms as adults. Generally speaking 75 % of persistent wheezers in children can be predicted to have persistent wheezing by 35 years of age. Children who have recurrent episodes of airway obstruction during early years of life as a consequence of viral respiratory infections as in respiratory syncytial virus (RSV) infections but who do not become sensitized to local aeroallergens are highly likely to remit in their airway symptoms by early adolescent years. However, these same patients are highly likely to have recurrences of their asthma symptoms if they should start smoking even if they have been in remission for an extended period of time. Those early wheezers who eventually become atopic are at risk for developing persistent asthma. Transient wheezers do not wheeze as adolescents or adults. However, if they become atopic, they are at increased risk of having mild persistent asthma as adults. Persistent asthma in childhood continues to maintain reduced airway function as adults and, if inflammation persists, may end up having severe asthma in adulthood.

Epidemiology of Pediatric Asthma

About five million youngsters under 18 years of age in the USA have asthma. This figure includes 825,000 children under 5 years of age. Each year children with asthma miss 1.4 million school days, three times the school absences of children without asthma. Asthma interferes with school sporting events, school trips, and play activities. Asthma accounts for 3,537,000 doctor visits for children under 15 years of age, 658,000 emergency room (ER) visits for wheezing under 15 years of age, and over 8.7 million prescriptions for children under 15 years of age.

The cost for asthma care for the average patient with asthma also rises as a result of time lost from work for parents and caregivers. Worldwide, the incidence of asthma has risen particularly in the pediatric age group.

Because asthma is the leading cause of school absences, time lost over an extended period of time ultimately reflects on the overall performance of the student during their formative years and in the end the asthmatics' role and contribution to society as an adult.

Asthma in the Preschool Age

By definition, asthma is a "chronic inflammatory disease characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Additionally, there is widespread but variable air flow obstruction." Strunk points out in defining asthma in the preschooler that the difficulty with this definition is that a number of other respiratory conditions meet some of these features and yet may not be asthma. Not all that wheezes is asthma, so goes an old teaching. In arriving at a diagnosis in this age group, it has been suggested that one starts with a concept that asthma belongs to a group of conditions exhibiting hyperactive airways (also meaning responding to medications like albuterol). There is no specific test for asthma. Rather, one goes through a series of elimination processes until the diagnosis is arrived at. To this end are three necessary ingredients in the process, namely, a chest X-ray, sweat test to rule our cystic fibrosis, and allergy skin tests to determine sensitization to offending aeroallergens or food antigens. A barium swallow under fluoroscopy is desirable to rule out structural abnormalities of the mediastinum and/or cardiovascular abnormalities as in the vascular ring, all of which may produce the same symptoms. A sweat test, the second part of a cost-effective assessment, is deemed necessary in spite of the much lower incidence of this disease because there are a number of clinical features shared by both conditions. Then of course there is always the possibility of the youngster suffering from both conditions.

With regard to skin testing, the question that always arises both from the clinicians' and parent's perspective is, how early does one justify skin testing? Skin testing can be performed at any age when the clinical history especially the family history warrants it or when history suggests the possibility of sensitization to an aeroallergen or food allergens. Certainly we are all aware that atopic dermatitis is the first leg of the atopic march and would make skin testing an even more reasonable option. At the minimum, skin test for dust mites, cockroach, and in inner city patients even mouse antigen would be reasonable. The most common food allergens include milk, egg, wheat, peanut, tree nuts, soy, fish, and sesame seed. Pollen allergy appears to herald allergic rhinitis rather than asthma, while sensitization to dust mite may antedate asthma. When the history of food allergy suggests a frightening reaction to a particular food, it is good practice to resort to in vitro testing for that suspected food, as a skin test by itself can have the potential for a violent systemic reaction. Anaphylaxis from peanut allergy comes under this category. In a typical office setting, a patient is generally brought to the office because of "allergies" manifested by persistent cough/interspaced with wheezing, nasal stuffiness, and presence or absence of fever. There may be a history of prior spitting up or a "choking spell" after ingestion of a suspected food allergen, unresponsive to repeated courses of antibiotics.

In some cases the diagnosis of asthma had already been arrived at because a sibling has asthma or because there is a strong history of asthma in the family. In this scenario, three conditions immediately come to mind. First is the possibility of asthma, second the possibility of chronic sinus disease, and third the possibility of

aspiration or a foreign body in the lower respiratory tract. Sinus disease in the preschooler may present itself as a persistent cough. Although wheezing may be reported, cough is more often than not the presenting symptom. Invariably previous caregivers had given a course of antibiotics, and the parents would more often report a transitory response only to end up in a relapse a few days later. This bit of information in the history can be a valuable clue for the presence of sinus infection (a temporary relief of symptoms followed by a relapse or a concomitant sinus disease may be the reason for poorly controlled asthma). Sinus disease is generally poorly responsive to bronchodilator therapy or even steroids and often seen by caregivers as exacerbated by upper respiratory infections (URI). The presence of nasal polyps at any age in the pediatric population makes a sweat test mandatory. Aspiration may be suggested by a history of a frequent practice of "propping the bottle during feedings, a history of choking spells following food, and the unwise practice of offering nuts or popcorn to toddlers less than 4 years of age. Response to medication may be similar to asthma. If one inquires further about stains of vomited material in the beddings especially after heavy meals (picnics, parties, birthday parties in particular where birthday cakes are often laced with various nuts of various sizes), foreign body in the lower respiratory tract enters the differential diagnosis. A chest fluoroscopy is always an essential part of a workup when foreign body is under consideration since a simple chest radiograph may miss a foreign especially if it was very recent episode.

Asthma usually presents exacerbations following viral respiratory illness, exposure to irritants and pollution, and tobacco smoke and will show dramatic response to steroids, inhaled corticosteroids (ICS), and bronchodilators. All causes of reactive airway disease need to be considered and these include (1) food-induced asthma, (2) bronchopulmonary dysphasia, (3) cystic fibrosis, (4) anatomic abnormalities in the mediastinum (vascular rings), (5) congestive heart failure, (6) bronchiolitis, and (7) pertussis. Just a word about the first episode of bronchiolitis occurring for the first time in any infant. Here, bronchiolitis is clinically indistinguishable from bronchial asthma. There are laboratory studies designed to identify viral antigens to pinpoint any of the six different viruses that can cause acute bronchiolitis. The clinical picture of pertussis may not be typical because of the attenuation of the disease by previous immunizations, but the presence of leukocytosis with preponderance of the lymphocytic series may provide the clue.

Natural History of Childhood Asthma

There are risk factors in the development of asthma. First, among them is that (1) males have a higher incidence of asthma but the female sex has a higher deficit in pulmonary function. (2) Atopic status is strongly associated with attacks of wheezing and dyspnea. Children with atopic dermatitis (after all, this is the first lag of the atopic march) or elevation of total serum IgE are strongly associated with the increased prevalence of asthma. (3) A potential genetic component appears likely in

the face of the old time observation that asthma tends to cluster in families. (4) History of viral infections especially respiratory syncytial virus (RSV), although other viruses may produce the clinical picture of bronchiolitis, especially those hospitalized for bronchiolitis, has been shown to have reduced pulmonary functions, a feature which appears to be a predictor of bronchial hyperreactivity. (5) Outdoor air pollution. It has been shown that oxidant pollution such as nitrogen dioxide and ozone may enhance the effects of aeroallergens by increasing airway permeability. (6) Indoor pollution such as increased levels of house dust mite exposure may affect the incidence of asthma and wheezing. (7) Maternal cigarette smoking definitely increases the risk both for the onset or exacerbation of asthma. (8) A recent study investigating genetic polymorphisms among Chinese preschool-age and school-age children found a higher frequency of the RANTES-28G allele among children with near-fatal asthma compared with children with mild to moderate asthma.

Will My Child Outgrow His/Her Asthma?

This is a question often asked. Current figures show that 50 % of adults who report having had childhood asthma no longer have symptoms. Airway responsiveness in childhood tends to predict airway responsiveness in adulthood.

Diagnosis of Asthma in the Older Child or Adolescent

The first step in arriving at a diagnosis of asthma, like any other medical condition, is a detailed history. What are the symptoms of concern to the parent or caregiver? When do they occur? Are they repetitive? When they have been in progress for a number of months, it helps to know if a seasonal variation exists. One favorite method in getting an accurate idea of the seasonality of asthma symptoms in any given patient is to refer to the holidays as landmarks (since most parents often do not remember the exact dates asthma exacerbations occur). How was the patient on New Year's Day? On Valentine's Day? On April fools? On Labor Day? On Memorial Day? On the fourth of July? On school opening day? After the first frost? On Thanksgiving? Christmas Day and New Year's Day? By using these holidays as benchmarks for dates, a more accurate idea of approximate dates of wellness or exacerbations can be obtained. The caregiver's assessment of the severity of the patient's problem can be obtained by asking him or her to give a "grade." Give him/her a grade on how well you think he/she is, 10 being the best and 1 or 2 the poorest or 5 in-between. This allows one to gauge the caregiver's ability to judge the patients wellness state. It is necessary to ask how often the patient has symptoms, how much he has restricted in play/or sports activities, and how much school he misses over a month or all year since he started. It is important to have a list of medications currently used or previously used. One

reliable source of this (as often the parents or patient has had so many drugs used he has lost tract) is the pharmacy who usually has a computerized list of drugs used in the preceding 6 or 12 months. It is important to know how many canisters of albuterol have been used in the preceding months, whether the patient/caregiver fully understands the difference between the "controller medication" and the "rescue medication," and whether they have been given refillable rescue medication or as on as-needed basis (PRN) or as a nonrefillable item. I stress this point because sooner or later the patient or caregiver finds that the rescue inhaler works immediately and soon the controller medication is neglected and often missed and at times even entirely omitted. The number of visits to the emergency room (ER) is important information as is the number of unscheduled visits to the primary care clinician. There are patients who resort to unconventional or alternative caregivers like a chiropractic care or herbalist or acupuncturist. One sure way to alienate a patient is to speak disparagingly about an alternative care provider that the patient may have already developed a close relationship with. One wants to make certain that the patient is not on any asthmogenic drugs like beta-blockers for migraine prophylaxis or hypertension.

On physical examination, the common stigmas of allergy may already be apparent in an allergic child (as described by Meyers many years ago as the allergic salute, dark circles under the eyes, allergic shiners, Dennie's sign, transverse crease at the dorsum of the nose and adenoid fascie, and the pale nasal mucosa of allergic rhinitis). There may already be a history of several sets of ventilation tubes installed to alleviate middle ear effusion. A tuning fork in the older child may betray the presence of effusion or pneumatic insufflations with a pneumo-otoscope to detect the degree of mobility of the tympanic membranes. One detects pain over the sinus areas (the maxillary sinuses and frontal) by pressure over the areas, and this should include a digital palpation of the roof of the mouth (which when exquisitely tender is a common finding in acute or subacute maxillary sinus disease). The search for concomitant sinus disease can be rewarding in making the differential diagnosis in the preschool child and in looking for clues as to why an asthmatic child remains uncontrolled. Tachypnea may or may not be present along with hyper-expansion of the chest. Widespread wheezing may be noted even on tidal breathing, and when absent one can often be elicited by having the patient forcefully blow a lighted match or pretend to blow a birthday candle on a cake. Pay close attention to examination of the fingernail beds and toenail beds for cyanosis and early evidence of clubbing, hardly ever seen in asthma but when present may suggest another differential diagnosis.

Objective measurements: A pulmonary function test using standard spirometry is the gold standard in establishing the presence of airway obstruction and demonstrating reversibility after a bronchodilator. It is also a desirable measurement for demonstration of airway obstruction following exercise. This parameter, however, is not adaptable to all ages but may be attempted as early as 4–7 years of age. Remember too that giggling, laughing, and crying can be considered the equivalent of exercise in the asthmatic toddler/infant.

Assessing Severity of the Disease Before Initiation of Therapy

Any treatment plan needs to be based on the physician's assessment of the severity of the disease. Reproduced below is the classification of asthma severity, from the National Asthma Expert Asthma Expert Panels (NAEP) guidelines. See Table 14.1.

In children, a recent survey reveals that majority of pediatric asthma patients have mild persistent or mild intermittent asthma symptoms. An important point to remember is that mild persistent asthma in children should not be considered a benign disease as mild persistent asthma in children can have life-threatening exacerbations. Reliance on symptom severity as a guide as to who to treat is often of limited usefulness. This is clearly pointed out in studies showing poor correlation between symptoms and airway obstruction. Furthermore, in one study forced expiratory volume, the first second (FEV1), has been found generally normal in children classified as severe persistent asthma on the basis of symptoms.

A word about exercise-induced asthma (EIA) in children. EIA is often not formally recognized as a diagnosis in children. EIA is discussed in detail elsewhere in this text, but some points regarding EIA in children is appropriate at this time. While premedication with short-acting beta-adrenergic drugs is effective in the management of most EIA, special consideration should be mentioned about EIA in children. There are studies assessing the effect of ICS use in exercised-induced symptoms in mild asthma demonstrating that ICS when used daily (instead of as needed before exercise) can protect against exercise-induced bronchoconstriction in children with near-normal pulmonary function.

Once a determination of the severity of asthma is arrived at, initiation of therapy may be started at the highest dose, and as control is achieved, the dose of the inhaled corticosteroid (ICS) selected can then be gradually titrated to the least amount of the drug to achieve control. In some instances, a short pulse of oral corticosteroid (OCS) may be justified to tide over the patient at his worst.

Table 14.1 Classification of asthma severity in children 5–11 years of age

Severity	Symptoms	Nighttime awakening	Using short-acting beta-2 agonist	Lung function
Severe persistent	All day	7 × week	Several times a day	FEV1 <60 % predicted
				FEV1/FVC <75 %
Moderate persistent	Daily	>1/week but not every night	Daily	FEV1 = 60–80 % predicted
				FEV1/FVC = 75–80 %
Mild persistent	>2 days/ weeks not daily	3–4 × a month	> Days a week not daily	FEV1= >80 % predicted
				FEV1/FVC >80 %
Intermittent	≤2 days a week	≤2 × a month	≤2 days a week	Normal FEV1 between exacerbation; FEV1 >80 % predicted; FEV1/FVC >85 %

Goals of Treatment

Total control is possible in 40 % of cases. It is possible to achieve well-controlled asthma in 80 % of patients. To achieve total control or good control however requires sustained treatment. When goals are not achieved in spite of maximum dose of ICS, an "add-on drug" (combination therapy) may be in order. Combination therapy may result in lowered doses of ICS. The goals of treatment include the following: (1) prevention of chronic and troublesome symptoms, (2) maintaining normal activity levels, (3) providing optimal pharmacotherapy with minimal adverse effects, and (4) meeting the patients and/ or his family's expectations. From the expert panel guidelines, the definition of a well-controlled asthma includes (1) asthma symptoms twice a week or less; (2) use of rescue medication twice a week or less; (3) no nighttime or early morning awakenings; (4) no limitation of activity at school, home, or place of work; and (5) asthma that is well controlled from the assessment of patient, family, and caregiver.

The addition of newly approved drugs may be a consideration in patients who are already using the maximum doses on ICS or ICS with long-acting beta-adrenergic drugs (LABA) or patients requiring oral corticosteroids (OCS). Coexisting sinus disease or gastroesophageal reflux disease (GERD) should also be ruled out in such cases. When severe symptoms are associated with infiltrates and high levels of serum IgE, bronchopulmonary aspergillosis enters the differential diagnosis. Details on the nature of this complication are discussed elsewhere in this text.

Managing Bronchial Asthma in Children

Managing the child with asthma as outlined in the *Guide for managing asthma in children* covers four components. The first component entails assessment and monitoring.

History is paramount in the assessment of the asthmatic child. One needs to obtain information about nighttime and morning symptoms, school absences, and whether the patient is able to keep up with his peers in play or sports. Older children may report "not feeling well" a good part of the time. In general, information about the youngster's performance in school and whether or not he limits his participation in sports and play, tailored to what degree his asthma allows him to do, are of value in assessing the patient's status.

In the older child capable of performing spirometry, periodic assessment is recommended. Spirometry should be done on the initial visit and after treatment. It will also serve to establish when normal or near-normal pulmonary function has been attained. Performing a spirometry every year thereafter assures the clinician that a normal or near-normal pulmonary function test (PFT) has been maintained or restored following modifications of any regimen.

Every child if old enough or his parent or caregiver should be able to recognize through adequacy of symptom control. Based on preconceived perceptions on what is acceptable control, previously agreed upon modifications in medication can be added or modified and/or when the clinician should be consulted.

The second component in the management of asthma in children addresses *Controlling factors contributing to severity*. For viral upper respiratory infections, utilizing currently available vaccines like the flu vaccine and reducing exposure to infections is desirable. The preschool nursery is a common conduit for these respiratory infections. Utilization of these facilities should be thoroughly weighed as to its practicality to any individual family and above all affordability, which varies from one family to another.

Tobacco smoke is certainly a completely avoidable irritant, and most parents when told that smoking cessation is really something they are doing not just for themselves but principally for their love ones invariably are more than willing to make the necessary changes in their lifestyles. Woodstoves are likewise avoidable.

Dust mite antigens are present in every home in the country, and while eliminating this antigen completely is an impossible task, dust control measures significantly contribute to the well-being of the dust mite-sensitive patient. Dust mites dwell where food for them is abundant. Human dander being the source of food for mites, mites understandably are mostly found in pillows, mattresses, and box springs. Of equal importance is the need to lower the humidity in the home to below 50 %. Parents need to know that high humidity is conducive to enhanced mite growth. In parts of the country often experiencing freezing weathers, it might be a worthwhile effort to have the mattresses, box springs, and pillows taken outdoors overnight as freezing weather significantly reduces the mite population. Often overlooked is the need to use a mattress cover, box spring covers, and pillow covers in other beds other than the patient's where the patient shares the room with someone else, usually the parents.

In inner city dwellings, cockroach antigen and mouse antigens can be an important part of the environmental milieu. Cockroaches thrive best when garbage and food leftovers are left exposed. The use of boric acid traps allows one to avoid using poisons as this method adds another hazard for accidental ingestions. For mold allergens, attentions can be directed to leaky faucets and wet areas. As in dust mite avoidance, reducing humidity to less than 50 % can minimize mold exposure.

For patients sensitized to pollens, confinement in air-conditioned rooms is undoubtedly the best barrier to pollen exposure but is not practical. In areas where clothesline drying of laundry is commonly practiced, the moist laundry allowed to dry on a clothesline collects pollens, bringing into the home quantities of pollen where it is recirculated for an indefinite period. The hair collects pollens so a typical pollen allergic patient may bring in a bagful of pollens to bed. So asking patients to wash their hair at night instead of in the morning can be helpful. In patients with coexisting allergic conjunctivitis, contact lenses are a drawback. Pollen grains can potentially be trapped underneath these lenses creating an ever-present reservoir of antigens. On the contrary, eyeglasses act as a windshield and thus theoretically block the entry of allergen directly to the eyes.

As you can imagine, all these measures cost money to implement and perhaps the greatest obstacle to all the above is *Poverty*. And the greatest number of poorly controlled asthma in children is found in poverty-stricken areas.

The third component in managing asthma in children is *Pharmacologic theraphy*. Attention has been called earlier for the need to assess the severity of the child's asthma before embarking on treatment (Table 14.1).

There are two approaches to the pharmacologic management of asthma in children. The one that is preferred by most practitioners is an aggressive approach where one attempts to control symptoms as rapidly as possible by using a dose higher than the perceived requirement for any given level of severity. This is usually accomplished by adding short burst of oral corticosteroid (usually prednisone or prednisolone) for a 3–10-day period added to the selected ICS. As soon as control is achieved, the dose is then titrated to a level that will maintain control.

The alternative approach is to select a dose level appropriate for the perceived severity of the condition as outlined in Table 14.1, gradually titrating the dose upward until the desired level of control has achieved. Elsewhere in this text are the various preparations currently available for use in children in the USA. The use of inhaled corticosteroids remains the gold standard for the treatment of chronic persistent asthma. In making the selection from the various preparations available, the following considerations are worth mentioning:

1. All currently available inhaled corticosteroids (ICS) are efficacious.
2. The safety profile of ICS is clearly superior to oral corticosteroids (OCS).
3. The currently available ICS are beclomethasone dipropionate, budesonide, flunisolide, fluticasone, triamcinolone, and mometasone.
4. Fluticasone is minimally suppressive even in high doses but is very cortisol suppressive when administered by metered-dose inhaler (MDI).
5. One study determined that a 10 % cortisol suppressive effect was produced by:
   (a) 936 ug for flunisolide (47 % of highest recommended dose via chlorofluorocarbon (CFC) MDI
   (b) 787 ug of triamcinolone (49 % of highest recommended dose via MDI)
   (c) 548 ug of beclomethasone dipropionate (65 % of highest recommended dose via CFC MDI
   (d) 445 ug (22 % of highest recommended dose) of fluticasone dipropionate via dry powder inhaler
   (e) 268 ug of budesonide (17 % of highest recommended dose via dry powder inhaler)
   (f) 111 ug of flunisolide (6 % of highest recommended dose) via a CFC MDI

These figures suggest that flunisolide delivered via a CFC MDI, fluticasone via dry powder inhaler, and budesonide via dry powder inhaler have a relatively wide margin of safety with regard to cortical suppression if administered with the recommended dosing limits.

Asthma is a condition associated with significant morbidity and mortality. The benefits of ICS in this disease have been well established over the years, and the all

too familiar side effects should not deter anyone from using these drugs. The adverse effects can be minimized by using the least amount of the drug to bring about the desired result, as undesirable side effects tend to increase with increasing doses. There comes a time when further increasing the dose, the desired effects plateau and further increases produce no further improvement in symptom scores and objective measurements. This would make the ideal time to introduce currently available non-steroidal drugs to the regimen. This includes the long-acting beta agonists (LABA), the leukotriene antagonists (LKTR), and theophylline. When theophylline is added as a steroid-sparing drug, serum levels not to exceed 5 mcg/ml would be preferred.

The fourth component in the management of asthma in children is patient education. There are important steps to forming a partnership with the patient and his family and or/caregivers. This can be achieved by providing clear and easily understandable written information to all relevant caregivers including older children, parents, caregivers, day care providers, teachers, coaches, scout leaders, camp counselors, and school and camp nurses.

Written instructions can be given at each visit, allowing ample time for people to study and understand implications of all information. It may be helpful to provide patients and caregivers who have access to the WEB, website addresses like those of the American Academy of Allergy, Asthma, and Immunology or the American College of Allergy, Asthma, and Immunology or similar organization websites where appropriate printed information are available.

Even medically trained individuals can absorb only so much information during any given time, so it is always good practice to offer information a little bit at a time as a short discussion at each subsequent visit. Provide information in a way that is easily understood and accepted, respecting cultural differences among patients at all times. *All of these can easily be delegated to trained personal in the clinicians' offices given the proper training*.

Patient Education

The fourth component in the management of asthma in children is patient education. The asthmatic patient should learn more and more about asthma like the diabetic patient learns more and more about diabetes. The patient must learn the nature of the drugs being taken and the reasons for its use. Such patients should be made familiar with the modes of delivery of each inhaled drug. When a patient fully understands reasons for any advice given, he/she is more likely to be receptive to his/her doctor's recommendations.

I have purposely omitted peak flow monitoring as part of the patient's educational program because I have found it to produce or magnify my instructions even more.

I have devised a plan where the patient's caregiver should keep track of whether the patient is symptomatic or not. Complete cessation of all symptoms of coughing or wheezing remains the main goal of therapy.

I have experienced a lot of delay resulting from denial of insurance coverage for drugs. The insurance coverage of any given patient which specifies specific drugs often causes so much delay that I have preferred to inquire what particular drugs any given patient's insurance covers. That way I do not lose valuable time communicating with insurance companies whether a patient's preferred drugs for asthma appear in the formulary of any given company.

I think that most physicians will agree that no particular inhaled steroid preparation is more efficacious than other brands in the same drug category.

I put particular emphasis on the delivery system used. I make certain that the patient returns to show me that he is capable of using the drug appropriately.

As a general rule, all infants need to have an electric nebulizer for delivery of maintenance controller drugs and inhaled rescue medication. For patients 4 years and older, they may be taught to use an inhaler delivered with an aerochamber. Even then, I always require that the patient uses the inhaler appropriately by demonstrating to my satisfaction that an aerochamber is used properly.

More importantly, every patient and/or his mikucaregiver should know the purpose of a "controller" medication as the word implies and the use of a "rescue" medication.

I have found through particularly among teenagers that because they experience immediate relief of symptoms with the rescue medication, there is always a tendency for them to use the rescue medication at the expense of omitting the controller medication. This leads to a worsening condition because the use of the controller medication has been omitted from the patient's regimen.

In this regard, I make it a point that rescue medications are refillable no more often than one unit per month.

It is obvious that when a patient calls for rescue medication refills more often than once a month, that patient can be presumed to be omitting the use of his controller medication.

I always ask a patient: "What is it you want to do at home or at school that you cannot do?" Regardless of how he answers this question, I get a general idea of how good or adequate the control of his asthma can be.

When Is Immunotherapy as a Part of the Treatment Plan an Option?

Immunotherapy (IMT) as a treatment option dates back to the early 1900s. Most clinicians prefer to wait until a patient is at least 5 years old before immunotherapy is given serious consideration. This seems primarily from the overall "fear of shots" in all age groups. However, when there is a distinct cause-and-effect relationship between an antigen identified either in vitro or in vivo, and when undesirable side effects have been experienced with conventional therapy, immunotherapy certainly is a viable option.

In a family violently opposed to getting rid of a cat is one instance. Cat antigen immunotherapy has been demonstrated to be efficacious. A number of studies have also repeatedly shown similar effects with dust mite immunotherapy. In some

instances, IMT has allowed clinicians to successfully eliminate medication. In others, clinicians have been able to reduce the doses of controller medication used. There is data to suggest that immunotherapy in the dust mite (DM)-sensitized patients appears to prevent the development of new sensitivities. Lesser established is the role of pollen immunotherapy in bronchial asthma. Immunotherapy (IMT) for allergic rhinoconjunctivitis has had a favorable effect on bronchial asthma. In the final analysis, the decision is dictated by the families' expressed desires. The mechanism underlying amelioration of symptoms following IMT has been established and described elsewhere in this text.

When Does Referral to an Asthma Specialist Become Desirable?

1. When the asthma is severe by definition, the following define severe asthma:
   (a) Treatment with continuous or near continuous OCS (>50 % of the year)
   (b) Requirement of high-dose ICS to achieve control of mild to moderate persistent asthma

   The above in association with two of the minor criteria listed below:
2. When the goals of treatment are not being met after three to 6 months of treatment, earlier if the child appears unresponsive to treatment
3. When signs and symptoms are atypical or there are problems in the differential diagnosis
4. When there are other comorbid conditions (sinusitis, allergic rhinoconjunctivitis)
5. When additional diagnostic testing is deemed necessary as (pulmonary function tests (PFT), skin testing, immunodeficiency workup)
6. When immunotherapy as part of the contemplated treatment is an option
7. When the child is below 3 years of age and has severe persistent asthma

Evidence-Based Medicine

Is there a link between atopic disease and cardiovascular risk factors in US children?

Dr. Jonathan Silverberg at the Northwestern University Eczema Center seems to think so and definitely calls for future studies using clinical examination, objective measures of adiposity, and metabolic syndromes.

In a letter to the editor appearing in the December 15, 2015 issue of JACI, he outlines the following observations: (1) Pediatric allergic disease was found to be associated with increased odds of obesity, hypertension, and hyperlipidemia. (2) In a multicenter study of 132 children with moderate to severe atopic dermatitis and

143 age-matched healthy controlled, which found higher overall systolic and diastolic blood pressures and increased odds of systolic blood pressure (greater than 90 %) in moderate-severe atopic disease. (3) The lack of association between atopic disease and diabetes may be related to reduce power owing to the relative rarity of childhood diabetes and/or heterogeneity from type 1 and 2 diabetes.

He believes that the case definitions for allergic disease are sufficiently valid for epidemiological study.

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Chapter 15
Adult Asthma

Daniel E. Maddox

Introduction

The adult population presents a different set of challenges than is seen in the pediatric asthmatic patient. Special considerations in adult asthmatic patients include numerous potential medical comorbidities, medication conflicts, and complex differential diagnoses.

The concept of asthma as a disorder involving airway inflammation is now well established, and many scientists working in the field regard the earliest pathological changes leading to clinical asthma as involving inflammatory mechanisms, which initially create a state of airway hyperresponsiveness. Although there is heterogeneity in its presentation, the asthma phenotype is well defined and can usually be diagnosed without excessive difficulty. The goal of appropriate diagnosis and treatment is, of course, to normalize and maintain the quality of life for patients with asthma, including social and occupational considerations. Given the extensive current deficiencies in our understanding of the various pathophysiologic perturbations, it is perhaps no surprise that asthma remains a considerable cause of morbidity and, in some instances, even mortality.

The primary goals of this chapter will be to address basic diagnostic considerations (including differential diagnosis), classification of severity, and treatment of the adult asthmatic patient. A brief discussion regarding asthma pathogenesis will also be included, although a detailed review of asthma pathogenesis is beyond the scope of this chapter.

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Definition

Asthma is best thought of not as a single disorder, but as a term descriptive of a characteristic clinical syndrome, characterized by recurrent cough, wheeze, and shortness of breath. The number of molecular pathologies that eventuate in chronic airway inflammation associated with episodic and at least partially reversible airflow obstruction may be quite large. Each of these molecular pathologies may have characteristic and specific nuances associated with their clinical presentations, and this makes for a potentially diverse spectrum of associated clinical details. Thus, asthma is more a clinical rather than a laboratory diagnosis; it seems likely that only a systems biology approach is likely to ever take us far enough into understanding its molecular pathology to bring its diagnostics into the laboratory realm. It is essential to exclude other potential disease processes that may mimic asthma, thus reinforcing the importance of exploring potential alternative diagnoses.

Epidemiology

An estimated 18.5 million people in the United States suffer from asthma. Roughly two-thirds of these are adults. The prevalence of asthma continues to increase in most industrialized nations [although the dramatic rate of rise seen in the last 80 years has begun to level off], while there has been no change in asthma incidence or prevalence in any of the aboriginal people of the earth [unless they have been touched by Western technology]. Some recent research has raised the question of whether the rising incidence and prevalence of asthma and allergy might be related to distortions in the microbiome that correlate with or are induced by the lifestyle exposures of humans living in Western, industrialized countries. Much more research in this arena will be necessary before this hypothesis can be robustly evaluated, but it remains an intriguing concept. According to US Department of Health and Human Services data, the prevalence increased significantly in all groups measured between 1940 and 2010. In addition to an increase in asthma prevalence, the overall age-adjusted asthma mortality rate appears to be increasing as well. The increase in asthma death rates appears to be higher for some demographic groups than others and is consistently lower for Hispanic groups than any other American demographic, which has underscored the possibility of strong participation in asthma pathogenesis of environmental/nutritional factors, which may reach far beyond simple allergic sensitivities. Similar trends seem to be emergent throughout most industrialized nations. The overall cost of asthma in the United States has recently been estimated at approximately $56 billion annually.

Pathogenesis

The pathogenesis of asthma is incompletely understood. Considering the variable clinical manifestations and the pattern of clustering within families, it seems likely that epigenetic factors play a major role in triggering the syndrome, and it seems increasingly probable that the innate immune system may play a prominent role in asthma susceptibility. That said, the clinical features among asthmatic patients seem to be similar enough to allow us the luxury of some clinically useful generalizations regarding asthma pathogenesis.

Historically, the focus of thought regarding asthma pathogenesis was on airflow obstruction secondary to transient smooth muscle-mediated bronchoconstriction. While this is clearly a component of asthma and is an element of asthma diagnosis, the emphasis has now shifted to the chronic inflammatory nature of the illness. Now, the bronchoconstriction or airway hyperresponsiveness (AHR) is often viewed as a marker of underlying inflammation.

Many different cell types have been implicated in asthma pathogenesis. These include eosinophils, basophils, neutrophils, lymphocytes [T cells and innate lymphoid cells in the bronchial mucosal infiltrate and B cells fostering IgE-mediated allergen responses], platelets, dendritic cells [DCs], pulmonary smooth muscle cells, pulmonary epithelial and pulmonary endothelial cells, and macrophages. In point of fact, almost certainly all of these cell types participate in both the pathogenesis and the pathophysiology of asthma, and the current challenge is to understand the whole network with sufficient insight so as to recognize where the most important nodes are active.

For example, many asthmatic patients tend to develop an eosinophilic infiltration of the airway submucosa. Additionally, the recruitment of TH2-type T cells seems to play a significant role in the initiation and maintenance of this eosinophil-mediated airway inflammation. Variations in T cell responsiveness to corticosteroids may correlate with clinical steroid-resistant asthma. DCs also appear to play a central role in the development of the asthma phenotype, particularly in extrinsic asthma. This is not surprising, considering the role of the dendritic cell in providing a link between innate and adaptive immunity. DCs appear to aid in directing the type of adaptive immune response (TH1 versus TH2). In asthma, a TH2 response [IL-4, IL-5, IL-13] seems to predominate in those cases in which the bronchial submucosa is extensively infiltrated with eosinophils. In allergic asthma, experimental models suggest that the earliest steps in development of the inflammatory infiltrate depend on histamine- and leukotriene-induced changes in adhesion molecule expression in vascular endothelial cells, promoting arrest of circulating leukocytes, and then egress from the vascular space into the bronchial submucosal tissues. In some cases, the bronchial submucosal inflammatory infiltrate is predominantly polymorphonuclear neutrophils, and in these cases TH17 T lymphocytes may be playing a more prominent role than the TH2 T cells. As might be predicted, cases demonstrating this type of histopathology are often much less responsive to corticosteroid therapy.

In general, asthma is considered to be a TH2-type inflammatory condition. Analysis of mRNA transcripts in bronchial T cell infiltrates shows submucosal lymphocyte expression of the cytokines which are usually secreted by TH2-type T cells (IL-4, IL-5, IL-13, and GM-CSF). However, recent studies suggest that there may be a significant role for innate lymphoid cells [these are cells which bear no markers for either T or B cells, but appear capable of secreting large amounts of cytokines in response to local factors, which are presently understood poorly], in addition to traditional T cell types, in the pathogenetic process. Additional mediators of inflammation such as histamine, leukotrienes, neuropeptides, and platelet-activating factor are released by local mast cells, by eosinophils, and possibly by airway epithelial cells. These factors in turn may initiate proinflammatory cascades in the extracellular milieu leading to the formation of vasoactive species such as kallikrein. The release of these inflammatory mediators results in changes favoring both smooth muscle contraction and proliferation, resulting in bronchoconstriction, airway narrowing, and airway glandular hypersecretion. Although a complex array of cytokines, inflammatory mediators, second messengers, and transcription factors have been shown to have significant roles in the development and pathogenesis of asthma, much work is still required to understand the global process as well as the factors that individualize the process in each patient. Ultimately, chronic airway inflammation may lead to irreversible airway narrowing ("remodeling") in a subset of patients, with much of the caliber change attributable to fibroblast proliferation, and it is this response that carries the greatest adverse impact on prognosis.

Also of interest is the question of whether IgE has a direct role to play in asthma. In addition to the role of allergen-specific IgE in allergic asthma, there appears to be a correlation between total IgE level and asthma [at least the type of asthma characterized by eosinophil dominance in the submucosal infiltrate], even in patients without evidence of allergic sensitivity. This may form a rationale for measuring total serum IgE in all asthmatic patients, as part of the basic initial evaluation.

Asthma Diagnosis

As with any illness, an accurate diagnosis is necessary to allow for appropriate treatment. The cornerstone of asthma diagnosis is patient history, supplemented with a limited number of diagnostic studies. It is helpful to remember the working definition of asthma as being a disorder of chronic airway inflammation with associated, intermittent episodes of symptomatic airflow obstruction that is at least partially reversible. These intermittent episodes of airflow obstruction may be manifest by coughing, a sensation of breathlessness, and chest tightness. Symptoms tend to be worse at night and/or associated with specific triggers, such as exercise.

A careful history is necessary to look not only for clues to possible asthma, but more importantly to exclude other diseases that may be causing or contributing to the patient's symptoms. It is essential to ask questions pertaining to potential coronary artery disease, thromboembolic disease (especially pulmonary embolism),

infectious diseases, malignant processes, and other potential pulmonary diseases (Table 15.1).

It is surprisingly common to find multiple systemic and pulmonary processes leading to respiratory symptoms, particularly in older patients. One should always be mindful of overall activity level and conditioning, tobacco use, and drugs of abuse. A complete occupational history is essential. Potential comorbidities also need to be considered, such as chronic obstructive pulmonary disease (COPD), heart disease, anemia, connective tissue disease, risk factors for infectious diseases, and potential malignancies. Although the differential is quite extensive, it is usually possible to focus on important historical elements.

A detailed physical exam, focused by historical information, is essential. This should include careful cardiac and pulmonary auscultation. Wheezing in asthma is typically expiratory and musical in nature. However, wheezing is not always present. When asthma is well controlled or the patient is not suffering an acute exacerbation, wheezing will generally not be heard. Never forget, however, that if an asthma exacerbation becomes severe enough to critically limit airflow (either directly or due to patient fatigue), wheezing may resolve. This can be an ominous sign and suggests impending respiratory collapse. The quality of airflow is also important. Many diseases including asthma and COPD may result in diminished airflow noted on auscultation. The presence of stridor suggests an upper airway process. Inspiratory Velcro-type crackles may represent an interstitial process such as idiopathic pulmonary fibrosis. Expiratory crackles often represent an alveolar process such as infectious infiltrate or pulmonary edema. The neck should be examined for evidence of jugular venous distention, which suggests a volume overload state that may be commonly seen in various cardiac diseases and renal failure. Extremities should also be examined closely for signs of clubbing, cyanosis, and edema. The presence of clubbing suggests an alternative pulmonary process other than asthma, such as idiopathic pulmonary fibrosis or cystic fibrosis. Clubbing is not

Table 15.1 Considerations in the differential diagnosis of asthmatic adults

System	Selected diseases
Cardiovascular	Coronary artery disease, heart failure, valvulopathy, pulmonary hypertension, pulmonary embolism
Infectious	Pneumonia, particularly atypical organisms, acute bronchitis
Neoplastic	Lung cancer, carcinoid
Other pulmonary diseases	Chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary eosinophilia, cystic fibrosis, pulmonary manifestations of connective tissue diseases, hypersensitivity pneumonitis, sarcoidosis, asbestosis
Gastroesophageal	Gastroesophageal reflux disease
Hematologic	Anemia, systemic mastocytosis
General	Deconditioning, obesity
Psychiatric	Anxiety, vocal cord dysfunction

It is important to remember that although many of these disease processes may mimic asthma, they (or their treatments) may also coexist with and contribute to the severity of asthma

a characteristic of asthma, even when asthma is severe. Dependent edema is another sign of cardiac, renal, or other processes resulting in a volume overload state. The ENT components of physical examination are also important, with particular attention to possible rhinitis, sinusitis, nasal polyposis, and postnasal drip. It is important not to overlook vital signs (including weight, as asthma may be more severe in obese patients).

"Diagnostic" Studies

In addition to the history and physical examination, a limited set of diagnostic studies may be useful in supporting a clinical diagnosis of asthma. These include pulmonary function testing, measurement of sputum eosinophils, exhaled nitric oxide, allergy skin testing, chest radiography, and a complete blood count. Other diagnostic studies may be suggested by elements of the patient's history and physical examination. A thorough discussion of all of these modalities is beyond the scope of this chapter:

- *Pulmonary function testing* is essential at the time of initial diagnostic evaluation and is of cardinal importance in guiding the ongoing management of the patient. Ideally, the initial assessment of pulmonary function should include plethysmographic determination of total lung capacity as well as diffusing capacity. These parameters provide insight into the earliest abnormalities definable in asthma – specifically, elevations in residual volume and diffusing capacity that are reflective of air trapping. These changes often antedate any significant abnormalities in the spirometric flow-volume curve and can thus illuminate further the decision-making process surrounding the transition from as-needed medication to regular daily administration of "controllers" in patients with mild asthma. Once a thorough assessment of lung function has been made for the asthmatic patient, simple spirometry may suffice for continuing follow-up of the patient's response to therapy. Many asthmatics will subconsciously decrease their level of activity or avoid exercise completely as their asthma worsens; this tendency underscores the unreliability of symptoms reporting alone and highlights the importance of periodic reassessment of pulmonary function with spirometry:
  - *Spirometry* should generally include baseline and post-bronchodilator expiratory flow-volume loops. While the flow-volume curve may be normal in many asthmatics not suffering from an acute exacerbation, asthmatics often have a "scooped" or concave appearance to the descending limb of the expiratory flow-volume curve typical of obstructive lung disease. The FEV1/FVC ratio is generally below 0.7 in a patient with significant airflow obstruction at the time of testing. The degree of obstruction can then be further characterized by the FEV1. However, it is important to remember that airflow obstruction (at least in the absence of severe remodeling) is variable; thus many mild asthmatics will have a normal baseline spirometry. Of significant importance in

asthma is demonstration of bronchodilator responsiveness, which is defined as an increase in FEV1 of at least 200 mL and 12 %. FEF25-75 may also be reduced, suggesting small airway obstruction (Fig. 15.1).

– *Methacholine challenge*. In patients with a normal baseline spirometry whose primary presenting symptom is cough and whose history suggests bronchial hyperreactivity, a methacholine challenge may offer additional insight into the level of activity of the lower airway inflammatory process. However, methacholine challenge is neither sensitive nor specific for asthma. For example, a positive response, although expected in asthma, may simply reflect the occurrence of a respiratory viral infection or other inflammatory processes within the 6 weeks preceding the test. Similarly, a negative response does not entirely rule out the diagnosis of asthma. Methacholine challenge may be most useful in providing additional insight into the care of patients with persistent cough, if a positive test remains persistently positive. Methacholine challenge should not be done in patients who already demonstrate any significant degree of airway obstruction, as the diagnostic value is further substantially undermined, and there is some hazard to the patient (Fig. 15.2).

- *Exhaled nitric oxide* (eNO) is gaining increasing acceptance as a marker of airway inflammation in asthma. However, accurate interpretation is plagued by many

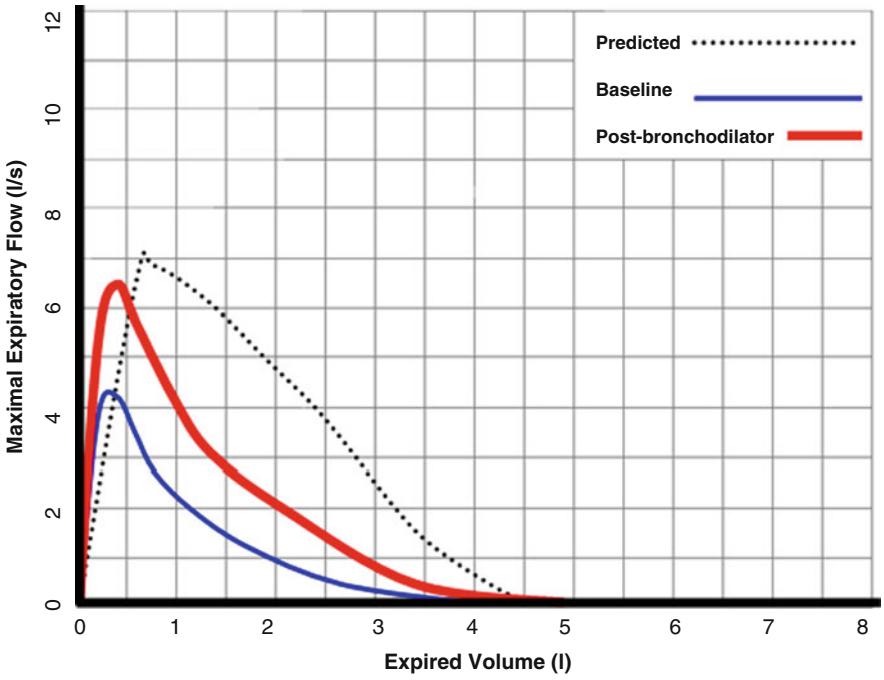

Fig. 15.1 Positive bronchodilator response in an asthmatic patient. Note shift upward and rightward of the red curve. Significant is 12 % and at least 200 mL

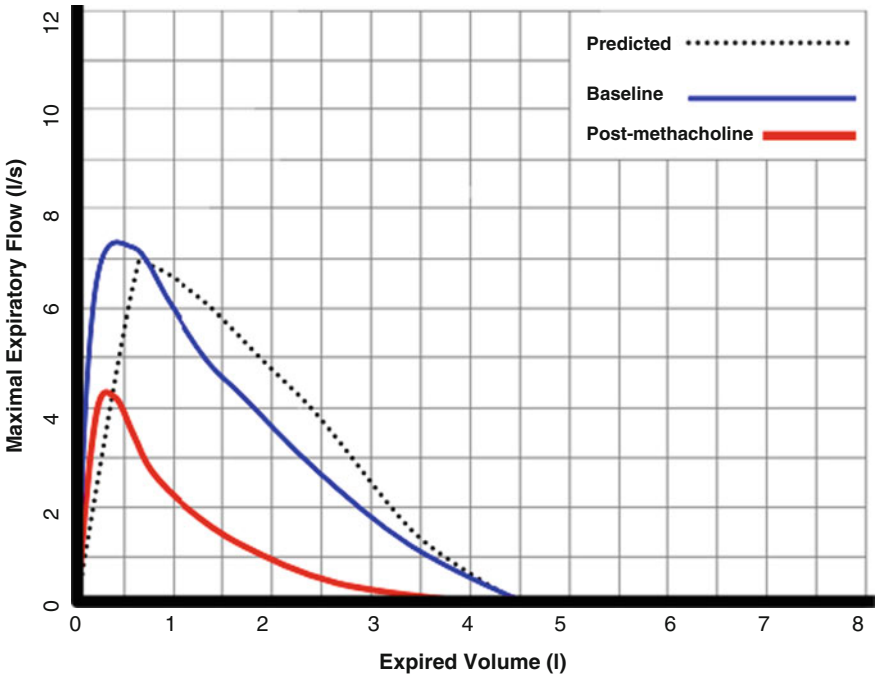

Fig. 15.2 Positive methacholine challenge in an asthmatic patient. Current practice is to qualify a 20% fall in FEV1 as a positive response

problems. The ambient nitric oxide (NO) level significantly impacts measurement. Results are often poorly reproducible between different pulmonary function laboratories. Additionally, there is a lack of consensus on values which define normal. Methodological challenges are presented by the fact that NO evolved from the nasal and sinus airways in much higher concentrations than are normally present in the lower airways, necessitating special procedures to avoid cross-contamination of sampling. It should also be noted that eNO may be elevated in other inflammatory airway diseases, including bronchiectasis, chronic bronchitis, and eosinophilic bronchitis. Thus, eNO measurement itself is *not* diagnostic of asthma. However, eNO may be helpful in monitoring an individual's response to therapy, as this marker is expected to decrease with successful therapy. Proponents have suggested that eNO might help predict which individuals with mild persistent asthma would respond better to an inhaled steroid versus a leukotriene antagonist, although data are presently too preliminary to make such a recommendation.

- *Chest radiography*. While the majority of patients with asthma will have normal chest films, too many competing diagnostic possibilities will be missed if chest radiography is overlooked in the initial evaluation. Important findings include hyperinflation, airway wall changes, alveolar and interstitial processes, nodules, masses, and adenopathy. Abnormalities of the cardiac silhouette and cardiothoracic ratio require further evaluation. Acute processes, such as pneumonia, may be present and can lead to a more difficult course in all asthmatic patients presenting

with a flare of respiratory symptoms. When asthma is in flare, atelectasis is a very frequent finding because of mucus plugging of airways. This may often lead to a radiographic diagnosis of pneumonia, which is erroneous. The best means of distinguishing atelectasis from true pneumonia is by serial imaging. An area of atelectasis will usually have radiographically resolved by the third to fifth day of therapy, while a true pneumonic infiltrate will require two full weeks or longer for complete resolution. Therefore, ideally all radiographic diagnoses of pneumonitis should have a fifth-day follow-up film to correct for this error.

- *Sputum eosinophils* are another marker of airway inflammation in asthma. However, these may also be elevated in chronic rhinosinusitis and eosinophilic bronchitis. It is usually necessary to induce sputum to provide an appropriate sample with the exception of some patients presenting with an asthma flare. While simple Wright's staining of sputum smears may be helpful when eosinophils predominate, a more reliable assessment is provided by processing sputum samples to yield homogenous fluids which permit comprehensive counting of all cellular elements in the sputum. This provides an accurate expression of eosinophils reported as a percentage of total sputum leukocytes. While helpful as an adjunctive measure of control of airway inflammation in asthma, measurement of sputum eosinophils is insufficient alone to diagnose asthma or initiate therapy.
- *Allergy testing*. Evaluation for allergic sensitivity is often of significant benefit to patients with asthma and should be considered an essential component of a thorough diagnostic evaluation. While relying on clinical history may help guide a decision about testing for seasonal allergens, there are no reliable historical features that identify patients with dust mite, animal dander, or indoor mold sensitivity. Allergy testing must be done to accurately recognize such patients. While not a diagnostic test for asthma per se, the information provided may greatly assist in management. Allergy testing should primarily evaluate sensitivity to aeroallergens. This can include perennial allergens such as house dust mite, animal danders (as directed by history), molds, and cockroach. Assessment of seasonal allergens such as tree, grass, and weed pollens is also helpful, but can be guided by the patient's history. Determination of total serum IgE can be beneficial, particularly in patients with severe persistent asthma and evidence of aeroallergen sensitivity, as the level may impact therapeutic options [and provides needed information if anti-IgE therapy, omalizumab, is being considered].

Asthma Management

Classification of Severity

Because decision-making surrounding asthma therapy is today closely tied to asthma severity, some scheme for stratifying new patients is useful. In the 2007 National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma, asthma severity was stratified on the basis of whether symptoms were intermittent or persistent. Persistent asthma was then

further stratified as mild, moderate, or severe based on severity and frequency of symptoms. This classification has been helpful in identifying appropriate initial therapeutic interventions for asthmatic patients (Table 15.2). It is critical to understand that all asthmatics can, at times, have severe exacerbations; these may be life threatening. This is independent of the classification of asthma severity.

Asthma control should be reevaluated on a regular basis, the frequency of which should be determined by the patient's overall severity. Whenever possible, medications, particularly oral or inhaled steroids, should be titrated downward to minimize potential side effects. The stepping up and down of asthma therapy will be discussed in more detail below.

Management

As previously mentioned, asthma management should be tailored according to a patient's needs and asthma severity. The guidelines should be followed whenever possible, tempered by the specific circumstances of each case. Asthmatics of all severities should have ready access to inhaled short-acting β-agonists. Additionally,

Table 15.2 Classification of asthma severity

- **Classifying severity for patients who are not currently taking long-term control medications.**

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Modified from *NAEPP Expert Panel Report 3: Guidelines for the diagnosis and management of asthma*; document available at URL http://www.nhlbi.nih.gov/files/docs/guidelines/04_sec3_comp.pdf

a plan should be in place for monitoring of asthma control and treatment of exacerbations. Many clinicians approach this with an "asthma action plan," governed by both asthma symptoms and serial home peak-flow measurements. Sample asthma action plans are included in the NIH NAEPP practice guidelines (executive summary available online at http://www.nhlbi.nih.gov/files/docs/guidelines/asthmsumm.pdf or the full report at the American Lung Association website, at http://www.lung.org/lung-disease/asthma/for-health-professionals-and-volunteers/strategies-for-addressing-asthma.html). Although commonly recommended, there is insufficient evidence to state that asthma action plans are effective or necessary for all patients. Studies suggest that those patients who present for unscheduled office visits or emergency department care of asthma on a recurring basis benefit most from the creation of asthma action plans. Therefore, this approach should be carefully tailored to each situation.

Education is critical in achieving appropriate asthma control. Patients should be instructed on appropriate use of inhaler devices, including spacer use where relevant. Oral hygiene following the use of inhaled steroids is encouraged for prevention of thrush. Perhaps the most critical educational point which patients must learn early, and be frequently reminded, is the difference between daily or "controller" medications and rescue medications. Daily (controller) medications include corticosteroids (generally inhaled), leukotriene modifiers, and less commonly cromolyn and theophylline. These may be used in conjunction with long-acting β-agonists (LABAs), particularly in moderate or severe asthma. Short-acting β-agonists, such as albuterol, should generally be used as rescue medications for prompt relief of symptom exacerbation and as premedication prior to exercise.

A subset of asthmatic patients may respond favorably to inhaled quaternary amine anticholinergic medications such as ipratropium bromide. While this class of medications alone is not considered sufficient as therapy in asthmatic patients, it may be a useful adjunct in some patients. There is limited experimental evidence in animal models that this class of medications may potentially limit airway remodeling, thus potentially expanding the future role of these drugs in asthma. However, at present there is not enough evidence in human asthma to make such a recommendation.

Some patients with refractory allergic asthma may respond to treatment with the anti-IgE monoclonal antibody omalizumab. Dosing is based on body weight and pretreatment total serum IgE level (consult the manufacturer's recommendations) and typically consists in subcutaneous injections once or twice per month. It is generally reserved for severe asthma, largely because of cost and convenience factors, which impacted the FDA approval application. Once given, it is no longer possible to follow the patient's IgE levels as a reflection of the activity of their disease, because IgE complexed with omalizumab exhibits delayed clearance from the circulation.

Allergy vaccine immunotherapy has been shown to be beneficial in asthmatics with known aeroallergen sensitivities, resulting in improvement in both nonspecific bronchial hyperreactivity and in reductions in responsiveness to specific aeroallergens. There is also evidence that this may result in decreased symptoms and medi-

cation use. However, immunotherapy should not be started in patients with unstable asthma. Generally, allergen immunotherapy is best managed by allergists trained in this modality.

Exercise-Induced Asthma

This topic is covered thoroughly in Chap. 16. Suffice it to say here that virtually all asthmatics can be provoked to symptoms given a sufficiently strenuous task in cool, dry air environments. Patients whose asthma symptoms only occur in circumstances of exercise should not be considered as having a separate disorder – they simply have asthma which is mild enough to require a potent provoking stimulus to manifest symptoms. Patients who engage in a regular exercise program that predictably provokes asthma symptoms usually benefit from premedicating themselves prior to exercise. This is helpful not only in preventing symptoms, but allows the patient to exercise more comfortably, thus encouraging a higher activity level and healthier lifestyle.

Asthma Exacerbations

Severe asthma exacerbations may occur in patients of any asthma severity or perceived level of control. In order to ameliorate exacerbations, which may occur in spite of the health-care provider's best efforts, an asthma action plan may be helpful, allowing interventions to be initiated prior to the development of severe or even life-threatening symptoms.

Exacerbations may be caused by common respiratory infections, especially viruses and atypical bacteria, especially *Chlamydophila pneumoniae* (formerly known as *Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*. Other factors such as environmental allergens (perennial and seasonal) and occupational exposures are also common causes of exacerbation. Complicating conditions such as allergic bronchopulmonary aspergillosis or minimal bronchiectasis of other causes, as well as other comorbid diseases, should be considered as well.

Evaluation of an exacerbation should include a focused history and physical examination including vital signs. Capillary oxygen saturation, spirometry (or PEF whenever spirometry is not available), and chest X-rays are also important in the evaluation of asthma exacerbations. In patients with a severe exacerbation, an arterial blood gas may be considered. Further evaluation should be guided by the patient's history and findings. Patients should always be asked whether they feel the same as they usually do when their asthma flares. Diagnosis of pulmonary embolism is almost always delayed in patients with asthma unless the alert physician elicits a comment such as "this doesn't quite feel the same as my usual asthma flare."

Initial therapy should be aimed at maintaining adequate ventilatory mechanics and tissue oxygenation. Inhaled β-agonists are necessary early on; however patient's response to bronchodilators must be closely monitored, since some patients will present in an advanced state of tachyphylaxis to β-agonists. Oxygen supplementation should usually be provided to the tight asthmatic with the goal of maintaining capillary oxygen saturation of at least 90 %.

For moderate exacerbations (PEF 51–80 % of personal best), it may be necessary to increase inhaled steroids or initiate systemic steroids. For severe exacerbation (PEF 50 % or less of personal best), systemic steroids and immediate emergency medical attention are necessary. If patients with severe exacerbations fail to achieve an adequate response after the first hour of intervention, hospital admission is necessary. Patients with moderate exacerbations with inadequate response to therapy may also be considered for emergent medical evaluation and hospital admission if necessary.

A short course of oral prednisone, in divided daily doses in the range of 40 mg per day for a period of 5–10 days, is sufficient for most exacerbations, but duration should be tailored to fit the clinical scenario. Experience with the individual patient's history will generally be required to establish whether a taper is necessary (to prevent a rebound exacerbation of the asthma) after a short course of oral steroid therapy. Mention should be made of the popular blister-pack steroid taper which provides only 1 day of top-dose treatment and begins the taper immediately thereafter – this is highly unlikely to provide an adequate therapeutic result for asthma exacerbation management and thus should be avoided.

Patients whose asthma relentlessly worsens and who present in a tight hyperinflated state of breathlessness with little or no favorable response to β-agonist bronchodilators are said to be in *status asthmaticus*. This is a true medical emergency. Such patients should be managed in a hospital emergency department and/or intensive care unit. Simultaneous pursuit of emergent studies and therapy is needed. The evaluation should include arterial blood gases, chest radiography, and visualization of the laryngeal airway. Generalized fatigue, normal to elevated $PaCO_2$, and mental status changes are generally considered indications for endotracheal intubation and initiation of either mechanical ventilation or high-frequency oscillation [HFO]. A recent task force concluded that there was insufficient experience with noninvasive ventilation [HFO] to officially endorse that as a recommendation in status asthmaticus. Aggressive use of β-agonist may trigger a significant, albeit transient, hypokalemia, necessitating electrocardiographic monitoring. The addition of inhaled anticholinergic medications (ipratropium bromide) may provide additional benefit when combined with inhaled β-agonists. The Expert Panel Report 3 sets forth guidelines for management of asthma exacerbations which have been embraced by the American Academy of Allergy, Asthma, and Immunology, as well as the American College of Allergy, Asthma, and Immunology (accessed here: http://www.nhlbi.nih.gov/files/docs/guidelines/11_sec5_exacerb.pdf).

Maintaining Asthma Control

As with other chronic health problems, regular follow-up and assessment of control is crucial to appropriately manage asthma. Asthma control issues should be addressed at every office visit. Additionally, follow-up visits should be scheduled at regular intervals, with the frequency determined by asthma severity. These should occur at least once per year for all asthmatics.

Because asthma symptoms do not always correlate with asthma severity, more objective parameters, such as spirometry, are necessary to ascertain the current degree of control. Questions addressing degree of control should generally include the frequency of asthma symptoms, rescue bronchodilator use, nighttime or early-morning symptoms, limitations on work, school or exercise, home PEF measurements, and patient/family member assessment of overall control and comfort (Table 15.3).

Discussions of medication use should not be limited to the frequency of rescue bronchodilator use alone. It is important to ask whether a patient has previously required oral steroids (particularly within the past year), hospitalization, or intubation. Many patients are poorly compliant with controller therapies, particularly inhaled corticosteroids. This may be due to side effects, such as thrush or dysphonia, or other factors, such as inconvenience or medication cost. Alternatively, poor compliance with controller therapies may suggest inadequate asthma education. The patient's inhaler and peak-flow techniques should be regularly reviewed.

The asthma checkup visit should include periodic spirometry. This should be done at least yearly, particularly in patients on regular, daily controller therapies and may be done more frequently if necessary. Other measurements such as exhaled nitric oxide and sputum eosinophils may provide additional helpful information, although no consensus regarding the indication and timing of such testing has yet emerged.

If the patient's asthma is well controlled, then therapy may either remain unchanged or attempts to "step down" may occur. For example, a patient on high-dose inhaled corticosteroids whose asthma has remained well controlled may warrant a change to intermediate- or low-dose inhaled corticosteroids. On the other hand, if a patient's asthma symptoms are not well controlled and if the patient is appropriately compliant with the current prescribed regimen, then stepping up the level of therapy may be necessary. Recent studies suggest that the dose-response curve of inhaled corticosteroids in asthma is quite shallow. Therefore, addition of a long-acting β-agonist (LABA) or leukotriene blockade may provide more advan-

Table 15.3 Characteristics of well-controlled asthma

Asthma symptoms ≤ twice per week
Rescue bronchodilator use ≤ twice per week
No nighttime or early-morning awakening
No limitations on exercise, work, or school
Patient and provider both describe asthma as well controlled
Normal or personal best (after aggressive therapy) PEF or FEV_1

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tage than doubling the dose of inhaled corticosteroids. If a LABA is added, a period of close monitoring is indicated in case the patient should have the Arg/Arg genotype for the β-receptor and as a result suffer worsening of asthma control with regular β-agonist use. Asthmatic patients should not receive LABA without concomitant inhaled corticosteroid administration, as the use of LABA alone is associated with an increased mortality rate.

In many instances, lack of control is due to poor compliance with the prescribed regimen. Again, in these situations, it is necessary to discover the reasons leading to poor compliance and provide further education.

Special Considerations in the Management of Adult Asthma

Pregnancy and Asthma

This topic will be covered in detail in Chap. 18. This is an area of significant importance in the management of asthmatic adults. Suffice it to say here that poorly controlled asthma during pregnancy increases the rate of both maternal and fetal complications. Thus, although there is always potential risk associated with any medical intervention during pregnancy, appropriate medical management of asthma prior to and during pregnancy is considered essential. While there will likely never be randomized prospective placebo-controlled clinical trials of drugs for asthma in pregnancy, the available retrospective data suggest that few if any of the currently used pharmacologic agents are associated with adverse side effects in pregnancy, in terms of fetal anomalies or adverse outcomes of pregnancy.

Heart Disease and Asthma

Aside from providing additional triggers for dyspnea, heart disease complicates asthma management largely as a result of opposing goals in pharmacologic management. β-Antagonists (β-blockers) are a component of standard care for many patients with heart disease, including coronary artery disease (CAD), prior myocardial infarction, and heart failure. Unfortunately, even medications which are considered to be β_1 selective do exhibit some β_2 antagonism. This commonly results in exacerbation of asthma and complicates management. The additional physiological stress due to asthma may also exacerbate the comorbid cardiac condition. Patients with moderate or severe asthma should not be treated with β-blockers. When this class of medications is necessary in mild asthmatics, the lowest possible dose should be used, and the patient must be closely monitored, preferably with before and after spirometry. If the β-blocker can be shown to eliminate a favorable β-agonist response or decrease the baseline flow-volume curve in the well asthmatic, then the β-blocker may prove catastrophic if the patient were to have an asthma flare. In the setting of β-blocker-induced

asthma, the administration of glucagon and carefully titrated epinephrine may be necessary. Quaternary amine inhaled anticholinergics such as ipratropium bromide may also be helpful in the treatment of β-blocker-associated bronchospasm, although first priority should be to avoid an exacerbation. Mild asthmatics that must be treated with β-adrenergic blockade for cardiac conditions should have access to inhaled anticholinergic medications. Even without concurrent β-blocker administration, it is always necessary to consider both the asthma and any comorbid cardiac diseases as potential causes in any increase in respiratory complaints.

Another major class of cardiovascular drugs that cause major trouble for asthmatics is the ACE inhibitors. Angiotensin-converting enzyme and bradykinin-catabolizing enzyme are the same molecule, so when an ACE inhibitor drug poisons the enzyme, if bradykinin is being produced anywhere in the body, its levels will rise. While this may eventuate in nothing more serious than a hacking cough in a normal individual, it may make controlling asthma [and particularly recovering from an exacerbation] a great deal more difficult. There are few circumstances where the advantages of the ACE inhibitors cannot be fully supplied by the appropriate angiotensin receptor blocker [ARB] as an alternative drug, and we always advocate for that option, since it does not elevate bradykinin levels.

COPD and Asthma

Long-term asthma may result in airway remodeling with resulting irreversible obstruction similar to COPD. Furthermore, many asthmatics, particularly elderly asthmatics with a history of tobacco use, develop a significant component of COPD. Evaluation of such patients is more complex. Complete pulmonary function testing with plethysmographically derived lung volumes and measurements of diffusing capacity, along with chest radiography and in some cases high-resolution chest CT (for quantification of emphysematous changes), is needed in evaluation of this group of patients. It is important to remember that the optimal treatment of COPD is generally regarded as distinct from that of asthma; thus treatment decisions may become more complex. Collection of additional data, such as a sputum cellular profile and blood eosinophil enumeration, may help to determine which disease pattern more closely describes the patient. Treatment should be tailored accordingly. This may be a subclass of patients that derive additional benefit from the addition of inhaled long-acting quaternary amine inhaled anticholinergic medications such as tiotropium.

Evidence-Based Medicine

While there certainly has been no dearth of meta-analyses performed since the last edition of this text was published, there have been no stunning breakthroughs in asthma diagnosis or management in this interval either. Several more clinical trials

of new biologicals have provided largely disappointing results, with some critics pointing out that targeting single molecules in complex inflammatory pathways cannot be expected to have substantial impact on the overall inflammatory process, particularly given the broad field of individual variations in molecular pathogenesis suspected to be presenting across the asthmatic population. As systems biology approaches become more entrenched in asthma research, we anticipate that deeper understanding of complex networks' dysfunctions will become more recognized, and we expect that treatment will increasingly consist of "suites" of several therapeutic compounds administered simultaneously. These multicomponent therapies will be coordinated in their ability to push whole networks crucial to the inflammatory pathways activated in asthma back to a more quiescent state, which reduces or eliminates disease.

The two areas of greatest change since the last edition of this text was published relate to recent investigations into the microbiome of the respiratory tract and the role it may play in asthma development and activity and the use of bronchial thermoplasty in management of severe asthma. A complete discussion of these two major developments is beyond the scope of this chapter, but readers are encouraged to peruse the several recent excellent reviews.

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Chapter 16
Exercise-Induced Bronchoconstriction

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Exercise-induced asthma (EIA), now referred to as exercise-induced bronchospasm (EIB), is extremely common. The terms *EIA* and *EIB,* although not identical, are often used interchangeably in much of the literature. *EIB* is now the accepted term to avoid the mistaken impression that exercise causes asthma. Rather, exercise leads to bronchospasm in susceptible individuals, who may or may not have asthma. In this light, all patients with EIA have EIB, but the reverse is not true. This is especially true of athletes who demonstrate airway bronchial hyperactivity that may be a consequence of extreme performance conditions and hyperventilation.

Prevalence varies, depending on location, investigational criteria, and specific population studied, with increased incidence in developed countries, urban locations, and in those in high-performance athletics. The prevalence of EIB in the general population is likely between 6 and 20 %. Up to 90 % of asthmatics suffer from EIB. This increase in EIB parallels the overall increase in asthma over the past several decades. EIB is also frequently underdiagnosed, and in a study of Australian children, 19.5 % experienced a fall in forced expiratory volume in 1 s (FEV_1) greater than 15 % with exercise. Only 60 % of those who had this decline in FEV_1 were known asthmatics.

EIB can significantly impair social function and exercise in children. At times, half of children with asthma were unable to compete secondary to symptoms, especially those who participated in outdoor running sports. Furthermore, asthma inhibited life activities in a third of students over a random 2-week period in Australia.

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EIB is also a concern in high-performance athletes. Although the incidence of asthma in the general population is 4–7 %, a much higher proportion of competitive athletes have been diagnosed with asthma, up to 55 %, depending on the study.

EIB is second only to viral infections as a cause of acute airway obstruction. Often, EIB is the first presentation of asthma in an individual. Several factors may increase the risk of EIB. Atopy, as measured by positive skin tests, correlates with EIB incidence, and up to 40 % of patients with allergic rhinitis have EIB. Genetics is also important, and relatives of asthmatics, who do not have asthma themselves, often have an obstructive pattern on pulmonary function testing with exertion. The increase in obesity and a parallel overall reduction in physical activity and conditioning appear to be associated with an increased risk of EIB.

Clinical Characteristics

EIB may present with traditional symptoms such as coughing, wheezing, or chest tightness during or within 5–10 min after exercise. However, the clinician should be aware of atypical presentations such as fatigue, chest pain, persistent post exercise cough, or stomachache (Table 16.1). The differential diagnoses of EIB include cardiac disease, intra- and extrathoracic causes of tracheal narrowing, lung disease, neuromuscular disease, metabolic disorders, and deconditioning (Table 16.2). Vocal cord dysfunction frequently mimics EIB and must be considered especially in adolescents undergoing highly stressful athletic performances. In contrast to EIB, patients with vocal cord dysfunction often have more difficulty on inspiration, often with loud stridor, rather than on expiration, and they may also demonstrate trouble with phonation during the event. Spirometry done at the time of symptoms often reveals saw-toothed pattern on the inspiratory flow loop. Direct visualization of the

Table 16.1 Symptoms of exercise-induced bronchoconstriction

Typical	Atypical
Coughing	Fatigue
Wheezing	Headache
Chest tightness	Chest pain
Dyspnea/air hunger	Stomachache

Table 16.2 Differential diagnosis of exercise-induced bronchoconstriction

Respiratory	Intra- and extrathoracic tracheal disorders causing tracheal narrowing, uncontrolled asthma, viral or bacterial respiratory infection, emphysema
Cardiac	Coronary artery disease, arrhythmia/tachycardia, congenital defect, idiopathic arterial hypoxemia of exercise, valvular heart disease, congestive heart failure
Neuro/muscular	Deconditioning, metabolic disorders, neuromuscular disorders
Psychogenic	Vocal cord dysfunction, malingering for secondary gain
Gastrointestinal	Gastroesophageal reflux disease

vocal cords at the time of symptoms can confirm the diagnosis. Physicians should be cautious of overdiagnosis of EIB since some literature suggests that the most common cause of exercise-induced symptoms is deconditioning. As suggested by the differential, physical examination is important to rule out other etiologies as well as comorbid conditions, such as rhinosinusitis. Baseline spirometry is often normal in patients with EIB, especially in highly conditioned athletes.

Diagnosis

Diagnosis based on symptoms alone, which is neither specific nor sensitive, is often unreliable because different patients have different subjective symptoms that may or may not correlate with objective measures of EIB. Confirmation of asthma with a reversal of 12 % FEV_1 on spirometry and a response of exercise-related symptoms with therapy, such as with a β-agonist, suggests the diagnosis of EIB. In some cases, challenge tests may be necessary to confirm EIB.

Direct bronchoprovocation testing with methacholine or an indirect challenge, such as eucapnic voluntary hyperpnea, hypertonic inhalation, exercise, and mannitol, can be used to assess the presence of airway hyperresponsiveness; however, direct changes are more appropriate to rule out asthma than to diagnose EIB. An exercise challenge test, sport specific if possible, may be the most reliable method of diagnosing EIB in high-intensity athletes.

Exercise challenge tests (ECTs) are contraindicated in those with severe airflow limitation and other unstable medical conditions (Table 16.3). Before the ECT screening baseline electrocardiogram should be considered in those older than 60 years. Patients should be advised to arrive at the test dressed to exercise, after eating only a light meal, and they should not have exercised within 2 h of the exercise challenge test. This latter requirement is secondary to a "refractory period" which is induced by the release of protective prostaglandins, which cause airway smooth muscle tachyphylaxis to mediators of bronchoconstriction. The refractory period may persist up to 2 h following exercise and raises the risk of false-negative ECT results.

During testing, the patient's FEV_1 is measured at baseline and then at frequent intervals after exercise. Pulmonary function testing should be done while the patient is in a seated position. Tests are performed at 5, 10, 15, 20, and 30 min after

Table 16.3 Contraindications to exercise challenge test

Respiratory	Low FEV_1 <50–60 % predicted; technical inability to perform spirometry
Cardiovascular	Myocardial infarction or stroke within 3 months; unstable angina; malignant arrhythmia; uncontrolled blood pressure >200/100; aortic aneurysm
Orthopedic	Inability to perform specified exercise

FEV_1 forced expiratory volume in 1 s

exercise, and, some suggest even at 1 and 3 min post exercise. Two to three tests are performed at each time interval, with variability of an accurate test of less than 0.2 L between the two top tests. The diagnosis of EIB is suggested by a reproducible decline of 10 % in FEV_1, even though some researchers prefer a 15 % decline of FEV_1. The response of the normal individual to exercise should be an increase in FEV_1. Peak flow may be used if spirometry is not available, but the results are less valid.

Exercise challenge may be performed via cycle ergometer, treadmill, free running, or step testing. Bronchoconstriction may be easier to provoke with treadmill exercise due to a faster increase in minute ventilation. Cycling is easier than treadmill testing, especially for those with lower extremity weakness or arthritis, and it will identify most patients with EIB. Field testing of the athlete in his or her chosen event would be most specific although not always practical. To achieve adequate exercise level for testing, patients should reach 80–90 % of their maximum predicted heart rate (220 minus age), or 30–40 mL/kg oxygen consumption. It is important for the patient to reach target heart rate quickly to prevent the development of the refractory period. With the exception of field testing, inspiration of dry, cold compressed air and use of a nose clip to force mouth breathing provide more sensitive testing and are recommended by the American Thoracic Society. The goal is 8 min of exercise with 6 min near the desired target rate.

If a patient is unable to exercise for whatever reason, stationary hyperventilation may be an adequate alternative. This is usually performed with the patient breathing air with a fixed concentration of carbon dioxide to prevent hypocapnia from hyperventilation. The goal is to achieve 60–70 % maximal voluntary ventilation. Eucapnic voluntary hyperventilation (EVH) is sensitive and may be equal or superior to cold air exercise challenge in the identification of airway hyperresponsiveness in elite cold-weather athletes. The eucapnic hyperventilation testing has a limited role because it is expensive and difficult to perform and equipment is rarely available; however, most consider it the best surrogate marker for EIB.

Airway Hyperreactivity Testing as a Surrogate to EST

Direct Tests

As noted above direct challenges and indirect challenges have been used as surrogate markers for diagnosing EIB when ECT is not available. The direct challenges to include histamine and methacholine are very sensitive and should identify most asthmatic patients and are best to use to exclude the diagnosis of asthma. Because the mechanism is direct stimulation of bronchoconstriction, it is considered less appropriate to use as a surrogate of EIB.

Indirect tests, to include mannitol, EVH, and hypertonic saline, cause an osmolarity strain across the epithelial cells resulting in similar changes in the airway that EIB causes. For this reason indirect tests are preferred. Some have suggested that

mannitol inhalation testing may be ideal for the diagnosis of EIB. It has correlated well when compared to eucapnic hyperventilation in a study of EIB in summer athletes, remaining sensitive for diagnosis, but is less expensive and easier to perform than hyperventilation testing. The concern is that manufacturing mannitol is extremely difficult and it is no longer produced in the USA.

Pathophysiology

Within the first few minutes of exercise, bronchodilation secondary to endogenous catecholamine release occurs as a reflexive response, even in some asthmatic patients. This lasts through exercise and even up to 20 min post exercise in some patients. Contrary to this dilation is that airway obstruction in those with EIB usually peaks 5–10 min after aerobic exercise with recovery after 30–60 min. The clinician should be aware that some patients present with symptoms during, instead of after, exercise. Unlike asthma exacerbations secondary to other etiologies, the occurrence of a late reaction following pure EIB in the absence of allergen challenge is unusual, but it has been reported. Boulet et al. and Chhabra et al. showed a late response in 30 % and 50 % of EIB patients, respectively, following exercise. Unfortunately, there were no predictors as to who was at risk for this phenomenon.

Two theories have been described to explain the pathophysiology of EIB. They are not mutually exclusive and may or may not be the same as the pathology involved in chronic asthma. The first was described in 1986 and is often referred to in the literature as the thermal hypothesis. According to this theory, airway cooling is less of a problem than the rapid rewarming of the airways that follows exercise. Rapid rewarming leads to reactive hyperemia and airway wall edema that contributes to airway narrowing and bronchoconstriction with mediator release. By preventing airway rewarming, the obstructive bronchial response is abrogated. If athletes avoid rewarming by breathing cold air instead of warm air during their recovery period post exercise, FEV_1 decline was reduced from 25 % to less than 10 %. This thermal theory has been debated since EIB occurs with hot, dry air as well.

The second theory, the osmotic hypothesis, states that neither cooling nor rewarming is necessary. The osmotic theory espouses water loss in the airway following hyperpnea as the pathologic cause. This leads to increased airway osmolarity and dehydration of airway epithelial cells and activation of mast cells. In support of the osmotic hypothesis, lung mast cells have been demonstrated to release histamine with a transient osmotic stimulus, and products of mast cells are increased in EIB. Cysteinyl leukotrienes (LTC4, LTD4, and LTE4), prostaglandins, histamines, and cytokines are released from mast cells and facilitate bronchoconstriction, increase mucus secretion, influx of eosinophils, and increase vascular permeability. The end result is influx of inflammatory cells, contraction of smooth muscle, increased mucus production, airway wall edema, and epithelial cell desquamation, all compromising the caliber of the airway.

Treatment

With proper treatment, EIB should not limit physical activity. A management plan for EIB includes pharmacologic and nonpharmacologic treatments. If possible, athletes should schedule exercise to avoid the coolest time of the day since cold air carries less water content, high pollen time for those with coexistent allergies and high pollution times. Patients should warm up and cool down following exercise for 10–15 min. Warming up may induce the refractory period and protect from EIB for several hours. Boulet and O'Bryne in a 2015 manuscript in the NEJM suggest that short sprints may be more effective warm-up than lower aerobic exercise.

If possible, breathing through the nose, rather than the mouth, facilitates the warming and humidification of dry air, minimizing the osmotic changes that can trigger EIB. Facemasks during sports in cold environments may decrease EIB for the same reasons. Interestingly, by improving overall aerobic fitness, athletes decrease their minute ventilation required for the same amount of work, limiting airway drying and EIB. By this method, regular exercise may help reduce EIB. For this reason, regular exercise and conditioning should be encouraged and not limited in those with EIB.

As alternative medicine becomes more popular, some patients may inquire about other nonmedicinal treatment modalities, such as diet. There are some preliminary, although not conclusive, data that suggest dietary salt restriction may improve EIB. Other alternative therapies that *may* have some merit include vitamin C, other antioxidants, fish oil, and magnesium. The best dietary intervention is hydration to reduce the possibility of dehydrating the airway.

Short acting β-agonists (SABAs) inhibit EIB for up to 3–4 h and are the first-line prevention and treatment of EIB. Usually two to four puffs of a short-acting inhaled bronchodilator, such as albuterol, 15 min before exercise will inhibit EIB. The regular use of SABA may lead to refractoriness to the protective effects and reduce the rescue effect of SABA for EIB.

Long-acting bronchodilators may also provide protection from EIB symptoms. Formoterol decreases symptoms of EIB after a single dose and with regular use. Formoterol has a faster onset of action than salmeterol and may be given 15 min prior to exercise, whereas salmeterol requires earlier administration at least 60–90 min before anticipated activity. These long-acting bronchodilators and the newer ultra-long-acting beta-agonists provide protection for a longer duration of time, up to 12 h after administration, and may be an option for activities that may last longer than a few hours. However, the regular use of long-acting bronchodilators should be discouraged as solo therapy if used regularly because of tolerance and decrease response to albuterol. The benefits and disadvantages of the newly released once-a-day beta-agonists are anticipated to be similar, and it is expected that the adverse effects on EIB will outweigh their benefits. Other side effects of β-agonists commonly include tremor and increased heart rate, which could adversely affect performance in some athletes.

Mast cell stabilizers may also be used prophylactically for EIB. Two puffs of either nedocromil sodium or cromolyn sodium before exercise provide significant protection from EIB and were superior to placebo. A meta-analysis by the Cochrane Database regarding mast cell-stabilizing agents in the prevention of EIB involved 518 participants in 24 trials in 13 countries. Patients on mast cell stabilizers had a 7.1 % decline in FEV_1 versus a 13.8 % decline with anticholinergic agents, but neither was as effective as β-adrenergic agonists. Mast cell stabilizers are not effective for aborting symptoms of EIB and are useful as prophylactic agents only. The mechanism of action of sodium cromoglycate and nedocromil sodium may include action on ion channels involved in cell volume regulation as well as inhibition of mediator release. The mast cell stabilizers have a very favorable and minimal side effect profile, but neither is presently available in the USA.

Leukotriene receptor antagonists (montelukast and zafirlukast) and the 5-lipoxygenase inhibitor zileuton also have proven efficacy in the treatment of EIB. Urinary leukotrienes, which are increased following exercise in those with EIB, decline with montelukast treatment. Montelukast and zafirlukast provide protection from EIB within 1 h of ingestion and provide protection from EIB up to at least 12 h, with efficacy proven to 20 and 24 h for montelukast. Zileuton, because of a shorter half-life, provided protection only up to 4 h. In a comparison of montelukast and salmeterol, although initial efficacy in reduction of EIB was similar with both medications, at 8 weeks, montelukast was superior to salmeterol, as a result of tolerance to salmeterol.

Other effective treatments for EIB include inhaled corticosteroids. Inhaled corticosteroids decrease asthma exacerbations, including exacerbations secondary to exercise. For example, budesonide, at a dose of 100–400 μg per day, provided 80 % protection from EIB symptoms. Corticosteroids decrease mast cells and eosinophils and improve integrity of the epithelial cell airway lining. When used regularly, an inhaled steroid demonstrated better protection from EIB than montelukast.

Experimental therapies such as inhaled furosemide, indomethacin, and heparin have also been described in the treatment of EIB but require further study. Furosemide inhibits NAK2CL transport and may inhibit EIB by a mechanism similar to cromolyn. Inhaled indomethacin may inhibit local prostaglandin synthesis and/or ion transport, protecting against EIB. Inhaled heparin may inhibit mast cell mediator release. These latter treatments should only be used in research at this time.

Special Considerations

Many famous sports figures, such as Pittsburgh Steeler Jerome Bettis and track and field athlete Jackie Joyner-Kersee, have succeeded in competitive sports despite having asthma. Elite athletes compose of a special group at risk for EIB. A high prevalence of bronchial hyperreactivity to methacholine of almost 50 % has been demonstrated in elite athletes. The majority of these athletes had no personal or

Table 16.4 Sports and risk for exercise-induced asthma

High-risk sport	Lower risk sport
Cross-country skiing	Baseball
Figure skating	Swimming
Ice hockey	Football (American)
Distance running	
Basketball	
Swimming	

family history of asthma prior to this testing. The pathologic findings in this population are the result of the extreme conditions under which these athletes compete and train, rather than the asthma that is typical of that seen in allergic asthma. The changes described in detail earlier, especially in response to airway dehydration with hyperpnea, can occur in normal individuals without a history of asthma. Repetitive exercise, especially, but not limited to, elite athletes, can cause an increase in IL-8, a potent neutrophil chemoattractant, leading to an influx of neutrophils.

Environmental factors, including pollutants, may further worsen the changes in the airway. These changes are noted in 76 % of elite swimmers secondary to the effects of chlorine. Similarly, ice skaters are exposed to increased levels of nanoparticles from the ice cleaners as well as dry cold air. Alpine skiers and cross-country skiers are also at risk secondary to the extreme cold and dry air. As elite athletes show pathologic changes in their airways consistent with chronic inflammation, regular treatment with inhaled corticosteroids is often suggested; however, since the inflammation is often neutrophilic, it is often refractory to inhaled corticosteroids (Table 16.4). Seasonal outdoor activities are also more likely to expose athletes to high pollen and mold counts, which could worsen bronchospasm in susceptible atopic individuals.

Scuba

Scuba divers are at particular theoretical risk for EIB, which may be life threatening during dives. Since there are nearly nine million sport divers in the USA alone, this is an important consideration for physicians. Approximately 7 % of scuba divers have asthma, similar to the incidence of asthma in the general population. These asthmatic divers may risk higher chance of decompression-related illness and arterial gas embolism by the following mechanism. According to Boyle's law, there is an inverse relationship between the pressure and the volume of a gas. As ascent occurs and pressure decreases, the gas expands, increasing its volume, which with air trapping can cause barotrauma. Furthermore, scuba divers breathe cold, dry air that may exacerbate EIB by mechanisms described earlier in this chapter. This, along with possible inhalation of aerosolized hypertonic saline from faulty regulators, aeroallergens introduced when tanks are filled, as well as increased exertional work of breathing, may lead to bronchospasm. The concern of barotraumas is the

risk of pneumothorax and pneumomediastinum. In addition there is a high risk of sinus and ear barotrauma in those with asthma due to rhinitis. The Thoracic Society of Australia and New Zealand recommends that at-risk divers undergo pulmonary function testing with a cold, dry air inhalation challenge. For those with a positive challenge test, diving should not be advised. A history of recent active asthma within the past 5 years may also be a contraindication (see section "Evidence-Based Medicine" for more information).

Hiking

High-altitude sports also require special consideration for those with EIB. At higher altitudes, the air is cooler and drier, and high elevation hikers are at risk for hypoxia. However, Boner et al. documented improved function in asthmatics at higher altitude, hypothesizing that it may be secondary to decreased pollen and dust mite allergen concentrations, less pollution at these altitudes, and decrease density of air.

Conclusion

EIB is very common in the general population as well as in elite athletes. Exercise should be encouraged rather than limited because with proper diagnosis and treatment, EIB should not limit performance. Part of the responsibility of the physician caring for patients with EIB includes education of the public. In several studies, despite the high prevalence of EIB in children, teachers and coaches did not demonstrate knowledge of the condition or its management. Even physicians are rarely aware of the benefits of exercise for those with asthma. Meta-analysis suggests that exercise has multiple benefits for patients with asthma and routine daily exercise should be encouraged. Warming up, hydration, cooling down, using anti-inflammatory therapy when indicated, and pretreatment with albuterol should allow the vast majority of patients with asthma to exercise.

Evidence-Based Medicine

Recent studies have demonstrated that regular aerobic exercise can improve asthma. A study by Franca-Pinto et al. demonstrated that regular aerobic exercise could reduce asthma exacerbations and symptoms. In the study 58 patients were randomly assigned to a "sham" group or an aerobic training group and followed for 3 months. Bronchial hyperresponsiveness (BHR), serum cytokine, and the Asthma Quality of Life Questionnaire (AQLQ) were evaluated at the beginning and end of the study. It was found that the treatment group had decreased BHR, interleukin 6 (IL-6), and

monocyte chemoattractant protein 1 (MCP-1) and improved AQLQ ($p > 0.05$) compared to the control group. A murine animal model by Lowder et al. demonstrated that regular exercise increased T-regulatory cells and with this decreased inflammation of the airways. Lowder et al. sensitized mice with ovalbumin (OVA) prior to exercise and then repeatedly OVA challenged throughout the three times per week for 4-week exercise protocol. The mice were analyzed at study completion for the number and suppression function of Treg cells. The results showed that there was enhanced suppression function by the Treg cells on CD4 (+)(CD25−) cell proliferation and Th2 cytokine production in the exercise OVA-treated exercise mice compared to the sedentary controls. This suggests that Treg cell may play a role in airway inflammation. Although similar cellular changes have not been elucidated in human airways, benefits of exercise are apparent in increased asthma-free days and oxygen consumption and improved quality of life and asthma control. For the reasons noted, all patients with asthma should be encouraged to participate in aerobic, isotonic exercise for 30–60 min at least 5 days a week.

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Chapter 17
Occupational Asthma

Jonathan A. Bernstein

Definition of Occupational Asthma

Occupational asthma has been defined as "a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace." Two types of OA need to be distinguished based on the presence of a latency period (includes most high molecular weight agents and some low molecular weight agents) or absence of a latency period (includes irritant-induced asthma aka reactive airways dysfunction syndrome). High molecular weight (HMW) agents refer to plant or animal proteins >1,000 Kd in size such as natural rubber latex, enzymes, or laboratory animal allergens. Low molecular weight (LMW) agents refer to chemicals <1000 Kd in size that usually require conjugation with endogenous proteins to form a complete hapten capable of eliciting an immunogenic response. Examples include isocyanates, acid anhydrides, and metallic salts. It is important to emphasize that preexisting asthma does not preclude a diagnosis of OA. The term "work-exacerbated asthma" has been recommended for patients with this presentation.

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History and Epidemiology

The first reference to asthma in workers was cited by Hippocrates (460–370 BC) in reference to metal workers, tailors, horsemen, farmhands, and fishermen. Throughout history, physicians have increasingly recognized the relationship between asthma and a variety of occupations.

The incidence of OA is difficult to estimate as there are significant differences between countries, ranging between 10 and 114 per million per year. These differences are largely due to methodological differences in calculating incidence and the types of occupations and employment opportunities in each country. The Sentinel Event Notification System for Occupational Risks (SENSOR) was developed in several states within the United States in the 1980s to encourage reporting of OA cases by physicians and to put them in contact with public health agencies responsible for investigating high-risk workplaces. This program was successful at increasing awareness among physicians about OA; however, as with other notification systems, underreporting was a problem. Other countries have developed voluntary reporting registries to identify an ongoing incidence and prevalence of OA with varying degrees of success. Asthma cases being evaluated for work-related medicolegal benefits have been another source for estimating the incidence of OA.

Overall, it has been estimated that 5–20 % of all new diagnoses of asthma are occupationally related. Over 250 agents in the workplace have now been associated with causing OA. Cross-sectional studies have provided much of the prevalence data available for many of these agents known to cause OA. The prevalence of OA varies between occupations. For example, studies have found the prevalence of OA among laboratory animal workers is approximately 20 %, whereas western red cedar asthma occurs in approximately 5 % of workers. The prevalence of OA has been estimated to occur in 7–9 % of bakers for baker's asthma, 5–10 % of isocyanate-exposed workers, 20–50 % of platinum-exposed workers, and in up to 60 % of enzyme-exposed workers.

The prevalence for OA within a specific occupation depends on many factors including environmental conditions within the plant, exposure levels, and the number of exposed workers. For example, at first glance, it might appear that isocyanate-exposed workers have a lower prevalence of OA compared to platinum-exposed workers. However, the absolute number of workers exposed to isocyanates (>100,000) each year results in a greater absolute number of workers who develop isocyanate-induced OA compared to platinum-exposed workers.

Unfortunately, cross-sectional studies can underestimate the prevalence of OA due to the "healthy worker effect." This phenomenon occurs as the result of symptomatic workers leaving the workplace because of illness which results in a misleading healthier workforce. Therefore, in order to obtain more accurate prevalence statistics and information about the causes, risk factors, and natural course of OA, surveillance programs have been established in developed countries including the United Kingdom, the United States, and Finland. The "SWORD" (Surveillance of Work-Related and Occupational Respiratory Disease) program established in the

United Kingdom involves voluntary reporting of occupational illnesses from a variety of industries by pulmonologists and occupational medicine physicians. This program has already yielded useful prevalence data due to the excellent response rate from participating physicians. Thus far, SWORD has identified OA as the most frequently reported occupational respiratory illness and isocyanates as the most common specific cause of OA. As mentioned, the "SENSOR" (Sentinel Health Notification System for Occupational Risks) program established in the United States has not been as successful in obtaining useful epidemiological data due to a poor response rate from participating physicians. This is in contrast to Finland's program, which has already compiled enough data to estimate the country's yearly incidence of OA and hypersensitivity pneumonitis. Currently immunosurveillance programs implemented by companies manufacturing potentially sensitizing chemicals and enzymes are ongoing and have proven very effective at reducing and/or preventing occupational respiratory diseases.

Pathogenesis

Our understanding of asthma has been greatly enhanced with the advent of bronchoscopy, bronchoalveolar lavage, and bronchial biopsies. The pathogenic features of OA are similar to what has been observed in non-OA patients. In general, lung biopsies of patients with OA demonstrate increased numbers of inflammatory cells with a predominance of eosinophils and lymphocytes, increased intercellular spaces between epithelial cells, and thickening of the reticular basement membrane due to deposition of collagen (types I, III, and V). Interestingly, the degree of reticular basement membrane thickening has been demonstrated to differ between different forms of OA. For example, workers with reactive airways dysfunction syndrome (RADS) have thickening that can reach 30–40 μm compared to 6–15 μm in workers with diisocyanate asthma and 3–8 μm in normal subjects. Airway inflammation associated with OA involves similar bioactive mediators and proinflammatory cytokines identified in non-OA. Certain causes of work-related lower respiratory symptoms have been reported to manifest as eosinophilic bronchitis, characterized as a chronic cough with sputum eosinophilia in the absence of bronchial airway hyperresponsiveness. For example, natural rubber latex, mushroom spores, acrylates, and epoxy resins have been reported to present as eosinophilic bronchitis. Occupational asthma manifesting as neutrophilic inflammation is less common but has been reported with some low molecular weight agents. For non-OA the presence of neutrophils is believed to be a marker of severity, but their role in different causes of OA is still unclear.

Patients with OA can exhibit the inflammatory phases of asthma similar to non-OA. However, some forms of OA are more commonly associated with either the early airway response (EAR), the late airway response (LAR), or a dual airway response (DAR). For example, whereas an EAR may be more characteristic of high molecular weight (HMW) agents, an LAR or DAR may be more commonly seen in

workers with isocyanate-induced OA. Therefore, it is important for the clinician to be familiar with these different disease presentations to avoid missing a diagnosis of OA because symptoms by history begin after leaving the workplace.

Mechanisms

In general, many HMW and LMW agents known to cause OA involve Th2 proinflammatory cytokines characteristic of IgE-mediated allergic asthma. For example, enzymes commonly used in the detergent manufacturing industry are proteins that have been well documented to cause OA through IgE-mediated mechanism. Acid anhydrides are examples of LMW agents known to cause IgE-mediated OA. However, some LMW chemicals (plicatic acid and diisocyanates) cause OA in nonatopic workers through non-IgE-mediated mechanisms. The mechanism(s) by which these agents cause OA is unknown. The mechanism(s) for irritant-induced asthma (aka reactive airways dysfunction syndrome or RADS) also remains elusive. It is believed chronic inflammatory changes occur in these workers as the result of toxic injury to bronchial epithelial cells leading to loss of epithelial-derived relaxing factors combined with neurogenic inflammation and release of bioactive mediators and proinflammatory cytokines by nonspecific activation of mast cells. Ongoing research using a variety of animal models is trying to further elucidate the role of innate and adaptive immune responses in causing a variety of non-IgE-mediated forms of OA.

Genetics

Several studies have now reported potential and important genetic associations in workers who develop OA. For example, workers with acid anhydride OA have been shown to express the class II HLA molecule, DQB1*501, while this same molecule may be protective against developing OA from isocyanates or plicatic acid. Furthermore, the HLA-DRB1*07 phenotype was more commonly expressed in laboratory animal handlers sensitized to rat lipocalin allergens. Glutathione S-transferase polymorphisms, important for protecting cells from reactive oxygen species, have been postulated to protect workers exposed to isocyanates from developing OA and are also believed to play a protective role against developing non-OA from ozone and diesel exhaust particulate exposures. Finally, N-acetyltransferase genotypes may also be important in OA as recent studies have found that individuals with a slow acetylator genotype had a 7.8-fold risk of developing toluene diisocyanate-induced (TDI) asthma. A variety of other candidate gene polymorphisms found to be associated with non-OA phenotypes have also been investigated to a lesser extent in OA such as IL-4Rα S478P and IL-4-589. In a more recent study, subjects with diisocyanate asthma were found to have elevated levels of

IFN-γ promoter methylation than those who did not have diisocyanate asthma. However, the role of increased methylation in diisocyanate asthma remains unclear at this time.

Diagnosis

History

The criteria for defining occupational asthma proposed by the American College of Chest Physicians are summarized in Table 17.1. The diagnosis of OA requires a detailed and comprehensive history (Table 17.2). An inadequate history can often delay the diagnosis of OA for months or years. To prevent omission of important historical data, administration of a physician-directed history in conjunction with a structured questionnaire is recommended. The occupational history should elicit comprehensive demographic data about the worker; present and past employment history; the nature, duration, and temporal pattern of symptoms; and finally, any potential risk factors for OA. It is essential that the physician be familiar with most of the known causative HMW and LMW agents of OA and methodologies used for diagnosis (Table 17.3).

Table 17.1 Criteria for defining occupational asthma proposed by the American College of Chest Physicians

A. Diagnosis of asthma
B. Onset of symptoms after entering the workplace
C. Association between symptoms of asthma and work
D. One or more of the following criteria:
1. Workplace exposure to an agent or process known to give rise to occupational asthma
2. Significant work-related changes in FEV1 or peak expiratory flow rate
3. Significant work-related changes in nonspecific airway responsiveness
4. Positive response to specific inhalation challenge tests with an agent to which the patient is exposed at work
5. Onset of asthma with a clear association with a symptomatic exposure to an irritant agent in the workplace RADS
Requirements
Occupational asthma:
Surveillance case definition: A + B + C + D1 or D2 or D3 or D4 or D5
Medical case definition: A + B + C + D2 or D3 or D4 or D5
Likely occupational asthma: A + B + C + D1
Work-aggravated asthma: A + C (i.e., the subject was symptomatic or required medication before and had an increase in symptoms or medication requirement after entering a new occupational exposure setting)

RADS reactive airways dysfunction syndrome, *FEV1* forced expiratory volume in 1 s

Table 17.2 Key elements of the occupational history in the evaluation of occupational asthma

I. Demographic information
A. Identification and address
B. Personal data including sex, race, and age
C. Educational background with quantitation of the number of school years completed
II. Employment history
A. Current department and job description including dates begun, interrupted, and ended
B. List of all other work processes and substances used in the employee's work environment. A schematic diagram of the workplace is helpful to identify indirect exposure to substances emanating from adjacent work stations
C. List of prior jobs at current workplace with description of job, duration, and identification of material used
D. Work history describing employment preceding current workplace. Job descriptions and exposure history must be included
III. Symptoms
A. Categories:
1. Chest tightness, wheezing, cough, shortness of breath
2. Nasal rhinorrhea, sneezing, lacrimation, ocular itching
3. Systemic symptoms such as fever, arthralgias, and myalgias
B. Duration should be quantitated
C. Duration of employment at current job prior to onset of symptoms
D. Identify temporal pattern of symptoms in relationship to work
1. Immediate onset beginning at work with resolution soon after coming home
2. Delayed onset beginning 4–12 h after starting work or after coming home
3. Immediate onset followed by recovery with symptoms recurring 4–12 h after initial exposure to suspect agent at work
E. Improvement away from work
IV. Identify potential risk factors
A. Obtain a smoking history along with current smoking status and quantitate number of pack years
B. Asthmatic symptoms preceding current work exposure
C. Atopic status
1. Identify consistent history of seasonal nasal or ocular symptoms
2. Family history of atopic disease
3. Confirmation by epicutaneous testing to a panel of common aeroallergens
D. History of accidental exposures to substances such as heated fumes or chemical spills

Although questionnaires are essential, they have limitations. Occupational questionnaires are sensitive but not specific and, therefore, cannot be used to make a diagnosis of OA without confirmatory objective testing. The poor correlation between a history of OA and OA confirmed by specific challenge testing emphasizes the limitations of the medical history. While several itemized questionnaires have been utilized for obtaining an occupational history by different investigators, there is as yet no standardized instrument available for this purpose. However, several groups of experienced investigators have developed questionnaires, which have been validated by repeated use in cross-sectional or longitudinal studies. Recently,

Table 17.3 Etiologic agents of occupational asthma and reported immunologic tests

Agent	In vivo	In vitro
Azodicarbonamide	Prick tests with 0.1, 1, and 5 % azodicarbonamide	Not done
Baby's breath	Intradermal titration testing	RAST/histamine release
Bacillus subtilis enzymes	Prick tests with 0.05, 0.5, 5, and 10 mg/ml	RAST/radial immunodiffusion
Buckwheat flour	Prick test with 10 mg/ml	Reverse enzyme immunoassay/histamine release
Carmine dye	Skin test with coccus cactus	RAST to dyes
Castor bean	Prick test with 1:100 extract	Not done
Chloramine-T, halazone	Scratch test at 10^{-5} dilution	Not done
Chromate	Prick test at 10, 5, 1, and 0.1 mg/ml $Cr_2(SO_4)_3$	RAST to HSA-chromium sulfate
Cobalt	Patch tests	RAST to HSA-cobalt sulfate
Coffee bean	Intradermal titration to coffee bean extract	RAST to coffee bean extract
Diazonium tetrafluoroborate (DTFB)	Not done	RAST to HSA-DTFB
Dimethylethanolamine	Prick tests to dimethylethanolamine undiluted at 1:10, 1:100, and 1:1000	Not done
Douglas-fir tussock moth	Cutaneous tests with 1:25 extract	Histamine release
Dyes, textiles	Prick or scratch tests to dyes at 10 mg/ml in 50 % glycerine	HSA-dye
Egg proteins	Prick tests with 1:10 w/v egg white, egg yolk, whole egg; prick tests to 10 mg/ml egg white fractions	RAST to egg proteins
Ethylenediamine	Intracutaneous test to 1:100 ethylenediamine	Not done
Furan binder	Not done	RAST to catalyst, sand, and furfuryl alcohol
Garlic	Prick test titrations beginning at 10^{-5} garlic extract	PTRIA for IgE against garlic extract
Grain dust, grain dust mite	Prick and intracutaneous tests with grain dust and grain mite	Not done
Grain weevil	Skin test to weevil extract	Not done
Gum acacia	Skin tests with gum arabic	Not done
Guar gum	Prick tests with 1 mg/ml guar gum	RAST with guar gum
Hexamethylene diisocyanate (HDI)	Prick tests to HSA-HDI	ELISA to HSA-HDI
Hexahydrophthalic anhydride (HHPA)	Not done	RAST to HSA-HHPA
Hog trypsin	Skin test to trypsin	Histamine release
Laboratory animals	Skin tests with serum and urine extracts from animals	ELISA

(continued)

Table 17.3 (continued)

Agent	In vivo	In vitro
Latex	Prick test using low ammonia latex solution	Not done
Locusts	Prick tests with locust extract at 0.1, 1, and 10 mg/ml	ELISA
Mealworm	Prick test titration beginning at 1:20 w/v Tenebrio molitor (TM) extract	RAST to TM extract
Diphenylmethane diisocyanate (MDI)	Prick test with 5 mg/ml HSA-MDI; intradermal test with 1 μg/ml and 10 μg/ml	ELISA to HSA-MDI
Mushroom	Prick test with mushroom extract	Not done
Nickel	Prick tests with $NiSO_4$ at 100, 10, 5, 1, and 0.1 mg/ml	RAST to HSA-$NiSO_4$
Papain	Skin test with papain at 1.25–20 mg/ml	RAST to papain
Pancreatic extract	Prick tests with 1:100 and 1:1,000 extracts	Not done
Penicillin	Prick tests to ampicillin at 10^{-3} to 10^{-2} mol/l, benzylpenicilloyl polylysine at 10^{-6} mol/l and minor determinants at 10^{-2} mol/l	Not done
Penicillamine	Prick tests with penicillamine, major and minor penicillin determinants at 0.01, 0.1, and 1 mg/ml	Not done
Phthalic anhydride (PA) and tetrachlorophthalic anhydride (TCPA)	Prick and intradermal tests to HSA-PA and HSA-TCPA	ELISA; PTRIA to HSA-PA only
Platinum	Prick tests with complex platinum salts from 10^{-3} to 10^{-11} g/ml	RAST to $(NH_4)_2PtCl_2$, RAST to HSA-platinum, and histamine release
Poultry mites	Skin tests with 1:10 w/v Northern fowl mite (NFM)	RAST to NFM
Protease bromelain	Prick test with bromelain at 10 mg/ml	RAST to bromelain
Redwood	Prick test to redwood sawdust extract	Not done
Spiramycin	Prick tests with 10 and 100 mg/ml spiramycin	Not done
Tobacco	Skin tests with green tobacco extract 10 mg/ml	RAST with green tobacco extract
Toluene diisocyanate (TDI)	Prick test to 5 mg/ml HSA-TDI	RAST and ELISA to HSA-TDI, histamine release
Trimellitic anhydride (TMA)	Prick tests to 3.4 mg/ml HSA-TMA and TMA in acetone	PTRIA with HSA-TMA
Western red cedar (WRC)	Prick tests with 25 mg/ml WRC extract; intracutaneous testing with 2.5 mg/ml WRC	Not done
Wheat flour	Prick tests with 10 % w/v extract	RAST to wheat flour and wheat flour components

validated questionnaires are now available to help primary care physicians recognize a case of work-related asthma.

The basic components of a structured occupational questionnaire include an employment history and medical history. The employment history should ascertain information regarding the individual's work process including all jobs that could be related to specific exposures, work processes in adjacent areas, work shift hours, and previous jobs where the worker may have been exposed to similar or identical agents. The medical history should determine any relationship of symptoms experienced before, during, or after work to a specific exposure in the workplace; duration of symptoms after leaving the workplace; improvement of symptoms on weekends or vacations; associated upper respiratory and dermatologic symptoms; systemic symptoms such as fever, chills, or temperature; smoking history; preexisting allergy/asthma history; and previous chemical spill exposure.

The classic presentation of a worker with OA often consists of symptoms which begin at work and resolve or improve either shortly after leaving the workplace at night, during weekends, or while on vacation. However, a worker with OA may not improve away from the workplace because of chronic airway inflammation as a result of persistent workplace exposure to an agent for months or years after the initial onset of symptoms. In addition, patients with the reactive airways dysfunction syndrome (RADS) typically do not improve away from work. Therefore, the diagnosis of OA should not be overlooked because of the apparent lack of correlation of symptoms to workplace exposure.

Material Safety Data Sheet (MSDS) are an essential part of the occupational history. They provide valuable information regarding generic chemical names and specific constituents of raw materials being used in the workplace. They also provide standard information about threshold limit values (TLVs) and permissible exposure levels (PELs) of potentially toxic and/or sensitizing agents. When available, assistance from industrial hygienists or safety officers familiar with the workplace and the worker's exposure history should be sought. Occasionally these documents have proprietary agents that are not specifically listed which may cause OA, and therefore, it may be necessary for the clinician to contact the company to obtain additional exposure information.

Differential Diagnosis

A diagnosis of OA can be incorrectly made in individuals with preexisting asthma or allergic asthma due to non-workplace allergens. However, workers with preexisting asthma can still have work-exacerbated asthma. In these cases, symptoms are aggravated by exposure to irritants, physical factors (e.g., cold air), or common indoor allergens (e.g., dust mites) in the workplace. It is important to differentiate OA from other diseases such as chronic obstructive lung disease, pneumoconiosis, bronchiolitis obliterans, and endotoxin-induced asthma-like syndromes such as grain fever or byssinosis using appropriate

diagnostic testing. Whereas many of these disorders are associated with abnormal chest x-rays and diffusing capacity (DLCO), these tests are usually normal in workers with OA.

Immunologic Assessment

Immunologic mechanisms have been confirmed for many causes of OA. Therefore, it is important to investigate whether specific immune responses to suspected agents with allergenic potential are involved. Although identification of an immunologic response to a specific agent helps to phenotype different forms of OA, it is usually not diagnostic. Such a response may only reflect exposure and/or the immunogenic nature of the inciting agent. Cutaneous sensitization to an offending agent indicates a high risk for OA but lacks the specificity needed to diagnose OA. Several types of immune responses have been associated with high molecular weight (HMW) and low molecular weight (LMW) agents that cause OA. Type I, IgE-mediated immune responses have been identified for the majority of HMW proteins derived from a variety of plant and animal sources known to cause OA. IgE-mediated immune responses have also been identified as the underlying mechanism for several LMW chemical agents such as acid anhydrides and platinum salts. Although type II cytotoxic, type III immune-complex, and type IV cell-mediated immune responses have been linked to certain causes of OA, measures of specific IgE are usually the simplest and most readily available tests for diagnosing OA.

High molecular weight antigens are considered complete allergens since they do not require structural modification to elicit a specific immune response. In vivo skin testing and in vitro immunoassays have been used to identify sensitized individuals to these specific allergens. High molecular weight allergens include proteins from animal dander, insect scales, food products, and enzymes used in the food manufacturing and pharmaceutical industries. Low molecular chemical agents require structural modification to act as complete antigens. Traditionally, these reactive chemicals are coupled to a carrier molecule such as an autologous human protein (e.g., human serum albumin or HSA). The chemical hapten-protein conjugate forms new antigenic determinants, which are capable of inducing an IgE-mediated response.

It is important that the test reagents used in the diagnosis of OA be characterized and standardized. Standardization of an allergen extract requires identification of the allergen source, the extraction procedure, and its biochemical composition. The allergen source should be fresh and free of contaminants. The extraction process should record characteristics such as temperature, the medium used for extraction, the extraction time period, and the filtration methods utilized. Proper characterization should include total protein content, molecular weight range of proteins, isoelectric points of each protein, and identification of immunologic and allergenic components. The latter can be determined by a variety of techniques such as ELISA inhibition assays, Western blotting, leukocyte histamine release assays, and endpoint skin test titration techniques.

Low molecular weight chemicals can be conjugated to a carrier protein and used as an antigen for use in immunodiagnostic tests. Platinum chloride salts and sulfonechloramide represent two examples where LMW agents have been directly used as skin test reagents without prior conjugation to proteins. The most common protein carrier used is human serum albumin (HSA). Successful hapten-protein conjugation depends on the buffers used, the amount of protein and chemicals used, and the duration and temperature of the reaction. To determine the degree of chemical linkage to protein, the ratio of chemical ligand to protein carrier (mols/mole) must be established. This analysis is essential since antigenicity and allergenicity of the final conjugate may vary with ligand density. The method of analysis depends on the chemical structure of the compound. For example, spectrophotometric analysis is used to assess aromatic compounds, and free amino analysis is used for chemicals that bind to carrier amines. Gas chromatography and mass spectroscopy are the preferred methods for the analysis of aliphatic chemical-protein antigens. The ideal range of ligand binding should fall between 10 and 20 molecules of chemical per molecule of protein. Over- or under-conjugation of ligand to protein binding can result in poor test antigens. The methods described for biochemical composition of HMW complete proteins can also be used for the analysis of hapten-protein conjugates.

Clinical immunologic assessment of workers suspected for OA should include in vivo and in vitro tests when they are available. The prick skin test is the most commonly used in vivo test to assess IgE-mediated hypersensitivity responses to occupational protein allergens. The prick test concentration usually ranges between 0.1 and 10 mg/ml.

In vitro tests can detect specific IgG and IgE antibody responses to a suspected causative occupational agent. For the ELISA, allergen is bound to a plastic well with high binding avidity and then incubated with the subject's serum and antihuman IgE conjugated to alkaline phosphatase. This results in a colorimetric change, which is measured by spectrophotometry. The optical density is proportional to the amount of specific IgE in the subject's serum.

For natural protein allergens such as enzymes, ELISA-specific IgE assays are specific assays but tend to be less sensitive than skin prick testing. False-positive reactions can occur in the presence of high serum total IgE levels due to nonspecific binding, and false negatives can occur as the result of binding of a specific isotypic antibody other than IgE.

ELISA assays are also used to measure specific IgG antibodies. The significance of elevated specific IgG antibodies to a workplace allergen is less clear. There is some evidence to suggest it could represent a biological marker of exposure to chemicals such as MDI. Specific IgG antibodies to TMA-HSA conjugated antigens have been found in both trimellitic anhydride-exposed workers with hemolytic anemia and pulmonary hemorrhage and in workers with late systemic symptoms, suggesting that such antibodies may have a mechanistic role in cytotoxic or immune complex-mediated responses.

The proper interpretation of an immunologic test used in the diagnosis of OA requires validation against an accepted benchmark, such as the specific bronchoprovocation test (SBPT). Furthermore, proper standardization of an immunoassay always requires the use of well-established positive and negative control sera.

Other in vitro assays such as MCP-1, lymphocyte proliferation, and leukocyte histamine release have been used primarily as research tools in the investigation of workers with OA. Table 17.2 lists several high and low molecular weight agents known to induce OA in workers and the reported immunologic tests, which have been performed as part of their assessment. It should be emphasized that skin test responses and in vitro specific antibody responses may decline within months or years after removal from exposure from the causative agent which may limit their clinical utility in the evaluation of workers remotely exposed to a specific agent.

Physiologic Assessment

Many approaches have been used in measuring lung function in workers suspected of OA. Ideally, lung function should be monitored in the workplace during a known exposure to a suspected causative agent. However, this may present logistical problems when conditions in the workplace are not suitable for pulmonary function testing. Often, personnel experienced in proper performance of pulmonary function testing are not readily available to conduct serial testing of lung function or employers are not cooperative with such testing.

Spirometry should include the forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and the maximum midexpiratory flow rate ($FEF_{25–75}$). Assessment of cross-shift lung function (i.e., pre- and post- shift FEV1) has been used to correlate asthma symptoms to workplace exposure, but this approach lacks sensitivity for confirming OA. Multiple assessments of PEFR at work (four to five times/day) often capture enough data to diagnose or exclude OA. Furthermore, cross-shift changes in a worker's lung function have been found to be directly proportional to their level of exposure to the sensitizing agent.

Serial measurements of peak expiratory flow rates (PEFR) performed properly correlate moderately well with results of specific bronchoprovocation testing used in the diagnosis of OA. Serial PEFR measurements should be interpreted with caution due to patient noncompliance or the potential for falsification of measurements. Computerized peak flow meters which record effort and time of each measurement can improve the reproducibility and potential for unreliable readings.

Nonspecific bronchial hyperresponsiveness (NSBH) testing with methacholine or histamine is essential for confirming the presence or absence of airway hyperresponsiveness, a central feature of asthma. Subjects with a positive methacholine test and evidence of specific IgE to an HMW have been demonstrated to more likely exhibit a positive SBPT to that agent. Negative tests of NSBH are most useful in excluding a current diagnosis of OA in a currently symptomatic exposed worker.

The SBPT is considered the gold standard for the diagnosis of OA. This test should only be administered in specially equipped centers under the supervision of physicians experienced in conducting this procedure. Specific provocation testing is very time consuming and expensive to perform and therefore not readily available. However, if performed properly, the SBPT can be performed with minimal risk.

Several airway response patterns may be elicited that are characteristics for workers presenting with OA. An isolated early asthmatic response (EAR) is characterized by the immediate onset of asthma symptoms after exposure to an agent that is more commonly associated with IgE-mediated OA. An isolated late asthmatic response (LAR), which occurs until 4–12 h after exposure to the challenge agent, is more characteristic of non-immunologic OA induced by LMW chemical agents. Finally, workers with OA may exhibit a dual asthmatic response (DAR) characterized by an EAR followed by recovery period and then a LAR. Multiple physiologic patterns have been observed in OA caused by chemicals. For example, workers with diisocyanate-induced OA present 30–50 % of the time with DARs, 40 % of the time with an isolated LAR, and less than 10 % of the time with an isolated EAR.

Asthma occurring in the workplace in the absence of a latency period is characteristic of reactive airways dysfunction syndrome (RADS), also referred to as irritant-induced OA. Reactive airways dysfunction syndrome typically occurs after one or more repetitive large inhalational exposure to a toxic chemical agent such as ammonia gas, acidic fumes, smoke, or spray paints. Reactive airways dysfunction syndrome must be differentiated from the irritant symptoms which occur in patients with preexisting asthma. Irritant symptoms disappear promptly after cessation of exposure and are not associated with prolonged bronchoconstriction or bronchial hyperresponsiveness, characteristic of RADS. Workers with RADS typically do not manifest airway response patterns seen with OA induced by HMW and LMW agents. Being familiar with the different airway responses associated with various agents known to cause OA can greatly facilitate the correct diagnosis of OA.

Clinical Assessment

The first step for assessing a suspected case of OA is to obtain a careful physician-administered history. As mentioned, an occupational questionnaire is useful in capturing the necessary clinical and exposure information and to help validate information obtained by the physician-administered history. Workers with OA may present with dyspnea, chest tightness, wheezing, and cough in or out of the workplace. Upper airway symptoms such as rhinorrhea, nasal congestion, or ocular pruritus preceding the onset of asthmatic symptoms are especially characteristic of IgE-mediated sensitization to HMW agents. Symptoms may begin after immediately starting a work-shift (within 1–2 h) or several hours after starting work. Review of Material Safety Data Sheet (MSDS) is often very helpful for identifying agents known to cause OA.

If the history is positive for OA, a test of NSBH (i.e., methacholine or histamine provocation) should be performed at work or within 2 h after the work-shift. Results of this test are usually reported as PC_{20} measurements (provocative concentration of methacholine or histamine causing a 20 % decrease in FEV1). A negative methacholine test (PC_{20} >10 mg/ml) would exclude airway hyperresponsiveness (AHR) and is a good negative predictor for asthma. A positive methacholine test indicates

the presence of AHR suggestive of asthma but is nonspecific and does not confirm a diagnosis of OA. In this case, assessment of lung function performed at and away from the workplace to demonstrate airway hyperresponsiveness around the suspected agent is very useful for supporting a diagnosis of OA. When possible, a workplace challenge, which consists of supervised measurements of lung function (i.e., FEV1) in the actual work site before and during work-shifts for at least 1 week of work exposure, should be conducted. Improvement of symptoms and lung function after removal from the workplace with subsequent deterioration after reintroduction into the workplace further supports a diagnosis of OA, except in the case of RADS.

If a workplace challenge cannot be performed, peak expiratory flow rate monitoring should be conducted over 2–3 weeks at work. The worker should measure and record his/her PEFR every 3 h while awake or at least four times a day. Work exposure, symptoms, and medication usage should be recorded in a diary during this time. Diurnal variability of greater than 20 % at work as compared to normal variability at home is consistent with OA. Visual analysis of weekly plots of PEFR measurements by a blinded physician is the most reliable method of analysis. A consistent pattern of declining PEFRs at work and improvement away from work is strong evidence supporting a diagnosis of OA. Peak expiratory flow rate measurements should be interpreted with caution as workers who are seeking compensation could potentially falsify their readings.

The gold standard for the diagnosis of OA is the SBPT. If a specific substance in the workplace is suspected of causing OA and the workplace challenge is equivocal, an SBPT may be necessary. The PC_{20} ascertained by methacholine or histamine testing may be helpful for estimating the initial dose of an occupational agent prior to the specific inhalation challenge test. Because these tests are very time consuming and potentially risky, they should be performed only by experienced individuals. An SBPT should not be performed in workers with severe cardiac or pulmonary disease (FEV1 <60 %). Specific inhalation challenge tests have also been used to document causation of OA by new substances in index cases and for medical/legal purposes in proving or excluding a worker's eligibility for workmen's compensation. Although specific challenge tests confirm a diagnosis of OA if positive, negative tests do not always exclude the diagnosis in workers who have been removed from the workplace for a period of time during which bronchial AHR to the suspected agent may have resolved. It is therefore important to perform an SBPT either before or shortly after removing the workers from their workplace exposure. Another potential problem with specific inhalation challenge testing is poor standardization of methods used between different centers. Furthermore, it may not be possible to reproduce workplace exposure conditions in the laboratory since a number of technical factors such as temperature, atmospheric pressure, and concentration must be controlled in order to assure consistent exposures to chemical agents (i.e., toluene diisocyanate). In Canada, regional centers have adapted standardized methodologies for performing inhalational challenges that obviate this problem.

In addition to lung function assessment, it is important to identify whether the worker is atopic by skin testing with common aeroallergens and other appropriate allergens, especially when HMW substances are suspected of causing OA. These workers can often be skin tested using the actual agent they are exposed to such as flour, coffee beans, castor beans, and egg enzymes (Table 17.3). In vitro assays to measure specific IgE to these proteins can also be performed but are less specific than in vivo skin testing. As previously mentioned, the presence of either a positive prick skin test or serum-specific IgE only indicates IgE-mediated sensitization has occurred and does not prove a clinical diagnosis of OA.

Immunologic testing by ELISA using serum from workers exposed to LMW reactive chemicals is also useful for supporting IgE-mediated sensitization when present. IgG antibodies may represent markers of exposure to a particular chemical antigen. In vivo skin testing to LMW chemical agents has been less reliable for confirming IgE-mediated sensitization. Other in vitro techniques, such a leukocyte histamine release, leukocyte inhibitory factor, and MCP-1, have thus far been reserved for research purposes only.

Treatment

Once the diagnosis of OA has been confirmed, the treatment of choice should be to remove the worker from further exposure. Studies evaluating the clinical course of workers after removal from the workplace have found that persistence of their asthma correlated with the duration of exposure and symptoms prior to diagnosis. Individuals with OA caused by diisocyanates or western red cedar wood dust had a better prognosis if they were diagnosed early and had relatively well-preserved lung function and a less AHR. In contrast, symptomatic workers who remained in the workplace for longer periods of time experienced greater deterioration of their lung function leading to chronic persistent asthma requiring increased medication use even after being removed from further exposure. Use of respirators in the work environment generally does not reduce exposure or prevent clinical deterioration. Some studies have suggested that certain types of respirators such as airstream helmets may offer adequate protection for the worker from the offending agent; however, they are generally not considered to be adequate substitutes for absolute avoidance measures. Pharmacologic treatment of acute or chronic OA is similar to non-occupational asthma, which involves inhaled corticosteroids with or without selective long-acting β_2-agonists, leukotriene-modifying agents, theophylline, cromolyn, or nedocromil sodium; however, the latter two medications are not readily available as metered dose inhalers or dry powder inhalers in the United States. Medications can be used in various combinations depending on the severity of the worker's symptoms. Immunotherapy may play a role in the treatment of some forms of OA caused by HMW protein allergens such as laboratory animal proteins.

Prevention and Immunosurveillance

The primary categories of prevention include reducing exposure to known occupational inciting agents, identifying susceptible workers and removing them from exposure, administering workplace controls to reduce the number of workers exposed or the duration of their exposure, providing personal protective equipment in the workplace, and educating "at-risk" atopic individuals about avoidance of occupations where the likelihood for developing OA would be increased (i.e., laboratory handlers). Effective prevention of OA requires the cooperation between management and workers in the implementation of good industrial measures aimed at preventing exposure to agents known to cause OA. Every attempt should be made to minimize a worker's exposure to potentially problematic agent(s) through the institution of strict handling procedures. Workers should be continually educated about the importance of adhering to those procedures in order to avoid inadvertent exposures such as chemical spills. Prescreening of already hired workers for atopy should be considered before assigning employees to jobs where they would have inhalational exposure to sensitizing proteins (e.g., latex, laboratory animal, and enzyme proteins). Comprehensive immunosurveillance programs for detecting and monitoring workers at increased risk for exposure to known inducers of OA need to be implemented in industries that commonly use agents known to cause OA. Industries that have implemented such comprehensive immunosurveillance programs have been successful in reducing the incidence of asthma in the workplace.

Evidence-Based Medicine

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   Asthma in the Workplace is a comprehensive authoritative book on all aspects of occupational asthma. This book is an excellent resource for any individual who is interested in learning more about occupational lung diseases. Asthma in the Workplace goes into detail regarding pathophysiology, genetics, epidemiology, disease mechanisms, specific causes of occupational asthma, clinical diagnosis, treatment, prevention, and surveillance. It is considered the most up-to-date resource on this topic.
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   Material Safety Data Sheets are an integral part of evaluating workers suspected of having occupational asthma. Unfortunately, these documents frequently have limitations that may thwart the clinician's ability to make a correct diagnosis of this disease. Health care individuals should understand how to interpret information provided by MSDS and recognize that they often contain incomplete information.

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This study sought to evaluate the utility of screening TMA skin testing as part of an ongoing immunosurveillance program to screen workers for IgE-mediated sensitization. The results indicated that TMA skin testing correlates very well with serologic TMA-specific IgE, but when both tests are used together, the sensitivity and specificity of these screening tests are increased.

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Chapter 18
Asthma and Pregnancy

Peg Strub

Asthma and Pregnancy

Asthma is one of the most common chronic diseases and affects up to 8 % of pregnancies. The "one-third rule" states that in pregnancies with asthma, a third of the patients will improve, a third will get worse, and a third will stay the same.

Asthma in two-thirds of pregnant women will either worsen or show no improvement; the importance of treating all persistent asthmatics with Inhaled corticosteroids (ICS) must be emphasized. One large study shows that in women using Inhaled corticosteroids (ICS) prior to pregnancy, the number of emergency department visits for asthma remained unchanged, and the rate of physician visits for asthma actually decreased after pregnancy.

Despite worsening or unchanged asthma in two-thirds of the patients, pregnant women in general report a decrease in asthma symptoms throughout the pregnancy particularly in the last 4 weeks of pregnancy. This perceived improvement may be explained by hormonal changes or other factors and may lead to difficulties with medication adherence.

Adverse Pregnancy Outcomes for Patients with Asthma

Studies have shown that pregnant women with asthma are at increased risk for pregnancy-induced hypertension, preeclampsia, eclampsia, vaginal bleeding, perinatal mortalities, premature birth, low birth weights, and neonatal sepsis as well as

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pulmonary embolism and depression. For pregnancies complicated by moderate to severe asthma, studies report an increased incidence of cesarean section deliveries. Pregnancies with poorly controlled asthma are at risk for intrauterine growth retardation (IUGR).

Physiology

During pregnancy, many physiologic changes occur in the mother. Understanding these changes is important not only for the care of the pregnant patient with asthma but also for the fetus.

Maternal Respiratory Physiology

In early pregnancy, 60–70 % of women feel dyspneic due to hyperventilation. The mechanism of the hyperventilation is progesterone mediated with a resultant increase in tidal volume. As pregnancy progresses, an up to 50 % increase in minute ventilation occurs with a corresponding increase in oxygen consumption and carbon dioxide production. The increase in carbon dioxide production is partially blunted by an increase in renal excretion of bicarbonate (explaining the polyuria of early pregnancy), resulting in a mild compensatory respiratory alkalosis. During pregnancy, arterial blood gases (ABGs) typically have pH levels of 7.42–7.46, PCO2 levels of 26–30 mmHg, and PO2 levels of 99–106 mmHg.

The increased size and pressure of the uterus limits diaphragmatic excursion, lowering residual volume and functional residual capacity. Compensation occurs by increased mobility and flaring of the ribs as well as by progesterone-mediated relaxation of bronchial smooth muscle. The net result is that pulmonary function test results remain unchanged for forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), the forced expiratory volume in 1 s to forced vital capacity ratio (FEV1/FVC), and peak expiratory flow rate (PEFR) (Table 18.1).

Maternal Cardiovascular Physiology

Although central venous pressure remains unchanged, there is a 40 % increase in maternal cardiac volume and cardiac output with a marked increase in left ventricular mass, compliance, and end-diastolic volume. Total blood volume increases by 40 %, but plasma volume increases more than red cell mass resulting in anemia of pregnancy or physiologic hemodilution (Table 18.2).

Table 18.1 Maternal respiratory physiology

60–70 % patients have dyspnea of early pregnancy due to hyperventilation
Progesterone-related tidal volume increase
Minute ventilation increases up to 50 % with increased O2 consumption and CO2 production
Compensatory respiratory alkalosis (pH 7.42–7.46, PCO2 26–30, and PO2 99–106)
Increased size and pressure of uterus limits diaphragmatic excursion
Increased mobility and flaring of ribs
Progesterone may relax bronchial smooth muscle
Pulmonary function tests remain essentially unchanged

Table 18.2 Maternal cardiovascular physiology

Central venous pressure remains unchanged
40 % increase in maternal cardiac volume
40 % increase in cardiac output
Increase in left ventricular mass, compliance, and end-diastolic volume
Plasma volume increases more than red cell mass: anemia of pregnancy

Table 18.3 Maternal gastroesophageal reflux

Common complaint during pregnancy
May be due to progesterone-mediated relaxation of smooth muscle of esophagus with resultant
Increase in intra-abdominal pressure

Maternal Gastroesophageal Reflux

Gastroesophageal reflux during pregnancy is a common complaint and may exacerbate asthma. The increase in gastroesophageal reflux may be due to progesterone-mediated relaxation of smooth muscle of the esophagus with a resultant increase in intra-abdominal pressure (Table 18.3).

Fetal Physiology

The fetus functions by aerobic metabolism even though the PO2 level of the fetus is one-fourth of the PO2 level of the mother. Mechanisms allowing the fetus to thrive include an increase in hemoglobin content and the oxygen affinity of fetal hemoglobin, preferential blood flow to vital organs, high cardiac output, and leftward shift of the oxygen dissociation curve.

Table 18.4 Fetal physiology

Fetus functions by aerobic metabolism
Mechanisms allowing fetus to thrive
Increase in hemoglobin content
Increase in oxygen affinity of fetal hemoglobin
Preferential blood flow to vital organs
High cardiac output
Leftward shift of oxygen dissociation curve
Low maternal PCo2 important to acid-base balance
Increase in maternal PCo2 may result in fetal acidosis, even with adequate oxygenation

A low maternal PCO2 is important to normal fetal acid–base balance. An increase in maternal PCO2 may affect this balance and result in fetal acidosis, even with adequate oxygenation (Table 18.4).

Asthma Treatment During Pregnancy

Treatment goals are providing optimal therapy to maintain control of asthma for maternal health and quality of life as well as for normal fetal maturation. As per the National Asthma Education Prevention Program (NAEPP), asthma control is defined as follows:

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities
- Maintenance of normal or near-normal pulmonary function
- Minimal use of short-acting inhaled B2-antagonist
- Minimal or no adverse effects from medications (always consult latest NAEPP guidelines)

Assessment of Asthma

Pregnant women with asthma should have a thorough assessment of their asthma control. Patients should be asked about the frequency of their symptoms both during the day and at night/early morning, how often symptoms interfere with normal activities, and the usage of short-acting B2-agonists for symptom relief (not for exercise-induced bronchospasm prevention). Validated questionnaires such as the ATAQ, ACQ, and ACT are particularly helpful in classifying the level of asthma control.

In addition, a complete assessment of asthma must include objective measurements. All patients should have pulmonary function testing at their initial evaluation to determine disease severity. At subsequent office visits, repeat pulmonary function testing is preferable, but at a minimum, assessment of peak expiratory flow rates (PEERs) should be checked. Patients should be prescribed a peak flow meter or a portable FEV1 device to monitor asthma variability.

Assessment of the Fetus

All pregnant women should be advised to be attentive to fetal activity. Serial ultrasound evaluations beginning at 32-week gestational age may be considered for women with moderate to severe asthma and women with poorly controlled asthma. In addition, after a severe exacerbation, an ultrasound evaluation may be reassuring.

Medication Reassurance

Patients need to be reassured that asthma medications are safe and advised that the risks of treatment are much less than the risks of untreated asthma. Concern about side effects in the fetus may interfere with medication adherence and lead to undertreatment of asthma.

Education

All pregnant women with asthma should receive asthma education emphasizing the important benefits of treatment and its impact on the fetus. Written and verbal instructions should be given for the proper use of medications, spacers, and peak flow meters. Patients should be taught how to monitor inhaler usage to avoid running out of medication. Patients should also be counseled on the dangers of overuse and over-reliance on short-acting B2-agonist (SABA) medications.

Smoking

Any patient who is smoking should be advised to quit and be referred to a smoking cessation program. Besides adversely affecting asthma. In addition to adversely has deleterious effects on the mother and the fetus.

Triggers

An assessment of common triggers with instructions on avoidance and control should be part of all patient evaluations. Patients with exposure to secondary smoke, including woodburning stoves and fireplaces, should also be counseled on the importance of avoidance. Patients should be advised to avoid exposure to irritants that trigger their symptoms including sprays, cleaning agents, and occupational sensitizers. Viral infections are the most common triggers causing severe exacerbations. Influenza vaccines and frequent hand washing are recommended, particularly during the flu season. Increased body weight and high-panic-fear state can worsen asthma and complicate treatment in asthma.

Treatment Plans

Together with the patient, providers should develop medication regimens that are effective and easy to follow. Providers need to be aware that pregnant patients with asthma may have difficulty following complicated treatment regimens.

All patients should receive a written self-management plan. The plan should emphasize home management of exacerbations, including instructions on when to start oral steroids and when and where to call for help. Ideally, these plans should be based on both symptoms and peak flow meter readings.

In addition, it is important to include the obstetrical provider in the asthma care team early on. The obstetrical provider will be assessing the patient more frequently.

Medications

Inhaled Short-Acting B2-Agonists (SABAs)

Inhaled short-acting B2-agonists (SABAs) are one of the mainstays of therapy but should be administered only as needed. The preferred medication is albuterol, based on more published data on safety.

Inhaled Long-Acting B2-Agonists (LABAs)

Inhaled long-acting B2-agonists (LABAs) have a profile similar to the inhaled short-acting B2-agonists (SABAs) with the exception that these drugs are retained longer in the lungs. The preferred medication is salmeterol (Serevent), due to the longer availability of the drug in the United States (Table 18.6).

There has been controversy about inhaled long-acting B2-agonists (LABAs) increasing risks of hospitalization and death in asthmatics. It would be prudent to use inhaled long-acting B2-agonists (LABAs) only as add-on therapy to medium- or high-dose inhaled corticosteroids (ICS), if asthma remains poorly controlled.

Inhaled Corticosteroids (ICS)

Inhaled corticosteroids (ICS) are the cornerstone of therapy for the pregnant woman with persistent asthma. Multiple studies have emphasized the decrease in asthma exacerbations and the improvement in FEV1 with the use of inhaled corticosteroids (ICS). Even studies in large birth registries have failed to relate the use of inhaled corticosteroids (ICS) in low–moderate doses to any unfavorable perinatal outcome, including increased incidence of congenital malformations. However, a study that looked at higher doses of inhaled corticosteroids (ICS) (>1000 mcg/day) during the first trimester showed a 63 % increase in risk of all congenital malformations. This study had multiple issues including a small number of patients with a daily dose over 1000 mcg, and it was difficult to determine whether the increased incidence of malformations was due to inadequately controlled asthma or due to high-dose inhaled corticosteroids (ICS). More studies are needed. The preferred medication is budesonide (Pulmicort), based on published data (Table 18.7).

Oral Corticosteroids

Oral corticosteroids are used in the treatment of poorly controlled severe persistent asthma or for the treatment of asthma exacerbations. On occasion, a short course of oral corticosteroids may be necessary to gain control of asthma (Table 18.6). Studies have shown that oral corticosteroid use has been associated with a decrease in birth weight of approximately 200 g without an increased incidence of small for gestational age (SGA) infants. In addition, there is an association with an increased incidence of isolated cleft lip (without cleft palate) especially when oral corticosteroids are taken during the first trimester. Systemic steroid use has also been associated with an increased incidence of preterm births and preeclampsia. Hypertension and gestational diabetes are potential maternal complications. The preferred drugs are prednisone and prednisolone due to limited placental transfer.

Cromolyn Sodium

Cromolyn sodium is safe for pregnancy. It is considered an alternative but not a preferred option for mild persistent asthma (Table 18.6). The availability of this drug is limited.

Nedocromil

Animals' studies have been reassuring on the use of nedocromil in pregnancy. It is considered an alternative, but not a preferred, option for mild persistent asthma. The availability of this drug is limited (Table 18.6).

Theophylline

Theophylline is safe for pregnancy in the usual therapeutic serum level range of 5–12 ug/mL. However, theophylline has many side effects and drug–drug interactions. Studies have shown that women treated with theophylline have a high rate of discontinuance of the drug. Inhaled corticosteroids (ICS) have greater efficacy with fewer side effects. Oral theophylline would be an alternative but not preferred option for the treatment of mild or moderate persistent asthma (Table 18.6).

Leukotriene Receptor Antagonists (LTRAs)

There are limited studies on treatment with leukotriene receptor antagonists during pregnancy available for review. There is more data on montelukast in pregnancy than zafirlukast and zileuton; montelukast is considered the preferred leukotriene receptor antagonist option. Animal data on zafirlukast shows no teratogenicity at high doses. Animal studies on zileuton do not support its use in pregnancy. Leukotriene receptor antagonists would be an alternative but not preferred option for the treatment of mild or moderate persistent asthma (Table 18.6).

Ipratropium

There are reassuring animal studies for ipratropium (Atrovent, Atrovent HFA). Inhaled ipratropium is considered safe for pregnancy. Note that when atropine is administered systemically to the mother, the fetus can develop tachycardia (Table 18.9).

Tiotropium

Tiotropium may be an option for asthma that is not well controlled during pregnancy on inhaled corticosteroids (ICS) and long-acting B2-agonists (LABAs). However, there is currently no safety data on the use of tiotropium during

pregnancy. Caution needs to be used and the benefits versus the risks need to be weighed if considering tiotropium during pregnancy (Table 18.6).

Anti-immunoglobulin E

Omalizumab is an IgG monoclonal antibody (recombinant DNA derived) which inhibits IgE binding to the high-affinity IgE receptors on mast cells and basophils. It is considered a potential option for add-on therapy for moderate to severe persistent asthma only when asthma is inadequately controlled. No human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. However, further studies are needed. Patients who are pregnant with inadequately controlled asthma on high-dose steroids who may be candidates for anti-immunoglobulin E therapy should be referred to a specialist (Table 18.6).

Treatment Guidelines

The pharmacologic treatment approach for pregnant woman with asthma is based on stepwise asthma care. This approach follows established guidelines for intermittent asthma and mild, moderate, and severe persistent asthma (Table 18.5). It recommends controller mediations for all levels of persistent asthma. Doses of medications used in pregnancy and lactation are included in Tables 18.6 and 18.7. These guidelines may be modified to fit the needs of individual patients (Table 18.8).

Intermittent Asthma (Step 1)

Patients with intermittent asthma should be treated with inhaled short-acting B2-agonists (SABAs), preferably albuterol, as needed. However, it is important to note that even patients with intermittent asthma can experience life-threatening exacerbations and should have treatment plans for exacerbations that include oral corticosteroids (Tables 18.5, 18.8, and 18.9).

Mild Persistent Asthma (Step 2)

Patients with mild persistent asthma should be treated with low-dose inhaled corticosteroids (ICS), preferably budesonide (Pulmicort), with inhaled short-acting B2-agonists (SABAs), preferably albuterol, used as needed. The alternative but less preferable treatments include leukotriene receptor antagonists (LTRAs), sustained-release theophylline, cromolyn, and nedocromil (Tables 18.5, 18.6, 18.7, and 18.8).

Table 18.5 Guide to asthma severity

Components of severity	Category	#Symptoms	#Symptoms/night	SABA use	Activity	FEV1 or PEFR	FEV1/FVC	Step
Impairment normal Fev1/FVC: 8– to 19 years 85 %	Intermittent	≤2 days/week	≤2 nights/month	≤2 days/week	None	≥80 %	Normal	1
20–39 years, 80 %	Mild persistent	>2 days/week but not daily	3–4×/month	>2 days/week not daily and not more than 1×/day	Minor	≥80 %	Normal	2
40–59 years, 75 %	Moderate persistent	Daily	>1×/week but not nightly	Daily	Some	>60–<80 %	Reduced 5 %	3
60–80 years, 70 %	Severe persistent	Continual	Often 7×/week	Several times/day	Extremely	≤60 %	Reduced >5 %	4, 5 or 6

Adapted from NAEPP Guidelines, 2007

Table 18.6 Usual dosages for long-term medications during pregnancy and lactation

Medication	Dosage form	Adult dose
Inhaled corticosteroids (*see estimated comparative daily dosages for inhaled corticosteroids* (Table 18.8))		
Systemic corticosteroids (*applies to all three corticosteroids*)		
Methylprednisolone	2-,4-,8-,16-, 32-mg tablets	7.5–60 mg daily in a single dose in AM or qod as needed for control
Prednisolone	5-mg tablets	
	5 mg/5 mL	Short-course "burst" to achieve control: 40–60 mg/day
	15 mg/5 mL	
Prednisone	1-,2.5-,5-,10-,20-,50-mg tablets	As single dose or two divided doses for 3–10 day
	5 mg/mL, 5 mg/5 mL	
Long-acting inhaled B2-agonists (*note*: *should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids*)		
Salmeterol Formoterol	DPI 50 μg/blister DPI 12 μg/single-use capsule	1 blister q 12 h 1 capsule q 12 h
Combined medication		
Fluticasone/salmeterol	DPI 100 mcg/50 mcg 250 mcg/50 mcg Or 500 mcg/50 mcg HFA 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	1 inhalation bid; dose depends on level of severity or control
Budesonide/formoterol	HFA MDI 80 mcg/4.5 mcg 160 mcg/4.5 mcg	2 puffs bid; dose depends on level of severity or control
Mometasone/formoterol	HFA MDI 100 mcg/4.5 mcg 200 mcg/4.5 mcg	
Cromolyn Cromolyn	MDI 5 mg/puff Nebulizer 20 mg/ampule	2–4 puffs qid 1 ampule qid
Nedocromil	MDI CFC free 2 mg/puff	2 puffs qid
Leukotriene receptor antagonists		
Montelukast Zafirlukast	10-mg tablet 20-mg tablet	10 mg q h 40 mg daily (20-mg tablet bid)
Methylxanthines (*serum monitoring is important* [*serum concentration of 5–12 μg/mL at steady state*])		
Theophylline	Liquids, sustained release	Starting dose, 10 mg/kg/day up to usual maximum; 16 mg/kg/day
	Tablets and capsules	

(continued)

Table 18.6 (continued)

Medication	Dosage form	Adult dose
Immunomodulators		
Omalizumab (anti-IgE)	Subcutaneous injection, 150 mg/1.2 mL, following reconstitution with 1.4 mL sterile water for injection	150–375 mg SC q 2–4 weeks, depending on body weight and pretreatment serum IgE level
		Note: no human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. Further studies are needed and the benefits versus the risks need to be weighed
Anticholinergics		
Tiotropium	18-mcg capsule 2.5 mcg/puff	18-mcg capsule by inhalation qd
		2 puffs qd
		Note: tiotropium may be an option for asthma that is not well controlled during pregnancy on ICS/LABA. Note there is currently no safety data on the use of tiotropium during pregnancy. Caution needs to be used and the benefits versus the risks need to be weighed

Adapted from NAEPP Guidelines, 2007

Moderate Persistent Asthma (Step 3)

Patients with moderate persistent asthma should be treated with medium-dose inhaled corticosteroids (ICS), preferably budesonide (Pulmicort). If control is difficult or cannot be achieved, inhaled corticosteroids (ICS) can be supplemented with an inhaled long-acting B2-agonist (LABA), preferably salmeterol (Serevent). Inhaled short-acting B2-agonists (SABAs), preferably albuterol, should be added as needed. Alternative, but less preferable, treatments include low-dose inhaled corticosteroids (ICS) with an inhaled long-acting B2-agonist (LABA), preferably salmeterol (Serevent). For those intolerant of long-acting B2-agonists (LABAs), either low-dose or medium-dose inhaled corticosteroids (ICS) can be supplemented with the addition of sustained-release theophylline or leukotriene receptor antagonist (LTRA) therapy (Tables 18.5, 18.6, 18.7, and 18.8).

Table 18.7 Estimated comparative daily dosages for inhaled corticosteroid

Medication – daily dose	Low	Medium	High
Beclomethasone MDI	80–240 mcg	More than 240–480 mcg	More than 480 mcg
40 mcg per puff	1–3 puffs twice a day	4–6 puffs twice a day	
80 mcg per puff	1 puff a.m. 2 puffs p.m.	2–3 puffs twice a day	4 or more puffs twice a day
Budesonide DPI	180–540 mcg	More than 540–1,080 mcg	More than 1,080 mcg
90 mcg per inhalation	1–3 inhalations twice a day		
180 mcg per inhalation	1 inhalation a.m. 2 inhalations p.m.	2–3 inhalations twice a day	4 or more inhalations twice a day
Budesonide Nebules	Not applicable	Not applicable	Not applicable
0.25 mg	Not applicable	Not applicable	Not applicable
0.5 mg	Not applicable	Not applicable	Not applicable
1.0 mg	Not applicable	Not applicable	Not applicable
Ciclesonide MDI	160–320 mcg	More than 320–640 mcg	More than 640 mcg
80 mcg per puff	1–2 puffs twice a day	3–4 puffs twice a day	
160 mcg per puff		2 puffs twice a day	3 or more puffs twice a day
Flunisolide MDI	320 mcg	More than 320–640 mcg	More than 640 mcg
80 mcg per puff	2 puffs twice a day	3–4 puffs twice a day	5 puffs or more twice a day
Fluticasone MDI	88–264 mcg	More than 264–440 mcg	More than 440 mcg
44 mcg per puff	1–3 puffs twice a day		
110 mcg per puff		2 puffs twice a day	3 puffs twice a day
220 mcg per puff		1 puff twice a day	2 or more puffs twice a day
Fluticasone DPI	100–300 mcg	More than 300–500 mcg	More than 500 mcg
50 mcg per inhalation	1–3 inhalations twice a day		
100 mcg per inhalation		2 inhalations twice a day	3 or more inhalations twice a day
250 mcg per inhalation		1 inhalations twice a day	2 or more inhalations twice a day
Mometasone DPI	110–220 mcg	More than 220–440 mcg	More than 440 mcg
110 mcg per inhalation	1–2 inhalations p.m.	3–4 inhalations p.m. or 2 inhalations twice a day	3 or more inhalations twice a day

(continued)

Table 18.7 (continued)

Medication – daily dose	Low	Medium	High
220 mcg per inhalation	1 inhalation p.m.	1 inhalation twice a day or 2 inhalations p.m.	3 or more inhalations divided in two doses
Mometasone HFA	100–200 mcg	More than 200–400 mcg	More than 400 mcg
100 mcg per puff	2 puffs once a day	2 puffs twice a day	
200 mcg per day	1 puff a day	2 puffs a day	2 puffs twice a day

Adapted from NAEPP Report (17.27)

Table 18.8 Stepwise approach for managing asthma during pregnancy and lactation: treatment

	Step 1	Step 2	Step 3	Step 4	Steps 5 and 6
Preferred controller choice	None needed	Low dose ICS	Med dose ICS	High ICS/ LABA	Refer for add-on treatment, e.g., anti-IgE[b]
Other controller options	Consider low-dose ICS	LTRA, low-dose theophylline, nedocromil, cromolyn	Low-dose ICS/ LABA, low-dose ICS + LTRA (or +theophylline) Med-dose ICS/ LABA	High-dose ICS +LTRA (or + theophylline) consider tiotropium although no safety studies on usage during pregnancy[a]	Add low-dose OCS; consider tiotropium although no safety studies on usage during pregnancy[a]
Reliever	As-needed short-acting beta 2-agonist (SABA)		As-needed SABA		

Modified from National Heart, Lung, and Blood Institute: National Asthma Education and Prevention Program Asthma and Pregnancy Working group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy ClinImmunol*. 2005;115 (1):36.q

Remember to …

Note presence of fetal activity

Provide guided self-management education (self-monitoring + written action plan + regular review)

Treat modifiable risk factors and comorbidities, e.g., smoking, obesity, and anxiety

Advise about nonpharmacological therapies and strategies, e.g., physical activity, weight loss, and avoidance of sensitizers where appropriate

Consider stepping up if…uncontrolled symptoms, exacerbations, or risks, but check diagnosis, inhaler technique, and adherence first

Consider stepping down if…symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised

[a]Tiotropium may be an option for asthma that is not well controlled during pregnancy on ICS/ LABA. Note there is currently no safety data on the use of tiotropium during pregnancy. Caution needs to be used and the benefits versus the risks need to be weighed

[b]No human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. The benefits versus the risks need to be weighed. Patients should be referred to an asthma specialist

Table 18.9 Medications and dosages for asthma exacerbations during pregnancy and lactation

Medications	Adult dosages	Comments
Short-acting inhaled β2-agonists		
Albuterol Nebulizer solution (5 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL) HFA (90 μg/puff)	2.5–5 mg q 29 min for doses, then 2.5–10 mg q 1–4 h PRN, or 10–15 mg/h continuously 4–8 puffs q 20 min up to 4 h, then q 1–4 h as needed	Only selective β2-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min As effective as nebulized therapy if patient is able to coordinate
Levalbuterol (*R-albuterol*) Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL) HFA 45 μg/puff	1.25–2.65 mg q 20 min for three doses, then 1.25–5 mg q 1–4 h as needed, or 5–7.5 mg/h continuously See albuterol dose	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects
Systemic (injected) β2-agonists		
Epinephrine 1:1000 (1 mg/mL)	0.3–0.5 mg q 20 min for three doses sq	No proven advantage of systemic therapy over aerosol
Terbutaline (1 mg/mL)	0.25 mg q 20 min for three doses sq	No proven advantage of systemic therapy over aerosol
Anticholinergics		
Ipratropium bromide Nebulizer solution (0.25 mg/mL) HFA (17 μg/puff)	0.5 mg q 30 min for three doses, then every 2–4 h as needed 4–8 puffs as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to β2-agonists therapy
Ipratropium with albuterol Nebulizer solution (each 3-mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol)	3 mL q 30 min for three doses, then every 2–4 h as needed	Contains EDTA to prevent discoloration. This additive does not induce bronchospasms
Ipratropium with albuterol MDI (each puff contains 18 μg ipratropium bromide and 90 μg albuterol)	4–8 puffs as needed	
Systemic corticosteroids (dosages and comments apply to all three corticosteroids)		
Prednisone *Methylprednisolone* *Prednisolone*	10–80 mg/d in 1 or 2 Divided doses until PEF reaches 70% of predicted or personal best	For our outpatient "burst," use 40–60 mg in 1 or 2 divided doses for 5–10 days in adults

Modified from the NAEPP Report. Child doses taken off table
MDI metered dose inhaler, *PEF* peak expiratory flow, *PRN* as needed

Severe Persistent Asthma (Step 4)

For patients with severe persistent asthma, the treatment of choice is high-dose inhaled corticosteroid therapy, preferably budesonide (Pulmicort), and an inhaled long-acting B2-agonist (LABA), preferably salmeterol (Serevent). Inhaled short-acting B2-agonists (SABAs), preferably albuterol, should be added as needed. Alternative but less preferable treatment would be high-dose inhaled corticosteroids (ICS) with sustained-release theophylline or leukotriene receptor antagonists (LTRAs). If control cannot be achieved with these drugs, oral corticosteroids should be added, as needed, to maintain control (Tables 18.5, 18.6, 18.7, and 18.8).

Tiotropium may be an option for moderate and severe persistent asthma that is not well controlled during pregnancy on dose inhaled corticosteroids (ICS) and long-acting B2-agonists. However, there is currently no safety data on the use of tiotropium during pregnancy. Caution needs to be used, and the benefits versus the risks need to be weighed (Tables 18.5, 18.6, and 18.8).

Addition of Anti-IgE Therapy to Moderate and Severe Persistent Asthma (Step 5 or 6)

For patients with moderate to severe asthma that is inadequately controlled on inhaled corticosteroids (ICS) and long-acting B2-agonists (LABAs), anti-IgE therapy is an option for add-on therapy. No human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. However, further studies are needed and caution is advised. Patients who may be candidates for anti-immunoglobulin E therapy should be referred to a specialist (Tables 18.5, 18.6, 18.7, and 18.8).

Addition of Oral Steroids to Severe Persistent Asthma (Step 5 or 6)

For patients with severe persistent asthma that is inadequately controlled on inhaled corticosteroids (ICS) and long-acting B2-agonists (LABAs), low dose oral corticosteroids are an option for add-on therapy. Patients who may be candidates for oral corticosteroid therapy should be referred to a specialist (Tables 18.5, 18.6, 18.7, and 18.8).

Assignment of Severity Step

All patients should be assigned to the highest step in which any single feature occurs. For example, nighttime symptoms twice a week will increase the severity assignment to moderate persistent asthma, even if all other symptoms and objective measures are in the mild persistent asthma category (Tables 18.5 and 18.8).

Overuse of Albuterol

Patients need to be specifically asked about their use of albuterol or other inhaled short-acting bronchodilators (SABAs). Overuse of albuterol indicates inadequate asthma control and the need to increase the asthma severity assignment to a higher level. Pharmacy records, if available, can be invaluable in analyzing refill patterns and determining if patients are refilling their inhaled short-acting B2-agonists (SABAs) too frequently (Table 18.5).

The extent of albuterol overuse can be easily estimated by multiplying the number of canisters used by 200 (puffs per canister) and dividing the result by the number of days between refills. The use of one canister, every 2 months, indicates an average of more than 3 puffs of albuterol per day, suggesting suboptimal control that should be evaluated (Tables 18.5 and 18.8).

Patients often experience worsening of asthma symptoms during exercise. These patients may require albuterol use prior to exercise as well as during and after exercise. Ideally, patients with asthma that is well controlled won't require additional albuterol. A step-up in the asthma medication regimen may be required to allow for exercise without additional albuterol (Table 18.8).

Gaining Control of Asthma

Most asthma specialists start a patient at a higher dose of medication to gain control quickly and even consider a short course of oral steroids if needed. Once control is gained, the dosage should be lowered to the minimal medication needed to maintain good control. Reassessment should occur frequently to determine if control can be maintained at a lower dose of medications (Table 18.8).

Specialty Care

The NAEPP guidelines recommend that pregnant women with asthma be referred to an asthma specialist if there is difficulty controlling their asthma. The guidelines specifically advise that patients with severe persistent asthma or those requiring step 4 treatment be referred to an asthma clinic or a specialist. Patients with moderate persistent asthma or who require step 3 treatment should be considered for referral. If anti-IgE therapy is being considered, the patient should be referred for specialty care (Table 18.8).

Exacerbations

During the course of their pregnancy, studies show that 20 % of asthma patients have exacerbations severe enough to seek urgent medical care. Approximately 6 % require hospital admissions. Severe exacerbations such as those requiring hospital

admission, urgent physician visits, or systemic corticosteroids are significantly more likely to occur with severe asthma.

Exacerbations are most common in the late second trimester to early third trimester. The most common reasons for exacerbation are viral infections and noncompliance with inhaled corticosteroid treatment. The importance of regular usage of inhaled corticosteroids (ICS) for persistent asthma cannot be overemphasized. Studies show that for patients using inhaled corticosteroids (ICS) before pregnancy, the rate of asthma-related physician visits decreased and the number of emergency department visits was unchanged after pregnancy.

Management of Exacerbations

The management of the pregnant woman having an asthma exacerbation is set forth in Figs. 18.1 and 18.2. Treatment depends on the severity of the exacerbation with inhaled albuterol and oral steroids used as the primary treatment, particularly at home. For pregnant women with severe exacerbations in the emergency department, nebulized ipratropium can be added to albuterol. Table 18.9 lists the doses of medications for acute exacerbations.

Mechanical Ventilation

Fortunately, it is rare for a pregnant woman to require intubation and mechanical ventilation. If needed, intubation should be oral instead of nasal due to airway narrowing. Preoxygenation with 100 % oxygen prior to intubation is important to avoid a precipitous drop in oxygen that may occur after even a short period of apnea. Studies show that it is important to maintain cricoid pressure before and after intubation to avoid aspiration and gastric insufflation. Patients should be ventilated with respiratory rates of 8–12 breaths per minute, tidal volumes of 6–8 mL/kg, and high inspiratory flow rates of 100–120 per minute. Hyperventilation should be avoided because a respiratory alkalosis may decrease uterine blood flow and impair oxygenation of the fetus. In addition, it is important to avoid volutrauma and barotrauma.

Evidence-Based Medicine

Global Strategy for Asthma Management and Prevention 2015. Retrieved 11 Aug 2015. http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_May19.pdf. Accessed 1/16

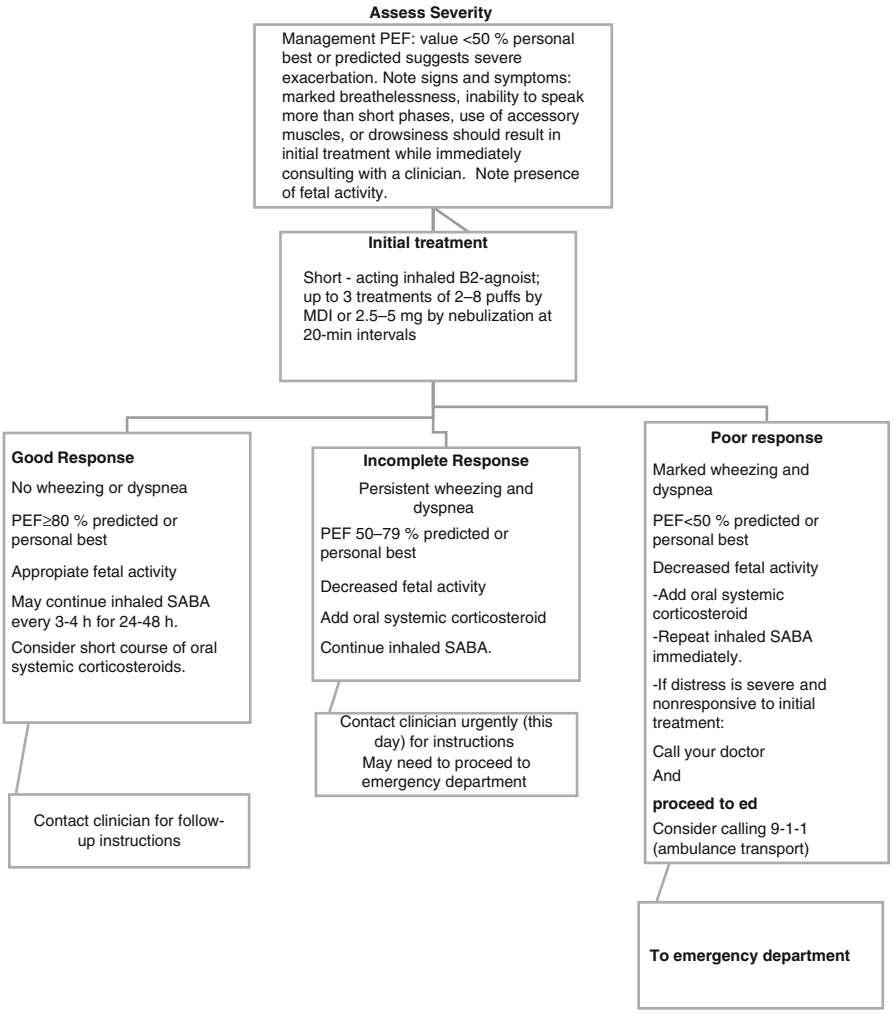

Fig. 18.1 Management of asthma exacerbations: home treatment (Adapted from NAEPP Guidelines, 2007)

This is an updated guideline from the GINA Report 2015 and is a systemic evidenced review of asthma. This is a very thorough, well-presented guideline. There are several changes from the NAEPP 2007 Guidelines.

Blais L, Beauchesne MF, Lemière C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformation. *J Allergy Clin Immunol*. 2009;124(6):1229.

This is a very interesting study that looked at higher doses of inhaled steroids (>1000 mcg/day) during the first trimester and showed a 63 % increase in risk of all congenital malformations. This study had multiple issues including a small number

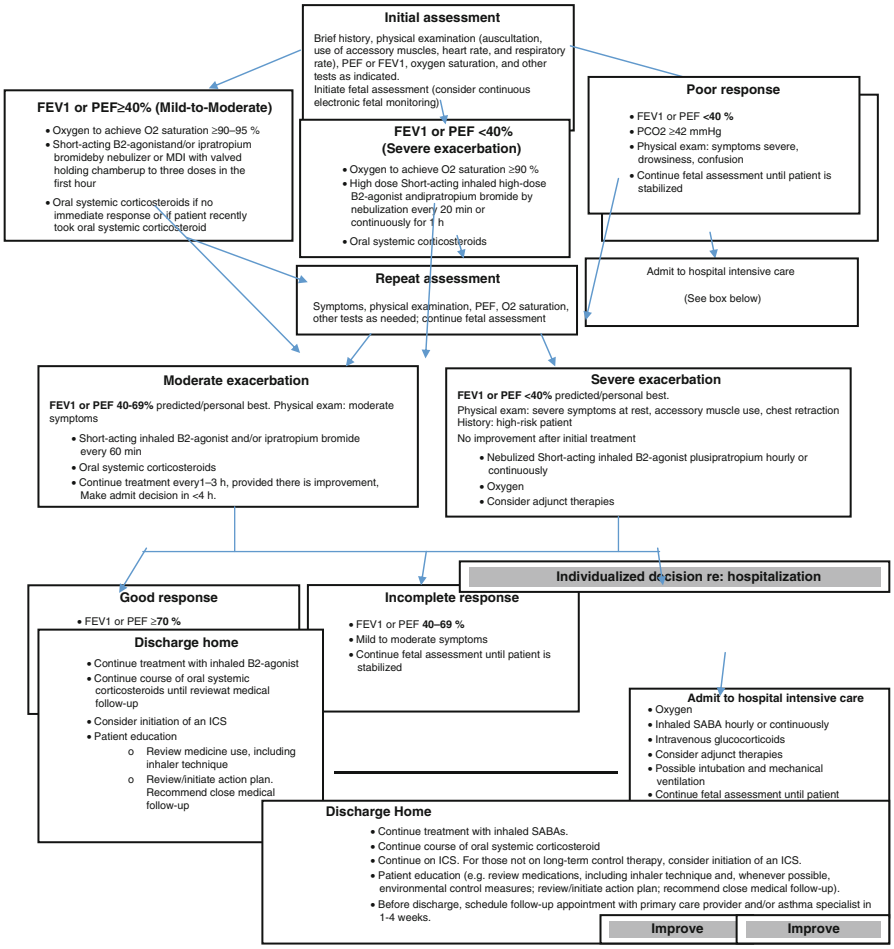

Fig. 18.2 Management of asthma exacerbations: emergency department and hospital-based care (Modified from NAEPP Asthma Guidelines, 2007)

of patients with a daily dose over 1000 mcg, and it was difficult to determine whether the increased incidence of malformations was due to inadequately controlled asthma or due to high-dose inhaled steroids.

Conclusion

Optimal asthma control during pregnancy is very important for both the mother and the fetus. To achieve this goal, thorough assessments and evaluations are critical, including monitoring with pulmonary function testing and peak flow meters. Avoidance and control of common triggers needs to be addressed with an emphasis on smoking cessation. Effective treatment must include asthma education and

reassurance that treatment is much safer for the fetus than maternal asthma exacerbations and symptoms. The obstetrical provider should be involved as part of the asthma care management team from the start of pregnancy.

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Chapter 19
Asthma and Pseudo-Asthma

Miles Weinberger

When Is It Asthma?

What is asthma? This question is of particular importance in evaluating respiratory disease in the young child where euphemisms for asthma have been common, including reactive airway disease (RAD), wheezy bronchitis, obstructive bronchitis, recurrent bronchiolitis, etc. Sometimes describing or defining asthma is like the parable of the blind men describing the elephant who felt it was like a tree, a snake, or a rope depending on whether they were feeling a leg, the trunk, or the tail. Like the blind men examining only one part of the elephant, asthma is sufficiently diverse in its presentation that its perception depends on the experience of the observer. Some have suggested that, like love, it can't be defined but it's recognizable when confronted. But is that either medically or operationally acceptable? Can we truly recognize, optimally treat, or study asthma without a definition?

The complexity and challenge of defining asthma have been discussed. In examining the 12 definitions and references in a review, a common theme to all is the presence of airway disease that varies over time either spontaneously or as a result of treatment. A committee of the American Thoracic Society agreed upon the definition that "Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that change in severity either spontaneously or as a result of therapy." This definition was expanded by a subsequent committee of the American Thoracic Society to include "The major symptoms of asthma are paroxysms of dyspnea, wheezing and cough, which may vary from mild and almost undetectable to severe and unremitting…" That definition and others added to the definition that the airflow

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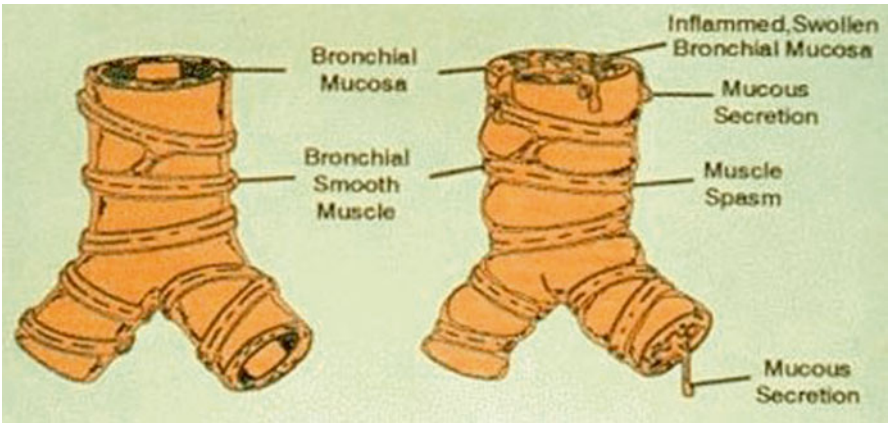

Fig. 19.1 Artist's rendition of the two components of airway obstruction in asthma: bronchospasm and inflammation with mucosal edema and mucous secretions

obstruction and clinical symptoms are largely or completely reversed by treatment with bronchodilators or corticosteroids.

Inflammation was introduced into the definition and subsequently incorporated into the National Asthma Education Program Expert Panel Reports from the US National Institute of Health. However, a definition based on inflammation is not helpful in differential diagnosis or early disease identification since noninvasive measures of inflammation are neither readily available nor well validated. This is especially true for young children where even the ability to make physiologic measurements is limited. For a definition of a disease to be useful, it should provide a basis for making the diagnosis. While airway inflammation is certainly a component of asthma, the value of including this as a major component of the definition has also been challenged since inflammation and hyperresponsiveness are not unique to asthma. Airway narrowing in asthma is related to both smooth muscle constriction and airway inflammation to varying degrees (Fig. 19.1). Asthma has thus proved challenging to define because of the diversity in its clinical presentation, variability of its clinical course, and absence of any specific diagnostic test. This results in the potential for both over- and underdiagnosis.

Asthma Phenotypes

Within that definition of asthma are distinct clinical patterns of symptoms that constitute phenotypes. What is meant by the use of the term phenotype? It means that there are observable characteristics resulting from the interaction of the genotype with the environment. By far the most common phenotypes are those who have symptoms of asthma exclusively from the viral respiratory infections that cause the common cold. Intercurrent symptoms are absent in those individuals. This

phenotype occurs at all ages but is most troublesome in preschool-age children because of their high frequency of viral respiratory infections. Although an intermittent pattern, without intercurrent symptoms between viral respiratory infections, severity during those viral respiratory infections may range from mild to life threatening and contribute to the high hospitalization rate in the preschool-age group.

Since children in this age group have a particularly high frequency of acquiring viral respiratory infections, especially if they are in day care or have older siblings in school, it can be difficult at the peak times of the seasonal viral respiratory illnesses to distinguish this pattern from phenotypes with persistent asthma. Moreover, children with persistent symptoms also experience exacerbations from viral respiratory infections which compounds the diagnostic difficulty. An absence of specific IgE to major inhalant allergens is generally predictive at this age of a viral respiratory infection-induced pattern. When the pattern is unclear during the peak of the viral respiratory disease season, the marked decrease in the frequency of acute exacerbations during the summer months when viral respiratory illness is less common can eventually make the absence of intercurrent symptoms more apparent.

Other distinct phenotypes are those who develop allergen-specific immunoglobulin E (IgE) to inhalants that cause the bronchospasm and airway inflammation of asthma. However, phenotypes may not be isolated. Such children may start as the intermittent viral respiratory-induced pattern during the first few years of life and then develop allergen-specific IgE. That then causes either persistent seasonal or perennial symptoms or symptoms just upon specific allergenic exposure. Examples of major allergens that contribute to seasonal allergic asthma are grass pollen that peaks in May and June in the California and Pacific Northwest valley areas and *Alternaria* mold in the US Midwest farm country which is variably present throughout the growing season but peaks when the farmers are stirring up the decaying vegetation on which *Alternaria* thrives during harvest time. Some children who develop allergen-specific IgE will have had no problems with viral respiratory infections initially but may subsequently have exacerbations of asthma once sensitized if exposed to the relevant allergen and simultaneously develops a viral respiratory infection.

At least two phenotypes of persistent asthma can be identified. The most common, estimated to be about 85 % in school-age children with persistent symptoms of asthma, has extensive allergen-specific IgE and has perennial symptoms. Here again, clinical variables occur in this phenotype with some experiencing seasonal allergic exacerbations, depending again on the specifics of the allergen-specific IgE and local aerobiology. Exacerbations from viral respiratory infections are also common in these patients. Another phenotype is characterized by nonallergic children who appear to have exquisitely sensitive airways to irritants, exercise, and perhaps other nonspecific factors. It is most commonly seen starting in pubertal or prepubertal girls as exertional dyspnea and progressing on to persistent symptoms with no evidence of inhalant allergy contribution. Such patients contribute to the greater equality of asthma prevalence by gender postpuberty compared with the approximately two to one ratio of males to females in younger children. A manner of

conceptualizing the interaction of nonspecific airway responsiveness and allergic sensitivity can be seen by overlaying these two components.

Other phenotypes become apparent in adult asthma. Some women with asthma have been observed to experience exacerbations repeatedly with menses, consistent with a role of sex hormones involved in the disease process; this can start as early as adolescence. Sensitivity to aspirin and other nonsteroidal anti-inflammatory agents, commonly associated with nasal polyps, is another phenotype seen among a minority of adults with asthma. Late adult-onset nonallergic asthma is yet another rather distinct clinical phenotype.

Clinical Approach to Asthma Diagnosis and Phenotypical Characterization

Asthma should be suspected in any child with the following symptoms:

Cough
Wheeze
Dyspnea
Exertional dyspnea
Diagnoses of recurrent bronchitis or pneumonia without other explanations

However, each of those can have an extensive differential diagnosis. Description of answers to the following queries can assist in identifying the possibility that such symptoms occur as a manifestation of asthma:

Age of onset?
Frequency and duration of symptoms?
Frequency and duration of periods completely free of respiratory symptoms?
Associations with other signs of illness or exposures?

Symptoms that are of new onset cannot readily be identified as asthma since the clinical diagnosis of asthma requires evidence of a recurring pattern of symptoms. The frequency and duration provide essential information regarding the phenotypical pattern as does the association with apparent viral respiratory infections or association with specific seasons or environmental exposures. For those children capable of performing pulmonary function, such physiologic measurements can provide useful data. However, normal pulmonary function during an asymptomatic period does not exclude asthma, and the presence of airway obstruction or bronchodilator responsiveness does not, by itself, confirm a diagnosis of asthma.

Finally, the response to appropriate therapy provides the coup de grace for either confirming a diagnosis or indicating that the differential diagnosis needs to be expanded. A short course of an adequate dose of an oral corticosteroid should eliminate current symptoms of asthma (Table 19.1). For exertional dyspnea in a child with normal baseline pulmonary function measurements, a bronchodilator such as albuterol (salbutamol) or terbutaline should reliably block exercise-induced asthma.

Table 19.1 Suggested doses of systemic corticosteroid to use as a diagnostic test for asthma when cough, wheezing, or dyspnea persists

Age of patient	Dosage as prednisone or prednisolone
Infant under 6 months	10 mg b.i.d.
Infant 6–12 months	15 mg b.i.d.
1–3 year old	20 mg b.i.d.
3–13 year old	30 mg b.i.d.
>13 year old	40 mg. b.i.d.

Complete relief of signs and symptoms with these doses within an absolute maximum of a 10-day period (usually less) is supportive of the diagnosis of asthma, whereas failure to relieve symptoms and normalize physiology warrants pursing alternative diagnoses. These doses are empirical, based on our clinical experience as being sufficiently high to provide a definitive answer regarding the steroid responsiveness of the airway inflammation

Either an atypical history for an asthma phenotype or failure to respond to these therapeutic measures warrants consideration of "pseudo-asthma" clinical entities.

When Isn't It Asthma?

Asthma is diagnosed clinically and is suspected when there is cough, wheezing, or dyspnea. However, the same symptoms may be from other causes. The distinguishing characteristic of asthma from other causes of these symptoms is the response to bronchodilator or corticosteroids when the patient is symptomatic. For patients old enough to perform a pulmonary function test, substantial improvement of airway obstruction from an aerosol bronchodilator or a short course of reasonably high dose of systemic corticosteroid supports the diagnosis of asthma whereas the failure to completely relieve symptoms and substantially improve lung function argues against asthma as the etiology (Table 19.1). This will be apparent in the subsequent description of clinical problems initially misdiagnosed as asthma that we have indicated as "pseudo-asthma" syndromes.

Cough That Isn't Asthma

Asthma is the most common chronic or recurrent inflammatory airway disease and a major cause of cough in children. While there are causes of cough that are unlikely to be confused with asthma, there are several that characteristically are confused with asthma and result in overdiagnosis of asthma with consequent inappropriate treatment. Acute viral bronchitis, colloquially called a chest cold, is a common cause of a generally self-limited cough. Pertussis causes a more prolonged period of cough. It was known in the past as the hundred-day cough. Characteristically

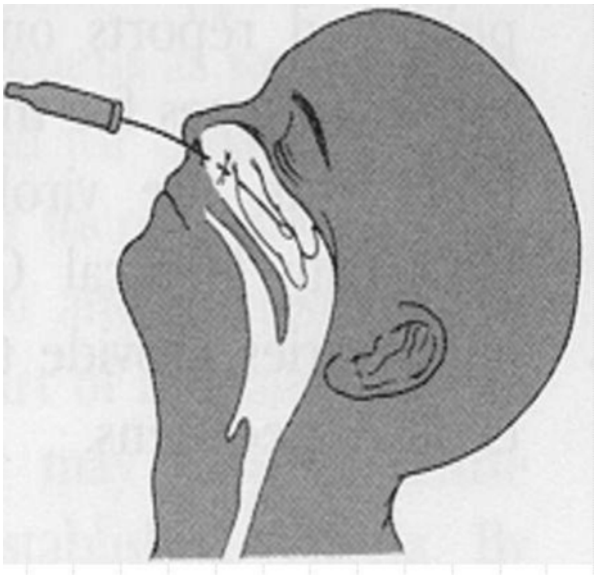

Fig. 19.2 Pertussis should be considered for any child with a prolonged period of cough in the absence of a prior history. A flexible wire with a cotton tip is inserted in a nare and left in the posterior nasopharynx for 30 seconds before being withdrawn, appropriately saved as instructed by the laboratory, and sent for polymerase chain reaction (PCR) detection of Pertussis. This is far more sensitive than culture. When performed early in the course of Pertussis infection, appropriate preventative measures can be provided to all contacts and thereby minimize the spread

spasmodic and associated with post-tussive, gagging, or emesis, diagnosis is important to prevent spread to contacts. Pertussis should be suspected for any cough persisting for more than 2 weeks. Diagnosis is most readily made by polymerase chain reaction (PCR) from a properly collected nasal swab (Fig. 19.2). Acute cough beyond infant and toddler years with no prior history will rarely be asthma. It is more likely that chronic long-standing cough will be confused with asthma.

Two common diagnoses for cough that need not be considered are postnasal drip and gastroesophageal (GE) reflux (GER). Both are highly controversial symptoms that are attributed to causes of cough and asthma. Evidence only demonstrates an association with asthma but not etiology. *Cystic Fibrosis*: Cystic fibrosis is the second most common inflammatory airway disease, occurring in about 1 in 2500 live births in Caucasian populations of Northern European descent with variable lesser incidence in other ethnic groups and races. Although the mechanisms of airway inflammation are different in these two diseases, both cause airway obstruction, cough, wheezing, and dyspnea. The classical clinical presentation of malabsorption is not always present, and the severity and progression of the airway disease are highly variable. Some degree of bronchodilator response may even be present.

Cystic fibrosis should be suspected when symptoms and signs of airway inflammatory disease persist despite a short course of systemic corticosteroid. The diagnosis of cystic fibrosis is most reliably made by performing a sweat chloride measurement using the classical quantitative pilocarpine iontophoresis method. Most of the various screening methods utilizing assessment by the conductivity of sweat are unreliable, having both false-positive and false-negative results. For the test to be valid, duplicate collections of at least 75 mg are required for the filter paper discs or gauze pads with 15 μl being sufficient with the Macroduct collection

coil. Measurement of 60 meq/l chloride with substantial agreement in both samples is generally diagnostic of cystic fibrosis. Measurements of less than 40 meq/l are generally reassuring that cystic fibrosis is not the cause of the patient's airway inflammatory disease. Levels of 40–60 meq/l should be considered sufficiently suspicious to justify genetic analysis for the presence of two mutations of the cystic fibrosis transmembrane regulator of which there are now over 1500. Some of the less common mutations are associated with a milder course of the pulmonary disease, and a few are not associated with elevated sweat chlorides. While rare, constituting less than 1 % of patients with cystic fibrosis, awareness of these exceptional cases permits specific treatment rather than fruitless use of antiasthmatic medications that only frustrate the patient and the physician.

Primary Ciliary Dyskinesia This disorder is rare and consequently may not be adequately considered when a persistent cough is present. It includes a variety of abnormalities in airway ciliary function that results in absence of normal mucociliary clearance, an important innate host-defense mechanism for the lungs. A continuous movement of the mucous layer of the respiratory mucosa is normally maintained by the rhythmic beating of ciliated respiratory epithelial cells. The absence of the coordinated ciliary movement results in pooling of mucous in the airway with low-grade chronic infection. Cough and slowly progressing bronchiectasis result from this defect. Half will have situs inversus totalis when it is then known as Kartagener's syndrome. As with cystic fibrosis, primary ciliary dyskinesia will not respond to usual antiasthmatic medications, and delayed diagnosis results in permanently damaged airways. The diagnosis should be highly suspect in the presence of situs inversus totalis, but the definitive diagnosis can be difficult in the absence of that anatomic abnormality. The classical means of diagnosing has been examination of ciliary structure by electron microscopy. However, this is fraught with errors in interpretation. Examination of coordinated ciliary movement from a nasal or tracheal epithelial sample by light or phase contrast microscopy is as means of evaluation. The diagnosis of primary ciliary dyskinesia by identifying pathogenic variants in one of the 32 genes known to be associated with PCD.

Protracted Bacterial Bronchitis This is an entity not well appreciated and only infrequently described. While chronic bacterial bronchitis is certainly a characteristic of cystic fibrosis, there are young children with no identifiable abnormalities in immunity or other underlying diseases who have prolonged periods of cough with neutrophilia and bacteria in their lower airways demonstrable by bronchoalveolar lavage. Some but not all have bronchomalacia that may be contributing both to cough and to retaining secretions in the lower airway which predisposes the child to secondary infection (Fig. 19.3). The bacteriology identified is most commonly the same ones commonly associated with otitis media, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. While responsive to appropriate antibiotics, some will require repeated courses or even maintenance prophylactic antibiotics for an extended period. Resolution with age is common in the absence of an underlying innate or acquired host-defense disorder. Diagnosis requires flexible bronchoscopy and bronchoalveolar lavage with cell count and

Fig. 19.3 Tracheomalacia, a softening of the tracheal rings that are to provide a degree of rigidity to the airway, occurs from either a defect in the cartilage itself or from external compression by the great vessels. The innominate artery (a.k.a. brachiocephalic trunk) crosses over the lower third of the trachea where a pulsating bulge can often be seen on bronchoscopy. This is a common location for tracheomalacia as in this picture. Persistent cough occurs when the repeated contact of the anterior and posterior walls of the trachea causes a focus of irritation with a consequent harsh barking cough characteristic of a tracheal cough. Cough may also occur because of inefficient clearing of secretions that results from the collapse of the airway when intrathoracic pressure is increased during coughing

differential of lavage fluid for evidence of significant neutrophilia and quantitative culture of the fluid.

Tracheomalacia (Fig. 19.3) **and Bronchomalacia** (Fig. 19.4) Inadequate rigidity of the tracheal or mainstem bronchial cartilage results in tracheal collapse which causes cough by at two mechanisms. When secretions are present in the airway, the airway collapse causes pooling of secretions distally. The secretions then act as a continued stimulus for cough. Additionally, collapse of the trachea or mainstem bronchi during increased intrathoracic pressure as in vigorous exhalation or coughing can cause the anterior and posterior walls to come into contact resulting in an irritable focus that stimulates the cough reflex. While tracheomalacia and bronchomalacia can be troublesome in the infant, some cases do not cause problems until later in childhood. In unusually severe cases of intractable cough from tracheomalacia, surgical aortopexy is needed. This involves placing a suture through the adventitial lining of the aortic arch and the periosteum of the sternum to pull the arch forward. Since the anterior tracheal wall is connected to the aortic arch with fascial tissue, it essentially pulls the anterior wall of the trachea forward, thereby maintaining a more normal tracheal lumen.

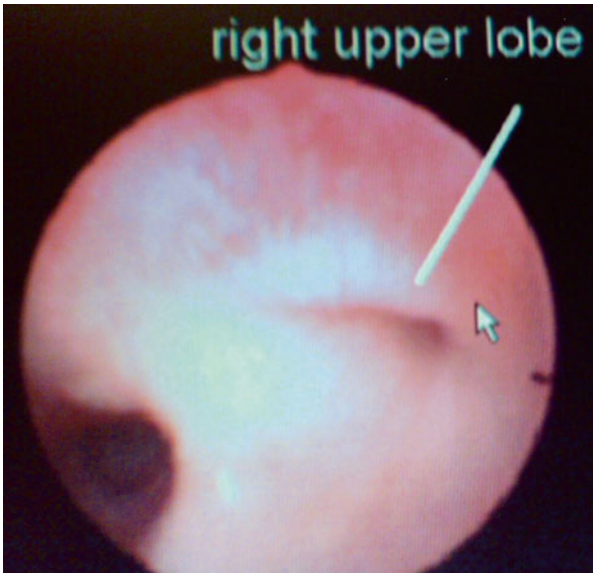

Fig. 19.4 Bronchomalacia of the right upper lobe (upper picture) and of the right mainsterm (lower picture). Depending on the degree of obstruction caused by the malacia, either cough or expiratory monophonic wheezing may be heard. Obstruction occurs on expiration with positive intrathoracic pressure during expiration while negative intrathoracic pressure during inspiration opens the airway. Complete airway obstruction during expiration can result in lobar emphysema from persistent hyperinflation of the lobe distal to the malacia. Decreased clearing of secretions distal to the malacia may result in purulent bacterial bronchitis

Habit Cough Syndrome This is a troublesome disorder commonly treated as asthma that often causes a great deal of morbidity and ineffective treatment and yet is readily rapidly curable with a simple behavioral technique. The classical presentation of the habit cough syndrome is that of a harsh barking repetitive cough occurring several times per minute for hours on end. It is extremely irritating to those in the presence of the cougher. Characteristic of the habit cough syndrome is the complete absence of cough once the patient is asleep. A variation of the habit cough is habit throat clearing. As with the classical habit cough, the softer throat clearing occurs up to several times a minute and is completely absent once asleep. Both of these are frequently subjected to multiple diagnostic tests and therapy with antiasthmatic medications.

This syndrome is sometimes misinterpreted as a tic. However, the so-called cough-tic syndrome will involve more vocalization characteristic of Tourette's syndrome and does not resemble the true cough or simple throat clearing of the habit cough or habit throat clearing syndrome. In considering treatment and discussing the issue with the family, it is important not to refer to this as a psychogenic cough, since that is likely to adversely affect the relationship with the therapist who will subsequently need the patient rapport to effectively utilize suggestion therapy. Moreover, there is no evidence in all but the rare case of other psychosomatic or

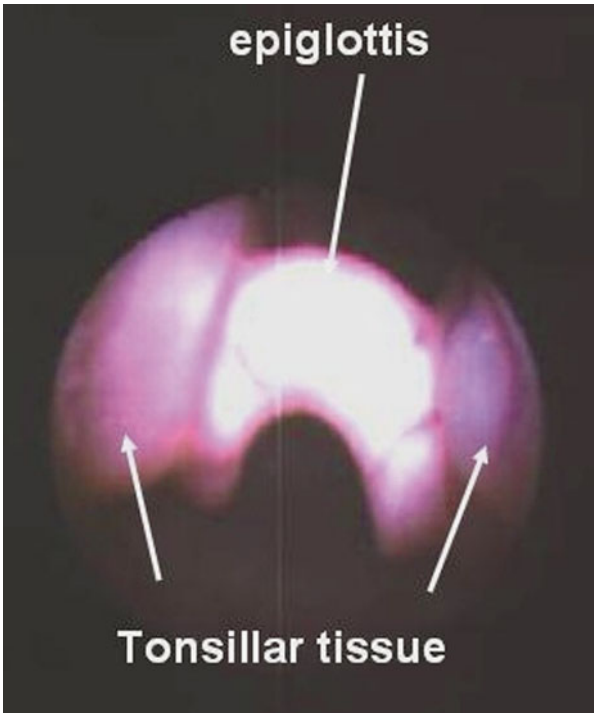

Fig. 19.5 Tonsils (the lateral masses in the image) impinging on the epiglottis in a 3 y.o. girl caused chronic cough initially treated unsuccessfully for asthma. Tonsillectomy cured her cough

psychological problems in these children and adolescents. Testing performed on our patients identified no tendency toward other somatization but some tendency to score high but not pathologically so on an obsessive-compulsive scale. Perhaps related to this personality characteristic is our observation that most of these patients were academically high achievers.

If not treated with appropriate behavioral intervention, symptoms can continue for months and can continue in some for years as was demonstrated in a follow-up of diagnoses of habit cough syndrome made at Mayo Clinic. Treatment with suggestion therapy can provide a sustained cure by the use of various modes of suggestion therapy. We have used a technique that results in complete cessation of symptoms within 15 min.

Other Rare Causes of Chronic Cough We have seen some particularly unusual causes of chronic cough that were misdiagnosed as asthma. While unlikely to be frequently encountered, awareness of these entities can encourage further investigation when the pattern of symptoms and response to treatment is not consistent with asthma (Figs. 19.5 and 19.6).

On the other hand, postnasal drip is often diagnosed as a cause of cough, whereas the cough is actually more likely to be a manifestation of lower airway inflammation from asthma with the postnasal mucous visualized simply a manifestation of accompanying upper airway inflammation. Similarly, the presence of gastroesophageal reflux is more likely to be a result of coughing rather than a cause.

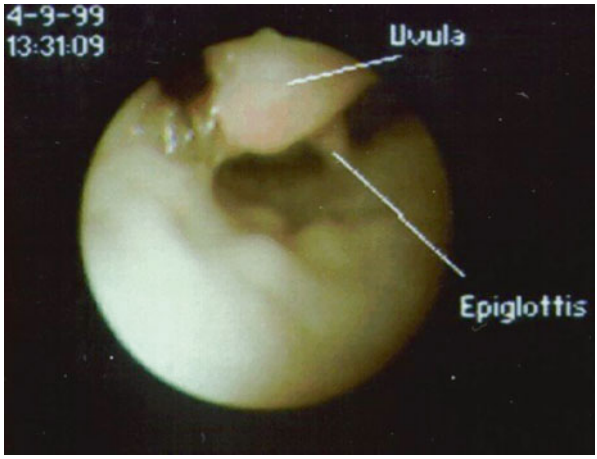

Fig. 19.6 The uvula making contact with the epiglottis caused a troublesome cough in this 4 y.o. boy treated unsuccessfully for asthma who was able to relate that he coughed because he felt something in the back of his throat. Uvulectomy cured his cough

Wheezing That Isn't Asthma

In considering wheezing, it's important to consider that patients, parents, and even physicians at times refer to various respiratory sounds as "wheezing" that are not, in fact, wheezing. Wheezing is defined as a continuous musical expiratory sound due to intrathoracic airway obstruction. However, parents will describe inspiratory rattling or stridor as wheezing, and there are many reports of inspiratory sounds from upper airway obstruction being called wheezing by medical personnel.

Partial Airway Obstruction A cause of true wheezing, partial obstruction of a bronchus can result in wheezing that is commonly misdiagnosed and treated as asthma. A *retained foreign body* in a bronchus is one cause. This needs to be distinguished from a *mucous plug* associated with asthma that can also obstruct a bronchus. Another is *bronchomalacia* (Fig. 19.4). Most commonly associated with wheezing in infants, this is associated with little respiratory distress. In contrast to a mucous plug from asthma or other airway inflammatory diseases, these causes of partial airway obstruction will cause unilateral wheezing that is persistent, whereas the localized wheezing from a mucous plug will vary from time to time.

When bronchomalacia occurs in an infant who also experiences recurrent viral respiratory infection-induced asthma, which occurs in 15–20 % of infants and toddlers to some degree, the persistent wheezing following the initial clearing of symptoms can result in frustrating attempts to clear the wheezing pharmacologically. However, once confirmed to be bronchomalacia by direct observation during flexible bronchoscopy with conscious sedation, no further treatment is indicated. It is important to consider that both tracheomalacia and bronchomalacia can be missed during rigid bronchoscopy where general anesthesia and positive pressure ventilation keep the airway open. That eliminates the increase in intrathoracic pressure from normal ventilator effort that will collapse an airway that is poorly supported because of defective cartilaginous rings.

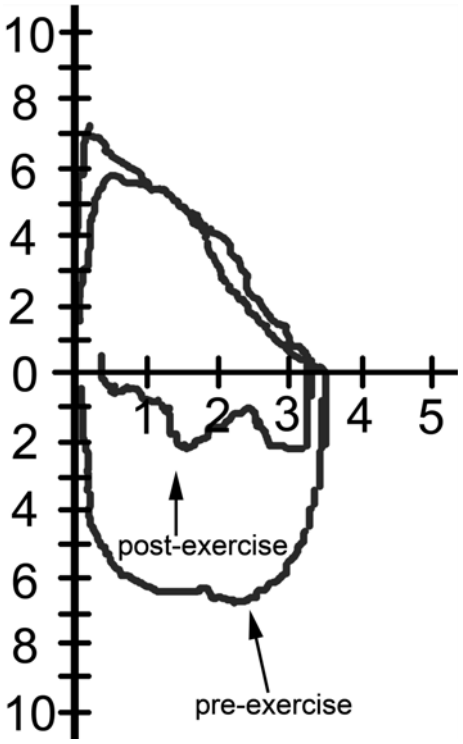

Fig. 19.7 Flow-volume loops obtained before and when symptomatic in Vocal Cord Dysfunction Syndrome. Before exercise, flow-volume loop with the mid-inspiratory and mid-expiratory flows were about equal. The post-exercise loop exhibited the typical flattening of the inspiratory portion of the flow-volume loop in a 15 y.o. girl with exercise induced inspiratory stridor (that had been described as "wheezing" by the patient's primary care physician). This indicates reversible upper airway obstruction typical of paradoxical vocal cord movement which was then confirmed by visualizing adduction of the vocal cords on inspiration with flexible laryngoscopy

The natural course of this is resolution with age, apparently as the airway increases in size. It is not known how many eventually become associated with cough as described above, but this is probably not an inevitable outcome.

Vocal Cord Dysfunction Syndrome This entity is a functional disorder of the vocal cords most commonly seen in adolescents. It is commonly misdiagnosed as asthma based on an inappropriate description of "wheezing." The respiratory noise, however, is actually a high-pitched inspiratory stridor due to paradoxical adduction of the vocal cords during inspiration. A variation of the vocal cord dysfunction syndrome manifests itself as abnormal continuous inspiratory and expiratory noise. This latter variation of the vocal cord dysfunction syndrome is characterized by spasmodic closure of the vocal cords with adduction persisting during both inspiration and expiration. Spirometry with a maximal inspiratory effort can readily distinguish the upper airway obstruction of vocal cord dysfunction from the lower airway obstruction of asthma (Fig. 19.7).

Two phenotypes of vocal cord dysfunction syndrome have been described. One type occurs spontaneously with the patient experiencing dyspnea and inspiratory stridor (often described as "wheezing") at various and often unpredictable times. Whether this is a panic or anxiety-induced reaction is speculative. It nonetheless is alarming for those experiencing this and for those observing the reaction. Urgent visits to an emergency room are common, and those who have the spasmodic closure

of the vocal cords are, more likely than those with just paradoxical movement, more likely to experience multiple emergency 911 calls because of the alarming appearance of their respiratory distress. Other phenotypes are those that occur only with exercise. This is commonly seen in adolescent athletes during competitive aerobic activities. Typically transient and relieved spontaneously with a period of rest, this phenotype of vocal cord dysfunction syndrome is troublesome predominantly because it interferes with their athletic activities. While most patients with vocal cord dysfunction syndrome will manifest only one of these two patterns, some will exhibit both patterns of vocal cord dysfunction.

The treatment for the spontaneously occurring phenotype of vocal cord dysfunction syndrome is instruction by a speech pathologist familiar with this disorder who can instruct techniques to voluntarily take control of the vocal cords. This is generally effective. Such techniques, however, are not practical for those with exercise-induced vocal cord dysfunction, since the techniques would require stopping the activity that was inducing the problem, which results in spontaneous resolution of symptoms anyway. We have found that an anticholinergic aerosol (Atrovent oral inhaler) when used prior to exercise prevents the vocal cord dysfunction in these patients, and this observation is consistent with evidence that a vagal reflux is involved in this pattern of vocal cord dysfunction. For both patterns of vocal cord dysfunction syndrome, the long-term outlook for resolution or accommodation appears favorable.

Dyspnea That Isn't Asthma

Hyperventilation Attacks of hyperventilation can be confused with asthma, both in those who have asthma and those who do not. Patients who have both asthma and experience hyperventilation attacks cannot readily distinguish the sensation of dyspnea associated with hyperventilation from that associated with their asthma. Spirometry at the time the patient is symptomatic can help distinguish the perception of dyspnea associated with a hyperventilation attack from asthma. A blood gas demonstrating low pCO_2 and high pH without evidence of airway obstruction at the time of symptoms provides supportive evidence for hyperventilation.

Exertional Dyspnea Dyspnea on exertion in children and adolescents is frequently part of the clinical course of asthma. However, asthma is rarely the diagnosis when there is dyspnea on exertion with no respiratory symptoms other than during exercise. In a study of 142 children and adolescents with exercise-induced dyspnea referred to us, 100 had been diagnosed and treated as asthma without clinical response. When treadmill exercise was performed with full cardiopulmonary monitoring on 112 of the 142 (Fig. 19.8), exercise-induced bronchospasm was rare despite having reproduced the patient's exercise-induced dyspnea. The most common cause of exercise-induced dyspnea in these patients was physiologic limitation in patients with a wide range of cardiovascular conditioning.

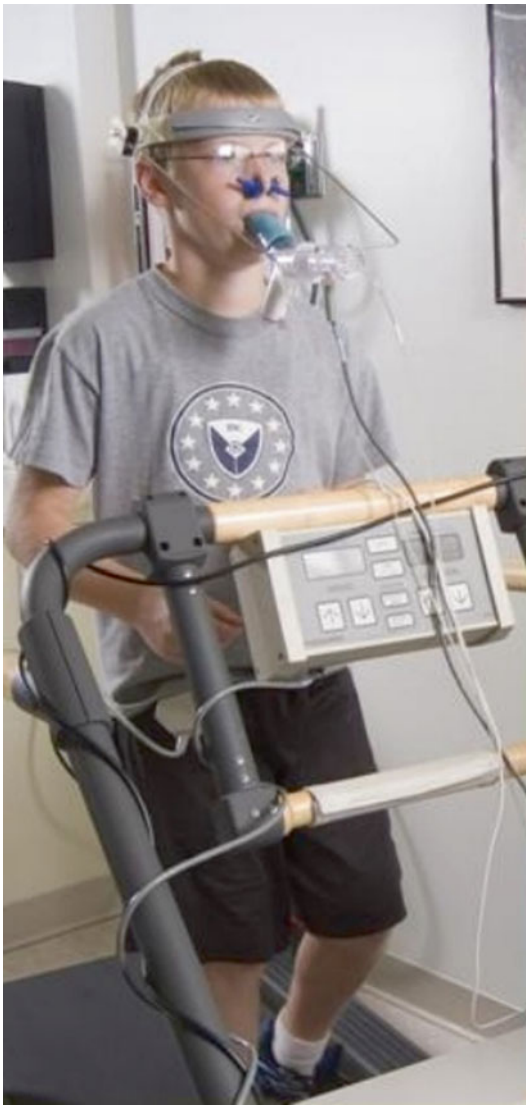

Fig. 19.8 Exercise test with cardiopulmonary monitoring. Continuous measurement is provided for inspiratory and expiratory flow, oxygen utilization, carbon dioxide production, ECG, and pulse oximetry during progressive treadmill exercise until the patient's symptoms are reproduced. A blood gas is routinely obtained at the completion of the test

Their perception of dyspnea results from the respiratory drive that occurs as a result of the lactic acidosis produced during anaerobic metabolism when exercise exceeds what is commonly called the aerobic threshold. The lowered pH from the metabolic acidosis stimulates the attempt to compensate by increasing respiratory drive to an extent that exceeds the patient's maximal respiratory effort. The result is the perception of dyspnea. Other abnormalities documented included vocal cord dysfunction, restrictive physiology associated with minor chest wall abnormalities, exercise-induced laryngomalacia, and exercise-induced supraventricular tachycardia (Fig. 19.9).

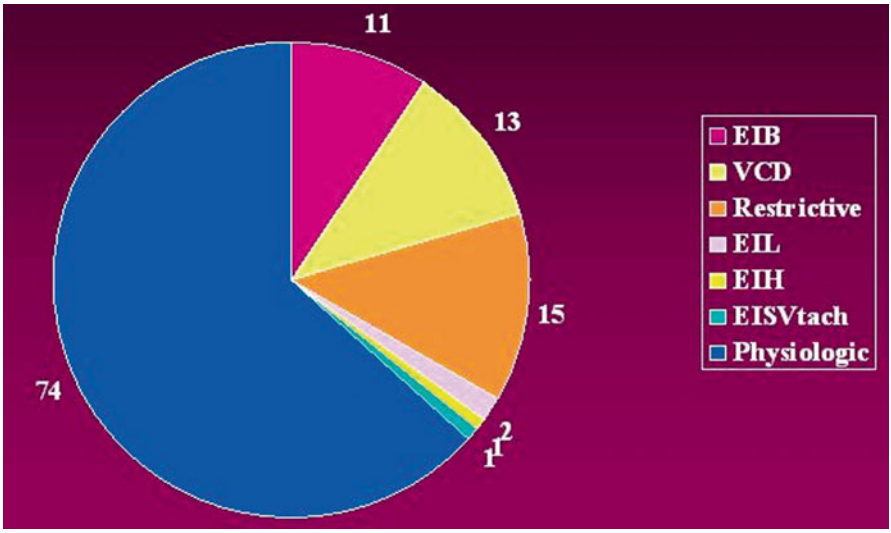

Fig. 19.9 Diagnoses determined by treadmill exercise testing with physiologic monitoring. *EIB* exercise-induced bronchospasm, *VCD* vocal cord dysfunction, *Restrictive* apparent restriction of chest wall movement, *EIL* exercise-induced laryngomalacia, *EIH* exercise-induced hyperventilation, *EIVTach* exercise-induced supraventricular tachycardia. *Physiologic* normal physiologic limitation without other abnormality. Reproduced with permission from Pediatrics

Making the correct diagnosis enables the cessation of ineffective asthma pharmacotherapy and appropriate corrective action. For those with physiologic dyspnea, counseling regarding cardiovascular conditioning and appropriate training can be of considerable value.

Evidence-Based Medicine

Kompare M, Weinberger M. Protracted bacterial bronchitis in young children: association with airway malacia. *J Pediatr*. 2012;160:88–92.

These children, primarily preschool age with predominance during the first 2 years of life, wheeze and cough and so can be initially suspected to have asthma. The cough is commonly characterized as a "wet cough." Since asthma will respond reliably to a 7-day course of an oral corticosteroid at an adequate dose, that can be used as a diagnostic test to distinguish asthma from this entity called protracted bacterial bronchitis.

Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia. requiring hospitalization among U.S. Children. *N Engl J Med*. 2015;372:835–845.

This study demonstrated that what is called pneumonia is predominantly illness from viral respiratory infections, especially in young children. It is notable that

33 % were already identified as having asthma or "reactive airway disease" (a term that should be abandoned). It would be of interest to know how many of these non-bacterial "pneumonias" were nonetheless treated with antibiotics whereas as least some may have benefited more by treatment for asthma.

Summary

While asthma is a common cause of various respiratory symptoms, all that coughs, wheezes, and causes shortness of breath or dyspnea is not asthma. Knowledge of the natural history of asthma and close observation of the response to therapy should quickly lead to an index of suspicion that diagnoses other than asthma need to be considered when there are characteristics that are atypical for asthma. Appropriate diagnostic tests including spirometry when symptomatic, flexible bronchoscopy with conscious sedation rather than general anesthesia, bronchoalveolar lavage, and treadmill exercise testing with full cardiopulmonary monitoring can generally result in the appropriate diagnosis and more specific treatment.

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Chapter 20
Hypersensitivity Pneumonitis

Jaison Jose and Timothy J. Craig

Introduction

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is an uncommon and complex syndrome that involves the interaction between the immune system and inhaled low molecular weight chemicals or organic particles. There have been numerous inhaled agents indicted, including agricultural dusts, reactive chemicals, microorganisms (bacterial, fungal, or protozoan), and bioaerosols.

Unlike other allergic diseases, the immune mechanisms do not involve an immunoglobulin E (IgE) response and eosinophilia is rare. Inhalation of environmental antigens stimulates IgG antibodies, and after binding to the antigen, the complement cascade and macrophages are activated. As a result, there is proliferation of $CD8^+$ cytotoxic lymphocytes and plasma cells that are stimulated by the $CD4^+$ T helper cell type 1 (TH1) response causing interstitial and alveolar inflammation. HP is considered a chronic disease with acute exacerbations. Host deposition of fibrotic tissue ensues in an attempt to repair the damage along with the consequence of progressive pulmonary dysfunction.

HP can occur in a variety of occupational, home, and recreational environments. It was initially associated with farming practices, and HP was first described by an Italian medical professor, Bernardino Ramazzini, in 1713 in grain workers who

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developed orthopnea and edema. More recently physicians while working with farmers with HP in the USA identified the source of the disease. With the ensuing education of farmers, the etiology of HP has shifted primarily to home-related exposures.

The most critical aspect of the treatment strategy is to first recognize the presence of HP and then to remove the subject from exposure to the offending antigen. The identification of the offending agent can pose a significant challenge to clinicians; however, if there is identification of the environment where exposure has taken place, remediation can be performed, which is usually successful in removing the antigen, thus preventing further exposures and progression of the disease. Treatment with systemic corticosteroids can reduce symptoms, but corticosteroids will not delay progression of the underlying disease process. This treatment modality should not replace identification and environmental control measures to avoid the progression of the disease.

Epidemiology

It is difficult to assess the incidence and prevalence of HP because presentation can vary considerably around the world. HP can mimic other histopathologic patterns, such as asthma, bronchiolitis obliterans with organizing pneumonia (BOOP), acute eosinophilic pneumonia, usual interstitial pneumonitis/idiopathic pulmonary fibrosis (UIP/IPF), and nonspecific interstitial pneumonitis (NSIP). Many exposed asymptomatic individuals have serum precipitins or elevated T cells in bronchoalveolar lavage (BAL) fluid. For this reason serum precipitins represent exposure as opposed to disease and cannot be used to diagnose HP, but in those with HP, it can help in identifying the exposure. An individual's ability to become sensitized to an antigen depends on factors such as antigenic potential of the inhaled particle, agricultural and industrial practices, type and intensity of exposure, host susceptibility, risk factors, and the ability of the antigen to disperse in the air. Because symptoms are often nonspecific and exposure unknown, many cases may go undetected or are misdiagnosed for many years.

Prevalence

Most epidemiologic data relate to occupational causes that vary depending on location and industry. Adding to the fact that many cases may go unnoticed or misdiagnosed, the prevalence of HP is uncertain. The reported prevalence of farmer's lung, the classic example of HP, ranges from 1.6 to 7 % of exposed farmers. It is estimated that 0.5–3 % of farmers will develop chronic HP, and this population has higher mortality rates, which was found in a surveillance study of occupational HP. *Thermophilic actinomycetes*, which was the most common organism that farmers

are exposed to, is associated with disease predominantly in warm (50–60 °C) and wet environments, especially when hay was stored in barns improperly. Multiple other antigens are able to induce HP and are derived from other microorganisms, animals, plants, and organic and inorganic chemicals (Table 20.1). Most of these antigens are derived from organisms that are ubiquitous in the natural environment. Bird handlers have a prevalence of HP that ranges from 20 to 20,000 affected individuals per 100,000 at-risk persons. This population appears to have an increased risk of the disease as compared to farmers because their exposure to the avian antigen is on a more routine basis and is less affected by season and geographic location. Unfortunately, there is an inconsistent and unstandardized epidemiologic approach for assessing the various antigens that can cause HP.

Incidence

The incidence of HP varies considerably from country to country and occupation and factors such as climate, seasonal changes, cultural differences, and workplace environments. One large, general population-based study in the UK revealed an HP incidence of 1 per 100,000 people. A report on children, for which HP is uncommon, out of Denmark showed an incidence of 2 per year and a prevalence of 4 per 1,000,000 children. Finland in particular seems to demonstrate significant variability based on season. Most cases of farmer's lung occur during April when the indoor feeding season for cattle is ending. The incidence is lowest in October when outdoor feeding for cattle is more common. There is also a positive correlation between the incidence of HP and the average daily rainfall during the preceding haymaking season. In contrast, low molecular weight chemicals have been implicated in various jobs such as paint refinishers and plastic workers year-round.

Immunopathogenesis

Overview

Proliferation of $CD8^+$ cytotoxic lymphocytes and significantly elevated IgG antibody are central to the pathogenesis of HP. The IgG is likely derived from plasma cells stimulated from $CD4^+$ T_H1 lymphocytes. Once inhaled antigen is deposited in the lower airway, macrophages and dendritic cells ingest the antigen and initiate the inflammatory cascade. $CD4^+$ T cells differentiate into Th1 and Th2 cells, as well as a variety of other effector subsets such as Th17 cells, follicular T helper cells, and induced regulatory T cells (Treg) that are all important in the mediation of HP. $CD4^+$ Th17 cells secrete IL-17 and IL-22, the former of which is associated with disease severity, and they play an important role in the subsequent development of lung fibrosis. In contrast, Tregs help downregulate the disease by suppressing the

Table 20.1 Antigens in hypersensitivity pneumonitis

Antigen	Disease	Source
Bacteria: *Thermophilic actinomycetes*		
Bacillus subtilis	Enzyme/detergent worker's lung	Enzyme dust, contaminated
	Familial hypersensitivity pneumonitis (HP)	House dust
Bacillus cereus	Humidifier's lung	Ultrasonic cool mist humidifiers
Klebsiella oxytoca		
Cephalosporium acremonium	Floor finisher's lung	Moldy wood floors
Mycobacterium avium complex	Hot tub lung	Detergent/cleaning agents
		Hot tub
Pseudomonas fluorescens *Acinetobacter calcoaceticus* *Mycobacterium chelonae*	Machine operator's lung	Contaminated metalworking fluids
Mycobacterium immunogenum		Metalworking fluids
T. candidus	Mushroom picker's lung	Mushroom compost
T. viridis		
T. sacchari	Ventilation pneumonitis	Humidifier, air conditioner
T. vulgaris	Residential composter's lung	Moldy residential compost
Thermoactinomyces vulgaris	Bagassosis	Moldy sugarcane
Faeni rectivirgula	Farmer's lung	Moldy hay, grain, compost, silage
	Potato riddler's lung	Moldy hay around potatoes
Fungi		
Aspergillus spp.	Malt worker's lung	Moldy malt dust
	Stipatosis	Moldy esparto grass
	Compost lung	Compost
	Tobacco worker's disease	Moldy tobacco Contaminated oxygen water humidifier Contaminated soy sauce
Alternaria spp.	Woodworker's lung	Moldy wood dust
Rhizopus and Mucor spp.	Wood trimmer's disease	Moldy wood trimmings
Botrytis cinerea	Wine grower's lung	Moldy grapes
Aureobasidium pullulans	Air-conditioner lung	Moldy water in HVAC systems
Cladosporium spp.	Sauna taker's lung	Contaminated sauna water
Cephalosporium spp.	*Cephalosporium* HP	Contaminated basement (sewage)
Penicillium frequentans	*Suberosis*	Moldy cork dust
P. caseii *P. roqueforti*	Cheese worker's/washer's lung	Cheese mold
P. brevicompactum *Fusarium* spp.	Farmer's lung	Moldy hay

(continued)

Table 20.1 (continued)

Antigen	Disease	Source
Fungi		
Absidia corymbifera *Wallemia sebi*	Farmer's lung in eastern France	Moldy cowshed fodder
P. expansum *P. cyclopium* *P. chrysogenum*	Farmer's lung in eastern France	Moldy wood dust
P. camemberti *P. nalgiovense* *P. chrysogenum*	Salami worker's lung	Salami seasoning
Penicillium and *Monocillium* spp.	Peat moss processor's lung Woodman's disease	Moldy peat moss Moldy oak and maple trees
Pleurotus ostreatus and *Hypsizygus marmoreus* Basidiospores	Mushroom worker's lung	Indoor mushroom cultivation
Trichosporon cutaneum *T. ovoides* *Cryptococcus albidus*	Summer-type/summer house HP	Japanese house dust
Cryptostroma corticale	Maple bark stripper's disease	Wet maple bark
Rhodotorula rubra		Moldy cellar/bathroom walls
Pullularia spp. *Graphium* spp. *Alternaria* spp.	Sequoiosis	Moldy redwood dust
Peziza domiciliana	El Niño lung	Moldy home from flooding
Lycoperdon puffballs	Lycoperdonosis	Puff ball spores
Candida spp., *Ulocladium botrytis*	Saxophonist's lung	Moldy reed
Epicoccum nigrum	Basement shower HP	Moldy basement shower
Fusarium napiforme		Moldy home
Saccharomonospora viridis	Thatched roof disease	Dried grasses and leaves
Streptomyces albus	*Streptomyces albus* HP	Contaminated fertilizer
Animal protein		
Avian proteins	Bird fancier/breeder/handler's lung, pigeon breeder's disease	Pigeon (pets and wild), duck, chicken, turkey, lovebird, dove, parrot, parakeet, Canada goose, owl
Bovine and porcine proteins	Pituitary snuff user's lung	Heterologous pituitary snuff
Animal protein		
Cat hair, animal pelts	Furrier's lung	Cat hair and fur dust
Rodent urinary proteins	Laboratory worker's lung Gerbil keeper's lung	Laboratory rat or gerbil urine
Oyster/mollusk shell protein	Oyster shell lung	Shell dust
Insect protein		

(continued)

Table 20.1 (continued)

Antigen	Disease	Source
Sitophilus granarius	Wheat weevil disease Miller disease	Infested wheat flour
Silkworm larvae	Sericulturist's lung disease	Cocoon fluff
Amoebae		
Naegleria gruberi *Acanthamoeba castellanii*	Ventilation pneumonitis	Contaminated ventilation system
Chemicals		
Toluene diisocyanate (TDI)	Paint refinisher's disease	Varnishes, lacquer, foundry, casting, polyurethane foam
	Bathtub refinisher's lung	
Diphenylmethane diisocyanate (MDI)	Chemical worker's lung	Urethane paint catalyst
Phthalic anhydride	Epoxy resin worker's lung	Resin, adhesive, foam
Trimellitic anhydride	Plastic worker's lung	Plastics industry
Pyrethrum	Pyrethrum lung	Insecticide
Medications or drugs		
Fluoxetine, mesalamine, intravesicular BCG, intranasal heroin, β-blockers, nitrofurantoin, HMG-CoA reductase inhibitors, sulfasalazine, minocycline, chlorambucil, procarbazine, cyclosporine, gold, clozapine, amiodarone	Drug-induced HP	Medications
Plant		
Soybean hull		Veterinary feed
Tobacco leaves	Tobacco grower's lung	Tobacco dust
Coffee and tea dust	Coffee/Tea worker's lung	Coffee bean dust or tea leaves

Adapted from *Middleton's allergy: principles & practice*, 8th Edition, Published 2014

BCG Bacille Calmette-Guérin (vaccine), *HVAC* heating, ventilating, and air conditioning

proliferative response of activated T cells and could explain why many individuals exposed to antigens that can cause HP do not develop the disease and also why some individuals who have HP continue to be exposed resolve their pneumonitis.

The majority of people exposed to the antigenic particles develop an IgG response. This alone is not sufficient to cause disease when not accompanied by a cytotoxic delayed hypersensitivity $CD8^+$ response. The factors that determine whether a person will develop the clinical manifestations of HP are not fully delineated. Increased production of macrophage-derived tumor necrosis factor alpha (TNF-α) and expression of the TNF A2 allele, which is associated with increased production of TNF-α, were found with increased frequency in patients with HP. Patients who had farmer's lung had an increased production of TNF-α after hay challenge, but asymptomatic controls with positive antibodies did not have this

exaggerated response. Recently, investigators have found that glucocorticoid-induced TNF receptor (GITR) expressed on natural killer T cells (NKT) can increase cytokine production in vitro. They have also demonstrated that this effect can protect against the development of HP in vivo.

There is also a role for cell activation signals. Toll-like receptors (TLRs) are immune cell receptors that initiate lung cellular influx and inflammatory responses. They are expressed on immune cells and recognize most antigens. When specific TLRs are activated in HP, they react through an intracellular pathway known as the MyD88 pathway, which contributes to the release of proinflammatory cytokines and mediators.

Acute Phase of Hypersensitivity Pneumonitis

Most divide HP into an acute, subacute, and chronic phase. The acute phase of HP is initiated when the inhaled antigen binds to a specific IgG antibody. This immune complex formation triggers the complement cascade, and the ensuing C5 activates macrophages. As a result, these macrophages secrete various chemokines, such as IL-8, and macrophage inflammatory protein-α1 (MIP-1α). Other cytokines are also elaborated, and they attract leukocytes, predominantly neutrophils. MIP-α1 contributes to the differentiation of T_H0 cells to T_H1 cells and acts as a chemotactic molecule for macrophages and lymphocytes. Mouse models of HP show that IFN-γ, which is usually produced by activated $CD4^+$ T_H1 lymphocytes, is required for the activation of macrophages. This activation leads to the formation of granulomas.

Other cytokines, such as IL-1 and TNF-α, derived from activated macrophages, act as pyrogens and cause fever. They also cause the acute-phase response seen in HP, which often can mimic a bacterial pneumonia. Macrophages also elaborate IL-6 and IL-12, the latter of which contributes to the differentiation of B cells into plasma cells and the development of $CD8^+$ cells into cytotoxic T lymphocytes. Lymphocytes usually appear 24–48 h after antigen sensitization and account for 60–90 % of recovered cells from BAL of patients with HP. IL-12 additionally contributes to the differentiation of T_H0 to T_H1 cells, amplifying the reaction and increasing its severity. Human subjects with HP have T lymphocytes in BAL fluid with increased IL-12 receptors and are usually $CD8^+$.

The adhesion molecule CD80/86, or B-7, is increased on activated macrophages. Activated T cells have increased CD28, which is the ligand for B-7. CD28 and B-7 function as critical costimulatory molecules for antigen presentation and for B-cell activation by $CD4^+$ T helper cells. Mouse models of HP show that antagonism of these ligands inhibits inflammation necessary to induce HP.

Endothelial adhesion molecules such as E- and P-selectin are involved in the rolling of leukocytes resulting in their accumulation at the inflammation site. ICAM-1 expression on macrophages enhances their antigen-presenting capacity. Inhibition of these molecules blocks the recruitment of lymphocytes into pulmonary tissue. Because of the pathophysiology noted above, the bronchoalveolar lavage

(BAL) from patients with HP usually has higher numbers of $CD8^+$ cells compared to $CD4^+$ cells; however, $CD4^+$ lymphocytes may predominate early in the immunologic response. Lastly, as noted above, during the acute phase, the patient often manifests cough, fever, elevated leukocyte count, elevated sedimentation rate, and symptoms that may mimic an autoimmune or infectious disease. On pulmonary function testing, the DLCO drops as symptoms increase and both the FEV_1 and FVC drop, which is consistent with restrictive lung disease.

Subacute Phase of Hypersensitivity Pneumonitis

The subacute phase of HP is characterized by granuloma formation. Macrophages that are attracted to lung tissue eventually develop into epithelioid cells and multinucleated giant cells. Lymphoid follicles containing plasma cells form in proximity to the granuloma. This phase of inflammation is also represented by proliferation of $CD4^+$ T_H1 lymphocytes, which contain the CD40 ligand on their surface. This ligand is critical for the activation of B cells and their subsequent development into plasma cells that produce antibody. Much of the antibody production in HP occurs locally in lung tissue primarily due to this immune response.

Macrophages also produce the lymphocyte chemoattractant, CCL18, which is most abundant during the subacute phase of HP. This results in a high lymphocyte count in BAL with severe inflammation. B lymphocytes play a crucial role in HP, and an increased number of antibodies correlate with severity of the disease. During this stage, the patient often presents with more chronic symptoms and may have significant shortness of breath and dyspnea on exertion alone with constitutional symptoms often mimicking a rheumatologic disease.

Chronic Phase of Hypersensitivity Pneumonitis

The extracellular matrix surrounding the granuloma contains myofibroblasts, which deposit collagen and the proteoglycan versican. The activated macrophages secrete high amounts of TGF-β, a potent inducer of fibrosis and angiogenesis. These pathologic changes are the hallmark of the chronic phase of inflammation.

Expression of Fas ligand and CD40 ligand also promotes fibrosis. Increased numbers of mast cells are present in the BAL fluid of mouse and human models of HP. They are also found in high numbers in the interstitial tissue in HP. Mast cells can also be found in the BAL fluid of other interstitial lung diseases. The mast cells in BAL fluid in HP have characteristics of the connective tissue type rather than the mucosal type. Mast cells of the connective tissue type may play more of a role in diseases characterized by fibrosis as opposed to diseases such as asthma. Mast cells elaborate inflammatory cytokines that promote fibrosis and recruitment of monocytes and lymphocytes.

Neutrophils may play a role in the development of fibrosis in HP. Recently, evidence indicates that alveolar macrophages in patients with pulmonary fibrosis and HP secrete high levels of CCL18, which is a potent inducer of fibroblast collagen deposition. These are possible mechanisms of why fibrosis develops in patients with chronic HP. Neutrophils also produce elastase, a serine protease that is a destructive and proinflammatory enzyme, that contributes to the breakdown of elastic fibers resulting in emphysematous changes. The influx of neutrophils also contributes to the production of oxygen-free radicals, which damages tissue and triggers the development of fibrosis. The end stage of chronic HP is diffuse fibrosis and honeycombing of the lung, which results in severe limitation of exercise and increasing shortness of breath and pulmonary hypertension.

Clinical Presentation

As noted above the presentation of HP has been conventionally classified into acute, subacute, or chronic forms. These various stages can overlap clinically (Fig. 20.1), and individuals can present with a combination of these forms, which are usually determined by level of antigenic and temporal exposures. Patients can present with different forms of HP despite being in the same setting and antigen exposure. Why some patients stay healthy, some develop acute HP, others develop progressive fibrosis, and still others asthma from the same exposure is presently unknown and is an important area of research.

Acute Presentation

Signs and Symptoms

During the acute phase, symptoms are typically characterized by an influenza-like syndrome that includes fever, cough, dyspnea, chest pain, myalgias, and fatigue. Other symptoms include loss of appetite, weight loss, and wheezing. Symptoms of the acute form are usually abrupt and occur within 4–6 h after exposure to the agent. When the subject is exposed to very large amounts of antigen, the acute presentation can be within only a few hours of exposure. Symptoms typically resolve within 12 h but may take up to several days after the subject is removed from the offending agent. Physical examination usually demonstrates crackles, but wheezing may be present. Resolution of symptoms with hospitalization often delays the diagnosis because the patient is removed from the source of antigen. Markers of inflammation, such as erythrocyte sedimentation rate, C-reactive protein, and white blood cell count, may be elevated during this phase. Neutrophilic leukocytosis usually predominates in acute HP. Elevated inflammatory markers may precede signs and symptoms and may also persist for several days after symptom resolution. In general, this form is nonprogressive and intermittent and spontaneously improves and/or resolves after antigen avoidance.

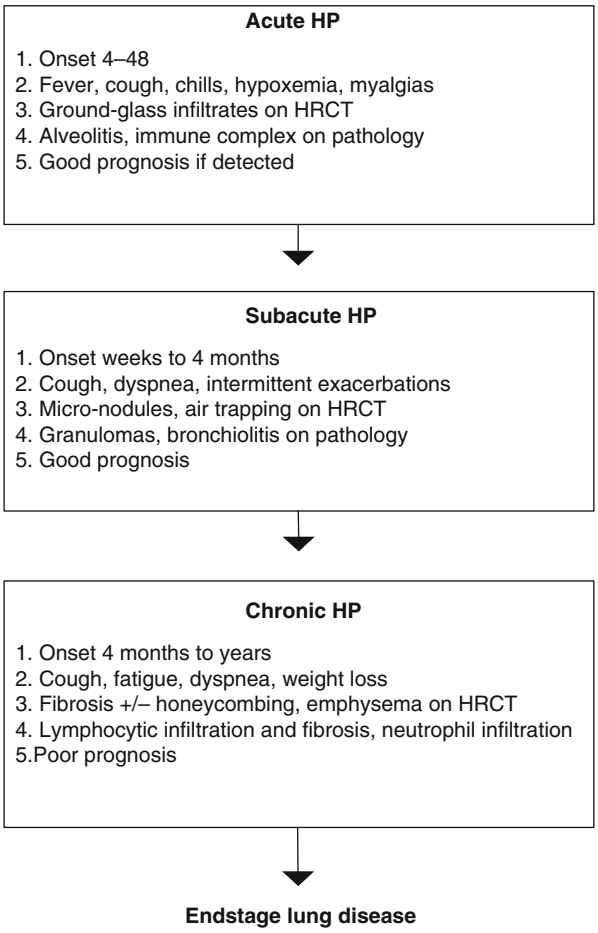

Fig. 20.1 Clinical presentation of hypersensitivity pneumonitis (*HP*). *HRCT* high-resolution computed tomography

Radiography and Pulmonary Function Testing

Chest radiograph is usually normal, but when abnormal, it can demonstrate ground-glass opacities or poorly defined small nodules. There are bilateral interstitial infiltrates in up to 90 % of patients, and hilar lymphadenopathy is present about 50 % of the time. Spirometry may be normal, but it can also show a restrictive functional pattern with decreased forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). The ratio of FEV_1 to FVC is usually preserved, and total lung volumes (TLC), along with diffusing capacity of the lung for carbon monoxide (D_{LCO}), are decreased. Radiographic abnormalities in acute HP usually resolve along with symptoms within 12 h to several days after removal from exposure.

Subacute Presentation

Signs and Symptoms

The subacute form is more difficult to diagnose because the associated signs and symptoms mimic many other respiratory disease states. It usually develops over weeks to 4 months with episodic flare-ups. It results from repeated, low-level exposure to inhaled antigens and, as a result, can progress insidiously. Symptoms begin with coughing, fever, dyspnea, and malaise that resemble bronchitis. The cough can become severe and productive. Wheezes, rales, and rhonchi may be present on examination as the disease severity fluctuates. Low-grade fever may also be present, but this is not a consistent finding in the subacute stage of the disease. Other symptoms, such as arthralgias, myalgias, and fatigue, may be significant, leading one to falsely suspect infectious pneumonia, or interstitial lung disease like sarcoidosis, or a rheumatologic disease.

Radiography and Pulmonary Function Testing

Chest radiographs may be normal or slightly abnormal in the subacute form. Computed tomography (CT) may be the preferred imaging study to identify any pulmonary abnormalities. Inflammatory markers may be elevated as in the acute form of HP. These markers may be particularly useful when monitoring avoidance challenge procedures.

Pulmonary function tests in the subacute form reveal a mixed obstructive-restrictive defect that may reverse with bronchodilators. Glucocorticoids often reverse the pulmonary function abnormalities as well. These findings often lead to the misdiagnosis of asthma. Interestingly, approximately 50 % of patients have a positive methacholine bronchial challenge, making the distinction with asthma even more difficult. Unlike patients with asthma, patients with HP do not attain control of their pulmonary symptoms with bronchodilators and inhaled corticosteroids. They require courses of systemic glucocorticoids to control their symptoms.

Chronic Presentation

Signs and Symptoms

In the chronic form of HP, patients often present to medical attention late in the course of the disease. Patients may be identified by routine chest radiography with minimal or no symptoms. The most common symptom is dyspnea with exertion and a nonproductive cough. Other complaints include weight loss, loss of appetite, and malaise. These nonspecific symptoms may be present for years before medical attention is sought. Lung exam often reveals crackles, but unlike

the other stages of HP, wheezes, rales, and rhonchi are unlikely to be found on lung auscultation. Digital clubbing is uncommon in the other two forms of HP but may be present in the chronic form and indicates severe disease and predicts clinical deterioration.

Radiography and Pulmonary Function Testing

Unlike the other forms of HP, inflammatory markers may be normal. Chest radiography often shows significant pulmonary fibrosis but may be normal. Pulmonary function test (PFT) demonstrates a restrictive pattern where the D_{LCO} will be reduced and hypoxemia is common. However, in cases of farmer's lung, there can be an obstructive pattern resulting from emphysema. CT will have characteristic mid-lung zone predominance of fibrosis which can be represented by irregular linear opacities, lobar volume loss, bronchiectasis, and nonspecific end-stage irreversible honeycombing and emphysema. In chronic farmer's lung, studies have shown that emphysema occurs more commonly than fibrosis.

Diagnosis

There is no single diagnostic test specific for HP (Table 20.2). The diagnosis is often entertained based on history, physical examination, and environmental and occupational exposure. Radiographic infiltrates that are intermittent in presentation should raise suspicion of HP. Physical examination may reveal crackles and occasionally wheezing on lung auscultation. These findings are nonspecific for HP but may be helpful if present with a compatible history.

Table 20.2 Evaluation and manifestation of HP

Evaluation	Findings
Laboratory investigation	IgG antibody specific for antigen (precipitin) Inflammatory markers: leukocytosis, hypergammaglobulinemia, elevated C-reactive protein, elevated erythrocyte sedimentation rate
Arterial blood gas	Possible hypoxemia
Chest radiography	Pulmonary infiltrates, fibrosis, nodules depending on stage of disease, level of antigen exposure, duration of exposure
Computerized tomography scan	Ground-glass opacities, air trapping, fibrosis
Pulmonary function	Restrictive defect, hypoxemia, impaired D_{LCO}, obstructive defect
Bronchoalveolar lavage fluid analysis	Initially neutrophilic predominance, followed by lymphocyte predominance (CD8+)
Lung biopsy	Lymphocytic infiltration, granulomas, fibrosis

Laboratory Findings

Laboratory testing is not particularly revealing in evaluating for the presence of HP. Inflammatory markers such as erythrocyte sedimentation rate and leukocyte count may be elevated. This elevation is most common in acute HP. Serum total IgG is elevated, but IgE and eosinophil count are usually normal. Rheumatoid factor may also be positive, especially with chronic HP secondary to lung fibrosis.

Serum-specific precipitating antibodies are found in many patients with HP. As many as 40–50 % of asymptomatic individuals exposed to the same antigens have serum IgG antibodies. Positive serum precipitins indicate past exposure to the implicated antigen in a sufficient amount to induce a humoral immunologic response, but not always the disease. Thus, serum precipitins are sensitive but not specific in diagnosing HP. Serum precipitin testing offered by commercial laboratories in general is only helpful in the evaluation of farmer's lung or bird fancier's disease. If exposure to the antigen is related to the home or work environment, this test most likely has little value. If precipitin testing is performed on suspected antigens from the environment where exposure has taken place, the diagnostic yield may be greatly increased. Precipitins can remain positive for months or years after the last known exposure.

Radiographic Evaluation

High-resolution computed tomography (HRCT) of the chest is more sensitive than chest radiography in supporting the diagnosis of HP. The findings on imaging vary according to the stage of HP. Acute HP typically demonstrates bilateral micronodular infiltrates or patchy ground-glass opacities on HRCT. Imaging may also show decreased attenuation and mosaic perfusion due to air trapping from bronchiolitis. These findings correlate on histopathology to peribronchiolar perilymphatic infiltration and active interstitial inflammation. In subacute HP, linear shadows and small nodules give a reticulonodular appearance on chest radiographs. Chronic HP demonstrates radiographic findings consistent with interstitial fibrosis or honeycombing. The distribution of fibrosis is in the upper and mid-lung zones. This is in contrast to idiopathic pulmonary fibrosis where the fibrosis is in the lower lung zones.

Pulmonary Function Testing

Pulmonary function testing typically demonstrates a restrictive defect with abnormal diffusion capacity. The FVC may be normal in early HP, but this value usually becomes progressively reduced as the disease process advances. The FVC can also be used to monitor the effects of glucocorticoids or removal from the environment.

The D_{LCO} is a more sensitive indicator of disease presence compared to FVC when measured early in the disease course. Serial measurements of D_{LCO} can also be

used to monitor intervention strategies. Pulse oximetry with exertion can be used in the office as an initial screen and may demonstrate oxygen desaturation with exercise, which may be an indicator of insidious interstitial involvement.

Because many other interstitial lung diseases produce a similar pattern on spirometry, these findings are not specific for HP. Chronic HP, particularly chronic farmer's lung, may show an obstructive defect with a reduced FEV_1 to FVC ratio as previously mentioned; however, most cases are restrictive.

Bronchoscopy

Clinical signs and symptoms that are consistent with HP in conjunction with relevant environmental exposure may be sufficient to establish the diagnosis of HP. If uncertainty persists, transbronchial biopsy specimens may help differentiate HP from entities such as sarcoidosis, alveolar hemorrhage, and lymphangitic carcinoma, which have their own characteristic findings that differ from HP. To increase the diagnostic yield of biopsy specimens, multiple biopsies should be performed on areas of the lung that demonstrate radiographic involvement. In addition, the classical finding on bronchoalveolar lavage, as noted earlier, is a predominance of CD8+ lymphocytes.

Histologic Analysis

The classic triad of HP on histopathologic analysis is cellular bronchiolitis or bronchiolitis obliterans, patchy NSIP, and scattered non-necrotizing granulomas. Despite the classic triad on histologic specimens, not all patients with HP demonstrate granulomas and bronchiolitis obliterans. The most common findings on histologic analysis found in farmer's lung as determined by Reyes et al. are listed in Table 20.3.

Table 20.3 Pathologic findings in hypersensitivity pneumonitis

Pathologic findings	% of cases
Patchy interstitial pneumonitis	100
Unresolved pneumonia with organizing intra-alveolar fibrinous exudates	65
Patchy interstitial fibrosis of varying severity	65
Bronchiolitis obliterans	50
Granulomas with Langhans-type giant cells	70
Birefringent foreign body material of uncertain nature	60
Pleural fibrosis	28
Intra-alveolar edema	52
Variable-sized collections of intra-alveolar foam cells	65

Adapted from Reyes CN, Wenzel FJ, Lawton BR, et al. The pulmonary pathology of farmer's lung disease. *Chest*. 1982;81:142

Neutrophilic inflammation and emphysema may be present if exposure is to a significant degree. Acute HP is characterized by neutrophils that infiltrate the alveoli and respiratory bronchioles. This evolves into a $CD8^+$ lymphocyte dominant presentation that is often noted on BAL. If the natural course of HP continues without intervention, fibrosis becomes the predominant finding and may resemble other fibrotic pulmonary diseases such as UIP.

Environmental History

The environmental history is an important aspect of the investigation when HP is suspected. In the past, HP was viewed as an entity that resulted from a significant exposure to an antigen found primarily in the agricultural, industrial, or hobbyist surroundings. Because practices in the workplace have been remedied by the addition of protective equipment, antigen exposure in the occupational setting has substantially diminished. For example, altering storage of hay has been very effective at decreasing HP in farmers.

The home is an integral part of the environmental investigation when HP is suspected. The investigator should clue in to areas of excessive moisture within the home environment when mold exposure is suspected. Seemingly irrelevant aspects of the home investigation should be considered, such as plumbing irregularities, humidifiers, hot tubs, bird antigens, saunas, animal exposures, forced air-heating and air-cooling system abnormalities, and roof leaks. These represent some reservoirs in the home that can provide enough antigen exposure to cause HP. The office or work environment should also be evaluated for these same conditions that can lead to antigen exposure.

In both the workplace and home environmental sampling of water, dust, soil, and air that is performed at suspected antigen exposure locations may be helpful and are best directed by an industrial hygienist. If an inspection is necessary, the data collected should be interpreted in relation to the history taken from the patient. If necessary a challenge may be utilized, but should only be done by experts in this disease state since patients can have severe symptoms from a challenge. Direct antigen inhalation, environmental exposure, and in vitro stimulation of lymphocytes are some of the various challenge methods used to help in the diagnosis of HP. Each of these methods has their own advantages and disadvantages.

In Vitro Challenge and Antigen and Specific Antibodies Detection

In vitro challenges have been used on blood lymphocytes and lymphocytes derived from BAL fluid. In vitro challenges, much like precipitin testing, do not discriminate between individuals who have been exposed to the antigen and those who are manifesting the clinical disease of HP.

Direct Antigen Inhalation

Direct antigen inhalation can be used to identify the causal antigen in all three stages of the disease. Because antigen concentrations are arbitrarily chosen, this procedure may deliver a potentially dangerous dose of antigen to a susceptible subject. It is imperative that patients be prick test negative to the antigen so a potentially lethal asthmatic response can be avoided. Provocative inhalational testing is usually not required for the diagnosis of HP, and if they are to be performed, they should be done in an appropriate setting, after a period of avoidance, where correct management can be obtained. To avoid poor outcomes, inhalational challenge is best reserved to be performed by those experienced with the technique.

Environmental Avoidance Challenge

Environmental avoidance challenge is another method to help detect the presence of HP. The disadvantage of this method is that the implicated antigen cannot be accurately determined. A typical environmental avoidance challenge would begin by inducing remission of the disease with a course of corticosteroids followed by restriction to the potential environment. Parameters such as chest radiograph, C-reactive protein, sedimentation rate, pulmonary function tests, and white blood cell count are monitored and followed as patient again enters the potential site where possible antigen exists. If symptoms occur, exploration and remediation is done to avoid further exposure.

Diagnostic Criteria

Diagnostic criteria for HP have been proposed by the American Academy of Allergy Asthma and Immunology. According to these diagnostic guidelines (Table 20.4), if four of the major criteria and two of the minor criteria are fulfilled, then the diagnosis of HP is made. Importantly, other disease processes with similar presentations must be excluded.

Treatment

Avoidance of Antigen

The primary objective in the treatment of HP is early identification of the disease and, most importantly, avoidance of the putative agents. Identifying the specific antigen is a challenging endeavor and may not be feasible. Equipment to protect the

Table 20.4 Major criteria for diagnosis

Major criteria:
1. History of compatible symptoms with hypersensitivity pneumonitis (HP) that develop or worsen within hours if exposed to antigen
2. Historical confirmation of exposure to the offending agent, investigation of the environment, serum precipitin testing, and/or bronchoalveolar lavage fluid antibody
3. Changes on chest radiography or high-resolution computerized tomography of the chest that is compatible with HP
4. If bronchoalveolar lavage is performed, the presence of fluid lymphocytosis
5. If lung biopsy is performed, compatible histologic findings with HP
6. Reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment or by controlled challenge
Minor criteria:
1. Basilar crackles on lung examination
2. Decreased diffusion capacity of pulmonary function testing
3. Arterial hypoxemia at rest or with exercise

Note: Four major and two minor criteria are required for diagnosis

subject from exposure such as laminar flow high-efficiency particle arrest-filtered helmets may be used. Electrostatic dust filters installed in the air-conditioning system can be effective in lowering mold antigen but may not provide adequate protection. High-efficiency particulate air (HEPA) filters when used in isolation are considered insufficient to remove antigen. For occupational-related HP, it is often difficult for patients to change profession, and in this instance, instead of avoidance, reduction in antigen exposure is necessary. In the farming industry, adequate drying of fodder, using silage instead of hay, and avoiding places where hay is stored can reduce the clinical manifestation of farmer's lung.

Environmental Remediation

Remediation of the environment is the next step in antigen avoidance. General contractors or the owner of the home is typically sufficient to perform a successful remediation. Once remediation has been implemented, the patient must be monitored for disease progression. Care must be taken to prevent progression to chronic HP or fibrosis by chronic low-level antigen exposure that is subclinical.

Corticosteroids

Corticosteroids may be used to treat acute and subacute HP but should not be substituted for avoidance measures. An appropriate time course and dose would be 2–4 weeks of prednisone, 0.5 mg/kg/day or doses equivalent to 40–60 mg daily.

Subacute HP may mandate higher doses of prednisone for a longer duration (3–6 months). The effect of corticosteroids on slowing the progression of the subacute and chronic forms of HP has not been clearly defined.

Lung Transplantation

Lung transplantation should be considered when there is no effective therapy and the risk of mortality is high such as in chronic advanced HP where there is progressive extensive lung scarring. The chronic fibrosis stage can lead to respiratory failure, cor pulmonale, and death.

Prognosis

Early recognition of HP and removal from the offending agent seem to be the most important factors in terms of prognosis, which can be highly variable. The prognosis is favorable if HP is detected early. Once the person is removed from the offending agent, improvement is typically observed within 1–6 months. If identified in the acute stage, the patient may demonstrate restrictive lung disease with reduced diffusion capacity that continues to improve over the course of several weeks. The granuloma and bronchiolitis that occurs in the subacute phase may take longer to resolve even if corticosteroids are implemented. Some patients with farmer's lung may continue to have disease progression and a decline in lung function despite removal from antigen exposure. Predictors of progressive decline in lung function in farmers include recurrent acute episodes of HP, exposure to areas of swine confinement, bacterial endotoxin exposure, allergy to mites/organic dust, and fungal infections. There also appears to be an increased risk of developing emphysema in farmers with farmer's lung.

Chronic HP can lead to pulmonary hypertension in approximately 20 % of patients, and as stated previously, chronic fibrotic HP is a slowly progressive disease that is irreversible and can lead to respiratory failure, right heart failure, and death. Further highlighting the importance of early recognition of the disease, preventing fibrosis in patients with HP can impact survival. In a cohort of patients with subacute and chronic HP, it was determined that the presence of fibrosis was related to a 5-year mortality of 27 % and a median survival of 12.8 years.

Evidence-Based Medicine

New advances in HP-related research have been due to two forms of HP secondary to exposure to environmental mycobacteria. Hot tub lung is due to M. avium that induces an HP-like reaction after hot tub exposure. This Mycobacterium genus has

been identified as the offending antigen in sputum, lung biopsy, and water cultures. Antimicrobial therapy is not required, and treatment is avoidance and corticosteroids. Metalworking fluid (MWF) HP is the second form, and it is found in workers in several industries. MWF is used to decrease heat from machine tools and their products. However, resistant microorganisms such as those from the Mycobacterium genus (most often *M. immunogenum*) survive and have been implicated in MWF HP. These mycobacteria have been shown to induce lung granulomas, peribronchiolar lymphocytosis, increased cell concentrations in BAL, and upregulation of cytokines in mice. Prevention strategies in the industry have been recommended.

In a prospective multicenter cohort study by Lacasse et al. in 2003, a diagnostic criteria and clinical prediction rule were developed for HP. Seven clinical sites from as many countries were involved, and the study population included patients 18 years and older with suspected diagnosis of HP from 1998 through 2001. This study concluded with significant predictors of HP: (1) exposure to a known offending antigen, (2) positive precipitating antibodies, (3) recurrent episodes of symptoms, (4) inspiratory crackles, (5) symptoms 4–8 h after exposure, and (6) weight loss. Exposure to a known offending antigen is the strongest predictor. These predictors do not apply to chronic and inactive forms of HP.

In the pediatric population, HP is an uncommon entity, and as a result, treatment has been extrapolated from adults. Griese et al. in 2013 identified 23 children in Germany with HP, and the majority were due to bird and fungus allergens. Also, almost all of the children were treated with systemic steroids which improves symptoms, but does not prevent progression of the disease. Nowicka et al. in 2015 retrospectively reviewed records of patients in Poland with HP and separated them into 3 age groups: <30, 30–49, and >50 years old. Lung function, including diffusion capacity for carbon monoxide (DLCO), was more seriously impaired in the youngest age group, and they more often had a restrictive pattern to their disease. However, more studies need to be done in the pediatric population in order to understand and treat HP appropriately.

Conclusion

In summary, HP remains a diagnostic challenge for the clinician. The pathophysiology involves interaction with an inhaled antigen that is of animal, plant, microbial, organic material, or inorganic material origin. In susceptible individuals, the antigen induces an immune response dominated by a T_H1 cytokine profile including INF-γ and TNF-α. Some MHC class I loci have been identified that predispose the individual to develop HP if the correct exposure takes place. Once the inflammatory process begins, IgG specific for the antigen is elaborated and can be measured serologically. Aside from lymphocytes that tend to be $CD8^+$ in the case of HP, neutrophils and macrophages are also recruited to the site of inflammation and contribute to the pathogenesis of HP. HP is classified into three stages: acute, subacute, and chronic HP. Each stage has its typical clinical findings and associated radiographic

abnormalities including ground-glass opacities, nodules, and fibrosis. Serum precipitins can be measured to assist in the diagnosis but may be positive in exposed individuals without clinical symptoms. Obtaining PFTs and bronchoscopy with BAL analysis may be helpful, as well as lung biopsy for tissue diagnosis. Using techniques such as direct antigen inhalation or environmental avoidance challenge can help verify the diagnosis and the causative agent. Treatment is directed toward identifying the antigen in the environment and avoiding it. Remediation of the exposure environment may be necessary. Oral corticosteroids can be used to treat symptoms but should not replace removal from exposure to the antigen.

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Chapter 21
Allergic Bronchopulmonary Aspergillosis

Satoshi Yoshida

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disorder caused by hypersensitivity response to *Aspergillus* antigens in the lung which is an uncommon but serious respiratory condition characterized by chronic airway inflammation and airway damage resulting from persistent colonization by and sensitization to the fungus *Aspergillus fumigatus* (*A. fumigatus*). The first cases of ABPA in the United States were identified more than 40 years ago, whereas the initial literature report in the United Kingdom was in 1952. The prevalence of ABPA is as high as 1–2 % of patients with persistent asthma if screening is carried out, although even higher rates have been reported. Especially in corticosteroid-dependent asthma patients, it has been reported that ABPA might be complicated as high as 7–14 %. In cystic fibrosis, the prevalence of ABPA ranges from 2 to 15 %. ABPA is sometimes recognized in patients with allergic fungal sinusitis, though such an association is unusual. ABPA has been identified in patients with hyper-immunoglobulin E (IgE) syndrome and chronic granulomatous disease, which might create management dilemmas because of concerns about administration of prednisone. In patients with asthma, ABPA is sometimes diagnosed in the absence of the typical proximal bronchiectasis; in such cases, it is designated ABPA seropositive. Often, ABPA is suspected (1) because of an episode of "pulmonary eosinophilia" or tenacious mucus plugging, (2) when a chest roentgenogram and an unexpected infiltrate are obtained, or (3) after skin testing and serologic testing.

The prevalence of ABPA in patients admitted with acute severe asthma is even higher. In a recent study of 57 patients with acute severe asthma admitted in the respiratory ICUs, we demonstrated the prevalence of *Aspergillus* hypersensitivity

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(AH) and ABPA to be around 51 % and 39 %, respectively. The occurrence of AH and ABPA was significantly higher in patients with acute asthma compared to the outpatient bronchial asthma (around 39 % and 21 %, respectively).

Pathogenesis

Discussions on pathogenesis are available in greater detail in several additional references. After inhalation of spores of *A. fumigatus*, there is saprophytic growth in the hyphal form, which is a result of immune response to *A. fumigatus* colonization of airway and poor clearance of mucus secretions. It remains unclear what survival factors there might be in *A. fumigatus*, or what abnormalities there might be in bronchial mucus, that permit its growth in contrast to the clearing seen in all other patients with asthma who do not develop ABPA. The array of antibody production, cytokine generation, cellular proliferation (*A. fumigatus* can function as a growth factor for eosinophils in vitro), and effector molecules creates an intense immunologically mediated set of reactions. Many issues remain unclear, including how on histologic examination of patients with ABPA there can be, either individually or in combination, eosinophilic pneumonia, bronchocentric granulomatosis, granulomatous bronchiolitis, exudative bronchiolitis, *A. fumigatus* hyphae in microabscesses, lipid pneumonia, lymphocytic or desquamative interstitial pneumonia, pulmonary vasculitis, and bronchiolitis obliterans. Thus, ABPA leads to subsequent bronchiectasis, pulmonary fibrosis, and compromise of pulmonary function.

Environmental factors are not considered the main pathogenetic factors because not all asthmatics develop ABPA despite being exposed to the same environment. In a genetically predisposed individual 42–54 (Table 21.2), inhaled conidia of *A. fumigatus* persist and germinate into hyphae with release of antigens that compromise the mucociliary clearance, stimulate and breach the airway epithelial barrier, and activate the innate immunity of the lung. This leads to inflammatory cell influx and a resultant early- and late-phase inflammatory reaction. The antigens are also processed presented to T cells with activation of Th2 CD4+ T-cell responses. The Th2 cytokines (interleukin [IL]-4, IL-5, and IL-13) lead to total and *A. fumigatus*-specific IgE synthesis, mast cell degranulation, and promotion of a strong eosinophilic response. This causes the characteristic pathology of ABPA.

Clinical Features

There is no gender predilection and majority of the cases present in the third to fourth decade of life. A family history of ABPA may be elicited occasionally. Most patients present with low-grade fever, wheezing, bronchial hyperreactivity, hemoptysis, or productive cough. Expectoration of brownish black mucus plugs is seen in 31–69 % of patients. The symptoms of hemoptysis, expectoration of brownish black mucus plugs, and history of pulmonary opacities in an asthmatic patient suggest ABPA. Patients can occasionally be asymptomatic, and the disorder is diagnosed on

routine screening of asthmatic patients. Physical examination can be normal or may reveal polyphonic wheeze. Clubbing is rare and is seen in only 16 % of patients. On auscultation, coarse crackles can be heard in 15 % of patients. Physical examination can also detect complications such as pulmonary hypertension and/or respiratory failure. During exacerbations of ABPA, localized findings of consolidation and atelectasis can occur that needs to be differentiated from other conditions.

The Diagnosis

Classic criteria for the diagnosis of ABPA have been published by Rosenberg and colleagues in 1977 as mentioned in Table 21.1. Japanese allergist-immunologist or pulmonologist still usually uses these criteria for the diagnosis of ABPA. Such cases will have other features as well, including chest roentgenographic infiltrates (Fig. 21.1), peripheral blood eosinophilia in the absence of oral corticosteroids, precipitating antibodies to *A. fumigatus*, and production of mucus plugs containing *A. fumigatus*. In such cases, the allergist-immunologist or pulmonologist should have little difficulty with the diagnosis. Failure of the chest roentgenographic or chest CT infiltrates to clear over a 2-month period of prednisone therapy suggests noncompliance, another ABPA exacerbation, or possibly other diagnoses, such as cystic fibrosis. Proposed criteria for the diagnosis of ABPA in patients with cystic fibrosis are presented in Table 21.2, which is based on the work of a Consensus Conference of the Cystic Fibrosis Foundation. Of note, the prevalence of ABPA is higher in patients with cystic fibrosis than in patients with persistent asthma. Another criterion proposed for the diagnosis of ABPA in patients with asthma is presented in Table 21.3. Some patients who seem to have had no history of asthma or cystic fibrosis and then present with chest roentgenographic infiltrates and lobar collapse are found to have ABPA. Some patients with ABPA have had histories of intermittent mild asthma (exercise-induced bronchospasm) before their ABPA was diagnosed. Conversely, the asthma might have been persistent moderate or severe (corticosteroid dependent).

Table 21.1 Criteria for the diagnosis of allergic bronchopulmonary aspergillosis

Primary
Episodic bronchial obstruction (asthma)
Peripheral blood eosinophilia
Immediate skin reactivity to *Aspergillus* antigen
Precipitate skin reactivity to *Aspergillus* antigen
Elevated serum immunoglobulin E concentrations
History of pulmonary infiltrates (transient or fixed)
Central bronchiectasis
Secondary
Aspergillus fumigatus in sputum (by microscopic examination)
History of expectoration of brown plugs or flecks
Arthus reactivity (late skin reactivity) to *Aspergillus* antigens

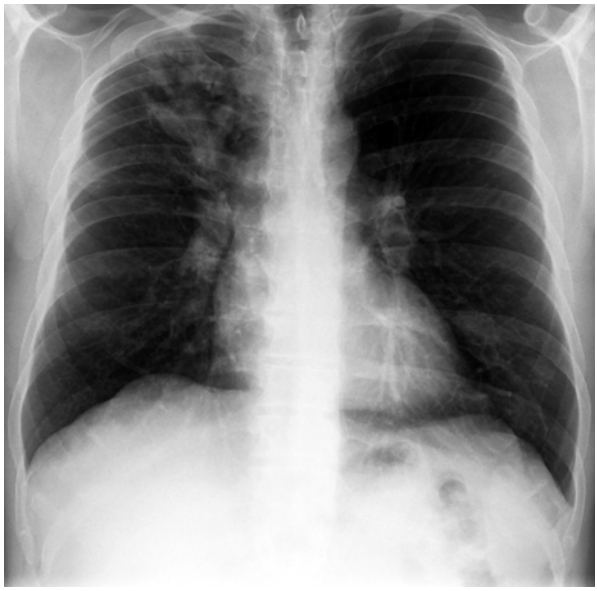

Fig. 21.1 Chest roentgenography showed pulmonary infiltrates, central bronchiectasis, glove-finger shadow, and nodular opacities

Table 21.2 Criteria for the diagnosis of ABPA in patients with cystic fibrosis

Classic case criteria
Clinical deterioration (increased cough, wheezing, exercise intolerance, increased sputum, decrease in pulmonary function)
Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE-*A. fumigatus*
Total serum IgE concentration >1000 kU/L
Precipitating antibodies to *A. fumigatus* or serum IgG-*A. fumigatus*
Abnormal chest roentgenogram (infiltrates, mucus plugging, or a change from earlier films)
Suggestions for screening on annual phlebotomy for ABPA
Maintain clinical suspicion for ABPA
Annual total serum IgE determination: If it is >500 kU/L, test for immediate cutaneous reactivity to *Aspergillus* or by an in vitro test for serum IgE-*A. fumigatus*
If the total serum IgE is <500 kU/L, repeat if clinical suspicion is high

From the ABPA Consensus Conference of the Cystic Fibrosis Foundation

Differential Diagnosis and Complications

The ABPA needs to be differentiated from the following conditions: *Aspergillus* hypersensitive bronchial asthma, pulmonary tuberculosis in endemic areas, community-acquired pneumonia (especially acute presentations), and other inflammatory pulmonary disorders such as eosinophilic pneumonia, bronchocentric granulomatosis, and Churg-Strauss syndrome.

The complications of ABPA include recurrent asthma exacerbations and, if untreated, the development of bronchiectasis with subsequent pulmonary hypertension and respiratory failure. In fact, this is the reason why routine screening is recommended in bronchial asthma to prevent the complications just described.

Table 21.3 Criteria for the diagnosis of ABPA in patients with asthma

Criteria for ABPA-central bronchiectasis/minimal essential criteria	
1. Asthma	Yes
2. Central bronchiectasis (inner two thirds of chest CT field)	Yes
3. Immediate cutaneous reactivity to *Aspergillus* species or *A. fumigatus*	Yes
4. Total serum IgE concentration >417 kU/L (1000 ng/mL)	Yes
5. Elevated serum IgE-*A. fumigatus* and/or IgG-*A. fumigatus*	Yes
6. Chest roentgenographic infiltrates	No
7. Serum precipitating antibodies to *A. fumigatus*	No
Criteria for the diagnosis of ABPA seropositive	
1. Asthma	Yes
2. Immediate cutaneous reactivity to *Aspergillus* species or *A. fumigatus*	Yes
3. Total serum IgE concentration >417 kU/L (1000 ng/mL)	Yes
4. Elevated serum IgE-*A. fumigatus* and/or IgG-*A. fumigatus*	Yes
5. Chest roentgenographic infiltrates	No

Staging of ABPA

The five stages proposed by Patterson et al. remain useful. These stages are not phases of a disease, and in each case, the physician should attempt to determine the stage that is present. The stages are presented in Table 21.4. Most patients who have classic findings and current chest roentgenographic or CT infiltrates are in stage III (recurrent exacerbation). Other patients with current infiltrates are in stage IV (corticosteroid-dependent asthma) or possibly stage I (acute) for first-time recognized infiltrates. High doses of inhaled corticosteroids have not prevented the emergence of infiltrates. Similarly, despite its widespread administration, the antifungal agent itraconazole has not prevented new infiltrates consistently. Patients who are in stage I or stage III with acute infiltrates should respond to prednisone administration, with clearing of the chest roentgenographic or CT infiltrates over 1–2 months, and they should become less symptomatic (reduced dyspnea and cough and improved spirometry results). Total serum IgE, if obtained serially, will decline by at least 35 % over 6 weeks. One should not attempt to administer prednisone indefinitely in an attempt to reduce the total serum IgE concentration into the normal range. Unless the patient enters stage II (remission) or stage V (end stage), it is doubtful that the total serum IgE concentration will return to normal ranges. Conversely, knowing the ranges of total serum IgE when there are no chest roentgenographic infiltrates will establish a baseline from which increases of 100 % or greater can alert one to an exacerbation. Patients with fibrocavitary ABPA (stage V) can have extensive bronchiectasis resembling end-stage cystic fibrosis. Infiltrates can be from *Pseudomonas aeruginosa* or *Staphylococcus aureus* pneumonias or from rare

Table 21.4 Stages of ABPA

Stage	Description	Radiographic infiltrates	Total serum IgE
I	Acute	Lobes or middle lobe	Sharply elevated
II	Remission	No infiltrate and patient off prednisone for >6 months	Elevated or normal
III	Exacerbation	Upper lobes or middle lobe	Sharply elevated
IV	Corticosteroid-dependent asthma	Often without infiltrates, but intermittent infiltrates might occur	Elevated or normal
V	End stage	Fibrotic, bullous, or cavitary lesions	Might be normal

species that have colonized the bronchi. Response to prednisone is limited, and additional modalities, such as bronchial hygiene, coughing or sputum assist devices, inhaled RNAase, and antipseudomonal antibiotic coverage, might be required. An earlier diagnosis of ABPA will result in fewer stage V patients. Noncompliant patients who refuse to take prednisone for infiltrates might develop a greater number of bronchiectatic areas that can eventually lead to stage V ABPA with a poor prognosis. Similarly, delays in diagnosis of ABPA are known to have resulted in patients presenting in stage V.

Radiology

Computed tomography (CT) scan with thin (1–2 mm) (HRCT, high-resolution CT scan) rather than conventional (10 mm) sections is extremely valuable in the diagnosis of ABPA (Fig. 21.2). Proximal (central) bronchiectasis is defined as being present when there are bronchi that are dilated in comparison with the caliber of an adjacent bronchial artery in the inner two thirds of the lung CT field. Bronchiectasis is described as cylindrical when the bronchus does not taper and is 1.5 to >3 times the caliber of diameter of an adjacent artery. Bronchiectasis can also be varicoid or cystic. Ring shadows on chest roentgenograms are 1–2 cm in diameter; they represent dilated bronchi seen in an en face orientation. When the same dilated bronchus is visualized in a tangential (coronal) plane, it is called a parallel line shadow. These findings are consistent with bronchiectasis. Some of the other findings include mucus plugs or mucoid impactions, bronchial wall thickening as occurs in asthma, atelectasis, lobar or whole lung collapse, pulmonary fibrosis, and cavities with or without air-fluid levels. Patients with ABPA can have cylindrical, varicose, and cystic bronchiectasis that involves multiple bronchi. When patients with asthma were examined, bronchial wall thickening was noted, and as many as 29 % of patients had localized areas of cylindrical bronchiectasis. Typically, just one or two lobes are affected in patients with asthma.

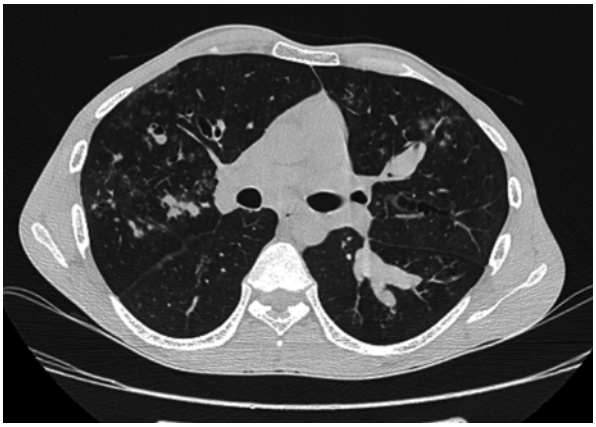

Fig. 21.2 High-resolution CT scan (*HRCT*). Proximal bronchiectasis is defined as being present when there are bronchi that are dilated in comparison with the caliber of an adjacent bronchial artery in the inner two thirds of the lung CT field

Laboratory Findings

Laboratory assays depend on a number of factors; one of the most important is the source material used for sensitization of the solid phases. Antibody assays (and skin test results) will be falsely negative when poorly reactive extracts are used. Furthermore, some laboratories do not use a specific positive control serum for each assay when panels are performed. In this scenario, it is possible that the positive control serum in an assay for IgE of *A. fumigatus* is a ragweed-positive serum. This positive serum might or might not have detectable IgE of *A. fumigatus* antibodies. Thus, interpretation of a negative result in such an assay could be misleading, inasmuch as the assay could be insensitive and the technician unaware of this fact. Advances in the characterization and molecular detection of *A. fumigatus* allergens have led to the hope that certain reactive recombinant allergens might serve as superior source material. Depending on the conditions under which these fungi are grown, the reactivity might or might not be acceptable for precise use in laboratory assays. It is hoped that in the near future, a sensitive and specific test will be developed that will involve the use of selected recombinant allergens and that will be available for widespread application. Sputum cultures might reveal *A. fumigatus* when plugs are expectorated. Often, the patient will stop producing plugs after the initial 2-month course of prednisone administration. CT examinations of the lung will show clearance of mucus plugs as well. Other patients expectorate plugs despite continued prednisone administration, and it is not always apparent that itraconazole has helped the elimination of the plugs. Conversely, while demonstration of *A. fumigatus* is not required for the diagnosis of ABPA, some microbiology technicians do not report out *A. fumigatus* because they do not think that the ordering physician is interested in a fungus that is so frequently recovered in the microbiology laboratory. However, generally

speaking in patients with bronchiectasis, the isolation of mucoid strains of *Pseudomonas* suggests the diagnosis of cystic fibrosis, isolation of *A. fumigatus* suggests ABPA, and isolation of *Mycobacterium avium* complex suggests chronic infection with that organism; however, isolating these organisms is not specific for these disorders.

Pathology

The pathology of ABPA varies from patient to patient and in different areas of the lung in the same patient. Histological examination reveals the presence of mucus, fibrin, Curschmann's spirals, Charcot-Leyden crystals, and inflammatory cells. Scanty hyphae can often be demonstrated in the bronchiectatic cavities. The bronchial wall in ABPA is usually infiltrated by inflammatory cells, primarily the eosinophils. The peribronchial parenchyma shows an inflammatory response with conspicuous eosinophilia. Occasionally, fungal growth in the lung parenchyma can occur in some patients with ABPA. Patients can also demonstrate a pattern similar to that of bronchiolitis obliterans with organizing pneumonia. Bronchocentric granulomatosis, the presence of noncaseating granulomas containing eosinophils and multinucleated giant cells centered on the airway, is also seen. Rarely, invasive aspergillosis complicating the course of ABPA has also been described.

Treatment of ABPA

The current recommended treatment approach of ABPA is presented in Table 21.5. As the disease is a manifestation of a hypersensitivity reaction rather than an infection, treatment is aimed at immune modulation. The administration of oral prednisone to patients with ABPA is associated with the improvement of asthma, and the presence of pulmonary infiltrates and eosinophilia, with reduction in serum levels of IgE, and probably reduced progression of bronchiectasis. The optimal dose is unknown, but 0.5 mg/kg/day is recommended, followed by a gradual taper and adjustment based on the patient's condition. The long-term use of corticosteroids is often necessary, but carries risk, including the development of invasive *Aspergillus* infection. Therefore, the antifungal agent itraconazole was tested in patients with ABPA as an adjunctive, steroid-sparing agent in two randomized placebo-controlled studies. The dose was 200 mg daily for another 16 weeks. Both studies spanned 16 weeks of treatment and showed reduced levels of markers of systemic immune activation (serum IgE level and eosinophil count). The study by Wark et al. also showed reduced levels of markers of airway inflammation in induced sputum. Neither study showed significant changes in lung function, although Wark and

Table 21.5 Suggestions for initial treatment of ABPA

1. For new ABPA infiltrates, administer prednisone 0.5 mg/kg/day for 1–2 weeks and then on alternate days for 6–8 weeks. Then attempt to discontinue prednisone by tapering by 5–10 mg every 2 weeks
2. Repeat the total serum IgE concentration in 6–8 weeks and then every 8 weeks for 1 year to determine the range of IgE concentrations. Increases of ≧100 % over baseline can signify a silent ABPA exacerbation
3. Repeat the chest roentgenogram or CT of the lung after 4–8 weeks to demonstrate that infiltrates have cleared
4. Consider environmental sources of fungi (e.g., moldy basements, leaking roofs, water damage in walls) and recommend remediation
5. Monitor pulmonary function tests
6. If the patient cannot be tapered off prednisone despite optimal anti-asthma treatment and avoidance measures, then he or she has evolved into stage IV (corticosteroid-dependent asthma). Try to manage with alternate-day prednisone as opposed to daily prednisone
7. New ABPA infiltrates may be identified by:
(a) Cough, wheeze, or dyspnea with sputum production
(b) Unexplained declines in expiratory flow rates
(c) Sharp (>100 %) increases in total serum IgE concentration
(d) Absent symptoms but new infiltrates on chest roentgenograms or chest CT examinations
8. Diagnose and manage concomitant conditions such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease

colleagues showed that subjects receiving itraconazole experienced fewer exacerbations of disease requiring increased doses of corticosteroids. Therefore, while itraconazole appears to be promising as adjunctive treatment for patients with ABPA, long-term trials are needed to assess the clinical efficacy and safety in patients in different disease severity strata. There have been no randomized controlled trials to evaluate the use of antifungal therapies in patients with ABPA complicating cystic fibrosis. Optional effective antifungal agent for ABPA might be fluconazole, according to our clinical experiences. In addition, the American College of Chest Physicians has proposed a new guideline for the treatment of the patients with chronic cough due to bronchiectasis including ABPA. With early diagnosis and treatment, ABPA can enter a remission stage, a recurrent exacerbation stage, or perhaps a corticosteroid-dependent asthma stage. Patients who have end-stage fibrocavitary lung disease often present in that stage without having been identified and treated previously. The other modalities for management of asthma should be instituted and patients should be encouraged not to be overly pessimistic. The goal is to avoid progressive loss of lung function and maintain good respiratory status which is achievable for many patients.

Recent studies have shown successful treatment of patients with cystic fibrosis complicated by steroid-dependent chronic ABPA with monthly administration of omalizumab. Also other studies reported the efficacy of inhaled amphotericin and budesonide, voriconazole, and pulse doses of IV methylprednisolone for the treatment of severe ABPA.

Evidence-Based Medicine

Omalizumab is a humanized anti-IgE monoclonal antibody currently used to treat severe asthma. Patients with chronic ABPA were randomized to 4-month treatment with omalizumab (750 mg monthly) or placebo followed by a 3-month washout period in a cross-over design. The main endpoint was number of exacerbations. Other clinical endpoints included lung function, exhaled nitric oxide (FeNO), quality of life, and symptoms. In vitro basophil activation to *Aspergillus fumigatus* extract and basophil FcεR1 and surface-bound IgE levels was assessed by flow cytometry. Thirteen patients were recruited with mean total IgE 2314 ± 2125 IU/mL. Exacerbations occurred less frequently during the active treatment phase compared with the placebo period ($P = 0.048$). Mean FeNO decreased from 30.5 to 17.1 ppb during omalizumab treatment ($P = 0.03$). Basophil sensitivity to *A. fumigatus* and surface-bound IgE and FcεR1 levels decreased significantly after omalizumab but not after placebo. Omalizumab can be used safely to treat ABPA, despite high serum IgE levels. Clinical improvement was accompanied by decreased basophil reactivity to *A. fumigatus* and FcεR1 and surface-bound IgE levels.

Voskamp AL, Gillman A, Symons K, Sandrini A, Rolland JM, O'Hehir RE, Douglass JA. *J Allergy Clin Immunol Pract*. 2015;3:192–9. Epub 2015 Jan 29. Evidence grade: Ib.

Distinguishing between patients with allergic bronchopulmonary aspergillosis (ABPA) and *Aspergillus fumigatus* (Af)-sensitized asthmatic patients without ABPA is sometimes difficult owing to the IgE cross-reactivity between Af and other fungal allergens. The levels of IgE to Asp f 1 and/or Asp f 2 can effectively differentiate ABPA from Af-sensitized asthma, suggesting that the amounts of IgE specific for these molecules are markers for genuine Af sensitization in ABPA. However, comorbid AD must be taken into consideration in the interpretation of high IgE to Asp f 6. Establishing of IgE-sensitization profiles using panel of Af-allergen components provides valuable information for distinguishing genuine versus cross-reactive sensitization in Af-sensitized patients.

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Chapter 22
Serum Sickness

Ali Saad, Yoon Mi Kim, Robert Hostoffer, and Haig Tcheurekdjian

Abbreviations

ATG	Antithymocyte globulin
CBC	Complete blood count
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
iC3b	Inactivated C3b
ITAM	Immunoreceptor tyrosine-based activation motif
SSLR	Serum sickness-like reactions

History

In 1905, Clemens von Pirquet and Béla Schick, two pediatricians practicing in Vienna, Austria, published an article on serum sickness. They were using horse serum to treat diphtheria and scarlet fever but noted symptoms of rash, fever, swelling of the glands,

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edema, leukopenia, and joint pains 8–12 days after the injection. These symptoms were observed a few days quicker if the patients were reinjected with the horse serum. In some patients, the symptoms showed up within minutes of serum readministration.

Definition

Serum sickness is a type III hypersensitivity reaction that is mediated by formation of antigen-antibody immune complexes that deposit in the microvasculature of the body and cause an inflammatory response. The clinical signs from the inflammation of the vessels can affect multiple body systems causing the classic symptoms of malaise, rash, fever, arthralgias, and lymphadenopathy. Patients will also have elevated inflammation markers such as increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Serum sickness is a clinical diagnosis based on history and physical examination, but abnormal laboratory findings can support the diagnosis. Clinicians must exclude other causes for the patient's symptoms such as infections that can present with similar clinical manifestations as serum sickness.

Epidemiology

Serum sickness is uncommon and appears to occur more commonly in adults; however, there is no exact data on prevalence of disease. There is another disease entity called serum sickness-like reactions (SSLR), which is more common in children. This manifests clinically similarly to serum sickness; however the mechanism is not clearly understood and is believed to be not related to immune complexes. One clear distinguishing factor between SSLR and serum sickness is that SSLR patients do not have vasculitis involvement based on histopathology; however they can present with rash, fevers, and arthralgias.

Serum sickness reactions have been noted with vaccines, blood-derived products, medications, and monoclonal antibodies. With regard to monoclonal antibodies, not only the molecule seems to make a difference but also what the medication is being used to treat. For example, serum sickness can occur in less than 1 % and up to 20 % of patients treated with rituximab depending on the underlying medical disorder a patient is being treated for.

Documented prevalence of a particular antigen exposure causing a serum sickness reaction can range from 0.007 % with amoxicillin up to 87 % with horse antithymocyte globulin (ATG). Multiple studies have shown this high rate of serum sickness reaction with horse or rabbit ATG exposure. Patients who are treated with snake antivenom can also expect to have a high incidence of serum sickness of 13 %.

Pathophysiology

Immune Complexes

Serum sickness is characterized by antigen-antibody immune complex formation and tissue accretion following introduction of a foreign antigen. After primary inoculation with an antigen, antigen-specific IgM antibodies begin to develop within 7 days. Thereafter, this IgM binds to the foreign antigen to form immune complexes. This complex formation is a normal immune defense function against soluble protein antigens, although in this venue it plays a pathogenic role. Once formed these complexes deposit in various tissues, activate complement, and trigger the activation of leukocytes which in turn release several mediators ultimately leading to end-organ tissue damage. Antibodies other than IgM can also bind with foreign antigen to create immune complexes, and the type of antibody in the immune complex dictates the ensuing immunologic reaction. For example, IgM strongly activates the classic pathway of complement leading to production of anaphylatoxins and other complement mediators that cause inflammation. Conversely, IgA does not activate the classical pathway of complement but can bind to receptors on phagocytes leading to inflammation mediated by these effector cells.

Immune complexes are usually cleared by the reticuloendothelial system although the system may become oversaturated due to excess antigen or system malfunction such as with liver or splenic disease. Multiple factors can affect or influence immune complex formation and clearance. The chemical characteristics of the antigen will affect the immune response and complex formation, i.e., high-molecular-weight proteins and polysaccharides elicit stronger responses. Stronger responses are also elicited when exposure is prolonged. The charge of the antigen is also significant in determining tissue localization and pathophysiologic effects. The positively charged antigens tend to localize in the basement membranes of the skin and renal glomeruli, whereas neutral and negatively charged antigens do not.

Initially, the concentration of antigen during the early stages of immunization is in surplus over that of antibodies, but as the concentration of antibodies increases, the number of antibody and antigen molecules reaches an equilibrium or zone of equivalence. Ultimately as the concentration of antigen diminishes, the paradigm shifts toward antibody excess. Immune complexes are optimally formed during equilibrium. Complexes formed during slight antigen excess are larger and are more readily cleared by the reticuloendothelial system. During slight antibody excess, the complexes formed are smaller and are able to evade the reticuloendothelial system more effectively. These complexes, therefore, persist for longer periods and pose a greater risk for tissue deposition and end-organ damage (Fig. 22.1).

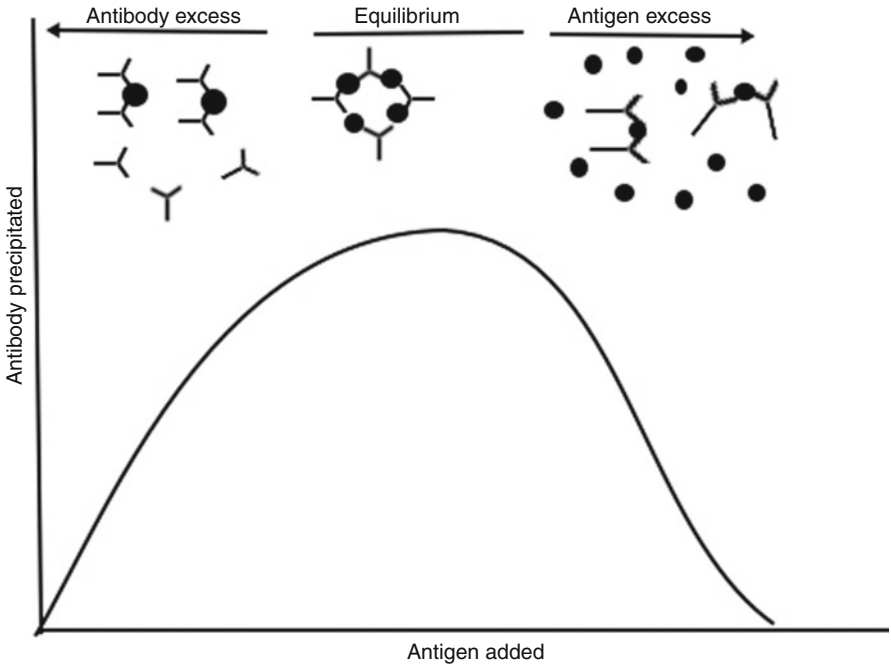

Fig. 22.1 Heidelberger precipitin curve illustrates effect of antigen/antibody ratios on the amount of immune complexes precipitated and size of immune complexes

Immune Complex-Mediated End-Organ Damage

As stated earlier, immune complex formation is a typical immunologic response to clear foreign antigen by the mononuclear phagocytic system. It is not until immune system activation by the immune complexes in deposited tissues that end-organ damage occurs. Progression from soluble antigen to immune complex formation and deposition is well defined as a Gell and Coombs type III hypersensitivity (Fig. 22.2). Immune complex-mediated injury is caused by a number of inflammatory processes including inflammatory cytokine production and complement activation.

IgG-containing immune complexes are potent activators of macrophages and phagocytes that produce inflammatory cytokines upon activation. For example, IgG-containing immune complexes cross-ligate the low-affinity FcγRIIA cell surface receptor on neutrophils triggering immune cell activation. FcγRIIA on the neutrophil cell surface has a cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM) which is important for signal transduction and activation of the neutrophil. Binding of the FcγRIIA receptor leads to phosphorylation of ITAM and various proinflammatory consequences including cell proliferation and production of cytokines such as IFNγ. IFNγ is correlated with increased FCγRIIA expression

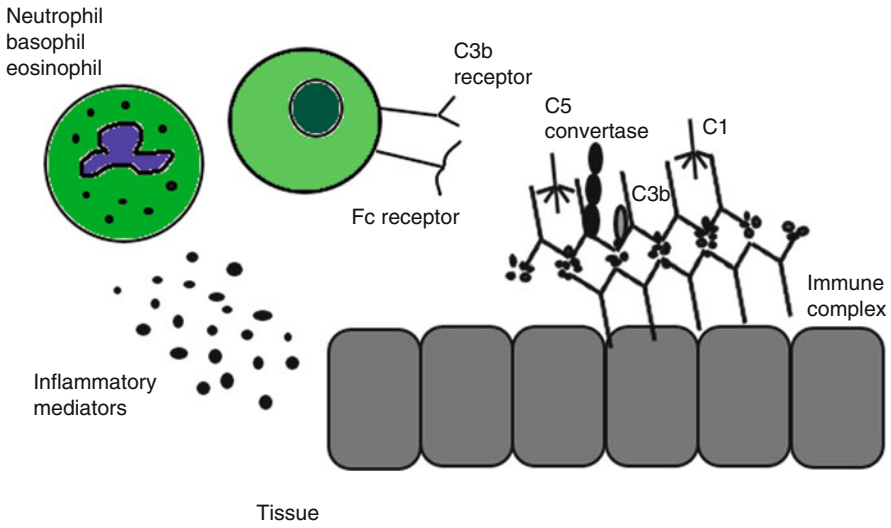

Fig. 22.2 Type III hypersensitivity reaction: binding of multiple IgM or IgG antibodies to a soluble antigen causes an insoluble complex to form which is deposited at the surface of various tissues. Complement opsonization and binding of Fc receptors on phagocytic cells induces inflammatory mediator release. Maturation and migration of other phagocytes lead to a vicious cycle and resultant tissue injury

on monocytes and greater antigen presentation which promotes greater immune system activation.

Both IgG and IgM containing immune complexes potently activate the classical pathway of complement, while IgA containing immune complexes activate the alternative pathway of complement. Complement activation leads to the increased synthesis of crucial complement components functioning as chemokines and potent anaphylatoxins such as C3a and C5a. Among other functions, these complement components lead to chemotaxis of neutrophils and degranulation of mast cells which leads to clinical findings seen in serum sickness such as fever and rash.

Triggers

The most common cause of serum sickness today is a hypersensitivity reaction to drugs. A vast host of medications and other agents have been reported as triggers. Table 22.1 lists some of the more frequently associated causes. Antibiotics, especially penicillins and cefaclor in children, are the most common medications linked with serum sickness. Blood products and foreign antisera, such as anti-snake venom antidotes, are also capable of inducing the reaction.

Antiserum is produced from the plasma of a human (homologous) or animal (heterologous) that has immunity against an infectious agent or poisonous substance.

Table 22.1 Representative drugs implicated in serum sickness

Antibiotics
Cefaclor
Ceftriaxone
Doxycycline
Fluoroquinolones
Metronidazole
Penicillins
Trimethoprim-sulfamethoxazole
Rifampin
Nonsteroidal antiflammatory
Aspirin
Naproxen
Antihypertensives
Captopril
Propranolol
Monoclonal antibodies
Infliximab
Omalizumab
Rituximab
Others
Allopurinol
Barbiturates
Bupropion
ATG (antithymocyte globulin)
Carbamazepine
Clopidogrel
Fluoxetine
Heparin
Hymenoptera
Methimazole
N-acetylcysteine
Phenytoin
Propylthiouracil
Pneumococcal vaccine
Sulfasalazine

The antiserum contains numerous proteins including antibodies directed against the infectious agent or poison of interest. In serum sickness, the recipient of the antiserum generates antibodies against proteins in the antiserum which leads to immune complex formation. A classic example is ATG used as an immunosuppressant for organ transplant patients. Transplant patients are infused with horse or rabbit ATG which contains antibodies against human T cells. This is done in an effort to deplete recipient T cells that could attack the transplanted organ leading to acute organ rejection. After exposure to ATG, recipient IgG and IgM specific for horse or rabbit

immunoglobulin develop resulting in the formation of immune complexes and the eventual deposition in various tissues.

A noteworthy and unusual cause of serum sickness is due to various stinging insects of the order *Hymenoptera* which includes bees, wasps, and vespids. Serum sickness may occur after a stinging event as well as during venom immunotherapy which is a treatment which uses your body's own immune system to develop protection to *Hymenoptera* venom allergy. Venom-specific IgG can be produced after stings and during immunotherapy. These IgG levels increase with immunotherapy and may in fact be responsible for the protection observed with therapy. It is likely that these IgG antibodies against venom proteins are the primary culprits underlying the development of serum sickness in these patients.

Unlike heterologous antisera, newer antibody-based therapies frequently use humanized antibodies. Humanized antibodies refer to antibodies from nonhuman species whose protein sequences are altered to be more similar to antibodies produced in humans. These human antibodies should theoretically carry a much lower risk of serum sickness because they are similar to human proteins and should therefore be less likely to elicit an immune response. Nonetheless, various monoclonal antibodies have been reported to cause serum sickness including rituximab, infliximab, and omalizumab, among others. Case reports involving rituximab-induced serum sickness have proposed that severe hypergammaglobulinemia due to autoimmune diseases may be a predisposing factor. The impaired humoral immunity and the altered immune responses to foreign antigens may predispose patients with autoimmune disease to the development of serum sickness.

Diagnosis

The diagnosis of serum sickness is based on a consistent history and clinical symptomatology. There are no set criteria that are needed to make the actual diagnosis. However, laboratory findings can support the clinical picture and make a stronger case for diagnosis.

Signs and Symptoms

Generally, the symptomatology of serum sickness appears 1–3 weeks after administration of the medication. However it can occur within 36 h if the patient has been sensitized with previous exposures. Usually the illness is more severe in this latter subset of patients. Organ-specific immune complex deposition is a main determinant of symptoms. The cardinal symptoms of serum sickness are rash, fever, malaise, and polyarthralgias or polyarthritis. Less common features include headache, edema, lymphadenopathy, splenomegaly, blurred vision, glomerulonephritis, gastrointestinal symptoms (i.e., bloating, cramping, nausea, vomiting), and peripheral neuropathy.

Cutaneous eruptions, the most common manifestation of disease, can be very variable. The most characteristic rashes are urticarial or morbilliform that start around the torso, groin, or axillary regions and spread to the back and extremities. Mucous membranes are not involved, which distinguishes it from other illnesses such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

The earliest symptoms of the disease include fever and malaise. Pyrexia is a universal symptom experienced in patients with serum sickness. The fevers spike and fall multiple times in the same day without any pattern. Rigors and chills, as well as headaches, uncommonly accompany the fever.

Arthralgias are found in about 30–50 % of patients. The knees, wrists, ankles, shoulders, and metacarpophalangeal joints are most commonly involved. Delayed-onset myalgias in the arms and thighs may occur following the arthralgia. The rheumatologic manifestations typically occur following cutaneous manifestations and resolve earlier than the cutaneous findings.

Laboratory

There is not a single laboratory value that will confirm a patient has serum sickness as this is a clinical diagnosis. However, there are multiple assays that are directed toward detecting immune complexes. The ^{125}I-C1Q binding assay measures immune complexes bound to the complement protein C1Q. This test also identifies autoantibodies directed toward C1Q, thus resulting in false-positive results. The solid-phase anti-C3 assay measures immune complexes that are bound to the complement protein C3 and is a very sensitive test. The Raji cell radioimmunoassay is derived from the B-cell line of Burkitt lymphoma that have cell surface C1q, C3b, C3bi, and C3d receptors. The Raji cell assay is sensitive; however, patients with certain diseases that have antilymphocyte antibodies such as in lupus can give false-positive results. The conglutinin assay is derived from bovine sera and binds to inactivated C3b (iC3b). This assay is rarely used because iC3b in the blood can get further metabolized and be present at too low a concentration to be identified by conglutinin.

Unfortunately, these assays to detect immune complexes are frequently not readily available at most hospitals, and they do not detect antigen-specific immune complexes. Therefore, there are indirect ways to determine if there are increased immune complexes in the serum. Decreased serum C3, C4, and CH50 levels are indicative of classical complement activation and suggest that there are increased immune complexes in the serum.

Other laboratory studies to consider during the evaluation of serum sickness include complete blood count (CBC) with differential, CRP, ESR, urinalysis, renal function, and liver function. CBC with differential may show neutropenia, thrombocytopenia, and eosinophilia. ESR and CRP are acute-phase reactants, and they are elevated in serum sickness. Urinalysis can show mild proteinuria and hematuria. Patients can also have mild elevation of creatinine suggestive of renal dysfunction along with hypoalbuminemia which leads to the clinical presentation of edema. Skin biopsies are usually unnecessary and are rarely helpful in aiding the diagnosis of serum sickness.

Differential Diagnosis

Due to the nonspecific signs and symptoms observed with serum sickness, the differential diagnosis is very extensive. Viral exanthems, bacterial infections, hypersensitivity vasculitis, acute rheumatic fever, acute meningococcal or gonococcal infection, and other drug eruptions are diagnoses to consider. In children, autoinflammatory disorders, Kawasaki's disease, and erythema multiforme should be included in the differential. Other diseases with related presentations include systemic lupus erythematosus, Still's disease, Henoch-Schonlein purpura, and mononucleosis. Additionally, hematologic malignancies, idiopathic urticaria, and lymphoproliferative disorders can present with similar imprecise constitutional symptomatology.

Natural History

After a patient gets exposed to an antigen, in 7–14 days IgM antibodies begin to form, and within a few days afterward, IgG antibodies appear. As the body makes more antibodies, immune complexes start to form with the antigens in the zone of equilibrium as demonstrated in Fig. 22.1. As the antigens and antibodies come together, clinical symptoms of malaise, fever, headache, and serpiginous erythema may be experienced by the patient. When the complexes deposit into the tissue, one can experience the more serious effects of serum sickness such as arthralgias and lymphadenopathy.

Small immune complexes appear to be the primary instigators of serum sickness. Medium- and large-sized complexes are cleared by the reticuloendothelial system. Once antibody production significantly exceeds antigen levels, immune complexes are harder to form; thus clinical symptoms improve as immune complex levels decrease. End-organ damage is usually reversible if patients are treated in a timely fashion.

Management

There are no formal studies on what therapy works best for the treatment of patients with serum sickness. Most of the management guidelines come from case reports and smaller studies that retrospectively describe what patients with serum sickness were given to alleviate the symptoms.

Monitoring

Serum sickness is a self-limited disease and only lasts until the immune complexes are cleared from the system. This frequently takes 1–2 weeks but can take up to 3 months. Patient suspected of having serum sickness should have a detailed

history focused on exposure to exogenous proteins or medications, history of prior exposures, and the timing of these exposures in relation to the symptoms. The physical exam should be thorough and focus on the organ systems noted in signs and symptoms above. Laboratory studies are used to assess end-organ dysfunction and follow markers of inflammation. Abnormal laboratory studies should be monitored throughout the disease process to ensure that the patient's condition is improving.

Therapeutic Options

Once the causative agent for the serum sickness has been identified, it must be discontinued immediately. Therapy for serum sickness is primarily supportive to alleviate symptoms. Antihistamines may be helpful for the dermatological manifestations such as pruritus. Bronchodilators can be administered for shortness of breath and wheezing. Nonsteroidal anti-inflammatory medications can help with the fever and pain relief.

If patients have severe symptoms or systemic manifestations such as vasculitis, severe arthritis, or persistently high fever, systemic glucocorticoids can be started. Oral prednisone can be used at a dose of 0.5–1 mg/kg/day in adults and 1–2 mg/kg/day in children. If needed, intravenous glucocorticoids can be used such as methylprednisolone at 1–2 mg/kg/day.

If patients are refractory to systemic glucocorticoid treatment, then plasmapheresis can be considered to help clear the immune complexes from circulation.

Prevention

Once the patient has had an episode of serum sickness, reintroduction of the offending agent may lead to a more severe and rapid reaction. For this reason, the patient needs to be educated on avoiding the medication and similar medications in the future. There is no consensus among experts whether drugs of similar classes can be given safely, although there are instances of patients with serum sickness following administration of cefaclor who are able to tolerate other cephalosporins. If there is no alternative to the medication and usage is compulsory, administration of antihistamines and glucocorticoids prior to and after the medication may help prevent reoccurrences. Skin testing and serum testing used in the diagnosis and prevention of IgE-mediated hypersensitivity have no role in projecting future risk in these patients.

Conclusion

Serum sickness is a type III hypersensitivity reaction. The classic symptoms are malaise, rash, fever, arthralgias, and lymphadenopathy that occur within 8–12 days of antigen exposure and sooner if it is a re-exposure. This is a self-limiting disease and therapy for serum sickness is primarily supportive to alleviate symptoms using anti-inflammatory medications. Prognosis is very good once the inciting agent has been stopped and rarely does one have end-organ damage as a result of serum sickness.

With future research and investigation, there is hope for identification of individuals at high risk of developing serum sickness, earlier detection of serum sickness, and a more nuanced understanding of the pathophysiology underlying the disease process. For example, further progress in the understanding of the interplay of various leukocytes and cluster of differentiation markers involved in the pathogenesis of serum sickness may aid in the development of specific flow cytometric assays for diagnosis and the development of specific molecular therapies for more directed treatment.

Evidence-Based Medicine

With the more frequent use of humanized monoclonal antibodies, it is necessary to investigate the true incidence of serum sickness with these medications. Although these medications theoretically carry a lower risk for the development of serum sickness because they are modified to closely resemble naturally produced human proteins, there have been multiple reports implicating humanized antibodies with serum sickness. In a recent systematic review, Karmacharya et al. investigated serum sickness induced by rituximab, a monoclonal antibody directed against CD20 used for the treatment of rheumatologic disorders and certain B-cell malignancies. The investigators identified 33 cases from the time of drug inception through September 2014. The majority of cases occurred in females, and mean age at presentation was 39 years. As would be expected in serum sickness, the time from drug exposure to symptom onset was significantly greater with the first dose of rituximab (10 days after exposure) compared to second dose (4 days after exposure).

Omalizumab, a humanized anti-IgE monoclonal antibody, inhibits the binding of IgE to high-affinity IgE receptors on the surface of mast cells and basophils. Since its approval in the United States in 2003, there have been four reported incidents of serum sickness as described by Harrison et al. Interestingly all the cases resolved despite continued medication use. In light of this observation, it is likely these

patients had a serum sickness-like reaction. This illustrates that the management approach of patients taking monoclonal antibodies who develop serum sickness-like reactions may differ from those who develop these reactions to other medications. Patients with serum sickness-like reactions and milder symptoms may be able to tolerate continued monoclonal therapy. Further studies are needed to investigate this in greater detail in order to appreciate if the above observation is consistently identified.

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Chapter 23
Complement Systems and Allergy Diseases

Marianne Frieri

The Complement System

Pathways and Physiologic Activities

The complement system consists of more than 30 plasma and cell membrane proteins both first discovered classic (C_1–C_9), activated by antigen–antibody complexes, alternative pathway components (properdin, factors B and D), inhibitors (C_1, factor 1, etc.), microbial cell walls, and regulatory proteins (C_4 binding, factor H, S protein (Fig. 23.1)). Complement is part of the innate immune system and is an important effector mechanism of humoral immunity. The main physiologic activities are listed which illustrates host defense against infection, bridging innate and adaptive immunity. The removal of immune complexes and inflammatory products is performed by C1q and covalently bound fragments of C_3 and C_4. Initiators of activation pathways for the classical pathway include apoptotic cells, viruses, gram-negative bacteria, and C-reactive protein in addition to immune complexes. The early steps of complement activation and classical pathways are illustrated in Fig. 23.2. The mannose-binding lectin or collectin, homologous to C_1q, is initiated by organisms with terminal mannose groups, and decreased levels have been noted in children with recurrent infections. The late steps of complement activation and the membrane attack complex (MAC) are shown in Fig. 23.3.

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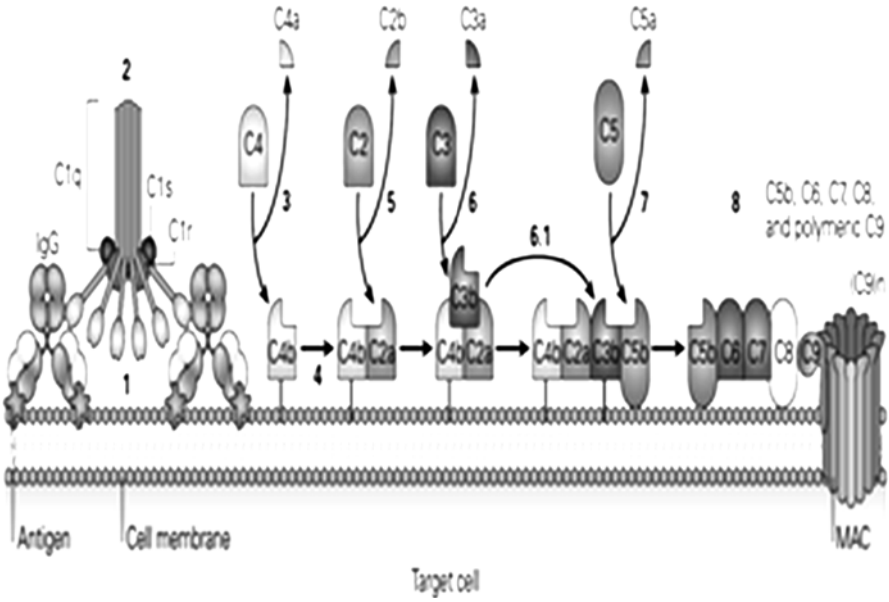

Fig. 23.1 Schematic representation of the classical complement cascade showing the initiation of the pathway by binding of the *C1q* component of *C1* binding to the *Fc* region of an *IgG* antibody molecule bound to an antigen on the surface of a target cell. The numbers in bold indicated the sequential steps which are involved in the activation of each of the components leading to the final lytic event carried out by the MAC. Some sources now use a revised nomenclature for the fragment of *C2*, in which *C2* is the small fragment diffuses away and *C2b* is the larger fragment that binds with *C4b* and acts in the convertase, *C4b2b* (Source: Immunology IV Text, Editor Bellanti, Berger)

Biologic Properties of Complement Fragments Related to Allergic Diseases

Complement cascade activation leads to generation of biologically active fragments (Table 23.1). The products of C_3 and C_5 are small polypeptide anaphylatoxins that have a variety of biologic properties; C_3a, C_4a, and C_5a release inflammatory mediators from mast cells, induce smooth muscle contraction, promote vascular permeability, and induce adhesion molecules on endothelial cells. C_3a can also lead to mucus secretion by goblet cells, and C_3a and C_3a des arg can modulate synthesis of tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β) by mononuclear cells to focus the production of proinflammatory cytokines that contribute to the pathophysiology of asthmatic inflammation. Anaphylatoxic peptides can trigger a variety of responses which contribute to allergic and inflammatory reactions. Anaphylaxis is an immediate systemic reaction due to rapid, IgE-mediated release of potent mediators from tissue mast cells and peripheral blood basophils. Anaphylactoid reactions are immediate systemic reactions that mimic anaphylaxis,

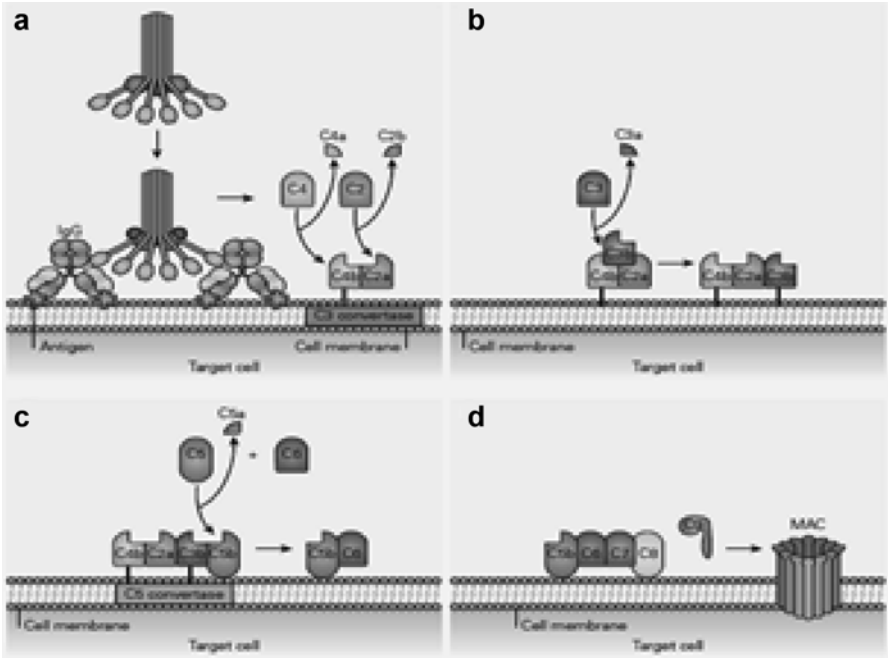

Fig. 23.2 Schematic representation of classical pathway activation. (**a**) Upon binding of *C1* to the Fc region of *IgG* or *IgM*, *C1r* and *C1s* are activated. *C1s* cleaves *C4* and *C2*, and the *C4b* binds covalently to the surface of a target cell and *C2a* subsequently binds to the *C4b* forming *C4b2a* complex, the *C3* convertase. (**b**) Following the binding of *C3* to the *C4b2a* complex, it is cleaved by the *C2a* component of the complex releasing *C3a*, which diffuses away, and *C3b*, which adheres to the *C4b2a* complex forming *C4b2a3b*, the *C5* convertase; note that *C4b2a* may deposit at a distance from the initial *C1* site and that many molecules of *C3b* may be deposited. Only a few will join with *C4b2a* to form the *C5* convertase. (**c**) Cleavage of *C5* by *C2a* releases *C5a* and allows *C5b* to bind with *C6*. The *C5b6* complex can insert into the plasma membrane; *C5b6* can also insert at a distance from the convertase that cleaved the *C5*. (**d**) *C7* and *C8* can bind with *C5b6*, forming a complex causing *C9* molecules to unfold, polymerize, and insert into the membrane, to a protein-linked pore (Source: Immunology IV Text, Editor Bellanti, Berger)

but are not caused by IgE-mediated immune responses. Mast cell and basophil mediators may play a role in anaphylaxis and anaphylactoid reactions through tryptase which may activate complement by cleavage of C3.

C_5a also plays an important role in recruiting phagocytic cells to sites of immune complex deposition in the lung leading to enhanced oxidative and lipoxygenase activity with leukotriene B_4 (LTβ4) production. LTβ4 and other leukotriene mediators are known to play important roles in asthma allergic rhinitis and cystic fibrosis. The presence of C_3a and C_5a in the lung can also induce respiratory distress through contraction of smooth muscle walls in bronchioles and pulmonary arteries. Animal studies have demonstrated the expression of C_3aR and C_5aR by cells in the lung suggesting a role for these receptors during lung inflammation both in sepsis and asthma (Table 23.2).

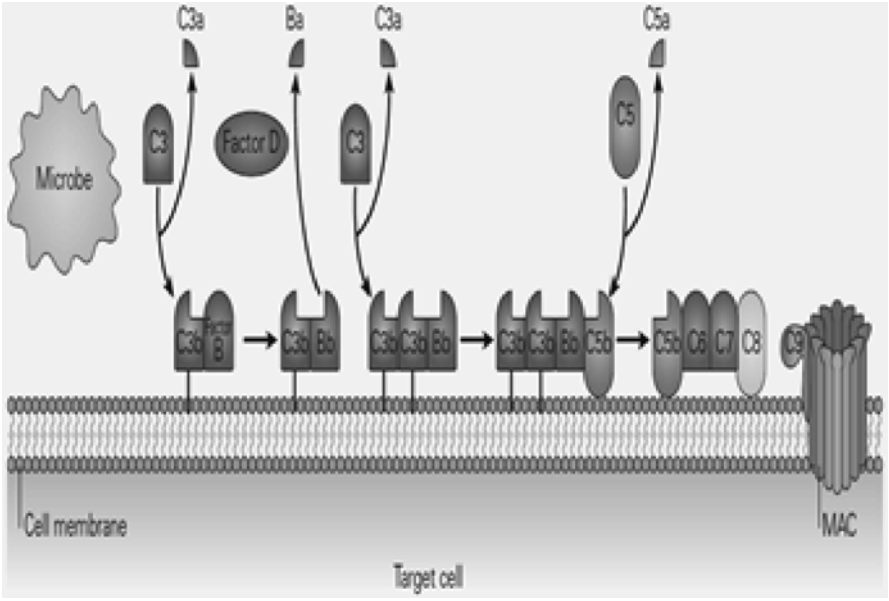

Fig. 23.3 Schematic representation of the alternative pathway showing the initiation of the pathway when *C3b*, which may be formed by one of the other pathways or by nonspecific proteolytic cleavage of *C3*, binds with Factor B, which is analogous to *C2*. When bound to *C3b*, B acquires a conformation that allows it to be cleaved of *C3*, binds with *Factor B*, which is analogous to *C2*. When bound to *C3b*, B acquires a conformation that allows it to be cleaved by the protease D following which the subsequent steps of the pathway are similar to those of the other two pathways (Source: Immunology IV Text, Editor Bellanti, Berger)

Table 23.1 Three main physiological activities of the complement system

Activity	Complement protein
Host defense Opsonization Chemotaxis and activation of leukocytes Lysis of bacteria and cells Interface between innate and adaptive immunity Augmentation of antibody responses Enhancement of immunologic memory	Covalently bound C3; C4 anaphylatoxins (C5a, C3a; C4a) receptors on leukocytes Membrane-attack complex (C5b–C9) C3b; C4b bound to immune complexes; AG; C3rc on B cells; APC C3b and C4b bound to immune complexes and to AG; C3rc on follicular dendritic cells
Disposal of waste Clearance of immune complexes from tissues Clearance of apoptotic cells	Clq; covalently bound fragments of C3 and C4 Clq; covalently bound fragments of C3 and C4

From Frieri
Modified from Walport

Cellular Receptors and Regulators

Receptors for complement components are expressed on many cells with important functions as listed in Table 23.3a. However, unlike most cellular receptors, some of the complement receptors also act as control molecules and interact with the molecule they bind to allow for further degradation of the bound fragment. Various inhibitors and regulators of complement activation and actions are listed in Table 23.3b. C_5a also acts as potent chemoattractant for LFA integrins (CD11a/CD18) to enhance leukocyte movement into tissues at the site of infection. There are four cell membrane receptors for bound C_3 or CR1, CR2, Cr3, and Cr4 that are within two gene families. CR1 or CD35 is found on mononuclear cells, neutrophils, mast cells, basophils, eosinophils, B and T lymphocytes, and kidney podocytes. It functions in phagocytosis and clearance of immune complexes. CR2 or CD35 expressed on B cell and follicular dendritic cells in addition to immature epithelial cells is utilized by Epstein–Barr viruses (EBVs) as a cellular receptor to promote cell entry.

Clinical Associations

Clinical effects of hereditary complement deficiencies related to infection, glomerulonephritis, angioedema, hemolysis, and systemic lupus erythematous (SLE) have been reported by Walport in articles on Complement. First and second of two parts

Table 23.2 Initiators of activation pathways

Pathway	Initiators
Classical	Immune complexes; apoptotic cells; certain viruses and gram-negative bacteria; CRP bound to ligand
Mannose-binding lectin	Microbes with terminal mannose groups
Alternative	Many bacteria, fungi, viruses, and tumor cells

Source: Frieri
Modified from Walport
CRP C reactive protein

Table 23.3a Major mechanisms of regulation of complement activation and function

Mechanism	Examples
Inhibition of active proteases	C1 inhibitor (C1NH)
Dissociation of convertases	DAF, CR1
Stabilization of convertases	Properdin (P)
Cleavage of active convertase subunits	Factor I
Promoters of cleavage by factor I	Factor H, C4 binding protein, CR1, membrane cofactor protein
Binding of lipophilic intermediates	S-protein (vitronectin), C8 binding protein (aka homologous restriction factor, HRF), protectin (CD59)

Source: Berger, Bellanti

Table 23.3b Regulatory proteins

Name(s)	Abbreviation or symbol	Family	Function
C1 inhibitor (C1 esterase inhibitor)	C1 INH	Serpin	Inhibits C1r, C1s, MASPs, noncomplement proteases
C4 binding protein	C4bp	RCA[a]	Binds to C4, inhibits classical pathway
Factor H (b-1-H)	H	RCA	Binds to C3b, inhibits alternative pathway
Properdin	P		Stabilizes alternative pathway convertases
C3b/C4b inactivator (Factor I)	I		Cleaves C4b and C3b
Decay accelerating factor	DAF, CD55	RCA	Destabilizes all convertases
Complement receptor type I	CR1, CD35	RCA	Binds to C3b, destabilizes convertases, and acts as cofactor for cleavage by I
Membrane cofactor protein	MCP, CD46	RCA	Cofactor for cleavage of C4b and C3 by I
S protein (vitronectin)			Inhibits insertion of C5b67
C8 binding protein (homologous restriction factor)			Inhibits addition and action of C8
Protectin (membrane inhibitor of reactive lysis)	CD59		Inhibits binding and polymerization of C9

Source: Berger, Bellanti
[a]*RCA* regulators of complement activation

N Engl J Med. 2001 Apr 5;344(14):1058–66 and *N Engl J Med.* 2001 Apr 12; 344(15):1140–4. Complement is part of the innate immune system and underlies one of the main effector mechanisms of antibody-mediated immunity. It has three overarching physiologic activities defending against pyogenic bacterial infection, bridging innate and adaptive immunity, and disposing of immune complexes and the products of inflammatory injury. In this review, each of these activities will be placed in a clinical context. The pathways leading to the cleavage of C3 are triggered enzyme cascades, analogous to the coagulation, fibrinolysis, and kinin pathways. The terminal complement pathway, leading to the formation of the membrane attack complex, is a unique system that builds up a lipophilic complex in cell membranes from several plasma proteins.

SLE can be associated with allergic disease such as urticaria and can masquerade as atopy.

Complement deficiency can lead to increased susceptibility to pyogenic infections such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, abnormality of function of the mannose-binding lectin, defective regulation of C_3 associated with membranoproliferative glomerulonephritis, or compromise of the lytic activity increasing neisserial infections. C_{3b} and iC_{3b} which are covalently bound cleavage

Table 23.4a Clinical effects of hereditary complement deficiencies

Complement deficiency	Consequence of complement activation
C3	Loss of major complement opsonin; failure to activate membrane-attack complex pathway
C3, properdin	Failure to form membrane-attack complex
C3 membrane attack complex proteins	Loss of regulation of C1 and failure to activate kallikrein
C1 inhibitor	Failure to prevent membrane attack complexes on autologous cells
CD59	
C1q, C1r; C1s; C4,C2	Failure to activate the classical pathway
Factor H and factor I	Failure to regulate the activation of C3; severe secondary C3 deficiency

Source: Frieri
Modified from Walport

Table 23.4b Clinical effects of hereditary complement deficiencies

Complement deficiency	Clinical association
C3	Pyrogenic bacterial infections, may have a distinctive rash; membranoproliferative GN
C3, properdin	Neisserial infection
C3 membrane attack complex proteins	Angioedema
C1 inhibitor	
CD59	Hemolysis, thrombosis
C1q, C1r; C1s; Cls; C4; C2	SLE
Factor H and factor I	Hemolytic uremic syndrome
	Membranoproliferative glomerulonephritis

Source: Frieri
Modified from Walport

fragments of C_3 are the most significant opsonins for bacterial host defense. Mannose-binding lectin as previously mentioned is low in recurrent infections but also involved in tissue inflammation and necrosis. The mechanism of entry used by various organisms involving complement is discussed in Walport's article as three pathways of activation of the complement system: the classical, mannose-binding lectin, and alternative pathways (Tables 23.4a and 23.4b).

Three types of complement deficiency can cause increased susceptibility to pyogenic infections: a deficiency of the opsonic activities of the complement system, which causes a general susceptibility to pyogenic organisms; any deficiency that compromises the lytic activity of complement, which can increase the susceptibility to neisserial infections; and deficient function of the mannose-binding lectin pathway.

EBV uses glycoprotein 350/20, measles and picornaviruses employ hemagglutinin and capsid, and *M. tuberculosis* uses C3 fragments.

Hereditary angioedema (HAE), an autosomal dominant disease, is a deficiency of the C_1 inhibitor with loss of regulation and failure to activate kallikrein. This disorder can lead to severe illness when it involves the intestinal submucosa or obstruction of the upper airway leading to death by suffocation. Symptoms usually

Table 23.5 Proteins of the complement system and entry in to human cells

Microorganisms	Mechanism of entry into host cell
Epstein-Barr virus	Glycoprotein 350/220
Measles	Hemagglutinin
Picornaviruses	Capsid
Mycobacterium tuberculosis	C3 fragments

Source: Frieri
Modified from Walport

begin in adolescence, and edema of the gastrointestinal tract results in severe colicky abdominal pain, nausea, and vomiting. Urticaria is not part of the syndrome, and swelling can be triggered by trauma, psychological stress with increased frequency with angiotensin inhibitors. Over 100 mutations in the C_1-INH gene have been described. Type 1 HAE is due to a mutation which prevents the transcription of the abnormal allele, whereas type 2 variant is due to a point mutation in the gene abolishing its activity as a serine protease inhibitor. Patients with the type 2 variant have normal or elevated antigenic levels but synthesize a dysfunctional protein with reduced or absent C_1-INH function.

A third type in women has clinical findings but normal C_1-INH levels and function. Acquired angioedema in older patients with lymphoproliferative or monoclonal gammopathies has consumption of C_1q. Laboratory features of HAE are decreased C_1-INH, C_2, and C4 levels.

A review by Khan was performed of historical and current literature of HAE. HAE I and II are related to insufficient production of C1-esterase inhibitor (C1-INH) or production of a dysfunctional C1-INH protein, respectively. HAE III is not related to C1-INH deficiency and the pathogenesis is unknown. Bradykinin appears to be the main mediator responsible for angioedema in patients with C1-INH deficiencies. Angioedema of the extremities, face, and upper airway along with gastrointestinal angioedema is the most common clinical feature in HAE. The laboratory tests that are most commonly used in the diagnosis of HAE include C4 and C1-INH concentration and C1-INH function. Advances in our understanding of the pathogenesis of HAE have led to several advances in the therapy of this disease. Despite our more thorough understanding of the genetics and pathophysiology of HAE, many questions remain unanswered.

Table 23.5 summarizes the complement profiles of the major forms of recurrent angioedema. As can be appreciated from this table, it is relatively easy to distinguish HAE with normal C1-INH from HAE due to C1-INH deficiency. The major challenge is distinguishing HAE with normal C1-INH from unknown or sporadic angioedema.

Treatment with infusion of C_1 inhibitor can be lifesaving for HAE as listed in Walport's article. Patients with complement deficiencies are also associated with various rheumatic diseases such as SLE, anaphylactoid purpura, dermatomyositis, and vasculitis (Table 23.6).

Paroxysmal nocturnal hemoglobinuria is a rare disease characterized by intravascular hemolysis, hemoglobinuria, and venous thrombosis due to the absence of decay accelerating factor (CD55) and inhibitor of the MAC (CD59).

Table 23.6 Angioedema laboratory characteristics

	C1-INH level	C1-INH function	C4 level	C3 level	C1q level
HAE type I	*<50 %*	*<50 %*	*Low*	*Normal*	*Normal*
HAE type II	Normal	<50 %	Low	Normal	Normal
HAE with normal C1-INH	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<50 %	Normal/low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

These characteristics can help to differentiate between types of HAE as well as distinguish between HAE and other forms of angioedema (such as ACE inhibitor-associated angioedema)
Modified from Khan

Hemolytic uremic syndrome is due to factor H and I deficiency. Total deficiency of C_3 and factor H mutations is associated with membranoproliferative glomerulonephritis. These patients have a complement consuming antibody called nephritic factor also found in partial lipodystrophy as listed in Walport's article. Apoptosis has been linked with autoimmune diseases associated with complement deficiencies. C_1q can bind to cells undergoing apoptosis with facilitation of elimination. Clearance of apoptotic cells has occurred through reactivity with collectin receptors or phagocytic cells that interact with C_1q and mannose-binding lectin.

Immunomodulation of Autoimmunity with Intravenous Immune Globulin and Mechanisms of Immunomodulation

The mode of action of immune globulin involves modulation of the expression and function of Fc receptors with complement activation and the cytokine network. The immunoregulatory effects of immune globulin which involve complement include blockade of Fc receptors on macrophages and other cell inhibitions of the Fcγ receptor IIB. The effect on inflammation includes the decrease of complement-mediated damage and immune complex-mediated inflammation, induction of anti-inflammatory cytokines, inhibition of endothelial cell activation, neutralization of bacterial toxins, and reduction in requirements of corticosteroids. The effects on B cells and antibody production, T cells and cell growth illustrated in immunomodulatory mechanisms, and agents for the treatment of autoimmune diseases include antigen-specific tolerance using intravenous or mucosal antigen application, altered peptides, or vaccines. In addition to immunoglobulin treatment, immunomodulation may also involve a change in the cytokine balance, administration of agents that suppress regulatory cytokines such as IL-10 and TGFß which can occur in allergen immunotherapy, and administration of agents that antagonize, TNFα or stem cell transplantation.

Table 23.7 Autoimmune/inflammatory diseases benefiting from immune globulin

Idiopathic thrombocytopenic purpura
Guillain–Barre' syndrome
Chronic demyelinating polyradiculoneuropathy
Myasthenia gravis
Multifocal motor neuropathy
Corticosteroid-resistant dermatomyositis
Kawasaki's disease
Prevention of graft-versus-host disease
Antineutrophil cytoplasmic vasculitis
Autoimmune uveitis
Multiple sclerosis

Modified from Kazatchkine

Table 23.8 Immunoregulatory effects of immune globulin

B cells and production of antibodies
Control of bone marrow B-cell lines
Negative signaling via Fc-y receptors
Selective downregulation and upregulation of antibody production
Neutralization by anti-idiotypes of circulating autoantibodies
T cells
Regulation of CD4-T-cell cytokine production
Neutralization of T-cell superantigens
Cells proliferation
Lymphocyte proliferation inhibition
Control of cell death

Modified from Kazatchkine and Kaven

Various autoimmune and inflammatory diseases benefiting from immune globulin and the immunomodulatory effects of immune globulin on B and T cells are illustrated in Walport's article (Tables 23.7 and 23.8).

Autoimmune Urticaria

Patients with SLE also can present with chronic urticaria, and a subpopulation of patients with chronic urticaria also possess IgG antibody directed to the α-subunit of high-affinity type I IgE receptor. IgG can activate basophils, which is dependent on or augmented by complement. SLE, a prototype of immune complex disease, and other autoimmune diseases are caused by a breakdown of tolerance and other factors. Factors that influence the pathogenesis of T-cell-mediated autoimmune diseases are due to genetic susceptibility, activation of autoreactive T cells or infiltration of target organs by T cells, and damage to target organs by T-cell effector molecules or other cell populations. Breakdown to tolerance can occur in SLE, autoimmune diabetes, and multiple sclerosis.

Evidenced-Based Medicine

Complement Therapeutics in Clinical Practice

Treatment of patients with congenital complement deficiencies focuses on the underlying problems of infection and autoimmunity. Recombinant complement components for a completely deficient patient are possible, and blood transfusion to replace missing components has been tried with some success in two SLE patients with C2 deficiency and several patients with factor H deficiency. Renal transplantation might be a viable therapy specifically for atypical HUS patients with an MCP mutation.

The success of animal studies led to clinical trials, with sCR1 being used for treatment of acute respiratory distress syndrome, myocardial infarction, and lung transplantation and post-cardiopulmonary bypass syndrome and anti-C5 mAb in multicentered trials for myocardial infarction, post-cardiopulmonary bypass syndrome, rheumatoid arthritis, membranous nephropathy, and lupus nephritis.

The complement system as part of innate immunity provides an important effector system for host defense, clearance of immune complexes, and regulation or acquired immune reactions. The future of complement therapy may include targeted gene therapy or replacement with recombinant proteins for patients with complement deficiencies.

Therapeutic complement inhibitor approaches have been considered for treatment of bulbous pemphigus, rejection of transplanted tissues, Alzheimer's disease since plaques contain high levels of classical and alternative pathway components as well as MAC components and immune-based fetal loss. As listed in an article by Tichaczek-Goska D on deficiencies and excessive human complement system activation in disorders of multifarious etiology in Adv Clin Exp Med. 2012 Jan–Feb;21(1):105–14 who described, selected diseases and syndromes are associated with excessive complement activation HIV and a great many other serious medical conditions. Other disorders that interface importantly with the complement system besides SLE include rheumatoid arthritis and related arthritides including cryoglobulinemia.

Complement also can be an important factor in tissue necrosis after ischemia. In addition, myocardial infarction and stroke are associated with complement activation in the area of tissue infarction. Complement participates in internal homeostasis by removing damaged, neoplastic, or infected cells. Thus, complement science is no longer thought to be just protein pathways involved in esoteric diseases but can be related to both autoimmune and cerebrovascular and myocardial disease. Deficiencies of the C3 and other complement components contribute to the emergence of recurrent bacterial, viral, and fungal infections and autoimmune diseases such as rheumatoid arthritis. The excessive activation of complement proteins is often discovered to be the reason for many diseases that include Alzheimer's syndrome, schizophrenia, atypical hemolytic uremic syndrome, angioedema, macular degeneration, and Crohn's disease that was also described by Tichaczek-Goska D etiology in *Adv Clin Exp Med*. 2012 Jan–Feb;21(1):105–14.

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Chapter 24
Food Allergy

Oscar L. Frick

Peanut, tree nut, and shellfish allergies cause life-threatening anaphylaxis and thus present a significant public health problem. Foods can cause a spectrum of symptoms affecting several organ systems by both immunologic and non-immunologic mechanisms. Such adverse reactions to foods may be toxic inherent in the food itself, like tyramine in aged cheeses and chocolate or caffeine in coffee, or toxic contaminants, such as histamine in scombroid fish or bacteria – *Salmonella*, *Shigella*, or *Corynebacterium* – that cause food poisoning. Host factors such as lactase deficiency or idiosyncratic reactions are non-immunologic.

Immunologic mechanisms include atopy, which is IgE antibody mediated, causing urticaria and anaphylaxis, and they are most common. Mixed IgE antibody and cellular immune mechanisms occur in atopic dermatitis and eosinophilic gastroenteropathies. IgA antibodies are involved in celiac disease. Cellular immunity is involved in inflammatory bowel diseases: regional enteritis (Crohn's disease) and ulcerative colitis.

About 8 % of infants and young children with immature gastrointestinal tracts are prone to develop food allergies, whereas in older children and adults, the incidence is about 2 %.

Peanut allergy has tripled in the past two decades. Many people think they have a food allergy, although it cannot be substantiated by tests and diets.

Mucosal Immunity and Tolerance

Ingested foods are processed all along the gastrointestinal tract beginning with salivary ptyalin converting starch to maltose, by stomach acid and pepsin and by intestinal trypsin and amylase and bile. Proteins are broken down into proteoses and

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amino acids for absorption and building host's tissues. Carbohydrates are broken down to sugars and fats to body lipids.

The gut-associated lymphoid tissue (GALT) is the mucosal immune system, consisting of M cells in Peyer's patches that "sip" antigens and transfer them to macrophages in the lamina propria, which then present antigens to T and B lymphocytes. Oral tolerance is effected by the mucosal immune system, which is able to distinguish pathogenic bacteria and viruses from the huge mass of commensal bacteria needed for digestion. Secretory IgA antibodies form a protective barrier that clumps incompletely digested proteins and harmful bacteria to be swept out in the stool. Mild anaphylaxis might have a physiologic function in increasing peristalsis to aid in removal of noxious materials from the gut.

Oral tolerance may be achieved by T-cell anergy in which intraepithelial cells (IELs) act as inefficient antigen-presenting cells (APCs) that present antigenic peptides to T cells as the first signal but lack the costimulatory second signals (CD-28 and ICAM-l) to effect an active immune response. Consequently, these partially activated T cells become anergic or tolerant. Furthermore, there may be stimulation of regulatory T cells secreting immunosuppressive cytokines, IL-10, and tumor necrosis factor-beta (TNFβ).

Pathogenesis

The intestinal mucosa of infants and young children is immature and "leaky" to incompletely digested proteins, especially to the large volumes of milk (l L/day in a 7 kg infant equals l0L/day in a 70 kg adult). The secretory IgA antibody barrier develops slowly over months in infants. Food antigens cross the leaky gut to IgE-coated mast cells that release histamine, which separates the intraepithelial cells to enhance gut permeability and presentation to IgE-forming B cells. As the intestinal barrier function matures, food allergens decrease and many children "outgrow" their milk, egg, and wheat allergies.

Allergens

The most common food allergens are cow's milk, egg, wheat, soy, and peanuts in children and tree nuts, fish, shellfish, and sesame seeds in adults. Specific allergen epitopes expressed in recombinant proteins have been identified (Table 24.1). These are usually glycoproteins of mol wt 10–70 Kd that are heat and acid stable and proteinase resistant, enabling them to bypass denaturation by cooking and by gastric and upper intestinal digestion.

Table 24.1 Classical (class 1) food allergens

Peanut	Ara h 1, Ara h 2, Ara h 3	
Cow's milk	Caseins a, b, k	Bos d8
	b-Lactoglobulin	Bos d5
	a-Lactalbumin	Bos d4
	Bovine serum albumin	Bos d6
Egg	Ovomucoid	Gal d1
	Ovalbumin	Gal d2
Shrimp	Tropomyosin	Pen a1
Codfish	Parvalbumin	Gad c1
Lipid transfer proteins		
	Apple	Mal d1, Mal d4
	Peach	Pru p1, Pru p2, Pru p3
	Hazelnut	Cor a1, Cor a2

Cross-Reacting Food Allergens

In food plant and some animal families, there may be considerable cross-reactivity among allergens. Patients should be made aware of these cross-reactions.

There is considerable public health concern about the potential allergenicity of genetically modified organism (GMO) foods. New GMO foods must be evaluated for those physical properties as well as comparison to six to eight amino acid sequences in known food allergen recombinant epitopes. The original example was transgenically inserting methionine into methionine-poor soybeans from the methionine-rich S2 protein of Brazil nuts. Such transgenic soybeans bound IgE antibodies from Brazil nut-allergic patients, which precluded further development of such transgenic soybeans for animal feeds (or human consumption). This alerted public health authorities about potential allergenicity in GMO foods.

Clinical Manifestations

Anaphylaxis is the most serious food allergy because it can be life-threatening.

It causes about 300 deaths annually in the United States with foods implicated in about 40 % of cases. Food allergens like peanut, tree nuts, and shrimp combine rapidly within seconds with IgE antibodies on ubiquitous vascular and tissue mast cells and circulating basophils to release massive amounts of histamine, PAF (platelet-activating factor), and leukotrienes.

Vascular endothelial cells are separated, allowing massive leakage of plasma into tissues that results in edema and circulatory collapse or shock. Smooth muscle cells

become spastic, leading to bronchospasm, intestinal motility (diarrhea), and urination. Laryngeal edema closes the airway leading to anoxia, asphyxia, and death.

Exercise-induced anaphylaxis occurs if a person sensitized to a particular food allergen, like celery, exercises within 2 h after ingesting that food.

Skin

Urticaria and *angioedema* commonly start in the face, eyelids, and lips and progress over the body and limbs. This is pruritic from histamine release and sometimes burning and painful from bradykinin formation. IgE antibodies and sometimes complement C4a and C2a anaphylatoxins contribute to symptoms. Handling or skin contact with food allergens may cause contact urticaria.

Atopic Dermatitis

A chronic pruritic rash on the face, limbs, and body usually begins in infancy and early childhood. This often clears by school age, although rashes may persist into adulthood. Due to intense itching, the skin is damaged from scratching and secondarily infected with *Staphylococci*. Older lesions become lichenified and discoloration may last for years.

Foods, especially egg and cow's milk, are common causes, as are other foods in about 40 % of cases, with dust mites and animal dander causing another major portion of cases. IgE antibodies cause an immediate reddening and itching that initiate a chronic inflammation with cellular infiltration with eosinophils and T cells. Initially, these Th2 cells elicit IL-4, IL-5, and IL-13 cytokines, but as chronicity occurs, Th1 cytokines IL-2 and IFN-γ perpetuate the inflammation.

Gastrointestinal Tract

Oral allergy syndrome (*OAS*) commonly from fruits or vegetables causes buccal mucosal and tongue itching and swelling but rarely proceeds further. This is due mostly to fruit and vegetable epitopes that cross-react with pollen allergens, like birch pollen Bet v1 in birch hay fever patients.

Vomiting, nausea, abdominal pain, and diarrhea are common symptoms of food allergy. Sometimes emesis is explosive. Infantile "colic" may be the first sign of an allergic child commonly due to cow's milk or a food in the nursing mother's diet. This may occur in 25 % of colicky infants.

Eosinophilic Esophagitis and Gastroenteritis

Infiltration of the mucosa of the esophagus and the mucosa, muscle, and serosa of the gastrointestinal tract is being increasingly recognized. Diagnosis is made by endoscopy and biopsy. Eosinophils in more than 15/HPF constitute gut eosinophilia. Peripheral blood may or may not express eosinophilia.

Symptoms in *eosinophilic esophagitis* (*EOE*) resemble those of gastric reflux with nausea, vomiting, dysphagia, and epigastric pain (heartburn), especially in children. Most patients with EOE exhibit other signs of allergy – eczema, rhinitis, or asthma. A pH probe is usually normal. A patient with gastroesophageal reflux and negative pH probe should have an endoscopy.

Both IgE-mediated and cell-mediated food allergy may be demonstrated by prick skin tests and atopy patch tests. Removal of positive foods may help in some cases; some may require an elemental diet for some weeks to quiet inflammation. They usually respond to oral corticosteroids but relapse when withdrawn.

Patients with *eosinophilic gastroenteritis* (*EOG*) have vomiting, abdominal pain, and diarrhea. The serosal form may have eosinophilic ascites. They may respond to elemental diet and corticosteroids.

Eosinophilic proctitis occurs in infants with flecks of blood in stool to bloody diarrhea. Implicated is cow's milk, soy, or food in the mother's diet if nursing. Changing to protein hydrolysate alleviates the condition.

Heiner syndrome in infants may also have melena and reflux with failure to thrive; hemosiderosis in bronchial washings indicates regurgitation of milk into bronchi and lungs. Blood contains milk-precipitating IgG antibodies. With removal of cow's milk and substituting an elemental formula, the condition resolves in weeks.

Irritable Bowel Disease

Crohn's disease and ulcerative colitis are beyond the scope of this chapter. But occasionally food hypersensitivity may be implicated.

Respiratory

Much less common symptoms from food allergy are rhinitis and asthma.

Wheezing or cough from a food ingestion is rare, but increased sensitivity to inhaled methacholine after food challenge is a more subtle indication of food-induced bronchial inflammation.

Genitourinary

The bladder is another smooth muscle organ, so urinary urgency and enuresis have been attributed to food allergy. Anaphylaxis following coitus with a partner who had ingested walnuts or peanuts has been reported.

Central Nervous System

Headaches have been attributed to foods, but there is little published data. Most headaches may be due to chronic sinusitis secondary to allergic rhinitis. Tyramine in aged cheeses and chocolate may cause headaches, as may monosodium glutamate (MSG) in restaurant-served Asian foods.

Diagnosis

Oral Food Challenges

The double-blind placebo-controlled food challenge (DBPCFC) is the gold standard in the diagnosis of food allergy. These are done in a controlled environment in a hospital or specialty clinic with emergency medications, equipment, and trained personnel at hand. Food in liquid or powdered form in a masking vehicle for blinding is given in a minute quantity and doubled every 15–30 min until allergic symptoms or signs occur. This indicates a positive reaction. If a maximum dose causes no symptoms, the test is negative.

Because DFPCFC requires considerable staff and time, several alternative simpler procedures have been proposed, for example, if cow's milk formula is mixed with placebo formula (l:2) to make it indistinguishable from placebo formula. At 30 min intervals, 2, 10, 50, and 100 mL are given blindly. If no symptoms occur in the following 2 h, the 60 mL per day for 4 days is given at home, watching for symptoms. If none occur, milk formula is resumed.

Prick Skin Tests

Prick skin tests are usually done in the initial workup with a screen testing with commercial extracts of the eight common foods – egg, cow's milk, wheat, peanut, tree nut, fish, seafood, and sesame seed – unless there is a history of anaphylaxis with one of these allergens, in which case an in vitro test is done. Various prick devices are available, but one should be standardized for use in a particular clinic. Positive reactions are a wheal larger than 3 mm with wheal and erythema size recorded after 10–20 min. These are compared with a histamine control. A negative

reaction is compared to a saline control. Certain food allergens are easily denatured. Therefore, pricking a fresh fruit or vegetable and then pricking the patient's skin (prick-to-prick method) yield more useful information. Intradermal skin tests with foods are contraindicated because of the danger of anaphylaxis.

Positive prick tests give useful information about a food causing a current problem in about 40 % of cases. The so-called false-positive prick tests indicate sensitization, but clinically a problem may be in the past or may occur in the future. If properly done, negative prick skin tests are about 95 % reliable that the food can be continued in the diet.

In Vitro Tests

In RAST (radioallergosorbent test) or ELISA (enzyme-linked immunosorbent assay test), food allergen is bound to a matrix that is bathed in the patient's serum. Food allergen-bound IgE antibodies are measured with a radioisotope-tagged or enzyme-tagged monoclonal anti-human IgE serum and developed with markers, such as alkaline phosphatase or horseradish peroxidase in ELISA. The CAP-RAST-FIEA (Pharmacia, Uppsala, Sweden) has been standardized so that above a given threshold the test would correlate well with a DBFCFC.

If anaphylaxis is suspected, in vitro testing is mandatory. One may follow the course of a food allergy with subsequent in vitro tests at intervals to determine if the food sensitivity has decreased or disappeared and when it might be safe to cautiously reintroduce that food into the diet.

Basophil Degranulation Tests

Several simplified versions of measurement of histamine released from sensitized basophils have been developed for clinical use.

Atopy Patch Tests

Dehydrated food is mixed one part with two parts petrolatum. This mixture (20 mg) is placed on a large (12 mm diameter) Finn chamber on Scanpor tape (Epitest, Tuusula, Finland) and applied to uninvolved skin of the back. Petrolatum in a Finn chamber is a negative control.

Occlusion time is 72 h and results are read 30–60 min after removal. The following scale is read: 1+=redness and erythema; 2+=redness, edema, and a few papules; 3+=redness, erythema, and papules covering most of the patch area; and 4+=papules spreading outside patch area or vesicles. The test may be useful in younger children with atopic dermatitis that has a cellular immune component.

Food Elimination Diets

Food elimination diets have been the major tool for diagnosis and management of food allergies for almost a century starting with the Rowe diets. Simpler elimination diets are available from the Food Allergy and Anaphylaxis Network (FAAN), www.foodallergy.org.

The suspect food in all forms is removed from the diet completely from 2 to 8 weeks to clear the food allergen from the patient's system. A simple symptom scoring is recorded daily or at intervals. At the end of this period, the physician evaluates positive or negative improvement. The food challenge is done cautiously in a controlled setting with epinephrine at hand. The patient is given a minute quantity of the suspect food. If he had been eating the food daily, he may have been partially desensitizing himself. During the elimination period, IgE antibodies may have built up so that, on reintroduction, anaphylaxis may occur. If the food is tolerated, the next day larger increments of the food may be given at intervals to determine if symptoms recur. If not, the food can be continued in the diet. If positive, the food must be kept out of the diet for months or even years. Adequate nutrition must be maintained, especially in growing children, where assistance of a dietician may be helpful. Other methods include the following:

Radiography with bowel contrast may detect ulcerations or irregularities in the bowel wall, especially in inflammatory bowel diseases.

Endoscopy with biopsy of esophagus, stomach intestine, and rectal mucosa for increased numbers of eosinophils and inflammation may be diagnostic in eosinophilic esophagogastroenteropathies.

Plasma histamine and/or tryptase. After a food challenge, plasma histamine and/or tryptase rises – histamine within minutes – but it is rapidly metabolized within 1 h. Plasma tryptase elevation persists for many hours to days and may be useful in determining whether anaphylaxis caused unexplained sudden death.

Management and Treatment

Elimination Diet

Removing the offending food allergen is the treatment of choice and is usually successful. If the food allergy is long-standing, there may be significant inflammatory damage to the gastrointestinal tract that may take months to heal.

Sometimes an elemental diet is necessary. The patient is given a protein hydrolysate (Nutramigen, Pregestimil, Elecare, Neocate, Alimentum, Vivonex) for 2 weeks to rest the gut. Then foods are gradually reintroduced one by one every 2 days and the patient is observed for symptoms. In children, protein hydrolysate and a lamb and rice diet can be used as baseline and the diet gradually expanded.

The patient should be educated to recognize the first signs of anaphylaxis and to read food labels for high-allergy risk foods. The patient should have a written action plan for management of anaphylaxis for home, school, and work.

Pharmaceuticals

Self-injectable *epinephrine* (EpiPen, Dey Laboratories, Napa, CA) is mandatory in treating anaphylaxis. *Antihistamines* are the second line of drugs in the acute treatment of anaphylaxis. They are inefficient in managing food allergy symptoms. But *hydroxyzin*e is helpful in alleviating pruritus in atopic dermatitis and urticaria. *Antileukotrienes* have been reported to help occasionally, but not consistently. *Cromolyn sodium* as a mast cell stabilizer has been helpful in individual cases but must be given in huge doses orally (100–200 mg) with each meal because only about 1 % is absorbed.

Hypoallergenic Foods

Different apple cultivars have either high or low Mal d1 content; this is the major apple allergen related to Bet v1. Hypoallergenic rice has been developed in Japan. A rice-based edible vaccine expressing multiple T-cell epitopes of cedar pollen has induced oral tolerance for inhibition of Th2-induced cedar pollen allergy. This might be applied to food allergens.

Evidence-Based Medicine

New Experimental Approaches

Immune Tolerance in Infancy

In infants born into highly allergic families, it has been customary to keep highly allergenic foods, such as egg, peanut, tree nuts, and shellfish, out of the child's diet for 1–3 years.

Recently, G. Lack observed that although peanut allergy is common among Jewish children, in Britain peanut is withheld from allergy-at-risk children for 2–3 years, whereas Israeli children are given peanut (Bamba) at 2–3 months of age and peanut allergy is rare in Israel.

In the prospective LEAP (Learning Early About Peanut) study, DuToit et al. reported on 640 infants with severe eczema or egg allergy split into two groups – one avoiding peanut and a second group eating peanut ad lib for 5 years. The peanut

avoidance group had 17 % peanut allergy vs 3 % for the peanut-eating group. In children with negative prick skin tests to peanut, the peanut avoidance group had 13 % peanut allergy vs 2 % in the peanut consumption group.

These results suggest that there may be an infant-tolerant period where early introduction of allergenic foods may induce tolerance to the foods and prevent food allergies. Somewhat similar was seen in infants born into dog- and/or cat-owning families, that such children failed to develop dog or cat allergy, again suggesting an infant tolerance period of some months of age. In families that acquired a dog or cat after the infant was 6 or more months old, pet allergy was common.

Immunotherapy for Food Allergy

Many studies are being reported of oral immunotherapy (OIT) whereby minute but increasing quantities of highly allergenic foods, such as peanut, egg, or cow's milk, are given orally that may desensitize or perhaps tolerize such patients with these food allergies. In anaphylaxis-prone patients having reactions with minute amounts of peanut, OIT has been successful in that such patients have been able to ingest eight to ten peanuts without reaction. Similar OIT results have been successful with egg and milk. This prevents anaphylaxis from accidental ingestion of the food allergen. However, moderate side effects are common in OIT causing pauses in increasing doses of allergenic food. Therefore, several groups are pretreating with omalizumab to cover OIT diminishing side effects. Sublingual immunotherapy with highly allergenic foods also induces desensitization, but less or minimal side effects.

Baked egg or cow's milk denatures the conformational epitopes in these foods and diminishes their allergenicity, but linear epitopes are not affected by baking.

Most recently, patients receiving epicutaneous immunotherapy (EPIT) using peanut skin patches (Viaskin) in 250 mg peanut repeatedly for 1 year had robust 19-fold increase in peanut-specific IgG antibody level. Such EPIT-treated peanut patients tolerated at least 1 g of peanut protein (four peanuts) or ten times the dose at the start of therapy. EPIT is safe and has few side effects, so further studies with other foods will be needed.

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Chapter 25
Insect Allergy

Donald F. German

Stinging Insect Allergy

Introduction

Systemic reactions to insect stings have been known for millennia. The lore is the first recorded reaction to an insect sting is found in ancient hieroglyphics; King Menes of Egypt apparently succumbed after a wasp sting in 2641 BC.

When stung, the majority of patients simply have an area of local pain and irritation lasting a few hours; others may have persistent local swelling and discomfort that may last for days, and few, like King Menes, have a systemic reaction. Studies demonstrate that sensitization is common after a sting. In the United States, 30 % of recently stung persons have transient evidence of IgE sensitivity to stinging insect venom, yet only 1 % of children and 3.3 % of adults have a history of systemic reaction to a sting. It is estimated that there are at least 40 insect sting caused mortalities each year. Patients with a history of a previous stinging insect systemic reaction, receiving beta-blockers or angiotensin-converting enzyme inhibitors, have elevated serum tryptase or mastocytosis are at increased risk for a systemic reaction. Since the 1970s there have been many advances in knowledge of the natural history and treatment of insect sting reactions.

Stinging insects belong to the order Hymenoptera. Their sting deposits venom, which contains proteins and low-molecular-weight compounds. The low-molecular-weight kinins and vasoactive amines cause much pain at the sting site and serve to protect both the insect and its nest.

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Stinging Insects: Classifications and Characteristics

Hymenoptera are classified into three main families: the *Apidae* (honeybees, bumblebees, and sweat bees), the *Vespidae* (comprised of two subfamilies, the Vespinae which includes yellow jackets, yellow hornets, and white-faced hornets and the Polistinae which include the paper wasps), and the *Formicidae* (imported fire ants and harvester ants). All hymenoptera have an ovipositor, which is modified into a retractable stinger (Table 25.1).

Domesticated honeybees and the bumblebees are not aggressive and rarely sting unless they are markedly provoked. Their barbed stinger is attached to the venom sac resulting in evisceration and death of the insect after stinging. The venom sac contains approximately 50 mcg of venom. Wild honeybees build their nests in the hollow of trees. Most honeybees are domesticated and are kept in boxed hives; wild insects live in the hollows of trees. Nests may contain up to 2000 insects. Bumblebees are not aggressive and rarely sting. Their ground-located nests contain 15–250 insects. When stimulated they are slow moving giving time for the potential sting victim to escape. In attempts to improve honey production, the docile domesticated European honeybee was hybridized with the African honeybee; these hybrids escaped into the wilds of South America and migrated to Central America, Mexico, and now are found in Texas, Arizona, and Southern California. They are easily provoked and very aggressive. They have five times more guards at the hive entrance and will pursue an intruder ten times farther (300 m) than a European honey bee; pheromones are released at the time of the sting, which attract a swarm of other bees subjecting the victim to multiple stings resulting in a toxic reaction, even death.

Members of the Vespinae subfamily (yellow jackets, yellow hornets, and white-faced hornets) are easily provoked, are aggressive, and frequently sting injecting up

Table 25.1 Classification of stinging insects

Class: Insecta
Order: Hymenoptera (ovipositor modified into a retractable stinger)
Family: Apidae
Genus: *Apis* (Honeybee)
Genus: *Bombus* (Bumblebee)
Family: Vespidae
Sub-Family: Vespinae
Genus: *Vespula* (Yellow jacket)
Genus: Dolichovespula (Yellow Hornet, White faced (bald) hornet)
Genus: *Vespa*
Sub-Family: Polistinae
Genus: *Polistes* (Paper wasp)
Family: Formicidae
Genus: *Solenopsis* (Imported fire ants)
Genus: *Pogonomyrmex* (Harvester ants)

to 20 mcg of venom. In much of the United States, they cause most stings. They are capable of inflicting multiple stings because their stingers are without barbs. Yellow jackets nest in the ground, whereas hornets build their nests in trees. They are attracted to meat, fish, and sweets, often congregate in garbage and orchard areas, and plague picnickers. The Polistinae subfamily includes wasps. They live in small nests containing 15–25 insects. Their nests, often found under eaves and window-sills of houses, contain 15–25 insects. They lack the aggressive tendencies of other vespids but will sting if provoked.

Formicidae include imported fire ants (IFAs), genus *Solenopsis*, and harvester ants, genus *Pogonomyrmex*. IFAs are the most important members of the family. They were inadvertently brought to the southeastern United States from South America, but now have migrated throughout the southern United States. They live in the ground in nests that are slightly raised with a diameter of up to 2 ft containing thousands of insects. The ants bite, hang on with their jaws, and then rotate their bodies inflicting multiple painful stings with their well-developed posterior sting apparatus. The sting sites form a characteristic sterile pseudo-pustule 24 h later due to alkaloids in the venom and may persist for a week. They are the most important cause of sting reactions along the Gulf Coast.

Venoms

Honeybee venom is collected by having insects sting through an electrically charged membrane at the hive entrance. Vespid venoms are obtained by collecting, then freezing an entire nest; the venom sack is extracted from each of the insects. The products ultimately are processed, standardized, and lyophilized. Formicidae venoms are not commercially available; hence a whole-body extract (WBE) is used both for testing and immunotherapy (Table 25.2).

The major allergens found in Apidae venom are phospholipase-A2 (PLA2), which is the most common sensitizer, and hyaluronidase. Other important allergens include melittin, acid phosphatase and allergen C. Apidae venom is standardized on the basis of PLA2 content. Bumblebee and honeybee venoms demonstrate little cross-reactivity.

Important Vespidae allergens include hyaluronidase which minimally cross-reacts with that of apids, phospholipase A1 (PLA1), which is the most common sensitizer, but lacks identity with Apidae PLA2, and antigen 5 which is unique to vespids. Vespid allergens have varying degrees of inter-genus identity ranging from 60% for phospholipases and antigen 5, and 80% for hyaluronidase. Vespid antigens are standardized on the basis of hyaluronidase content. Both apid and vespid venoms contain a number of nonallergenic toxic substances some of which include kinins, vasoactive amines, chemotactic peptides, mast cell activators, and pheromones. The Apidae and Vespidae venoms contain cross-reacting carbohydrate moieties, which share similarities, and, though probably not clinically important, may occasionally confound allergy testing. Testing using recombinant venom antigens would resolve this confusion.

Table 25.2 Important hymenoptera venom allergen components

Insect genus	Allergen	Comments
Apis	Phospholipase A2	Does not cross-react with vespid phospholipase A1
	Hyaluronidase	
	Melittin	Unique to *Apis*, 40–50 % of venom
	Acid phosphatase	
Vespula and Vespa	Phospholipase A1	Does no cross-react with *Apis* phospholipase A2
	Hyaluronidase	Very minimal sequence identity to *Apis* venom
	Acid phosphatase	
	Antigen 5	Unique to vespid venom, extensive sequence identity among species
Solenopsis	Sol i 1 phospholipase	
	Sol i 2	
	Sol i 3 antigen 5-like protein	Has 50 % sequence identity to vespid antigen 5
	Sol i 4	

Formicidae venoms are not commercially available. Studies show that nonallergic alkaloids, which comprise almost all of the venom, are responsible for the characteristic pseudo-pustule formation that occurs 24 h after a sting. The protein content of imported fire ant venom is less than 1 %. Four important allergens have been identified: Sol i 1 (a vespid-like phospholipase), Sol i 2, Sol i 3 (which shares partial identity with vespid antigen 5), and Sol i 4. There is a high degree of radioallergosorbent (RAST) cross-reactivity between various fire ant species. IFA WBE contains significant quantities of relevant antigens including lipase, phospholipase, esterase, hyaluronidase, and a number of non-antigenic toxic substances such as alkaloids.

Insect Sting Reactions: Classification

Stinging insect reactions are classified into normal, toxic, local, systemic, and unusual. The venoms are highly allergenic (Table 25.3).

Normal Reaction

Typically pain, erythema, and slight swelling may occur at the sting site. Pain is the predominant symptom. Imported fire ant (IFA) stings are characterized by a small sterile pseudo-pustule occurring at the sting site 24 h later.

Table 25.3 Stinging insect reactions

Normal	Transient pain and local erythema clearing within 24 h; fire ant sting causes a painful sterile pseudo-pustule at 24 h
Local	Local swelling and itching contiguous with the sting site, peaking within 24–48 h and persisting for up to a week or longer
Systemic	
Cutaneous	Urticaria as sole manifestation
Moderate-to-severe generalized	Immediate cardiovascular, respiratory, and/or other organ system involvement
Unusual	Serum sickness, Guillain-Barre syndrome, encephalopathy, nephrotic syndrome, acute renal failure, and cold urticaria
Toxic	Direct toxic effect of venom from multiple simultaneously occurring stings

Toxic Reaction

Toxic reactions occur as a result of multiple simultaneously occurring stings. The introduction of large quantities of potent venom proteins and nonprotein compounds may result in hypotension, shock, vascular collapse, and death. It is estimated that a 70 kg healthy person would have to simultaneously sustain 1500 stings to cause death.

Local Reactions

Local reactions are characterized initially by pain, followed by erythema, induration, and pruritus, all contiguous to the sting site. Usually these occur 12–24 h after the sting, peaking within 48 h and persisting for 7 days or longer. They are associated with IgE sensitization. Over 90 % of subsequent stings will result in a local reaction; however there is a 5–10 % risk of a systemic reaction.

Systemic Reactions

The incidence of systemic reactions to winged hymenoptera in the United States is 3.3 % in adults and 1 % in children. In the Southeastern United States, systemic reactions to IFA stings occur in 0.6–1 %. In two-thirds of patients, systemic reactions occur within 10 min after a sting.

Generally, the sooner the reaction occurs, the more severe it is. Systemic reactions are mediated by IgE antibody and vary from localized urticaria to anaphylaxis and death. Cutaneous reactions as the only manifestation of a systemic reaction are seen in 15 % of adults and 60 % of children. Systemic reactions are relatively consistent from one sting episode to another. Honeybee reactions are more severe and longer lasting, but yellow jacket reactions are more common. Anaphylactic deaths

are more common in adults and usually are caused by respiratory obstruction and circulatory collapse. Risk factors for a severe systemic reaction include older age, history of asthma, sensitization to honeybee, mastocytosis, elevated serum tryptase, and the use of antihypertensive medications (beta-blockers and angiotensin-converting enzyme inhibitors).

Unusual Reactions

Serum sickness, which is associated with IgE sensitivity occurring 7–10 days after a sting, has been reported. Other reported unusual reactions include persistent cold urticaria, acute encephalopathy, Guillain-Barre syndrome, nephrotic syndrome, and acute renal failure.

Natural History of Sensitivity

Sensitization to venom after a sting may occur at any age. Even after an uneventful sting, more than 30 % develop a positive venom skin test that is usually transient; venom skin tests return to negative in 30 % after 2–3 years and 50 % after 5 years. In one study 10 % of adults who were sensitized but had no reaction at the time of a sting had a systemic reaction up to 10 years later. Five to 10 % of persons with a history of a large local reaction will have a systemic reaction 10–20 years later.

In untreated patients with a history of a mild-to-moderate systemic reaction, the risk of a subsequent reaction gradually declines from a high of 50 % after a recent sting to 10–20 % 10 years later. Children with a cutaneous systemic reaction have a 10 % chance of a systemic reaction in the next 9 years and a 5 % chance 10–20 years after an initial reaction, but only a 1–2 % will have a more severe reaction. Little is known about the natural history of IFA sensitivity; however none of a group of patients under the age of 17 who initially experienced a cutaneous systemic or large local reaction developed a more severe reaction to a subsequent sting.

Diagnosis

History is important in determining the type and severity of the reaction. The presence and location of a nest at the site where the sting occurred, the time of year of the sting, and a stinger left at the sting site may help with identification but this is often thwart with error. Ideally, it would be helpful if the sting victim could provide the offending insect for identification. Testing is recommended for all individuals who have had a systemic reaction to an insect sting to determine the presence of venom-specific IgE. The exception is children under 17 who have

experienced only a cutaneous systemic reaction to a honeybee or vespid sting. Children who have had a cutaneous systemic reaction to an IFA or harvester ant and live in an area where these ants are endemic should be considered for testing and immunotherapy. Patients are at increased risk of a systemic reaction if they are adults, stung by a honeybee, are receiving angiotensin-converting enzyme inhibitor therapy or beta-blockers, or have mastocytosis. A serum tryptase determination should be obtained for patients who have suffered an anaphylactic reaction to a hymenoptera sting. An elevated serum tryptase may indicate systemic mastocytosis and is a risk factor for anaphylaxis both from an insect sting and from venom immunotherapy.

Extensive cross-reactivity exists among vespid venoms, particularly yellow jacket, yellow hornet, and white-faced hornet. Because of this most investigators recommend testing with all venoms. Still others recommend testing with the venom of the most likely stinging insect. To maximize the chance of a positive skin or in vitro test, there should be an interval of at least 4 weeks from the time of the sting.

For flying hymenoptera, skin *prick* tests are first performed with specific venoms at a concentration of 0.1–1.0 mcg/ml depending on the history of the severity of the reaction. If this is negative, *intradermal* tests are performed at an initial concentration of 0.001 mcg/ml and then repeated at increasing tenfold increments every 20 min until a venom concentration of 1.0 mcg/ml or a positive reaction is reached. *Intradermal* testing with venom at concentrations greater than 1.0 mcg/ml may cause nonspecific irritant reactions and is not diagnostic. The concentration of venom producing a positive skin test does not necessarily correlate with the clinical reaction.

The sting of an IFA results in a sterile non-immunologic pseudo-pustule 24 h later secondary to alkaloids in the venom. The diagnosis and treatment of IFA sensitivity are compromised by the lack of a commercially available venom antigen or a standardized WBE. Antigen quality varies among manufacturers. Skin tests with WBE are utilized for diagnosis. A skin *prick* test is initially performed at a concentration of 1:1000 weight/volume (w/v). If negative, *intradermal* testing is performed beginning at a concentration of 1:1,000,000 w/v and increased at tenfold increments until reaching a 1:1000 w/v level or there is a positive reaction.

For all hymenoptera, if there is a strong suggestion of a systemic reaction and the skin test is negative, an in vitro test (e.g., RAST) for venom-specific IgE should be performed. Skin testing is preferred and may be positive in 20 % of patients who have a negative RAST, whereas a RAST is positive in 10 % of skin test-negative patients. These tests supplement each other. If both the skin and the in vitro tests are negative and there is a strong suspicion of a systemic reaction, tests should be repeated after a 2–4-month interval.

There are occasions when a patient who suffered a systemic reaction to a honeybee demonstrates sensitivity not only to honeybee venom but also weak sensitivity to wasp or vespid venom yet has no history of clinical allergy to either. This limited cross-reactivity is of doubtful clinical significance and thought to be secondary to shared carbohydrate moieties. The dilemma could be resolved by in vitro testing

with recombinant antigens that do not contain the carbohydrate moieties, thus improving diagnosis and limiting the use of unnecessary immunotherapy.

Treatment of Insect Sting Reactions

Normal reactions and local reactions are treated with cold compresses, oral antihistamines, and nonsteroidal anti-inflammatory agents. Large local reactions may require the use of a short course of oral corticosteroids. Patients should be instructed regarding stinging insect avoidance. They should wear shoes and long pants when outdoors especially in grass or brush areas. IFA-sensitive patients should wear socks. Dark-colored clothing and flowery prints may attract stinging insects, whereas khaki color does not. Fragrances should be avoided. Foods especially sweets, meats, seafood, and sweet drinks attract vespids to outdoor eating areas, garbage cans, and fruit orchards. Insect repellants are of no value. Patients who have had a systemic reaction should have self-injectable epinephrine for intramuscular injection immediately available. In some studies over 20 % of patients experiencing a systemic reaction require a second dose of epinephrine. Commercially available products are available in two-dose forms, a pediatric dose of 0.15 ml of 1:1000 aqueous epinephrine for patients less than 30 kg and a standard dose of 0.3 ml for patients weighing more than 30 kg. Typically these are prescribed as a twin pack. If used the patient should seek immediate emergency care or 911 should be called. Patients with a history of a systemic reaction should wear a medical alert bracelet or necklace and should be considered for immunotherapy.

Immunotherapy

Immunotherapy is indicated for all patients with a history of systemic reaction to an insect sting who have IgE sensitivity to venom antigens. Typically it is not recommended for patients with a history of large local reactions where the risk of a subsequent systemic reaction is no more than 10 %. It is generally not indicated for children 16 years and younger who have only a cutaneous systemic reaction to the sting of a flying hymenoptera. It should be administered under the direction of a knowledgeable physician at a medical entity where appropriate personnel and equipment are available to treat anaphylaxis. Informed consent should be obtained and documented.

An exception is the use of IFA WBE immunotherapy. Moffitt et al., in a survey of allergists living in IFA-endemic areas, reported that 29 % would consider immunotherapy for children under 17 and 79 % for adults if they have had only a cutaneous systemic reaction to an IFA sting and live in an endemic area (Table 25.4).

The classic study by Hunt, Valentine, and Sobotka and subsequent studies by others demonstrate that venom immunotherapy reduces the rate of systemic reaction to 5 % or less in patients actively receiving maintenance immunotherapy.

Table 25.4 Standardized weekly dosage schedule for single hymenoptera venom therapy

Sting reaction	Skin test or RAST for venom	Immunotherapy indicated
Local	Positive or negative	No
Systemic (cutaneous only) Child <17 years	Positive or negative	No
Systemic (cutaneous only) Patient >16 years	Positive	Yes (United States)
		No (Europe)
Systemic (moderate to severe, other than just cutaneous)	Positive	Yes
Unusual immunologic	Positive	Uncertain[a]
Toxic	Positive or negative	Not indicated

[a]Reisman recommends immunotherapy for serum sickness reaction

Venom immunotherapy for children is particularly beneficial. Children with a history of a moderate-to-severe systemic reaction who received a mean of 3.5 years of venom immunotherapy had a 5 % incidence of a systemic reaction during a mean follow-up period of 18 years, compared to 32 % for a similar group who did not receive immunotherapy. According to Riesman, rare patients who experience a serum sickness reaction to an insect sting respond favorably to immunotherapy.

The choice of venom depends on a number of factors including the test reaction to specific insects; there is often much cross-reactivity among the vespids. Identification of the insect is often helpful, but is often flawed. Some allergists treat only with specific venoms if the insect can be identified. Others recommend treatment with all venoms to which the patient demonstrates sensitivity. Generally, venom immunotherapy is administered at weekly intervals beginning with a dose of 0.05–0.1 mcg and ultimately achieving a dose of 100 mcg for each venom used. For multiple vespid sensitivities, a venom antigen containing 100 mcg each of yellow hornet, white-faced hornet, and yellow jacket venoms (a total of 300 mcg) is available. The target dose is reached in 16–18 weeks. A "modified rush" regimen also has been successfully utilized enabling patients to achieve a target dose in 4–6 weeks with no significant difference in morbidity from the conventional regimen. Once the target dose has been reached, the interval is gradually increased to every 4 weeks for the first year. Some allergists will increase the interval to 6 week in the second and third year, and 6–8 weeks thereafter. In the small minority of patients who still have systemic stinging insect reactions at the recommended maintenance dose of venom, the dose needs to be advanced 50–100 % (Table 25.5).

Uncontrolled studies have demonstrated the effectiveness of immunotherapy with IFA WBE. Freeman reported only 1 of 47 patients receiving IFA WBE immunotherapy experienced a systemic reaction, whereas all 6 not receiving immunotherapy had a systemic reaction with a subsequent sting. Investigators recommend beginning with a concentration of 1:100,000 w/v of WBE and increasing weekly to a maximum tolerated level varying from 0.5 ml of 1:100 w/v to 0.5 ml of 1:10 w/v WBE; the interval then is gradually increased to every 4–6 weeks. Unblinded retrospective studies suggest that it is effective.

Table 25.5 Weekly dosage schedule for single hymenoptera venom immunotherapy

Dose	1 mcg/ml	Dose	10 mcg/ml	Dose	100 mcg/ml
1	0.05 ml	5	0.05 ml	9	0.05 ml
2	0.10 ml	6	0.10 ml	10	0.10 ml
3	0.20 ml	7	0.20 ml	11	0.20 ml
4	0.40 ml	8	0.40 ml	12	0.40 ml
				13	0.60 ml
				14	0.80 ml
				15	1.00 ml

Adapted from the insect venom package insert
Mixed vespid antigen contains three times the venom protein per ml shown here

Reactions to Immunotherapy

Reactions to immunotherapy vary from local to systemic. Systemic reactions occur in approximately 10 % of patients. Risk factors include female sex, history of atopy, mastocytosis, elevated serum tryptase, and honeybee venom immunotherapy. Concomitant beta-blocker therapy and possibly angiotensin-converting enzyme inhibitor therapy have been associated with increased risk; when possible alternative medications should be prescribed.

Systemic reactions require a temporary reduction in dose. Depending on the degree, local reactions may be mitigated by decreasing the dose or interval between injections, premedicating with antihistamines and leukotriene modifiers, or all these. Splitting the dose between two injection sites is helpful, especially when using mixed venom antigens. Venom immunotherapy is safe in pregnancy; however if pregnancy occurs, the initiation of immunotherapy should be deferred, and if already receiving immunotherapy, the dose should be maintained. Regular review of interval history, medications, antigen dosing, and insect sting reactions while on treatment helps to identify potential problems.

Duration of Immunotherapy

The duration of immunotherapy is controversial. The package insert for stinging insect venom immunotherapy recommends that it be continued indefinitely. However guidelines for discontinuing immunotherapy continue to evolve. It has been suggested that immunotherapy may be discontinued when skin and in vitro tests revert to negative; however this only occurs in 25 % of patients after 5 years and 50 % of patients after 10 years of treatment. For patients with a mild-to-moderate systemic reaction, a 5-year course of immunotherapy produces good protection, but not total loss of potential systemic reaction. In a 5–10-year follow-up study of patients who discontinued immunotherapy after at least 5 years of treatment, 16.7 %

sustained a mild-to-moderate systemic reaction to a subsequent sting. Immunotherapy should be considered indefinitely for those who are sensitive to honeybee venom, have an elevated serum tryptase, have a history of a severe anaphylactic sting episode, have a systemic reaction resulting in loss of consciousness, or have had a systemic reaction to immunotherapy.

In contrast with other stinging insects, there are no data concerning the duration of IFA WBE immunotherapy. In one report 36 % of allergists discontinue therapy after 4–5 years and 45 % after a negative test.

Biting Insect Hypersensitivity

Introduction

Biting insects utilize their developmentally unique needlelike proboscis to obtain a blood meal. This is inserted directly into a dermal capillary or a pool of extravasated blood. At the same time, they inject saliva, which contains both proteins and low-molecular-weight compounds. The secretions have anticoagulant, vasodilatory, and in some cases anesthetic activity. Often the victim is totally unaware of the bite. The bites of many insects result in a reaction varying from a small papule to an area of marked swelling and even necrosis. Many of these reactions have yet to be shown to have an immunologic origin; others, in particular flea and mosquito bite reactions, have been well studied and have an immunologic origin; their oral secretions are responsible for sensitization and allergic reactions. Though rare, there are credible reports of anaphylactic reactions, most commonly to the bite of the kissing bug (*Triatoma* sp.), but also rarely to the mosquito, blackfly, deerfly, and horsefly. Anaphylaxis due to the bite of a tick (an arachnid) has been reported. Bedbug bites may induce an IgE response.

Insect Bite Reactions

Reactions to insect bites vary greatly. Five stages of bite reactivity have been demonstrated. Stage I is the stage of induction in which there is no observable reaction. Stage II is the stage of delayed reactivity in which an erythematous papule develops at 18–24 h. Stage III is the stage of immediate followed by delayed reactivity. Stage IV is the stage of immediate reactivity. Stage V is the stage of non-reactivity (Table 25.6).

In a study by Feingold et al., guinea pigs, subjected to cat fleabites for five consecutive days and then twice weekly for 14 weeks, initially demonstrated no reaction. On day 6 they developed an erythematous papule at 18–24 h after the bite. On day 9, they developed an immediate reaction 20–60 min after a bite that cleared in 4 h, followed by a delayed reaction at 18–24 h; this immediate and delayed sequence

Table 25.6 Sequence of guinea pig allergic response to repetitive cat fleabites

Stage	Type of response	Time of onset
I	Induction	No reaction
II	Delayed reaction	Reaction at 18–24 h
III	Immediate followed by delayed reaction	Immediate followed by delayed reaction
IV	Immediate reaction	Immediate reaction
V	No reaction	No reaction

Adapted from Feingold B, Benjamin E, Michaela D. *Ann Rev Entomology*. 1968;13:137–158

persisted for the next 7 weeks. At 9 weeks only the immediate reaction was evident. At 13 weeks the bite sites became completely nonreactive. For the next 5 months, the animals were challenged every few weeks and exhibited no reaction. Peng and Simmons reported similar sequence in a human subject and a rabbit subjected to multiple mosquito bites every 2 weeks over a period 49 weeks; in the human subject, there was a loss of skin reactivity at 26 weeks, which persisted until the end of the study at 49 weeks. This loss of reactivity is observed in longtime residents living in areas of heavy endemic flea or mosquito bite exposure and possibly accounts for those patients who say they are "never bitten."

Thus the response to the bite depends on the victim's state of reactivity. In rare cases a systemic reaction may occur. Papular urticaria, which may persist for weeks, is seen most commonly with fleabites; it is hypothesized that it is the result of antibody reacting with residual antigen at bite sites in a previously unsensitized person. Simons and Peng have described "Skeeter syndrome" characterized by large local reactions involving an entire body part developing within hours after a mosquito bite. Bite victims who have immune aberrations such as Epstein-Barr virus, hematologic malignancies, and AIDS are at increased risk for mosquito bite reactions. There are no reports of retroviral transmission by biting insects.

Antigens

The antigens involved in the immune response generally are proteins found in the saliva. Up to 74 protein antigens have been identified in a study of various mosquito species; some are shared; others are species specific. Because of difficulties obtaining pure salivary antigens, cloned recombinant antigens have been developed in particular for the *Aedes aegypti* mosquito; at least three (rAed a 1, rAed a 2, rAed a 3) have been shown to possess immune activity in humans. The dominant salivary antigen for the cat flea is a hapten with a MW of 500 daltons, which binds with a carrier protein possibly found in collagen to form an immunogen; salivary protein antigens have also been isolated but apparently do not play a part in the human flea bite response.

Immune Response to Insect Bites

Studies of immunologic changes seen with mosquito bites demonstrate increases in antigen-specific IgG and IgE levels that mirror the development of the delayed and immediate reaction. There is no demonstrable antibody activity in stage I and almost total loss of specific IgE in the stage V nonreactive state. Histopathology studies of the various stages of mosquito and flea bite reactions demonstrated by biopsies at 20 min and 24 h revealed: stage I, no observable microscopic changes in either biopsy; stage II, no change at 20 min but an intense mononuclear and lymphocytic infiltration of the dermis and epidermis at 24 h; stage III, at 20 min edema and neutrophilic and massive eosinophilic infiltration followed at 24 h by the typical mononuclear infiltrate of the delayed reaction; stage IV, at 20 min edema and neutrophilic and massive eosinophilic infiltration and at 24 h only a minimal mononuclear infiltrate; and stage V, at 20 min and 24 h a negligible cellular response.

Diagnosis

The clinical diagnosis of insect bite reactions depends on many factors. Knowledge of the type of biting insects found in a given locale and at a given time is helpful. For example, mosquitoes are common in temperate climes during warmer months; in tropical climes they are found year-round; exposure is worse at dawn and dusk, but there are exceptions. Blackflies found in Canada and Northern United States and horseflies common throughout much of the United States inflict painful bites. Mosquitoes, blackflies, and stable flies bite exposed areas. *Triatoma* (kissing bugs), found in Texas, the Southwest, and California, bite at night. There are reports of anaphylaxis and even death as the result of *Triatoma* bites; this could be the result of unique characteristics of the antigens in the saliva, possibly the greater volume of antigen administered at the time of the bite and the frequency of the bites leading to a higher titer of specific IgE and/or to unique characteristics of the individual. Fleabites occur often in clusters under clothing, particularly where it constricts, such as a waistband/or the top of stockings; flea exposure is greatest in the late spring and during the summer, but may be year-round especially if there are pets in the environment.

In a few cases, the salivary antigens have been identified. However because of the difficulties collecting salivary antigens, the small amount of antigen available and the lack of a commercial supply, there is no practical way to test with purified antigens; hence whole-body extract (WBE) has been used both for testing and treatment. The available WBE antigens have limited in vitro and in vivo test reliability. The antigen is in the saliva and the amount in a whole-body extract is limited.

Treatment

The ideal treatment is bite avoidance. In the case of mosquitoes and other flying insects, screening and netting are helpful. Elimination of standing water in the area of the home is important. Wetlands pose a special hazard. Bite-sensitive individuals should wear clothing with long sleeves and pants and wear socks when outdoors at times when the insects are present. For special outdoor situations, permethrin-impregnated clothing is available. Insect repellants containing 20 % DEET (N,N-diethyl-meta-toluamide) are effective. Caution must be taken when DEET is used for young children; it is neurotoxic and has caused convulsions when applied in high concentrations on large surfaces. There are no known effective oral insect repellants. Appropriate use of insect sprays and "bug bombs" is often effective in controlling fleas and *Triatoma*; the use of "bug bombs" 14 days apart will destroy not only the adults but also the ova and pupae. The use of "flea collars" or topical insect repellants for pets is effective. For local bite reactions, cool compresses, topically applied menthol-containing products and corticosteroids, sedating antihistamines, and possibly NSAIDs may be helpful. Persons with a history of a systemic reaction to a bite should carry an emergency epinephrine kit. Reports of success of WBE immunotherapy to treat patients with a history of a systemic reaction to a biting insect are anecdotal and uncontrolled. In a small-uncontrolled study, immunotherapy with *Triatoma* salivary gland extract has been effective in treating anaphylaxis. Anecdotal reports of the value of mosquito WBE immunotherapy have been inconsistent. Uncontrolled studies to treat dogs sensitive to cat fleabites with purified salivary antigens have been shown to be effective. In some cases the favorable results that have been reported may be a manifestation in the natural course of insect bite sensitivity rather than the effect of immunotherapy.

The Future

An important goal for the future is the development of relevant recombinant insect venom and biting insect salivary antigens. This has the potential of opening new vistas particularly for diagnosis and treatment of hypersensitivity reactions. A major drawback will be cost.

Evidence-Based Medicine

These two articles by Rueff et al. detail the importance of obtaining a serum tryptase in the evaluation and treatment of a patient with a systemic reaction to a hymenoptera sting.

Rueff E, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum-tryptase-a study of

the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol*. 2009;124:1047

Severe anaphylaxis to hymenoptera stings is associated with a variety of risk factors. This observational study reviewed 206 patients with a history of severe anaphylactic reaction after a field sting. This is an observational study of 206 patients with a history of a severe systemic anaphylactic reaction after an insect sting. A serum tryptase was obtained 2 weeks or more after the index systemic reaction. The severity of the systemic reaction increased significantly with higher tryptase concentrations (>5 mcg/l). Thus an elevated serum tryptase is a risk factor for more severe systemic reaction to an insect sting. Measurement of baseline tryptase concentration is especially helpful when the diagnosis or indication for immunotherapy is controversial (patients who are fairly young, who have mild systemic reactions, or when both venom-specific IgE and skin tests are simultaneously negative).

Rueff F, et al. Predictors of side effects during the buildup of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol*. 2010;126:105

Severe side effects during venom immunotherapy are associated with a variety of risk factors. This observational study evaluated the association of baseline serum tryptase concentration with the frequency of severe reactions to immunotherapy requiring an emergency intervention during the buildup of venom immunotherapy. The majority of these patients were treated with a rush or ultra-rush immunotherapy program. Fifty-seven of the 680 hymenoptera-sensitive patients required an emergency intervention because of a severe systemic reaction to immunotherapy. The frequency of needed interventions increases significantly with higher serum tryptase concentrations. Other risk factors included honeybee sensitivity, older age, antihypertensive therapy, and an ultra-rush program of immunotherapy.

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Chapter 26
Latex Allergy

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Definition

Latex allergy is an IgE-mediated hypersensitivity disorder in which patients sensitized to natural rubber latex (NRL) have the potential of developing manifestations ranging from urticarial to anaphylaxis on reexposure to NRL.

History

Latex sensitivity was first reported in 1927 in Germany, but it was not until 1979 that the first skin test proven report of an allergic reaction, contact urticaria, to a natural rubber product was published in the English literature. Anaphylaxis was first reported in 1984 in two nurses who underwent surgical procedures; both had a positive skin test and radioallergosorbent test (RAST) to latex. In 1989 reports appeared of latex-induced anaphylaxis in children with spina bifida who had multiple surgeries. In 1991 there was a report of six anaphylactic reactions including one fatality due to the latex balloons of barium enema catheters. In that same year, because of these and other reports of allergic reactions in medical care settings, the FDA issued a warning concerning the risks of latex allergy.

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Epidemiology

It is important to distinguish between the prevalence of IgE *sensitization* and the prevalence of type I (IgE)-mediated *allergic reactions* to latex antigens. There are reports of both in the general population and in occupational settings, especially health-care workers. The prevalence of latex sensitization by skin testing in adults is approximately 1 %. Turjanmaa was the first to report the prevalence of latex sensitivity in hospital personnel, noting a high prevalence (6.2 %) in subjects regularly exposed to latex gloves. Sussman reported that 12.1 % of 1351 health-care workers exhibited sensitivity. In addition to health-care workers, persons who are employed in the rubber industry, housekeepers, and hairdressers are at higher risk. The presence of atopy is a major risk factor for sensitization. Latex sensitization increases in relation to the frequency and duration of exposure to latex. Multiple surgeries increase the risk of sensitization. Up to 64 % of patients who have had multiple procedures because of spina bifida or congenital urogenital abnormalities are sensitized to latex, and many of these have experienced severe, even life-threatening reactions. A group of dental hygiene students followed during their 3 years of training had a cumulative incidence rate of sensitization of 6.4 %, rhinoconjunctivitis 1.8 %, and asthma 4.5 %. Many reasons have been offered as a cause for the increase in NRL sensitivity; however, there is probably no one factor (Table 26.1).

There is a paucity of studies of the prevalence of IgE proven allergy to NRL latex. The prevalence of subject reported upper respiratory allergy symptoms was 7.8 % in a pooled population of 3567 health-care workers and 1.4 % for asthma in this same group. In a questionnaire survey, the annual incidence rate for contact urticaria was estimated to be 1.9 per 10,000 health-care workers. The prevalence of NRL-induced anaphylaxis during surgical procedures varies from 1 in 10,000 to 1 in 20,000. It is the second most common cause of intraoperative anaphylaxis. In the past decade, with the recognition of NRL allergy and efforts made to reduce exposure to latex allergens, there has been a reduction in the incidence of latex sensitization and allergy in health-care workers in developed countries.

Table 26.1 Reasons for increased sensitivity to natural rubber latex

1.	Institution of Universal Precautions (stimulated by the presence of HIV and viral hepatitis)
2.	Change in offshore production of latex gloves to country of origin of latex collection resulting in less time for degradation of native latex proteins by ammonia anticoagulant
3.	Increased latex protein contamination of the repeatedly used cornstarch slurry used in the manufacture of powdered latex gloves
4.	Increased use of latex gloves without appropriate indication
5.	Repeated tapping of a given rubber tree to augment latex production results in increased amounts of naturally occurring protective antigens in the collected latex

Natural Rubber Latex Products, Production, and Allergens

Rubber tree latex is harvested by tapping the *Hevea brasiliensis* tree. The milky latex flows from the site; it is thought to defend against pathogens and insects and to promote wound healing. Initially, the fluid is treated with ammonia to prevent coagulation. It is then centrifuged isolating the rubber phase. The majority of the latex is coagulated, washed, and sulfur heat vulcanized at high temperature. The resultant "*dry product*" is formed into rubber crumbs or sheets. These products have very low levels of latex antigen. The remaining latex liquid is compounded with various low-molecular-weight accelerators, preservatives, and antioxidants (thiurams, carbamates, benzothiazoles, paraphenylenediamine) (Table 26.2). Porcelain molds of the product to be produced (e.g., gloves, condoms, and balloons) are coated with a coagulant material and then dipped into the compounded latex liquid. The latex-coated molds are removed from the latex compound, washed to leach soluble latex proteins, and then sulfur-vulcanized to complete formation of the "*dipped product*" and in the case of gloves may be washed again. Gloves are then dipped into a cornstarch slurry. Finally the powdered gloves are stripped from the molds. Omitting the cornstarch application and using a chlorination wash produce powder-free gloves, which have a much lower quantity of latex proteins.

Raw natural rubber latex contains 1–2 % protein. Over 50 latex peptides have been described that induce IgE sensitization. Each varies in stability, bioavailability, and antigenicity. The International Allergen Nomenclature Committee has designated 14 of the proteins as major and minor allergens. Some are more likely to induce sensitization in specific groups of patients. Spina bifida patients are likely to be sensitized to Hev b 1, Hev b 3, Hev b 6, and Hev b 13; health-care workers are more likely to be sensitized to Hev b 2, Hev b 5, Hev b 6, and Hev b 13 (Table 26.3). Significant cross-sensitivity exists between latex allergens in particular profilin and several fruits, most commonly chestnut, avocado, potato, tomato, kiwi, banana, and tropical fruits (e.g., papaya, pineapple, mango, passion fruit, jackfruit, and star fruit) resulting in the latex-food allergy syndrome (Table 26.4).

Pathogenesis

Sensitization depends on the characteristics of the subject, the state of the integument, the quality of the antigen, and the degree, route, and duration of exposure. Atopy is an important risk factor. Latex allergens adsorbed onto cornstarch particles on "dipped rubber" products are the most common source of exposure.

Table 26.2 Classes of common additives used in fabrication of "dipped" latex products

Benzothiazoles
Carbamates
Paraphenylenediamine
Thiurams

Table 26.3 Important latex allergens

Antigen	Description	Importance as allergen		Cross-reactivity with other allergens
		HCW	Spina bifida	
Hev b 1	Elongation factor	++	++++	Papain
Hev b 2	Gluconase	++++	++	Bell pepper
Hev b 3		++	++++	
Hev b 4		++	++	
Hev b 5	Structural protein	++++	++++	Kiwi
Hev b 6	Prohevlin	++++	+++	Avocado, kiwi, banana
Hev b 7	Esterase	++	++	Potato
Hev b 8	Profilin	++	++	Banana, celery, pineapple, bell pepper, ragweed, melon, peach
Hev b 9	Encolase	+/–	–	Tomato, *Alternaria*, *Cladosporium*
Hev b 10		–	+/–	*Aspergillus fumigatus* and other fungi
Hev b 11	Chitinase	?	?	Avocado, banana, chestnut 60 % homology with Hev b 6
Hev b 12		?	?	Peach
Hev b 13	Esterase	++++	++++	?
Hev b 14	Chitinase	?	?	?

Reference: Sussman G. Allergens and natural rubber proteins. *J Allergy Clin Immunol*. 2002;110(Supplement):33
HCW health-care worker

Table 26.4 Common foods associated with food-latex allergy syndrome

Avocado
Banana
Chestnut
Hazelnut
Potato
Tropical fruits: passion fruit, mango, papaya, pineapple, jackfruit, star fruit

Repeated exposure facilitates sensitization. To induce IgE sensitization, sufficient amounts of latex allergens must come in contact with the immune system. The most important sites of exposure are through the skin and respiratory tract, and to a lesser degree the eyes, and the gastrointestinal and genitourinary tracts. The latex proteins are trapped and processed by antigen-presenting cells in the skin and mucous membranes, presented to TH-2 lymphocytes ultimately leading to the production of NRL-specific IgE by plasma cells. Once sensitized, the subject is at risk for IgE-mediated NRL allergy. Not all subjects who are exposed to NRL develop sensitivity and not all who are sensitized develop allergic symptoms. Atopy is a risk factor. Manifestations include urticaria, rhinoconjunctivitis, bronchial asthma, and anaphylaxis.

Persons employed in certain occupations or those with a history of repeated surgeries are especially vulnerable. Health-care personnel, particularly those working in surgical areas, are at increased risk for sensitization. The estimated threshold level of aerosolized latex antigen necessary for inhalant sensitization is 0.6 ng/m^3. This is at least 100-fold less than levels found in operating suites where powdered latex gloves are used. In past years many latex gloves contained very high levels of latex allergens. The latex antigen content of gloves has been drastically reduced in recent years. In the early 1990s, the soluble latex antigen content for many gloves was 100–1000 micrograms or even higher per square decimeter. The current recommendation for residual latex protein in gloves is 10 μg or less per square decimeter.

IgE-mediated dermatitis must be distinguished from *allergic delayed contact dermatitis* due to lymphocyte cell-mediated hypersensitivity to excipients compounded with latex in the formation of "dipped" products (Table 26.2) and *nonimmune irritant dermatitis*, the most common reaction to glove usage.

Diagnosis

The diagnosis of latex allergy depends on the presence of clinical findings confirmed by objective testing for latex sensitivity. A detailed history of the type of symptoms and clinical findings and their temporal relation to latex exposure are key. Problems associated with latex products include (1) *nonimmune irritant dermatitis*, the most common reaction to latex glove use; this often is the result of rubber glove use coupled with poor hand care, repeated handwashing, irritant soaps, and seasonal periods of low humidity leading to itchy, dry irritated dermatitis. Local dermatitis is the sole manifestation of latex glove use. Skin and in vitro tests for IgE sensitivity and patch tests for the excipients used in the fabrication of latex gloves do not reveal allergic sensitivity. (2) Lymphocyte-mediated *allergic delayed contact dermatitis* is the result of sensitivity to accelerators, antioxidants, and preservative chemicals used in manufacture of "dipped rubber" products. This dermatitis is evident at the site and close proximity to chronic latex contact. Diagnosis is facilitated by patch testing to these low-molecular-weight compounds (Table 26.2). (3) *IgE-mediated immune hypersensitivity reactions* to NRL proteins are associated with "dipped" rubber products. Diagnosis depends on presence of clinical findings confirmed by objective testing for latex sensitivity. A detailed history of the type of symptoms and clinical findings and their temporal relation to latex exposure are important. Some risk factors for sensitization include atopy, the presence of hand dermatitis, frequent surgeries (particularly urogenital surgeries and surgeries for spina bifida), and occupational exposure including those employed as rubber industry workers, cosmetologists, housekeepers, and health-care workers (especially those assigned to surgical units). Local pruritus, dermatitis, or edema after a gynecologic or dental procedure or blowing balloons and condom exposure suggests latex sensitization, as does food allergy (in particular to kiwi, avocado, banana, potato, and chestnut) (Table 26.5).

Table 26.5 Risk factors for latex sensitization

1. Occupational (health-care workers, rubber industry workers, housekeepers, beauticians
2. Repeated surgeries, in particular spina bifida, urogenital surgeries
3. Atopy
4. Hand dermatitis
5. Spina bifida
6. Food allergy (avocado, chestnut, banana, kiwi, potato, tropical fruits)

Ultimately confirmatory testing is necessary to establish the diagnosis of NRL allergy. In the United States, skin testing is thwarted by the lack of an FDA-approved commercially available extract. Typically an in vitro test for NRL IgE is performed. Three FDA-approved tests are currently available, ImmunoCAP-Phadia, AlaSTAT, and HY-TEC; there is relatively close agreement among the tests; however the incidence of a false-negative result may be as high as 27 %. High titers coupled with a positive history are indicative of latex allergy. If in vitro tests are negative, many allergists perform percutaneous and intracutaneous testing utilizing various dilutions of an antigen prepared by incubating pieces of powdered latex gloves in a diluent solution. If there is a strong suspicion of latex sensitivity and these tests are negative, a modified "glove-use" test described by Hamilton may be employed; a bifurcated needle is used to make three scratches on the dorsum of a saline-moistened hand and then a latex glove is placed on the hand for up to 30 min; the area over the scratch sites is rubbed repeatedly; finally the patient is observed for any cutaneous or respiratory symptoms. These latter tests are compromised by not knowing the concentration of latex allergen in the glove; newly manufactured gloves have very low levels of allergen. A work challenge monitoring the patient for symptoms and signs and following pulmonary function or peak flow has also been employed. Despite this there are still rare patients who have a convincing history and negative tests.

Management

Avoidance of NRL exposure is the primary goal of treatment. Sensitized patients need to be instructed regarding potential sources of contact and avoidance. Their health-care providers need to be informed of the sensitivity. When traveling to foreign countries, they should carry a supply of non-latex sterile surgical gloves.

Sensitized patients should be informed of the potential of the latex-food allergy syndrome (Table 26.4). Patients with a history of an anaphylactic reaction to latex or who have more than a cutaneous allergic reaction to the ingestion of

a cross-reacting food should carry an epinephrine self-injection emergency kit; a medical alert bracelet should be worn if there is a history of a severe reaction to NRL.

Surgical and other health-care procedures pose a special risk for latex-sensitive patients. Latex allergy is the second most common cause of intraoperative anaphylaxis. Latex aeroallergen content in the operating room gradually increases during the workday; this is dependent on the number of powdered latex gloves used and the amount of activity. A "latex-safe" environment should be provided for the sensitive patient undergoing surgery. Before the procedure the operating room should be "wiped down," the patient should be scheduled for the first case of the day, powdered latex products should not be used, and latex products should not come in contact with the patient. There are rare reports of sensitivity to solutions drawn through "dry" latex ports used in multidose vials. When possible products to be used parenterally should be drawn from unit dose vials and administered through non-latex ports. Butyl rubber products do not contain latex. The avoidance procedures should be carried through postoperative and hospital care. Both the patient and the hospital room should have latex precaution labeling. Latex avoidance procedures should be instituted for all patients and with spina bifida at birth. Protocols utilizing antihistamines and glucocorticoids preoperatively have been proposed but have not met with consistent success and are not recommended. The FDA now requires that all medical devices containing natural rubber latex be labeled.

A number of studies have shown that the highest prevalence NRL sensitivity is in medical personnel in particular nurses, working in where there is high utilization of powdered latex gloves. Not uncommonly the initial occurrence in health-care workers is at the time of childbirth or surgery. The incidence of latex sensitivity in this group seems to be leveling off probably because of both a reduction of NRL protein content in gloves and decreased frequency of powdered latex gloves exposure. When possible there should be a conversion to low NRL gloves or powder-free latex or nitrile gloves. Vinyl gloves are recommended when barrier protection is not necessary.

Latex-sensitive health-care workers must discontinue their use of latex gloves, and if necessary for barrier protection, use nitrile gloves; they should be assigned to well-ventilated areas where other personnel are using powder-free latex gloves. By making these accommodations, these personnel can successfully return to work.

The Future

Manufactures continue to make improvements in reducing the amount of latex allergens in natural rubber products. Many centers have switched to powder free latex gloves or nitrile gloves. While the prevalence of latex sensitivity is falling in developed countries, there is a risk of sensitivity increasing in developing countries with more frequent use of powdered latex gloves.

There are anecdotal reports of success using sublingual NRL immunotherapy. However controlled studies utilizing NRL or specific latex antigens are few in number and with variable results. Subcutaneous immunotherapy has been attempted but often resulted in severe allergic reactions.

Testing with recently developed specific recombinant component latex allergens has the potential of improved diagnostic capability identifying specific offending latex protein sensitization and eliminating irrelevant latex sensitization. NRL component antigens Hev b 1, Hev b 3, Hev b 5, and Hev b 6 indicates of clinically important latex sensitization, whereas sensitivity solely to Hev b 8 (profilin) by in vitro test and not by skin test is not associated with clinically important sensitivity. Recombinant NRL antigen components may offer an avenue to specific sublingual immunotherapy.

Evidence-Based Medicine

Noted below are two evidence-based articles: One addresses the effect of long-term avoidance of latex on continued sensitization to latex and the second presents the effect of sublingual immunotherapy in natural rubber latex allergic patients.

Smith Q, Amin M, et al. Percutaneous reactivity to natural rubber latex persists in health-care workers following avoidance of natural rubber latex. *Clin Exp Allergy*. 2007;37:1346.

In 2000, percutaneous sensitivity to NRL was measured in 34 health-care workers who were exposed and sensitized to NRL. Strict NRL avoidance was recommended. Five years later the prevalence of work-related symptoms significantly decreased. Percutaneous tests were repeated, and sera were assayed for NRL and non-ammoniated latex, and recombinant latex antigens using ImmunoCAP. Percutaneous tests remained positive, but with a decrease in sensitivity. In-vitro tests were still positive. The tests indicated continued sensitivity after 5 years. The authors recommended continued avoidance of NRL in sensitized workers.

Gastaminza G, Algorta J, et al. Randomized double-blind placebo-controlled clinical trial of sublingual immunotherapy in natural rubber latex allergic patients. *Trials*. 2011;12:191.

This European double-blind study demonstrates the lack of clinical effectiveness of a 2-year program of sublingual immunotherapy in a group of natural rubber latex allergy patients. Twenty-eight adults were randomized to receive sublingual immunotherapy with a commercial rubber latex antigen or placebo. At the end of the 2-year study period, there was no difference in clinical efficacy, prick test sensitivity, glove-use score, conjunctival challenge tests, and specific IgE between the two groups; however the basophil activation tests significantly improved in the active treatment group. During the study period, two active treatment patients dropped out, one due to pruritus and the other due to acute dermatitis.

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Chapter 27
Drug Allergy

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Introduction

Adverse drug reaction is a noxious and unintended response to a drug. Adverse drug reactions are separated into two major types: type A which is dose dependent and predictable and type B which is dose independent and usually unpredictable. The majority of adverse drug reactions are type A (e.g., bleeding secondary to warfarin). Type B reactions, which include hypersensitivity drug reaction, comprise of about 24 % of all adverse drug reactions. Drug allergy is considered a hypersensitivity reaction for which a definite immunologic mechanism, either IgE or T cell mediated, is demonstrated. An example is type I IgE-mediated allergic reaction to penicillin. True overall incidence of adverse drug reactions is unknown for the general population. The overall incidence of serious adverse drug reactions was 6.7 % of hospitalized patients and of fatal adverse drug reactions was 0.32 % of hospitalized patients. In 1994, fatal adverse drug reaction ranked the fifth leading cause of US deaths. In Singapore, a 2-year prospective study, using a network-based electronic notifications system for which each drug allergic case was verified by a trained allergist, detected the incidence of drug allergy was about 4.2 per 1000. Medication is the most common cause (58.8 %) of anaphylactic death in the USA from 1999 to 2010, and there was a significant increase in fatal drug-induced anaphylaxis from 0.27 per million in 1999–2001 to 0.51 per million in 2008–2010. Adverse drug reactions are encountered by physicians frequently. The reaction can be serious and fatal if not treated promptly and preventatively. Practitioners should be aware of therapeutic and preventive strategies for drug allergy.

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Classification

Type A Drug Reaction

Description

The majority (76 %) of adverse drug reactions are type A. It is dose dependent and predictable.

Subtypes and Examples

Overdose For example, hepatic failure secondary to high-dose acetaminophen.

Side Effects For example, bleeding or ecchymosis secondary to warfarin; nausea secondary to erythromycin.

Drug Interactions Concurrent usage of erythromycin and warfarin can increase INR and thus can increase the risk of bleeding.

Type B Drug Reaction

Description

The reactions are restricted to a small subset of the general population. They are dose independent and frequently unpredictable.

Subtypes and Examples

Intolerance Psychological disturbance after being on steroid.

Idiosyncrasy(Genetically Determined Drug Reactions/Pharmacogenetics) Caucasian with HLA-B5701 allele has high risk (positive predictive value of about 48 % and negative predictive value of 100 %) of developing hypersensitivity reaction after being started on abacavir. In this situation, this drug reaction is predictable based on a specific genetic code of a patient.

Immunological Drug Reaction (Drug Allergy) See next section.

Immunologic Drug Reaction (Drug Allergy)

Immunologic Drug Reaction Based on Gell and Coombs Classification

Type I IgE-Mediated Anaphylactic Reaction

Mechanism A complete antigen with multivalent epitopes, like an antibiotic, binds IgE antibodies on mast cells. If the antigen is small, it is called a hapten; it binds to an endogenous carrier protein to become a complete antigen with multiple epitopes. The binding pulls the IgE antibodies on the surface of a mast cell together. The process leads to degranulation of mast cells. Degranulation of mast cells releases mediators including histamine that can cause the typical presentation of an allergic reaction.

Clinical Manifestations The mediators released from the mast cells can cause urticaria, angioedema, and/or anaphylaxis with bronchospasm and/or hypotension. They can occur early or late in a course of therapy and even can persist for weeks or months after drug withdrawal.

Types of Complete Allergens Foreign macromolecules (e.g., insulin and vaccines) and functionally multivalent chemicals (e.g., succinylcholine).

Types of Incomplete Antigens (Haptens) The small antigens require binding to a carrier protein before being able to elicit an immune response (e.g., penicillin, antithyroid drugs, and quinidine).

Metabolism to Haptenic Form Some drugs, in their native forms, are unreactive macromolecules. They must be converted into reactive intermediates during drug metabolism. The intermediates then can be haptenated to become complete antigens that are capable of inducing type I IgE-mediated allergic reactions (e.g., acetylation and oxidation of sulfonamides to form N4-sulfonamidoyl haptens).

Type II IgG/IgM Antibody and Complement-Mediated Reaction

Mechanism Specific IgG or IgM antibody binds to a drug antigen located on cell membranes. In the presence of complement, the antibody-antigen complex is cleared by the monocyte-macrophage system and destroyed.

Clinical Manifestation Drug-induced hemolytic anemia and thrombocytopenia.

Type III Immune Complex Reaction

Mechanism Soluble complexes of a drug or its metabolite in slight antigen excess bind with IgG or IgM antibodies. Immune complexes are deposited in blood vessel walls and cause injury by activating the complement cascade.

Clinical Manifestations Fever, urticaria (usually persists more than 1 day and microscopically shows leukocytoclastic vasculitis), erythema multiforme, lymphadenopathy, and arthralgia. Symptoms typically appear 1–3 weeks after the last dose of an offending drug, although they can appear while the patient is taking the drug and subside when the drug is cleared from the body. The antigens can be any drug including penicillin and cephalosporins.

Type IV Delayed Hypersensitivity Reaction

Mechanism In classic delayed-type hypersensitivity, an antigen-presenting cell processes the medication (an antigen) and presents a piece of the antigen (peptide) in the context of HLA (covalently linked to the HLA) to the T cell via the T-cell receptor. However, not all drugs need to bind covalently to the MHC or HLA-peptide complex in order to trigger an immune response. Rather, some drugs may bind reversibly to the MHC or possibly to the T-cell receptor, eliciting immune reactions. The non-covalent drug presentation leads to the activation of drug-specific T cells. In some patients with hypersensitivity, such a response may occur within hours. Thus the reaction to the drug may not be the result of classic delayed-type hypersensitivity. This is called the p-i concept: pharmacologic interaction of drugs with immune receptors. This is first verified for sulfamethoxazole-specific T-cell clones and further confirmed for lidocaine, mepivacaine, celecoxib, carbamazepine, and quinolones. Thus, allergic drug reaction occurring within a few hours after drug administration may be T-cell-mediated rather than IgE-mast-cell-mediated allergic reaction.

Clinical Manifestations Classical T-cell-mediated hypersensitivity is contact dermatitis secondary to neomycin and topical antihistamine and maculopapular eruption (morbilliform eruption) secondary to antibiotics. An example of p-i concept of T lymphocyte activation is binding of abacavir onto HLA-B5701 and thereby stimulating T lymphocyte which can in turn cause tissue injury.

Pseudoallergic Drug Reaction

Mechanism This drug reaction cannot be classified under the Gell and Coombs classification as outlined earlier but can manifest similarly to an immunologic drug reaction. This type of reaction is also called an anaphylactoid reaction.

Clinical Manifestations Similar to type I IgE-mediated allergic reaction as previously described, with urticaria, angioedema, bronchospasm, and/or cardiovascular collapse.

Important Examples

Radiocontrast Media-Induced Anaphylactoid Reaction Adverse reactions are attributable to contrast's hypertonicity, which augments basophil and mast-cell histamine release. The release of histamine, upon binding to histamine receptors, can cause typical type I-like reactions. Risk factors include atopic background, underlying cardiovascular disease, and a previous history of radiocontrast reaction. Allergy to seafood is not a risk factor for anaphylactoid reaction to radiocontrast media. Usage of nonionic contrast media, which are almost isotonic, can reduce but not eliminate this pseudoallergic reaction. Addition of steroid and antihistamine before infusing the nonionic contrast can help to decrease the risk of reaction further (see Table 27.3).

Opiate-Induced Urticaria Narcotics such as morphine can induce direct mast-cell degranulation without involving the IgE-antigen process. Manifestation includes pruritus, urticaria, and occasionally wheezing. Management includes usage of non-narcotic medications, premedication with antihistamine, and graded challenge.

Vancomycin-Induced Red Man's Syndrome The mechanism is nonspecific non-IgE-mediated histamine release. Patients present with diffuse erythema, pruritus, and/or hypotension. Management includes slowing the rate of vancomycin infusion to about 2 h and preadministration with H1 blocker.

Colloid Volume Expanders Examples include dextran and human serum albumin. The mechanism is believed to be hyperosmolar-dependent histamine release. Manifestation is similar to reaction to radiocontrast media.

Aspirin (*ASA*)*/nonsteroidal anti-inflammatory drug* (*NSAID*):

1. Aspirin-exacerbated respiratory disease (AERD).
   (a) Mechanism: Overproduction of cysteinyl leukotrienes following inhibition of COX-1 by medications like aspirin or NSAIDs.
   (b) Clinical manifestation: Asthma, recurrent sinus disease with nasal polyps, and a sensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).
2. ASA/NSAID-induced urticaria and angioedema.
   (a) Mechanism: Blockage of cyclooxygenase enzyme leads to overproduction of leukotrienes.

(b) Clinical manifestation: Patient has underlying idiopathic urticaria/angioedema which can be further aggravated by ASA/NSAID usage. Patient, who reacts to one type of NSAID medication, tends to react to other types of NSAIDs.

3. ASA/NSAID single drug-induced anaphylaxis.

(a) This is a true IgE-mediated allergic reaction and not a pseudoallergic reaction.
(b) Mechanism: IgE-mediated allergic reaction to a specific NSAID or ASA. The reaction is specific to the NSAID drug in question. Cross-reaction to another kind of NSAID is rare, unless the chemical structures between the two NSAIDs are very similar.
(c) Usual clinical history: The patients do not have underlying chronic idiopathic urticaria which predisposes patients to cross-reactions with other NSAIDs. The history usually indicates that the patient has never had allergic reactions to other NSAIDs (not the one that causes the reaction). Therefore, this patient has a single drug reaction without cross-reaction with other NSAIDs. This suggests that the mechanism of the reaction is not by blocking the common cyclooxygenase pathway. The single drug reaction suggests specific IgE-mediated reaction to a specific NSAID. The classic allergic symptoms are urticaria, angioedema, wheezing, and hypotension. For organization purpose, ASA/NSAID single drug-induced anaphylaxis is listed under pseudoallergic drug reaction. However, immunologically, this unique type of NSAID reaction, mediated by IgE, should be listed under type I IgE-mediated allergic reaction.

Diagnosis of Drug Reaction/Allergy

Clinical Assessment

A detailed history is the most important tool in the diagnosis of drug reaction. Keep in mind the classification of drug reaction as mentioned above and as summarized diagrammatically (Fig. 27.1). It is important to know the pharmacologic property of the drug in question in order to distinguish between type A and type B reactions. Next, it is helpful to know if the patient has taken the medication in the past. If he or she has taken the medication in the past and now has a reaction, the patient may have been sensitized to the drug previously causing the current immunologic IgE-mediated allergic reaction. Next, it is important to know the clinical manifestation of the timing of the reaction. Does the patient have a typical IgE-mediated reaction, like urticaria, angioedema, hypotension, or bronchospasm? If you have a chance to examine the patient when he or she has the allergic reaction, it will be helpful. Sometimes, one has to rely on examination record from another physician who examined the patient at the time of the reaction. Immediate type I IgE-mediated allergic reaction occurs within minutes to hours after the administration of the drug. Delayed type IV T-cell-mediated drug reaction usually occurs days to weeks after the administration of the drug and may present with maculopapular, bullous, and

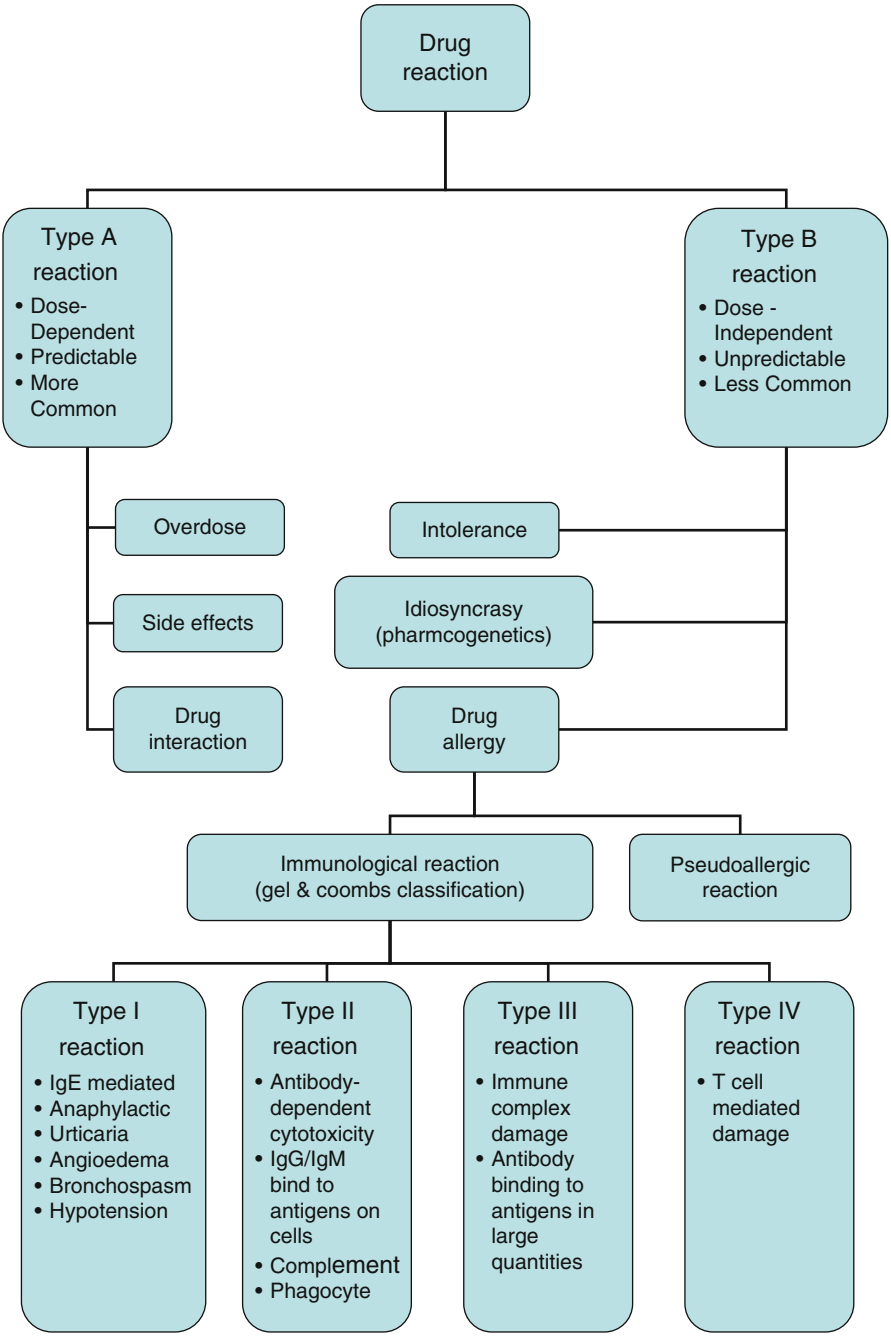

Fig. 27.1 Classification of drug reactions

pustular exanthem. It is important to know when a reaction occurs relative to the timing of the administration of the drug. One also has to consider other concurrent administered drugs and render a decision whether the reaction is caused by another drug. Therefore, temporal association between initiation of drug therapy and onset of allergic reaction is essential. It will also be important to know if the drug in question is the only drug available for the patient and if the patient requires using the medication without alternative. This will help a physician decide whether to proceed with desensitization. For example, a patient with type I diabetes mellitus has to take insulin for survival. In this situation, one has to continue using the medication by desensitization and/or premedication with antihistamine.

Diagnostic Investigation

Skin Testing

Not all drugs can be reliably skin tested. Frequently, the reaction to a drug can be secondary to the metabolite of the drug in question. In addition, false-positive and false-negative predictive values of skin testing of many drugs are not known. Therefore, a positive skin testing may be helpful with confirmation by history. A negative skin testing for a certain drug may be a false-negative finding. An exception to that is penicillin (PCN) skin testing utilizing the major and minor determinants of PCN. Allergic reactions observed in re-treatment of history-positive, skin test-negative patients have virtually all been mild and self-limited; no life-threatening false-negative reaction has been reported. The theoretic risk of a course of penicillin resensitizing the patient with a positive history but a negative skin test response is low and on the order of 3% or less. Thus once a patient with a positive history is shown to have a negative skin test response and has tolerated a course of penicillin or beta-lactam drug, future administration of such agents would not require additional skin testing.

Serum Tryptase

Tryptase is released by a mast cell and is an indication of mast-cell degranulation like seen in anaphylaxis. Measurement taken within 4 h of the reaction is helpful to confirm mast-cell degranulation or anaphylaxis.

Complements

CH50, C3, and C4 measurements are helpful to determine if the complement system is activated like what one would expect in type II and type III immunologic drug reactions.

Graded Drug Challenge (Test Dosing)

When skin testing is not available, one may have to perform a graded drug challenge under physician observation in case of anaphylaxis. This will help determine if the patient can safely tolerate the medication in question when diagnostic testing to determine the possibility of true drug allergic reaction is not available, the history is not definite for drug allergy, and/or the patient has to continue the medication without alternatives. The principles of incremental test dosing are to administer sufficiently small doses that would not cause a serious reaction initially and increase by safe increments, usually by tenfold, every 20–60 min over a few hours or a few days. The procedure is not a true desensitization as the dose is increased more rapidly compared to desensitization. The intent of a graded drug challenge is to assure that the patient can tolerate a small dose without allergic reaction before administering a higher dose safely. Repeated drug administration is contraindicated after any life-threatening reaction that is not mediated by IgE mechanism (e.g., drug-induced hemolytic anemia, immune complex reaction, and Stevens-Johnson syndrome).

Management

General Considerations

Based on the algorithm as shown diagrammatically in Fig. 27.1, one should be able to derive the correct type or classification of a drug reaction. If the patient has type A reaction because of overdose, dosage adjustment is all that is necessary. If the reaction is secondary to drug interaction, dose adjustment of the drug in question or the interacting drug will be sufficient. If the patient has type B reaction secondary to intolerance, an alternative drug should be administered if clinically indicated. If the drug is the only medication most appropriate for the patient, the medication can be given without type I IgE-mediated allergic reaction (the reaction is intolerance and not an allergic reaction). However, the patient may need to be warned regarding the reaction, which is not life threatening. If the patient's reaction is type B reaction secondary to drug allergy, one has to determine if the drug has to be given without alternative. If the administration of the drug is essential for the patient without alternative and the prior reaction was a type I IgE-mediated reaction, desensitization will be necessary so the essential drug can be given to the patient. Type II, type III, and type IV reactions cannot be desensitized. One has to be prepared to stop the medications if these reactions recur. If the patient has Steven-Johnson syndrome in the past, the responsible drug should not be readministered. Desensitization does not work for Steven-Johnson syndrome.

Desensitization

If a patient has a history of type I IgE-mediated reaction to a specific drug, the drug can be reintroduced via desensitization, provided that the medication is the one the patient needs without alternative. In other words, the benefit of administering the medication via desensitization is higher than the risk of complications associated with the desensitization. The best described desensitization is penicillin desensitization. The other drugs can be desensitized using the same principle. Table 27.1 is an example of penicillin desensitization procedure.

Special Considerations

Insulin Allergy

Systemic reactions to insulin are IgE mediated and characterized by urticaria, angioedema, shortness of breath, wheezing, and hypotension. The patient can have a mild form of reaction with rash only. Treatment may include antihistamine for symptomatic relief until reaction disappears. Systemic life-threatening allergic reaction may occur. In situations when insulin is crucial to a patient's health, insulin should not be discontinued after a systemic reaction if the last dose of insulin is given within 24 h. Rather, the dose should be reduced to about a tenth of the dose that caused the systemic reaction. The dose should then be slowly increased by 2 U per injection until a therapeutic dose is achieved. After that, the patient should receive insulin at least daily in order to keep him or her desensitized to the insulin.

If the patient who is allergic to insulin has not received insulin for more than 24 h, one may have to put the patient through the insulin desensitization protocol. The physician should be prepared to treat anaphylaxis and hypoglycemia during the desensitization procedure. Rapid desensitization like PCN desensitization in ICU may be necessary if the patient requires insulin urgently. If requirement for insulin is not critical, one can desensitize the patient via a modified protocol over a 6-day period with three doses each day.

Measles, Mumps, and Rubella Vaccine Allergy

Skin testing for MMR vaccine is indicated for a patient who has prior reaction to MMR or who has prior reaction to gelatin, which is also a stabilizer present in MMR. The risk for serious allergic reaction to the MMR in egg-allergic patients is extremely low and the vaccine may be administered to egg-allergic individuals.

Table 27.1 PCN desensitization

Time (min between doses)	Dose	Units/mg	Concentration (units/cc)	Vol (cc)	Total dose (units/mg)
0	1	50 U/0.03 mg (IV/PO)	100 units/cc (0.0625 mg/cc)	05	50 U/0.03 mg
15	2	100 U/0.06 mg (IV/PO)	100 units/cc (0.0625 mg/cc)	1	150 U/0.09 mg
30	3	200 U/0.13 mg (IV/PO)	100 units/cc (0.0625 mg/cc)	2	350 U/0.22 mg
45	4	400 U/0.25 mg (IV/PO)	100 units/cc (0.0625 mg/cc)	4	750 U/0.47 mg
60 (1 h)	5	800 U/0.5 mg (IV/PO)	100 units/cc (0.0625 mg/cc)	8	1550 U/0.97 mg
75	6	1600 U/1 mg (IV/PO)	1000 units/cc (0.625 mg/cc)	16	3125 U/1.97 mg
90	7	3200 U/2 mg (IV/PO)	1000 units/cc (0.625 mg/cc)	32	6350 U/3.97 mg
105	8	6400 U/4 mg (IV/PO)	1000 units/cc (0.625 mg/cc)	64	12,750 U/7.97 mg
120 (2 hr)	9	12,800 U/8 mg (IV/PO)	1000 units/cc (0.625 mg/cc)	128	25,550 U/15.97 mg
135	10	25,000 U/15.6 mg (IV/PO)	10,000 units/cc (6.25 mg/cc)	25	50,550 U/31.57 mg
150	11	50,000 U/31.3 mg (IV/PO)	10,000 units/cc (6.25 mg/cc)	5	100,550 U/62.9 mg
165	12	100,000 U/62.5 mg (IV/PO)	10,000 units/cc (6.25 mg/cc)	10	200,550 U/125 mg
180 (3 h)	13	200,000 U/125 mg (IV/PO)	40,000 units/cc (25 mg/cc)	5	400,550 U/250 mg
195	14	400,000 U/250 mg (IV/PO)	40,000 units/cc (25 mg/cc)	10	800,550 U/500 mg
210	15	800,000/500 mg (IV/PO)	40,000 units/cc (25 mg/cc)	20	1.6MU/1000 mg
225	16	800,000 (IV)	40,000 units/cc	20	2.4MU/
585	17	1,000,000 (IV)	40,000 units/cc	25	3.4MU/

After dose 17, then q 6 h without dose interruption

Requires the following penicillin concentrations: 100 unit/ml (0.0625 mg/cc); 1000 unit/ml (0.625 mg/cc); 10,000 unit/ml (6.25 mg/cc); 40,000 unit/ml (25 mg/cc); 1,000,000 unit/ml

PCN: VK: 125 mg = 200,000 units

No more than double the previous dose each time every 15 min. Decrease dose by a third if allergic reaction and continue to increase the dose

IV access and urgent medication (epinephrine, antihistamine, steroid). Double dose every 15 min IV

Increase dose in doses that are no more than double the previous dose at each administration. If a systemic reaction occurs, treat with epinephrine 0.3 mg IM of 1:1000. Then reduce the dose to a third the previous dose and slowly continue cautious increase in doses

Influenza Vaccine Allergy

The risk of an allergic reaction to influenza vaccine in a patient with egg allergy is very low, due to the very low amount of egg antigen (less than 1 mcg per 0.5 cc flu vaccine) in the vaccine in recent years. The risk of patients remaining unvaccinated is much higher than the theoretical allergic risk to the flu vaccine. Studies showed that the risk of allergic reaction due to the vaccine in egg-allergic patients is low. Skin testing with the vaccine and dividing the dose are not necessary. For those with a history of hives only after egg ingestion, full dose of the vaccine can be administered in the primary care office. For those with more serious reactions due to ingestion of egg, the vaccine should be administered in an allergist's office. In all cases, the patient should remain in the clinic for 30 min after vaccine administration and the practitioner should be prepared to treat anaphylaxis.

If the patient has a history of anaphylaxis secondary to vaccine, skin testing and divided dose of the vaccine may be necessary as determined by a trained allergist.

Tetanus Allergy

If an immediate type I allergic reaction occurs after tetanus immunization, a subsequent tetanus booster can be administered pending on skin testing result and possible desensitization. If skin testing is negative, 0.1 cc IM can be given then 0.4 cc IM 30 min later if the patient tolerates the previous dose. If skin testing is positive, tetanus desensitization is indicated starting from 1:1000 diluted tetanus vaccine. The rate of immunization can be given at weekly or biweekly intervals. For each administration day, up to five doses can be given every 20 min (Table 27.2).

Radiocontrast Anaphylactoid Reaction

If radiocontrast administration is medically indicated without other alternatives, premedication is indicated in addition to the usage of a lower osmolality radiocontrast (Table 27.3).

Table 27.2 Tetanus desensitization protocol

	1:1000 diluted dT	1:100 diluted dT	1:10 diluted dT	Undiluted dT
0 min	0.05 cc	0.05 cc	0.05 cc	0.05 cc
20 min	0.1 cc	0.1 cc	0.1 cc	0.1 cc
40 min	0.2 cc	0.2 cc	0.2 cc	0.15 cc
60 min	0.3 cc	0.3 cc	0.3 cc	0.2 cc
80 min	0.5 cc	0.5 cc	0.5 cc	

Note: May need to repeat the dose or to lower the dose if the patient has an allergic reaction. *dT* diphtheria-tetanus toxoid. May also use Tdap, tetanus/diphtheria/pertussis, in place of dT

Table 27.3 Radiocontrast pretreatment protocol

	Steroid	Antihistamine	Contrast agent
Non-emergent	Prednisone 50 mg PO 13 h, 7 h, and 1 h before procedure	Diphenhydramine 50 mg PO 1 h before procedure	Low osmolality
Emergent	Hydrocortisone 200 mg IV immediately and every 4 h until the procedure is completed	Diphenhydramine 50 mg IV 1 h before the procedure	Low osmolality

Local Anesthetic Reaction

True type I IgE-mediated allergic reaction is rare. Skin testing and test-dosing protocol are usually employed in order to assure that the patient can tolerate the anesthetic (Table 27.4).

NSAID Reactions

Aspirin-Exacerbated Respiratory Disease Figure 27.2 shows aspirin desensitization protocol in a patient who has AERD. Montelukast is frequently used to prevent airway complication. Antihistamine and decongestant are withheld to prevent the masking of rhinitis symptoms during the escalating phase of the desensitization. Onset of the symptom will confirm the diagnosis of AERD and thus successful desensitization and continuation of daily aspirin can improve a patient's respiratory

Table 27.4 Local anesthetic skin testing and test-dosing protocol

	Time Adm.	Site	VS BP//P	Prick test Erythema// Wheal// Result	Subcutaneous challenge Erythema// Wheal// Result
Diluent control				// //	Not applicable.
Histamine				// //	Not applicable.
*LA (undiluted) 0 min				// //	Not applicable.
*LA (0.1 ml of 1:100)@15min				Not applicable.	// //
*LA (0.1 ml of 1:10)@30 min				Not applicable.	// //
*LA (0.1 ml of 1:1)@45 min				Not applicable.	// //
*LA (1 ml of 1:1)@60 min				Not applicable.	// //
*LA (2 ml of 1:1)@75 min				Not applicable.	// //

*Local Anesthetic (LA) for Testing: 1 % Lidocaine HCL injection, USP 10 mg/ml (Preservative-Free)
LOT #:_____ EXP: _____

1) Local anesthetics used should be the same type to be used in the actual procedure;
2) Local anesthetics should have no epinephrine and no preservative;
3) Amount of dilution is designated as 1:1 (undiluted), 1:10 (10 fold dilution), 1:100 (100 fold dilution) using normal saline;
4) Erythema and wheal are measured in millimeter; result is histamine equivalent prick.

INTERPRETATION:
1) This patient has received 3 ml of the respective local anesthetic ( ) with no reaction and is at no greater risk for a subsequent allergic reaction than the general population (for the same type of local anesthetic tested without epinephrine and preservative).
2) Others:

_____
Dr.

Aspirin Desensitization Record

Dates: _____
Patient name:_____
Referral Doctor:_____ Primary Doctor: _____
Supervising physician for ASA desensitization: _____
Diagnosis (circled):Asthma Rhinitis Nasal polyps Anosmia Sinusitis AERD Anaphylaxis Urticaria Angioedema
(_____)
Type of Reaction to ASA/NSAID: _____
Indication for ASA desensitization:_____
Baseline FEV1 (>60% predicted & >1.5L): Yes/No (If no, treatment received to improve obstruction: _____)
Contraindication (pregnancy, unstable asthma, gastric ulcer, bleeding disorder): yes/no & if yes: _____

Date	Time	Dose of Aspirin (mg)	Symptoms	Nose	Throat	Skin	Lung	Vital Sign	PF/FEV1/FEF25-75%

Fig. 27.2 Aspirin-exacerbated respiratory disease desensitization protocol

Fig. 27.2 (continued)

Aspirin Desensitization Premedication and Treatment Record

Premedication: Montelukast 10 mg everyday starting 14 days before initiation of ASA desensitization: yes/no
Prednisone: yes/no and if yes, how much: _____

Asthma prophylaxis (usual controller + additional):

Rhinitis prophylaxis (usual controller + additional):

Medication to avoid: antihistamine x 3d, oral decongestant x 1d, short-acting bronchodilator x 4 hours before procedure

IV assess (saline) (good for 3 days after placement): yes/no

Escalation of aspirin: 20 mg, 40 mg, 80 mg, 100 mg, 160 mg, 325 mg, 650 mg every 2.5–3 hrs and 3 hrs observation after last dose before discharge to home; most reaction from 40 to 100 mg; if tolerating 325 mg, subsequent higher dose usually ok

Vital Sign (HR, bp, RR) q 1 h; PFT ½ h before each dose of aspirin

If reaction in larynx or bronchi, treat the reaction before repeating the dose that caused the reaction

If reaction limited to the nose, treat with oxymetazoline nasal spray then continue with next higher dose of aspirin

Target dose: ASA 650 mg two times per day for 1 month then taper by 325 mg monthly to the lowest 325 mg two times per day while maintaining improvement of upper and lower airway symptoms

Treatment: lung (beta agonist); Nasal (nasal antihistamine/decongestant); eye (pataday, etc); skin (antihistamine); GI (Pepcid); systemic reaction (epinephrine); hypotension (IV saline bolus)

Date	Time	Epinephrine SC/IM	Antihistamine PO/IM	Bronchodilator HHN	Bronchodilator nebulizer	Nasal Anti-histamine	Nasal Decong estant	Prednisone PO	Others

symptoms. The symptoms can be subsequently treated by antihistamine and decongestant in the clinic.

ASA/NSAID Single Drug-Induced Anaphylaxis If a patient has single drug-induced anaphylaxis as discussed above, he or she can tolerate another NSAID of different structure. The first dose, however, should be given in a doctor's office in case of anaphylaxis. If the reaction is a class effect, the patient may have to avoid all NSAIDs. If clinically indicated, ASA/NSAID desensitization can be performed by a specialist in the hospital.

Aspirin Challenge/Desensitization for a Patient Who Has Unstable Angina or Myocardial Infarction In a patient who has unstable angina or myocardial infarction with or without coronary stent placement, administration of aspirin is required. This presents a special problem in a patient who has a history of allergic reaction to aspirin. Table 27.5 shows the outline in managing this type of patient in the cardiac unit.

Table 27.5 Urgent aspirin desensitization protocol

Urgent aspirin challenge/desensitization for patient who is allergic to aspirin and who has unstable angina or acute myocardial infarction
1. AERD or not
(a) History
(b) Nasal exam
(c) Water view sinus (if patient has no sinusitis, AERD is unlikely)
2. If AERD: pretreat before challenge or desensitization
(a) Do not care about confirming diagnosis like in elective situation
(b) Want to prevent reaction in a patient who has active cardiovascular condition
(c) Montelukast to prevent lower airway reaction
(d) Inhaled steroid/LABA to prevent airway reaction
(e) Systemic steroid if patient has active asthma
(f) Antihistamine
(g) Start ASA at 40.5 mg (usually lower than provoking dose 60–90 mg)
(h) Repeat in 90 min: patient then received full 81 mg aspirin
(i) Treat reaction with beta agonist or IV antihistamine or other med
(j) Next day 81 mg then everyday
3. If not AERD: hives, rash
(a) Consider premedication with H1 antihistamine, H2 antihistamine, and montelukast
(b) Start 40.5 mg ASA also and repeat in 90 min
(i) Based on literature review and Scripps Clinic experience, ASA-induced anaphylaxis may not exist
(ii) Majority of patients with NSAID-induced cutaneous reaction will not react to 81 mg ASA
(iii) If practitioner concerns a very severe anaphylaxis based on history or the patient is hemodynamically unstable and may not tolerate an allergic reaction, one may start from 20.25 mg ASA
4. If cardiologist wants higher dose like 325 mg aspirin daily, one can escalate dose every 90 min: 121.1 mg, 202.5 mg, then 325 mg

Muscle Relaxant Reaction

Muscle relaxant allergic reaction accounts for 60–70 % of anaphylactic reactions during general anesthesia. Other causes to consider include latex, opioids, and antibiotics. A different muscle relaxant, especially one to which the patient has a negative skin test, should be used. It is preferable to use agents with lower histamine-releasing abilities like atracurium and pancuronium. Decreasing the rate of muscle relaxant administration may avoid cardiovascular collapse. Prior to general anesthesia, one should also premedicate patient with steroid (prednisone 50 mg orally 13 h, prednisone 50 mg orally 7 h, and hydrocortisone 200 mg intravenously 1 h prior to general anesthesia), an H1 receptor antagonist (diphenhydramine 50 mg IV 1 h before general anesthesia), and an H2 receptor antagonist (ranitidine 50 mg IV 1 h before general anesthesia).

Chemotherapeutic Agent Hypersensitivity

Table 27.6 shows the carboplatin desensitization protocol the author used to successfully desensitize a patient who is allergic to the agent.

Table 27.6 Desensitization protocol for carboplatin

Desensitization protocol for chemotherapy agent Carboplatin
Patient:_____Oncologists:_____PMD: _____

Premedication for allergic reaction

1. Evening before procedure (patient was given the medications)
    a. 10 mg Cetirizine
    b. 10 mg Montelukast
    c. 40 mg Prednisone
2. 1-2 hours before start of procedure
    a. 10 mg Cetirizine
    b. 10 mg Montelukast
    c. 20 mg Prednisone
    d. 150 mg Ranitidine

Premedication for chemotherapy chosen by oncologist (to be administered in ICU)

1. Ondansetron 8 mg within 15 min of the start of chemotherapy
2. Dexamethasone 8 mg IV within 15 min of the start of chemotherapy

Emergency medications available at patient's room

1. Epinephrine 1:1000 1 mg vial × 5 vials with IM needle/syringe available for 0.3. –0.5 cc increment doses
2. Benadryl for IV dosing: total of 100 mg available
3. Pepcid 20 mg IV available
4. Solumedrol 80 mg available on floor for IV dose
5. Albuterol nebulizer available: 2.5 mg/3cc vial × 5 ready to use (nebulizer machine available)
6. Oxygen available (nasal canula)
7. Usual resuscitation devices

Table 27.6 (continued)

Vital sign measurement

1. HR, bp, RR: baseline then eve ry 10 min x 3.5 h then every 15 min x 3 h, then every 30 min x 3 h, then every hour
2. Continuous oxygen saturation monitoring
3. Cardiac monitoring

Setting: ICU with MD present

Solutions to be prepared by pharmacy: Carboplatin

Carboplatin	Volume(ml or cc)	Concentration	Total amount (mg)
Solution 1	250 cc	0.012 mg/cc	3 mg
Solution 2	250 cc	0.12 mg/cc	30 mg
Solution 3	250 cc	1.2 mg/cc	300 mg

Desensitization: protocol for administration of Carboplatin

Step no.	**Solution no.**	**Rate (ml/h)**	**Time (min)**	**Volume infused per step (ml)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	1	2.0	15	0.50	0.006	0.06
2	1	5.0	15	1.25	0.015	0.075
3	1	10.0	15	2.50	0.03	0.105
4	1	20.0	15	5.00	0.06	0.165
5	2	5.0	15	1.25	0.15	0.315
6	2	10.0	15	2.50	0.30	0.615
7	2	20.0	15	5.00	0.60	1.215
8	2	40.0	15	10.00	1.20	2.415
9	3	10.0	15	2.50	3.00	5.415
10	3	20.0	15	5.00	6.00	11.415
11	3	40.0	15	10.00	12.00	23.415
12[a]	3	75.0	184.5	230.63	276.76	300.18

[a]Final cumulative dose and thus volume infused is determined by onc ologist and may be different for subsequent infusions

Total time: 349.5 min (5.825 h) and may be longer because of modification of above procedure by allergist during the desensitization period

Post-infusion monitoring: 6 h for this initial desensitization and may be shortened to 1.5 h in the future if the patient is doing well provided that he/she will carry epipen to go home in case of delayed allergic reaction

Evidence-Based Medicine

Chlorhexidine Allergy

Chlorhexidine is a disinfectant frequently used in the hospital setting to prevent infection. Chlorhexidine mouth care can reduce ventilator-associated pneumonia. Chlorhexidine is superior to povidone iodine in preventing surgical site infection (surgical hand scrub, skin cleansing, and preoperative bathing). Daily bathing with chlorhexidine can prevent central line-associated bloodstream infection. For center with high rate of central line-associated blood stream infection, use of chlorhexidine-coated catheter is advocated. In the outpatient setting, the chemical can be present in contact lens solution, mouth wash, and cosmetic. Based on PubMed search, there were 65 case reports of chlorhexidine-induced anaphylaxis. In the occupational setting, chlorhexidine-induced asthma has been reported. In a study in the UK reported by Nagendran et al., in 2009, 4 out of 86 health care workers (5 %) were confirmed to have chlorhexidine-induced skin rash. Although the incidence of chlorhexidine allergy is unknown, limited data showed that it may not be uncommon. A patient can present with urticaria or anaphylaxis of unknown cause. Clinicians have to keep this occult allergen in mind in evaluating a patient with urticaria or anaphylaxis. Serum-specific IgE for chlorhexidine or prick skin test using 0.05 % chlorhexidine may be helpful to confirm the diagnosis.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS is a rare, severe multi-organ adverse drug reaction. The syndrome is defined as the presence of fever, skin eruption, leukocytosis, eosinophilia, lymphocytosis, and systemic involvement including hepatitis, pulmonary infiltration, heart failure, and interstitial nephritis. The condition has a late onset up to 2–6 weeks after initiation of a specific drug and may persist for several weeks to even months. Funck-Brentano et al. in France conducted a retrospective study of 38 patients with confirmed DRESS syndrome from March 2005 to June 2009. In this study, the most common suspected causal drugs were allopurinol (34 %), antiepileptic drugs (26 %), sulfonamides (11 %), and minocycline (8 %). All subjects who had DRESS had cutaneous symptoms including exanthematous eruption, facial edema, purpura, pustules, erosions, or blisters. Seventy-nine percent of the subjects had fever. All subjects had hematologic abnormalities including leukocytosis, eosinophilia, atypical lymphocytes, or thrombocytopenia. Seventy-nine percent of the patients had lymphadenopathy involving more than two sites. Seventy-six percent of the subjects had hepatic involvement and 55 % had renal involvement. Twenty-one percent had pulmonary involvement and 8 % had cardiac involvement. Other less common systemic involvements included the gastrointestinal tract and nervous system. About

47 % of the subjects had evidence for viral reactivation including human herpes virus six, EBV, and CMV. Viral reactivation tended to occur more frequently in the group that had more severe presentation requiring systemic steroid than in the group that had less severe presentation requiring topical steroid. The more severe group which required systemic steroid also had a higher chance of infection or septicemia. In this study, the group of patients who was put on potent topical steroid tended to have milder form of DRESS. The group of patients who was put on systemic steroid tended to have more severe DRESS with visceral organ failure. It is not clear in this study whether it is the severity of DRESS or the usage of systemic steroid is the cause for higher chance of infection or viral reactivation. Of course, removing the offending drug that causes DRESS is most important. For less severe DRESS, the study showed that systemic steroid may not be required and potent topical steroid is sufficient for skin symptoms.

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Chapter 28
Smoke, Pollution, and Allergy

Jason Casselman, Massoud Mahmoudi, and Haig Tcheurekdjian

Introduction

The development and exacerbation of allergic disease are a multifaceted process involving an interplay between genetic and environmental factors. Airborne pollutants are nearly ubiquitous environmental hazards that have long been recognized as contributors to poor health outcomes in many disease processes. Recently, airborne pollutants have been implicated in the manifestations of allergic disease, especially those affecting the airways, such as asthma. The role of pollution in allergic disease is complex, and its effects vary based on a number of factors including the type of pollution and the attributes of the individual exposed to the pollution.

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Characteristics of Pollutants

Indoor Versus Outdoor Pollution

Pollution is generally categorized as being either indoor or outdoor pollution, although there is overlap between the two types. Most people spend the majority of their time indoors whether they are at home, school, or work; therefore, exposure to indoor pollutants is a significant problem. Common sources of indoor air pollutants are tobacco smoke, appliances (i.e., gas stoves, fireplaces), and building and renovating materials such as paint. Environmental tobacco smoke, also known as secondhand smoke, is the most prevalent of all the indoor pollutants and has been shown to increase the risk of a number of disorders including asthma. Fortunately, some of these sources are being diminished such as through bans on indoor smoking. Nonetheless, the levels of many indoor pollutants may be up to 2–5 times higher than those found outdoors, and indoor levels can even reach 1000 times higher than outdoor levels immediately after certain activities, such as paint stripping. Exposures to indoor pollutants may also be prolonged due to the more energy-efficient, airtight building designs being used today that do not allow air to circulate as efficiently between the indoor and outdoor environments. Although these building designs bring benefits such as a reduction in heating and cooling expenditures, they also do not allow pollutants generated indoors to escape to the outdoor environment.

Outdoor air pollution has been the subject of intense research because of its public health implications and the potential health benefits that can be achieved on a national scale if exposure to these pollutants is reduced. To this end, the Environmental Protection Agency of the United States has set the National Ambient Air Quality Standards (NAAQS) which identify and set the national standards for acceptable levels of major outdoor pollutants that are considered to be harmful to health. Four of the six pollutants identified in the NAAQS are known contributors to the exacerbation of asthma or allergic disease (Table 28.1). The NAAQS is periodically reviewed by the Environmental Protection Agency, and changes to these standards are designed to increase protection of public health and welfare.

It is important to note that pollution is frequently a complex mixture of various pollutants; therefore, its effects are significantly more complex than those of a single pollutant listed by the NAAQS. For example, diesel exhaust contains numerous pollutants, including particulate matter, nitrogen dioxide, and carbon monoxide, that may act in concert to initiate or worsen disease.

Actions of Pollution

In general, pollution can interact with allergic disease in three ways: by contributing to the development of disease, the exacerbation of established disease, or both (Fig. 28.1). A single pollutant may act alone in all of these processes, as seen with

Table 28.1 Outdoor pollutants identified by the National Ambient Air Quality Standards

Known contribution to asthma or allergic disease	**Major sources**
Nitrogen dioxide	*Primary*: fossil fuel use by automobiles *Secondary*: fossil fuel use by power plants, industrial plants, commercial plants
Ozone	Precursors produced by fossil fuel use by automobiles and industrial emissions
Particulate matter	*Primary*: fossil fuel use by power plants and automobiles *Secondary*: construction sites, fires, unpaved roads
Sulfur oxides	*Primary*: fossil fuel use by power plants *Secondary*: petroleum refineries, cement manufacturing, metal processing facilities, locomotives, large ships
No known contribution to asthma or allergic disease	**Major sources**
Carbon monoxide	*Primary*: fossil fuel use by automobiles *Secondary*: fossil fuel use by non-road vehicles (construction, boats, etc.), chemical processing
Lead	*Primary*: metal processing plants *Secondary*: fossil fuel use by power plants, waste incinerators

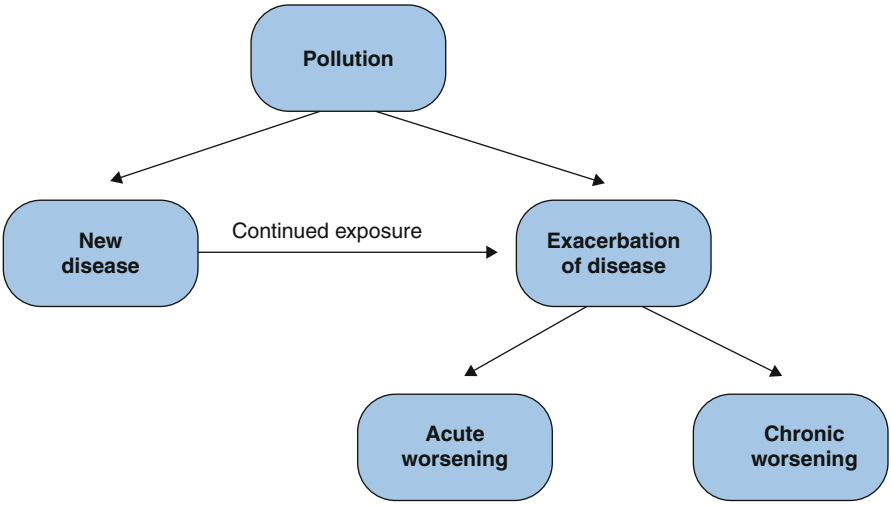

Fig. 28.1 Effects of pollution on allergic disease

tobacco smoke which contributes to both the development of asthma in exposed children and the exacerbation of asthma in individuals who already have the disease. On the other hand, pollutants may act in concert to initiate and exacerbate disease. For example, a child may develop asthma secondary to exposure to tobacco smoke and then develop an asthma exacerbation upon exposure to high levels of ozone.

The actions of pollutants are multifactorial. They can act in a nonspecific manner to worsen allergic disease, such as acting as simple irritants to worsen allergic rhinitis symptoms (see Chap. 6), or they can act in a more specific manner by contributing to allergic inflammation through the production of reactive oxygen species (ROS). This oxidative stress sets off a cascade of events marked by the production of pro-inflammatory products, which leads to the induction of Th2 responses and the downregulation of Th1 responses (see Chap. 1), both of which can promote the expression of allergic disease.

Characteristics of Individuals

The deleterious health effects of pollution are not only dependent on the specific features of the pollutant but also the features of the exposed population. Emerging research has shown an association between the genetic makeup of particular individuals and a predisposition to the development of allergic disease from pollution. Since airway inflammation and the response to oxidative stress are known to be genetically regulated, the variability of genes encoded to handle oxidative pathways is thought to contribute to the varying degrees of adverse health effects. In addition to genetic factors, the age of the exposed individual is one of the most important factors contributing to the effect of pollutants on an individual. The time period beginning in fetal life and extending throughout childhood is a period of marked vulnerability because this is when the respiratory tract and immune system are undergoing development and maturation. Furthermore, children usually have higher exposures to outdoor pollutants because they spend a larger portion of their time outdoors compared to adults. Children also have higher minute ventilation than adults leading to increased exposure to inhaled pollutants.

Respiratory Tract Development

The respiratory tract is only partially developed at birth and undergoes rapid changes postnatally. Development of the paranasal sinuses has only begun at birth with the presence of rudimentary ethmoid sinuses and early pneumatization of the maxillary sinuses. Complete development and pneumatization of all the sinuses do not occur until adolescence. Likewise, the lungs undergo significant changes after birth. Although the lungs are functional at birth, they are structurally immature with only a fraction of the alveoli present that will be present in adulthood. During the first 4 years of life, significant septation of the lung parenchyma occurs with the number of alveoli increasing by greater than tenfold. Pulmonary development continues to progress throughout adolescence with complete development being attained only in early adulthood. Due to the immaturity of the respiratory tract in utero and during childhood, exposure to pollution during this time period has the ability to alter

normal pulmonary development, potentially leading to adverse consequences for an individual's entire life. These adverse effects are not theoretical but are well-described events that will be discussed later in this chapter.

Immune System Development

Similar to the respiratory tract, the pediatric immune system is immature at birth and undergoes significant changes in the first few years of life. The healthy adult immune system maintains a fine balance between Th1 immune responses, which are important in cell-mediated immunity, and Th2 immune responses, which are important in humoral immunity and the development of allergic diseases. Infants naturally have a Th2-polarized immune system which later matures into an immune system which produces balanced Th1 and Th2 responses. Furthermore, atopic children maintain a Th2-polarized immune system for a longer period of time compared to nonatopic children indicating the central role of Th phenotype in allergic disease. Because the immune system continues to mature throughout early childhood, this is a time period during which children may be at heightened risk for the inappropriate skewing of immune responses toward the allergic, Th2 phenotype.

Specific Pollutants

In the following sections we will be reviewing the evidence implicating the role of various pollutants in the development of allergic disease and asthma. Tobacco smoke and diesel exhaust, two pollutants with complex mixtures of various compounds, will be discussed first, followed by the discussion of the four key pollutants affecting allergic disease identified in the NAAQS.

Tobacco Smoke

Exposure to tobacco smoke can occur through an active or passive process. Active exposure is through smoking a cigarette or other tobacco products. Passive exposure occurs by inhaling sidestream smoke (smoke released from the burning end of the cigarette) or inhaling smoke exhaled by the active smoker. This is referred to as secondhand smoke or environmental tobacco smoke (ETS).

ETS consists of a complex combination of hundreds of chemicals and pollutants. Exposure to ETS has been linked to numerous health problems affecting every age group starting from in utero development through adulthood. These health problems include intrauterine growth retardation, low birth weight, sudden infant death

syndrome, asthma, otitis media, pneumonia, chronic obstructive pulmonary disease, cardiovascular disease, and cancer. Both the conducting airways and lung parenchyma can be adversely affected during development by the effects of tobacco smoke. In sudden infant death syndrome patients, inner airway wall thickening is more severe in patients with smoking mothers, compared to nonsmoking mothers, suggesting airway remodeling due to in utero and early postnatal exposure. In regard to allergic disease, ETS has been shown to both cause and exacerbate allergic diseases and asthma.

Disease Development

Current evidence supports a causal relationship between in utero exposure to tobacco smoke and disruptions of fetal airway development. While gathering randomized data on smoking during pregnancy is difficult due to ethical concerns, the majority of studies demonstrate in utero tobacco smoke negatively influences respiratory function. In utero tobacco smoke exposure has been shown to be an independent risk factor in the development of asthma, wheeze, and impaired lung function. One meta-analysis demonstrated an increased risk of asthma at 6 years old, in children exposed to antenatal tobacco smoke. In addition to its harmful in utero effects, data also favors an association between ETS and asthma development. Variability exists in clearly defining asthma end points for study among researchers, and this has contributed to some inconsistencies among studies. The vast majority of research, however, supports the link between ETS exposure and an increased risk of asthma. Postnatal tobacco smoke exposure has been shown to increase risk of asthma development among children ages 6–18 years old. ETS exposure also increases both total and allergen-specific serum IgE levels, potentially contributing to the development of other allergic diseases. It is estimated that up to 26,000 cases of childhood asthma in the United States are secondary to exposure to ETS.

Disease Exacerbation

ETS exposure has long been linked to worsening of asthma symptoms and increased emergency department visits. A large body of research has evaluated the respiratory effects of involuntary ETS exposure; however distinguishing between acute and chronic ETS exposure can be difficult and has only been undertaken in adult subjects, using controlled chamber studies. For this reason, observational studies performed are considered to represent chronic ETS exposure.

Previously, studies favored a causal relationship between ETS exposure and asthma exacerbation. More recently, studies suggest the two are strongly associated, but ETS may not be a causal factor in isolation. For example, studies involving preschool-aged children failed to show a causal relationship between ETS and worsening asthma. Similarly, in older children and adults, ETS exposure has not consistently been demonstrated to worsen asthma symptoms. Conversely, in a study

of minority groups affected by asthma, in utero tobacco smoke exposure led to a higher incidence of persistent asthma in Mexican, Puerto Rican, and black patients, as well as poor asthma control in Latino and black patients. Recently published cross-sectional studies and one prospective study were able to demonstrate a worsening of asthma control and more frequent exacerbations in children exposed to ETS. Taken as a whole, these studies suggest that ETS exposure is associated with poor asthma control and asthma exacerbations in susceptible individuals, and these susceptibilities may be related to other environmental exposures or genetic factors. The lack of consistent concrete causal evidence despite the presence of the clear association that has been shown between ETS and asthma exacerbations is likely further compounded by inconsistent reporting of ETS by patients or their caregivers. A clear discrepancy has been shown between patient reporting of ETS exposure, in the form of parental surveys, and measurements of salivary cotinine levels, a nicotine metabolite.

ETS can also exacerbate allergic rhinitis and allergic conjunctivitis. ETS can act as an ocular irritant. In fact, ocular irritation is one of the most commonly reported effects of ETS by nonsmokers. The effects of ETS on the eye may be secondary to its ability to disrupt the thin, protective film of tear on the cornea. This is supported by experiments that document instability of the tear film after exposure to ETS and an increase in blinking and lacrimation (tearing), both of which act to reestablish the protective film of tear on the cornea. Although few studies have looked at ETS as the primary variable contributing to allergic conjunctivitis, symptoms of eye irritation and itching or tearing of the eyes have clearly been demonstrated in multiple studies on ETS-exposed patients.

Rhinitis symptoms also develop in many individuals upon exposure to ETS. ETS exposure can lead to the development of rhinorrhea and nasal congestion, and these symptoms coincide with objectively measured end points such as nasal airway resistance. Additionally, ETS promotes the production of allergen-specific IgE antibodies in nasal lavage, a hallmark of allergic rhinitis. Although these symptoms can occur in any individual upon exposure to ETS, they tend to be found predominately in atopic individuals.

Although different disorders of the respiratory tract have traditionally been thought of as isolated diseases, it is clear that disease activity in one part of the respiratory tract can adversely affect other parts. In other words, the respiratory tract may be envisioned as a unified system instead of as a combination of different components (i.e., nose, sinuses, lungs, etc.). For example, an episode of acute sinusitis, a disorder of the upper respiratory tract, can contribute to the development of an asthma exacerbation, a disorder of the lower respiratory tract. This concept of a unified respiratory system also extends to the effects of ETS, in that the effects of ETS that do not immediately affect the nasal cavity or lungs may still lead to exacerbations of allergic rhinitis or asthma. For example, evidence suggests the incidence of otitis media, adenoid hypertrophy, tonsillitis, and bronchitis is higher in children exposed to ETS in the home compared to those that are not. Secondary to the effects of the unified respiratory system, these disorders may contribute to the exacerbations of allergic rhinitis and asthma.

Diesel Exhaust

The burning of fuel by motor vehicles is one of the largest sources of airborne pollutants, and diesel exhaust accounts for a large portion of this pollution. Diesel exhaust consists of diesel exhaust particles (DEP) and gaseous combustion products. DEP are carbon particles of 0.1 μm or less to which numerous chemicals produced in the combustion process or already present in the atmosphere can attach. While each DEP particle is less than 0.1 μm, particles tend to combine to form aggregates with diameters of less than 0.25 μm. Gaseous combustion products include nitrogen dioxide, carbon monoxide, and hydrocarbons that are precursors to ozone production.

Like ETS, diesel exhaust has been linked to numerous adverse health outcomes including cardiovascular disease, leukemia, lymphoma, lung cancer, and wheezing. In regard to allergic disease, diesel exhaust is associated with the development and exacerbation of asthma, the promotion of sensitization to new allergens, and the enhancement of the allergic response to antigen.

Disease Development

There is significant epidemiologic and clinical research data indicating that exposure to diesel exhaust leads to the development of allergic disease. Accurate measurement of diesel exhaust exposure is difficult; therefore, studies have used proximity to automobile traffic and similar measures as a proxy for the measurement of diesel exhaust exposure. Infants exposed to traffic-related pollutants have 2.5 times the prevalence of wheezing compared to a nonexposed population. Of note, it is the proximity to traffic and the type of traffic (stop-and-go bus and truck traffic) that are the most significant risk factors for the development of disease, not the volume of traffic. Likewise, older children with exposure to traffic-related pollution have a prevalence of asthma twice as high as that compared to an unexposed population. As with asthma, exposure to DEP has been linked to the development of allergic disease. This has been clearly demonstrated in murine models in previous studies and more recently in humans where increased rates of allergic sensitization are found in individuals exposed to higher amounts of traffic-related pollutants.

From a mechanistic standpoint, there are numerous studies investigating the methods by which diesel exhaust induces the development of allergic disease. When atopic individuals are given an intranasal challenge of a new allergen plus DEP, they produce IgE specific to the allergen and upregulate Th2 cytokine production. On the other hand, atopic individuals challenged with a new allergen alone do not produce allergen-specific IgE, and there is no change in Th2 cytokine production. It has also been demonstrated that challenging individuals with DEP plus ragweed induces B lymphocytes producing ragweed-specific immunoglobulin to switch from the production of IgM to the production of IgE. This switch did not occur with challenge with ragweed alone. Therefore, diesel exhaust promotes the development of new

allergic disease by inducing the immune system to produce Th2-polarized responses to new allergens and inducing the production of allergen-specific IgE.

Disease Exacerbation

In addition to being associated with the development of disease, exposure to traffic-related pollution is also associated with exacerbations of asthma. High levels of DEP exposure in children with allergic asthma result in more frequent symptoms over a 12-month period. The role of diesel exhaust in the exacerbation of asthma is described in detail in the sections below discussing the individual pollutants which are products of combustion (i.e., particulate matter, nitrogen dioxide, ozone). In general, increased exposure to traffic-related pollution increases the risk of asthma exacerbations for both children and adults.

Multiple mechanisms by which diesel exhaust exacerbates allergic disease have been elucidated. In individuals sensitized to an allergen, challenge with that particular allergen plus DEP leads to the augmented production of IgE and Th2 cytokines and downregulation of Th1 cytokines. This shift in immunoglobulin and cytokine production is a potent promoter of allergic inflammation. Furthermore, DEP augments mast cell degranulation leading to increased amounts of mast cell mediators being released from activated mast cells. DEP also alters the secretion pattern of various cytokines leading to alterations of cellular infiltration of tissues, such as the respiratory epithelium. This may promote allergic inflammation, leading to disease exacerbation.

Nitrogen Dioxide

Nitrogen dioxide (NO_2) is a precursor to smog and ozone. It is both an important outdoor and indoor pollutant. Most NO_2 is produced by the burning of fossil fuels by automobiles, but other important outdoor sources include fossil fuel combustion by power plants and other industrial sources. Natural gas-burning stoves are a major indoor source of NO_2.

Although earlier studies evaluating the role of NO_2 in allergic disease have been conflicting, more recent data suggests that NO_2 does significantly influence the occurrence of asthma on elementary school-aged children. Exposure to NO_2 in the air significantly influences the development of childhood asthma and symptoms of wheezing. In addition to asthma development, NO_2 plays a role in the exacerbation of established disease. Indoor exposure from appliances using natural gas has been associated with an increased incidence of coughing and wheezing, and outdoor exposure has been linked to asthma exacerbations and diminished pulmonary development. NO_2 has also been shown to augment the allergic response to allergen when subjects are pretreated with NO_2. In addition to these direct effects, NO_2 also reacts with sunlight and hydrocarbons in the atmosphere to produce ozone, another important pollutant, discussed below.

Ozone

Ozone (O_3), which is naturally found in the upper parts of the atmosphere, has the beneficial effect of protecting the Earth's surface from ultraviolet radiation produced by the sun. On the other hand, O_3 is toxic when it is present in the lowest layer of the Earth's atmosphere, known as the troposphere. As described above, ground-level O_3 is produced primarily by the interaction of sunlight with by-products of fossil fuel combustion, namely, NO_2 and hydrocarbons. O_3 is a well-studied pollutant and has been associated with numerous adverse health outcomes including both the development and exacerbation of asthma.

Disease Development

In general, the evidence is lacking to sufficiently characterize O_3 as a causative agent in the development of asthma. Studies have shown variable results with regard to O_3 exposure and asthma prevalence in children. In a cohort of nearly 2500 asthma-free kindergarten and first-grade children with 3 years follow-up to evaluate the relationship between new-onset asthma and traffic-related pollution near homes and schools, there was no evidence to support that regional O_3 exposure leads to the development of asthma. On the contrary, a well-conducted study investigated the role of O_3 and other air pollutants on the incidence of asthma in children in southern California. Over 3500 children without asthma were followed prospectively for up to 5 years to determine if O_3 exposure had an effect on the prevalence of asthma. The investigators discovered that children who spent a large amount of their time playing outdoor sports in areas with high O_3 levels had greater than three times the risk of developing asthma than children who did not play outdoor sports. Outdoor sports activity had no effect on the development of asthma in areas with low O_3 levels suggesting increased exposure to O_3 may contribute to increased risk of asthma. Given the lack of consistent evidence directly pointing toward O_3 as a risk factor for asthma development, O_3 is not considered to be one of the pollutants strongly associated with increased asthma prevalence.

Disease Exacerbation

Despite the inconsistent evidence for disease development, the exacerbation of asthma secondary to exposure to O_3 is well documented in numerous studies. Chronic exposure to ambient O_3 is associated with a significantly increased risk of asthma hospitalizations. In addition to the deleterious effects of chronic exposure, short-term exposure to O_3 has also proved harmful. Hospital admissions for respiratory symptoms and emergency department visits for asthma exacerbations increase during periods of exposure to elevated O_3 levels. The use of asthma medications has also been reported to increase by nearly two times during periods of elevated O_3

levels compared to periods of time with low levels. An interesting event highlighting the effect of O_3 on asthma exacerbations in children occurred during the 1996 Summer Olympics in Atlanta, Georgia. During the Olympics, the city instituted citywide alternative traffic measures including expanded public transportation services and closure of the downtown area to private automobiles in an effort to decrease traffic congestion. These efforts led to a 28 % decrease in O_3 levels associated with a greater than 40 % decrease in emergency department visits and hospitalizations secondary to asthma exacerbations. This study not only highlights the adverse effects of high levels of O_3 but also demonstrates that reasonable changes in public policy can have a large positive impact on public health.

Of note, there may be up to a 2-day interval between O_3 exposure and an increase in asthma exacerbations indicating that the effects of O_3 on the respiratory system are more complex than just an irritant or bronchoconstrictive effect. This has been borne out in a number of studies involving challenges with O_3. O_3 exposure does lead to a rapid decrease in pulmonary function, but it also leads to pulmonary neutrophilic inflammation lasting for up to 1 day after exposure. In addition, studies have supported the notion that O_3 contributes to increased innate immune activation in asthmatics. This mix of bronchoconstriction plus tissue inflammation describes mechanisms by which O_3 exposure can lead to both early and delayed respiratory symptoms.

Particulate Matter

Particulate matter (PM) consists of tiny solid particles or liquid droplets that are suspended in the air and are, therefore, respirable. PM is classified into categories based on size by the US Environmental Protection Agency: <0.1 μm (ultrafine), 0.1–2.5 μm (fine), and 2.5–10 μm (coarse). PM >10 μm in diameter is not of significant concern in older children and adults because it is filtered out by the upper respiratory tract during nasal breathing. These particles may pose a problem for younger children because they are frequent mouth breathers, and the particles can therefore deposit in the lower respiratory tract. PM <0.1 μm (ultrafine) is found in relatively low levels in the environment because these particles tend to agglomerate quickly after production, yielding PM of larger sizes. When agglomeration does not occur, however, ultrafine PM can be inhaled deep into the small airways and alveoli of the lungs directly. This deposition causes penetration through the alveolar epithelial-endothelial layer, with the potential for hematogenous spread and adverse effect on a variety of organs. For example, a recently published study found that increased concentration of ultrafine particulate matter was associated with autonomic heart dysfunction in prediabetic and diabetic patients. On the other hand, PM <10 μm and <2.5 μm are considered significant pollutants because they are of a size that can easily penetrate the upper respiratory tract and deposit in the lungs, particularly PM <2.5 μm. Furthermore, PM <2.5 μm can remain airborne for many days, allowing it to be carried for many miles from its source of production.

PM is a major product of fossil fuel combustion and can be derived from a variety of traffic-related and industrial sources. PM is not a homogeneous pollutant, but rather is a combination of numerous constituents including metal ions, hydrocarbons, sulfates, nitrates, crustal materials (i.e., soil and ash), and biological contaminants. Furthermore, the composition of PM varies on a national scale due to its production from various sources in different locations. Due to this heterogeneous composition, it is difficult to identify the specific components that lead to adverse health outcomes. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study, however, tried to identify the importance of the different PM constituents using questionnaires, as well as lung function and allergic sensitization measurements in pediatric patients. The results indicated that certain PM constituents, particularly iron, copper, and zinc, increased the risk of allergy and asthma in school-aged children.

Disease Development

Epidemiologic studies have shown a correlation between increased levels of traffic-related air pollution and the incidence and prevalence of allergic disease. One study performed annual questionnaire reports on 3863 children during the first 8 years of life and estimated individual exposures to various pollutants, including particulate matter (PM) <2.5 μm. PM <2.5 μm levels were associated with an increased incidence and prevalence of asthma, as well as an increase in asthma symptoms. Increasing exposure to PM <10 μm has also been shown to be associated with an increased risk of developing allergic rhinitis. While further investigation is required to clearly define the role of PM in the development of allergic disease, it appears PM may be a risk factor for the development of a variety of allergic conditions.

Disease Exacerbation

Exposure to high levels of PM is associated with adverse outcomes in asthma. There is evidence that both short-term and long-term exposure to fine and ultrafine particulate matter can have detrimental effects on asthma symptomatology. There is an association between particulate matter exposure, as measured by air quality data, and increased asthma symptoms in children and adults. Elevated ambient PM levels have been associated with an increased number of hospitalizations secondary to asthma exacerbations in studies conducted in a number of countries. Elevated PM levels also lead to worsening asthma control as evidenced by increased nighttime symptoms, increased variability in peak expiratory flow rates, and lower forced expiratory volumes in 1 s. These effects may be more prominent in more severe asthmatics, defined as those requiring inhaled corticosteroids. PM exposure also leads to an increased need for asthma medication use and to increased hospitalizations secondary to respiratory infections.

Sulfur Oxides

Sulfur dioxide (SO_2) is the primary sulfur oxide implicated in causing adverse outcomes in respiratory diseases. SO_2 is an air pollutant derived from combustion of fossil fuels. Although SO_2 is primarily produced by fossil fuel-fired power plants, it is also a by-product of numerous industrial processes; therefore, significant occupational exposures can occur in addition to environmental exposures.

Disease Development

While the adverse effect of SO_2 on respiratory morbidity has been more completely defined, the association between exposure and asthma development has been more difficult to identify. Although mechanistic studies in humans are lacking, multiple animal studies have explored the mechanism by which SO_2 affects airway hyperresponsiveness (AHR). One particular study investigated the effects of chronic SO_2 exposure on AHR, airway inflammation, tissue remodeling, cell stiffness, and contractility of the airway smooth muscle on newborn rats. Comparisons were made between two groups of rats, those sensitized to ovalbumin (used as a model to mimic asthmatic symptoms) and normal rats. Ovalbumin-sensitized rats exposed to SO_2 exhibited increased AHR, airway smooth muscle mass, contractility, and stiffness compared to normal rats. In humans, occupational exposures to SO_2, such as in petroleum refineries, can lead to exposure to very high levels of the gas, which has been associated with nearly six times the risk of being diagnosed with asthma as compared to a nonexposed population. Exposure to the much lower levels of SO_2 found in the atmosphere is also associated with allergic disease and asthma. In school-aged children in France, a positive association was found between increasing levels of SO_2 exposure and the odds of being diagnosed with asthma or allergic rhinitis.

Disease Exacerbation

Studies evaluating the effects of SO_2 on respiratory morbidity have produced convincing evidence for an adverse association. According to the National Ambient Air Quality Standards put forth by the Environmental Protection Agency, a large body of evidence shows a causal relationship between SO_2 exposure and respiratory morbidity. Elevated SO_2 levels have been shown to increase the rate of hospitalization for asthma exacerbations in school-aged children. Further evidence has shown that the bronchoconstrictive response to SO_2 in asthmatic patients is concentration dependent, with increased responses to SO_2 concentrations between 0.2 and 1.0 ppm. As with O_3, this lag period until the onset of symptoms in certain individuals indicates that the effects of SO_2 on asthma exacerbations are complex and likely involve both bronchospastic and immunologic effects. One study sought to identify

possible mechanisms for these effects by examining asthma-related gene expression in human bronchial epithelial cells exposed to SO_2. Exposure to SO_2 resulted in higher ICAM-1 levels and increased EGF and EGFR expression, both of which have been implicated in the pathogenesis of asthma.

Much of the difficulty in finding associations between SO_2 exposure and asthma outcomes has been the difficulty in separating the effects of SO_2 from other pollutants. Furthermore, ambient SO_2 can lead to the formation of sulfuric acid aerosols which may themselves contribute to asthma exacerbations leading, in turn, to difficulties in gauging the true effects of SO_2.

In studies where individuals are intentionally challenged with SO_2, exposure has been shown to lead to bronchospasm and drops in measurements of pulmonary function. These findings have been accompanied by symptoms of wheezing and dyspnea. Furthermore, exposure to other pollutants, such as O_3, can increase the severity of adverse effects asthmatics experience upon exposure to SO_2.

Conclusions

Indoor and outdoor pollutants can lead to both the development and exacerbation of allergic disease and asthma. The effects of these pollutants can occur in utero or in early childhood, potentially leading to lifelong morbidity from allergic disease or asthma. Furthermore, these pollutants can lead to exacerbations of disease throughout an individual's life. Public policy changes to curb the adverse effects of airborne pollutants can lead to significant public health benefits by decreasing the morbidity associated with allergic and respiratory diseases.

Evidence-Based Medicine

The adverse effects of exposure to ultrafine PM were recently investigated by Peters et al. Ambulatory electrocardiograms were obtained on 64 individuals with type 2 diabetes and impaired glucose tolerance on 191 occasions over a 5–6-h time period. Personal exposure to particle number concentrations (PNC) during a 5-min time period was measured on each individual, as well as central monitoring of acquired PM <2.5 μm on an hourly basis. The results of the study showed heart rate variation associated with personally measured PNC and ambient PM <2.5 suggesting freshly emitted ultrafine PM and aged aerosol in urban areas are associated with changes in cardiac function.

Pedersen et al. evaluated the effects of low concentrations of ambient air pollution on low birth weight. Data was pooled from 14 population-based mother cohort studies in 12 European countries. Seventy-four thousand one hundred seventy-eight total women were included in the study from 1994 to 2011. Mean concentrations of PM with aerodynamic diameters of <2.5 μm, <10 μm, and 2.5–10 μm during

pregnancy were estimated at home addresses. Results of the study showed that a 5 μm/m^3 increase in concentration of PM <2.5 was associated with increased risk of low birth weight at term. These findings suggest air pollution and traffic exposure during pregnancy could contribute to restricted fetal growth.

While atopic dermatitis is one of the most prevalent of all the allergic diseases, it is less commonly the subject of intense research. Several cross-sectional and birth cohort studies have been performed, however, that indicate air pollution may contribute to atopic dermatitis prevalence. In one cross-sectional study involving 4907 French children aged 9–11 years old, with 3 or more years at their current residence, lifetime eczema was significantly associated with 3-year averaged concentrations of CO, NO_2, NO_x, and PM <10. In addition, two birth cohort studies were performed by Morgenstern et al. in Munich. Two thousand eight hundred sixty children at age 4 years old and 3061 children at age 6 years old were included in the two studies. Long-term exposure to PM <2.5, NO_2, and PM <2.5 adsorbance was evaluated using geographical information systems and air pollution measurements. A surrogate for traffic-related air pollution of distance to the nearest main road was used. Results of the studies showed strong positive associations between distance to the nearest main road and presence of atopic dermatitis.

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Chapter 29
Sick Building Syndrome

Massoud Mahmoudi

Exposure of building occupants to an unhealthy and hazardous environment may cause various symptoms, collectively known as "sick building syndrome." Any chemical, gas, fume, or smoke may potentially cause sickness or illness in occupants of such buildings; the term sick building syndrome, however, is usually referred to as nonspecific symptoms resulting from exposure to molds, bacteria, and their toxins or products. Many articles have associated the black mold "*Stachybotrys chartarum*" also known as "*Stachybotrys atra*" to this syndrome. However, the cause and effect has never been confirmed.

Is Sick Building Syndrome an Allergic Condition?

Although this syndrome is not an allergic condition, some of the symptoms mimic those of allergic rhinitis and allergic asthma. The affected individuals suffer from irritation and the effects of inhaled organisms, or their toxic by-products. Individuals with preexisting allergic rhinitis or asthma may experience exacerbation of their symptoms, while those without such conditions remain at risk for developing indoor allergies.

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Etiology of Sick Building Syndrome

Although no single organism or substance has been identified as a cause of this syndrome, mold exposure and specifically *Stachybotrys chartarum* have been mentioned more than the other organisms in the literature. The toxicity of this mold is due to the production of potent and lethal toxins known as stachybotryotoxin. Other factors such as poor building ventilation, polluted indoor air with chemicals such as detergents, pesticides, or others may also contribute to these nonspecific health problems.

Stachybotrys Chartarum and Human Diseases

In 1931, a disease of unknown etiology caused mortality of horse population in several villages in Ukraine. The etiology of this disease remained unknown until 1938 when investigators associated the disease with *Stachybotrys chartarum*. It turned out that the straws fed to animals were contaminated with *Stachybotrys* toxin.

In the 1990s, Center for Disease Control (CDC) published series of reports on "infant pulmonary hemorrhage/hemosiderosis" occurring in different regions of the United States; the reports noted that the affected individuals were living in unhealthy, moldy environments. However, the link between *Stachybotrys chartarum* and the infant pulmonary hemorrhage was never established.

Where Are the Molds Found?

Molds typically live in outdoor environments. They generally get indoors through open doors or windows. They can also attach themselves to hair, clothing, or pets and find their way indoors. When they get indoors, they settle on wet and damp surfaces. They need a humid environment and a constant source of moisture such as water leakage from a pipe or roof to grow. *Stachybotrys chartarum*, specifically, use materials that are rich in cellulose and low in nitrogen content as a nutrient source. Therefore, any object with such nutrients is subjected to mold contamination. Some examples of household materials of this category include insulation and paper products such as wallpapers. Any damp area of the house with enough moisture can support the growth of the molds. Places such as basements and bathrooms are particularly the target of such growth.

Identification of Molds in the Building

Damp and water-damaged buildings should be inspected for the presence of mold and bacteria. Occupational health inspectors need to visit the site and inspect the entire building. The following areas need specific attention:

1. Water-damaged areas: These are places where water leakage from a damaged pipe has caused destruction of wood, wall, or the flooring. Several areas such as bathrooms, areas under sinks, wallpapers, and flooring covers should be inspected. Areas under the carpet, linoleum, or hardwood may all be potential areas of mold growth.
2. Humidity: Areas with higher humidity such as basements need to be inspected for visible mold growth.
3. Heating, ventilation, and air-conditioning (HVAC) systems: This system may also be a potential source of mold contamination. Therefore these units/parts need to be inspected.

Inspectors take samples of obvious mold growth and other suspicious areas such as furniture or walls in the absence of visible molds. Then they grow the sample in an appropriate culture medium in the laboratory. After growth, the colonies are subjected to staining and microscopic evaluation. Identification is based on morphological characteristics of the grown mold.

Serological methods such as the use of serum immunoglobulin E (IgE) and serum immunoglobulin G (IgG) against molds such as *Stachybotrys chartarum* and their antigenic components are also reported. The use of monoclonal antibody has had some success for the identification of molds, but cross-reactivity among fungi makes species-specific identification a challenge.

Other methods of mold identification, such as polymerase chain reaction (PCR), have also been used. A recent study has introduced a multiplex polymerase chain reaction that has the capability of identifying *Stachybotrys chartarum*, *Aspergillus versicolor*, *Penicillium purpurogenum*, and *Cladosporium* species within an 8-h period.

Identification of fungi helps assess causal effect and their relationship with sick building syndrome, developed in water-damaged building. Table 29.1 summarizes the recommended areas of sampling for mold and bacteria and other organisms in water-damaged buildings.

Symptoms

The reported symptoms of sick building syndrome are nonspecific and may affect one or more of the following: the head, eyes, nose, sinuses, throat, chest, gastrointestinal system, skin, cognition, and senses. Table 29.2 lists examples of reported symptoms.

Characteristics of a Healthy Building Environment

A healthy building is an environment free of physical, biological, and psychosocial stressors. Such a building environment has the following characteristics (Table 29.3):

1. Free of environmental contaminants such as bacteria, fungi, and their by-products.
2. Free of pollutants such as smokes, fumes, gas, and chemical vapors.

Table 29.1 Recommended areas of sampling for mold and other organisms in a water-damaged building

Sampling location	Examples
Obvious mold growth	Walls, wallpapers, flooring, and bathtubs
Water-damaged area	These are water-damaged areas and may or may not have visible mold growth
Areas of high humidity	Bathrooms, basements, crawl spaces
Heating, ventilation, and air-conditioning system (HVAC)	Each unit or part of HVAC system with or without visible mold growth
Any reported area of the building by affected individuals	Furniture, desk or tables, countertops, and various parts of the building with or without obvious mold growth

Table 29.2 Examples of reported symptoms in sick building syndrome

Head	Headaches, dizziness
Eyes	Irritation, pruritus, watery
Nose	Congestion, blockage
Sinuses	Congestion
Throat	Irritation
Skin	Dry, pruritus
Respiratory	Cough, shortness of breath, wheezing
Gastrointestinal	Nausea, vomiting, diarrhea, constipation
Senses	Sensitivity to odor
Constitutional	Fatigue
Cognition	Difficulty to concentrate

3. Free of infestations such as cockroaches, ants, rats, and others.
4. Free of pets: Too many pets can cause health hazards such as exacerbation of allergy and asthma symptoms.
5. Good ventilation: Poor ventilation may trigger asthma symptoms.
6. Good lights throughout the building.
7. High or low humidity: Humidity below 55 % is recommended for people with dust mite or mold allergy.
8. Suitable temperature: High or low temperature can affect the building occupants and may cause health problems in addition to work performance.
9. Stress-free work environment: Work stress can affect the health of building occupants.

How to Prevent Sick Building Syndrome

1. Avoidance: The best strategy is to avoid living in an unhealthy environment; to do that, one should inspect the residence before moving in. This is also true for the office building and any work environment.
2. Plumbing inspection: This is perhaps the most important part of building inspection. Residents should look for water-damaged areas and then look for the possible sources. Damaged pipes need to be fixed or replaced. After fixing and

Table 29.3 Characteristics of a healthy building

Parameter	Examples	Comment
Contaminants	Bacteria, fungi, or their by-products, animal dander or pollens	The building should be free of such contaminants. The fungi, animal dander, or pollens can cause or exacerbate allergic rhinitis and asthma; bacterial or fungal toxins my cause nonspecific symptoms
Pollutants	Smoke, fumes, gas vapors	Such pollutants can trigger asthma or cause irritation of upper respiratory tract
Infestation	Cockroaches, rats, and others	Such infestations not only trigger or exacerbate allergic rhinitis or asthma but also may cause irritation of respiratory system
Pets	Cats, dogs, rabbits, and others	These are triggers of allergic diseases such as allergic rhinitis and asthma
Ventilation	Heating, ventilation, air-conditioning system (HVAC)	The HVAC system should be free of contaminants
Light	Different light sources used in the building	Too bright or too dark areas may cause physical stress
Humidity	Damp areas in basements, bathrooms, etc.	Keeping humidity below 55 % helps to control dust mites, fungi, and cockroaches
Temperature	Too high or too low temperature	Too high or too low temperature can cause discomfort for building occupants
Work stress	Job demand, workload, job performance	Work stress can affect well-being of the office worker

repairing the source, the damaged area such as carpets, wallpapers, ceilings, floors, and others should also be replaced.

3. Controlling humidity: Humidity should be kept below 55 %; this can be achieved by using a dehumidifier. In addition to molds, such low humidity can also control dust mites and cockroach populations.
4. HVAC system: This system can get contaminated with molds/bacteria and their toxins. Circulating air from this system can distribute such contaminants to other sites of the building. The contaminated parts of HVAC system should be identified and replaced. If any of the units damaged beyond the repair, the entire unit should be replaced.
5. Washing, disinfecting, and maintaining a healthy environment. This not only helps remove the organisms but also helps maintain a healthy environment.
6. Preventing entrance of outdoor molds: To prevent entrance of outdoor molds to indoor environment, windows and doors should be kept closed.

Management of Sick Building Syndrome

The best solution for the affected individuals is moving to a new environment, that is, a new or different building. Those who live in apartment complexes should move to a different unit, ideally to a different building complex because other units of the

same building may also have mold contamination. Individuals who suffer from sick building syndrome usually do better after moving to a healthy environment. If the symptoms persist in the new environment, other causes should be considered and investigated.

Evidence-Based Medicine

We have considered sick building syndrome as a biological phenomenon. However, it is important to consider other factors contributing to existence of such nonspecific symptoms. A series of publications have reviewed other parameters that may play roles in the development of sick building syndrome; they include physical factors such as light, temperature, and humidity of the buildings and psychosocial factors such as work-related stress affecting the occupants.

In a study by Petersen et al., the effect of ventilation rate on the performance of schoolwork children was studied. The authors studied the school performance of children aged 10–12 years in two different schools. This double-blind 2×2 cross-over intervention study investigated the performance of the subjects utilizing four different performance tests to assess the short-term concentration and logical thinking. The investigators noted that when the outdoor air supply rate was increased from an average of 1.7 (1.4–2.0) to 6.6 l/s per person, the number of correct answers was improved significantly in four of four performance tests: addition (6.3 %), number comparison (4.8 %), grammatical reasoning (3.2 %), and reading and comprehension (7.4 %).

Looking at a different angle, one study investigated the relationships between socioeconomic and lifestyle factors and indoor air quality. The study by Brown et. al. measured concentrations of 30 chemicals, biological, and physical parameters from 567 dwellings in France. Using a questionnaire, the investigators collected information on socioeconomic factors, building characteristics, and occupants' habits and activities. The authors showed that the household with lower income was more likely to have higher indoor concentration of formaldehyde and lower concentrations of perchloroethylene.

When managing the affected individuals, obtaining information such as past history of allergic diseases, family history of atopy, and detailed history of working environment including physical, such as light, temperature, ventilation; biological, such as fungal or bacterial contamination; and psychosocial factors such as work-related stress are crucial for better identification, diagnosis, and management.

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Chapter 30
Allergy in the Elderly

Marianne Frieri

Chronic Rhinitis and Sinusitis

Inflammatory and noninflammatory nonallergic rhinitis is more prevalent in the fifth decade and later in life. The elderly frequently have atrophic and medication-related rhinitis. Adults comprise the largest group with seasonal or perennial allergic rhinitis or both. In a survey by allergy immunology specialists of older adults, 6 % are older than 70 years, and these individuals represent the fastest growing population in the United States. There are many triggers for allergic rhinitis, but skin test reactivity decreases with age and symptoms tend to be milder. The elderly have variable nasal physiologic function and frequently have a dry nasal mucosa but complain of severe congestion, lack turbinate edema, and have negative skin tests. Structural changes can develop with aging due to atrophy of collagen and alterations in nasal cartilage. Other types of rhinitis in the elderly include idiopathic rhinitis and rhinitis due to granulomatous, collagen vascular diseases and neoplasia. The elderly often consume multiple medications, especially for chronic cardiac and gastrointestinal disorders. Rhinitis due to medications is a condition for elderly patients on chronic β-blockers, diuretics, and anti-reflux therapy.

Chronic nasal congestion can also lead to overuse of topical sympathomimetics, resulting in the development of rhinitis medicamentosa or, with oral α-adrenergic agonists, with hypertension or sleep disturbances. Local allergic rhinitis and allergic rhinitis are common in elderly patients. However, in this age group, these conditions are often underdiagnosed.

Chronic sinusitis, an inflammatory process, also contributes to the cough common in elderly asthmatics and affects more than 30 million Americans. Chronic or persistent sinusitis can overlap with recurrent sinusitis and be associated with

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anatomic abnormalities, rhinitis, aspirin sensitivity, and nasal polyps that can occur in the elderly. Treatment consists of hydration, nasal lavage, antibiotics, and topical corticosteroids. Comorbidities in chronic rhinosinusitis include asthma, aspirin sensitivity, and nasal polyposis. *Staphylococcus aureus* biofilms and exotoxins that act as superantigens have been implicated to play an important pathological role in the incidence, maintenance, and ongoing burden of chronic rhinosinusitis. A better understanding of the interplay between bacterial factors, host factors, and the environment will facilitate better management of this disease. Bacterial biofilms exist in chronic rhinosinusitis and can lead to ineffective antibiotic therapy.

The severity of asthma is caused by many factors such as lack of education, poor early recognition, decreased symptom awareness, improper medications, and phenotypic changes. Genetic variation, innate immune genes, those involved in tissue remodeling and arachidonic acid metabolism, and inflammatory mediators might contribute to the pathogenesis of chronic rhinosinusitis linked with asthma. An extensive review addressed concepts of the burden of asthma and sinusitis, altered innate immunity, adaptive immunity, asthma remodeling, the airway epithelium, the role of airway smooth muscle cells, united allergic airway, genetics, an integral part in asthma, and chronic rhinosinusitis. In addition, the role of vitamin D in both asthma and chronic rhinosinusitis in the elderly was briefly addressed.

Asthma in the Elderly

The prevalence of asthma in older adults is approximately 5 %, but the increased burden will increase. Evidence-based literature suggests asthma in older patients is often underdiagnosed and underrated, and older asthmatics have greater morbidity, mortality with a higher risk of hospitalization, and a lower quality of life. In addition, the elderly are more likely than younger patients to be poor perceivers of airway obstruction. A recent review on asthma in the geriatric populations stated factors that contribute to this include respiratory changes caused by aging, immunosenescence, lack of symptoms, polypharmacy, clinician unawareness, and lack of evidence-based guidelines for diagnosis and management that target this population.

Specific innate changes may affect severity of asthma in older patients, or the development of late-onset asthma includes impaired in mucociliary clearance and changes in airway neutrophil, eosinophil, and mast cell numbers and function. Age-related altered antigen presentation and decrease in specific antibody responses may increase the risk of respiratory infections that exacerbate asthma in older patients and increase the risk of death when both are present. Establishing these associations may inform interventions designed to reverse or prevent the progression of either condition and to reduce adverse outcomes.

Asthma is associated with significant morbidity and mortality in the geriatric population. Despite the rise frailty and respiratory impairment are strongly associated with one another.

Osteoporosis and osteopenia affect more than 40 million US individuals. Bone fracture is the most significant consequence of osteoporosis because it is associated with high mortality and morbidity rates. As specialists who frequently use corticosteroids, allergists/immunologists should include the assessment of fracture risk in the comprehensive care of asthmatic patients. This assessment should begin with a detailed history to identify risk factors, as noted above. In patients suspected of having a secondary cause of osteoporosis, the relevant blood or urine test (such as serum and urine calcium, serum thyrotropin and parathyroid hormone, serum 25-hydroxy vitamin D level, or IgA (antiendomysial antibodies) should be performed). Fracture Risk Assessment Tool (FRAX) has been validated in postmenopausal women and men 50 years and older. A clinically important feature of this tool is that it identifies patients in the low BMD range (T score of −1 to −2.5) who have the highest risk of fracture and would benefit from treatment. The importance of monitoring measures of control in the treatment of asthma is clear. Equal vigilance in monitoring long-term adverse effects, such as increased fracture risk, of the medications used to achieve that control is essential to the total care of asthmatic patients.

The incidence of asthma in people over 65 years of age occurs, and the diagnosis is frequently missed in this population. Factors that contribute to this include age-related changes to the respiratory and immune systems, lack of symptoms, clinician unawareness, and lack of evidence-based guidelines for diagnosis and management that target this population. A multidiscipline approach is needed to better manage these patients, and a broad set of goals is needed to guide future management of this growing population.

Elderly patients with asthma may have airway remodeling and nonreversible disease associated with matrix changes reminiscent of chronic obstructive pulmonary disease. The elderly with asthma and chronic obstructive pulmonary disease needs special attention because it is more common in women. Coexisting diseases can occur with asthma, such as hypertension, coronary artery disease, diabetes, glaucoma, osteoporosis, and nicotine dependence, that can complicate the diagnosis. Advanced age is also a risk factor for asthma mortality.

Other Allergic Conditions

Acquired Angioedema, Anaphylaxis, and Food and Drug Allergy

Chronic angioedema due to the acquired C1-INH deficiency can occur in the elderly, who can have adenocarcinoma of the colon or lymphoproliferative disease. Anti-idiotypic antibodies and monoclonal paraproteins can occur. A depressed C1q complement component with a decreased C1 esterase inhibitor or CH50 in an older individual should raise a high suspicion for a lymphoproliferative disorder. Therapy with angiotensin-converting enzyme (ACE) inhibitors in the elderly can also lead to facial angioedema even after long-term therapy.

Anaphylaxis is an immediate systemic reaction due to rapid IgE-mediated release of potent mediators from tissue mast cells and peripheral blood basophils. Anaphylactoid reactions are immediate systemic reactions that mimic anaphylaxis but are not caused by IgE-mediated immune responses. Causes of anaphylaxis/anaphylactoid reactions include foods, antibiotics and other drugs, foreign proteins (insulin, seminal proteins, latex, chymopapain), immunotherapy, Hymenoptera stings, exercise plus food ingestion, complement-mediated reactions, and blood and blood products.

Nonimmunologic mast cell activators such as opiates (narcotics), radiocontrast media, vancomycin (red man syndrome), and dextran are also involved in anaphylaxis. Other issues are related to modulators of arachidonic acid metabolism, nonsteroidal anti-inflammatory agents, tartrazine (possible) sulfiting agents, idiopathic causes, exercise, catamenial anaphylaxis, and idiopathic recurrent anaphylaxis.

Cardiovascular abnormalities that can occur in the elderly also develop during anaphylaxis. Because the differential diagnosis could include myocardial infarction, it is important to note that arrhythmias and coronary artery vasospasm with ischemia can occur during exercise-induced anaphylactic events without the presence of intrinsic coronary artery obstruction.

The capillary leak syndrome is a rare disorder usually associated with monoclonal gammopathy that can occur in the elderly. Clinical findings associated with both anaphylaxis and anaphylactoid reactions include cutaneous (flushing, urticaria, angioedema), cardiovascular (tachycardia, hypotension, shock, faintness, arrhythmias, syncope, palpitations, weakness), gastrointestinal (abdominal distension, vomiting, bloating, cramps, diarrhea, nausea), and respiratory (rhinorrhea, laryngeal edema, nasal congestion, shortness of breath, asphyxiation, hoarseness, difficulty in breathing, choking, cough). Other findings include diaphoresis, fecal or urinary incontinence impending doom, genital burning, and metallic taste.

Systemic symptoms suggestive of anaphylaxis can occur with hypotension, angioedema, and gastrointestinal signs. The differential diagnosis of anaphylaxis and anaphylactoid reactions include flushing disorders, exercise-related reactions, sulfites, idiopathic anaphylaxis, complement-mediated reactions, nonsteroidal anti-inflammatory reactions, vasovagal collapse, hereditary angioedema, serum sickness, systemic mastocytosis, urticaria pigmentosa, pheochromocytoma, carcinoid syndrome, panic reactions, and Münchausen syndrome.

The World Allergy Organization (WAO) Guidelines for the assessment and management of anaphylaxis are a widely disseminated and used resource for information about anaphylaxis that focused on patients at risk, triggers, clinical diagnosis, treatment in health-care settings, self-treatment in the community, and prevention of recurrences.

In older adults, systemic mastocytosis can result in leukemia, lymphoma, or carcinoma. Carcinoid-like symptoms can also be produced by oat cell carcinoma of the lung, medullary carcinoma, and pancreatic tumors such as insulinoma, glucagonoma, vasoactive intestinal polypeptide-secreting tumors, and gastrinoma. Many retired elderly play golf and can be exposed to insect allergy, and up to 3 % of the population are at risk for anaphylaxis to insect stings with approximately 40 deaths

per year. In addition, fire ants, biting insects, and mosquitoes can cause systemic reactions. A recent review by Simons on long-term management of anaphylaxis in the community suggests specialists play a pivotal role. Comorbidities and concurrent medications in the elderly might interfere with recognition of triggers or symptoms, such as impairment of vision or hearing, neurology disease, or depression, that might affect treatment of asthma, cardiovascular disease, or the inability to self-inject epinephrine. Concurrent administration of sedatives or hypnotics might affect treatment with β-adrenergic blockers or α-adrenergic blockers that decrease epinephrine efficacy by blocking effects at the adrenergic receptors. Although food allergy is more common in children, most IgE-mediated reactions to foods in adults are caused by peanuts, tree nuts, fish, and shellfish. Many retired elderly travel and can have adverse food reactions. Foods may be contaminated by a wide variety of hidden substances that can be confused with food allergy, and other disorders in the elderly, such as hiatal hernia, peptic ulcer disease, malignancy, toxins, or pharmacologic agents, can mimic food allergy. Sensitized individuals can unknowingly be exposed to allergenic proteins in foods through cross contact, food containing allergenic nonfood products, food additives, and cross-reactivity. The differential diagnosis of food hypersensitivity includes enzyme deficiencies, gastrointestinal diseases, additives, endogenous chemicals, and many toxins. Drug allergic reactions can be predictable or unpredictable due to an idiosyncratic reaction or intolerance, or they may be IgE mediated. Many elderly patients taking antibiotics, aspirin, nonselective nonsteroidal anti-inflammatory medications or immunomodulators for arthritis, cancer, and other immune diseases can develop adverse drug reactions. Such reactions could involve anaphylaxis or pseudoallergic reactions, angioedema, urticaria, maculopapular rashes, Stevens–Johnson syndrome, or toxic epidermal necrolysis. Rigors, dyspnea, or hypotension can also occur with immunomodulators used to treat elderly patients with rheumatoid arthritis or Crohn disease, psoriasis, and other inflammatory disorders.

Evidence-Based Medicine

According to Sackett (*BMJ*; 1996:312:71), "evidence based medicine is conscientious, explicit and judicious use of current best evidence in making decisions about care of individual patients. The practice of evidence based medicine means integrity, individual clinical experience with the best available clinical evidence from systematic research." This chapter has provided several references from the literature in terms of review articles and sections from textbooks that critically explain mechanisms and can also be applied to patient care, intervention, and outcome.

Vaz Fragoso reviewed frailty and respiratory impairment in older persons. Baseline assessments included frailty status and spirometry. Outcomes included development of frailty features and respiratory impairment. Mortality was highest among participants who were frail and had respiratory impairment compared with those who were non-frail and had no respiratory impairment. Frailty and respiratory

impairment were strongly associated with one another and substantially increase the risk of death when both are present. Establishing these associations may inform interventions designed to reverse or prevent the progression of either condition and to reduce adverse outcomes.

The occurrence of depression with asthma is very common, especially in women, and can influence behavioral factors such as treatment compliance, self-assessment, management of environmental triggers that can collectively result in poor asthma management, and control. This recent review by Frieri and others described the association and major clinical implications of stress, anxiety, and depression and associated hormonal changes frequently seen in women with poorly controlled asthma. Several validated instruments have been recently developed for screening patients for depression that can now be utilized in and benefit patients with asthma by earlier detection of these confounding risk factors. The review also highlights the need for further delineation and characterization of specific underlying pathophysiologic and immunologic mechanisms responsible for depression in women.

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Chapter 31
Diagnostic Testing in Allergic Diseases

Paul Cheng

When a medical history is suggestive of an allergic cause, proper testing is performed to identify clinically relevant allergens. The discovery of IgE antibody, along with the recognition of its central role in the allergic reaction, has established the identification of allergen-specific IgE as the key to the diagnosis of allergic diseases. Both in vivo skin testing and laboratory allergy testing are designed to detect allergen-specific IgE, although the pathophysiology of allergy is far more complex than just an IgE-mediated condition. Diagnostic testing for nonIgE-mediated allergic reactions and for allergies with predominant late-phase reaction and challenge testing with food or other allergens are beyond the scope of this chapter. Likewise, diagnostic tests for autoimmune conditions and immunodeficiencies are discussed in other chapters.

Percutaneous Allergy Testing

The abundance of cutaneous mast cells, predominantly the MCTC phenotype that contains both tryptase and chymase, makes skin an ideal place for in vivo allergy testing.

Mast cell degranulation with the release of histamine and other immediate mediators upon introduction of allergen extract to the skin is the hallmark of allergy skin testing. With the presence of allergen-specific IgE bound to its receptors on mast cells, an immediate wheal-and-flare response is elicited when two IgE-receptor molecules are cross-linked by its relevant allergens introduced to the skin. This

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immediate response is mediated mainly by histamine and, to a lesser extent, by tryptase. Through axon reflex, histamine released from mast cells can also trigger the release of neurogenic mediators, such as substance P and neurokinin A, which can further activate mast cell granulation and histamine release to intensify the wheal-and-flare response.

Prick-Puncture Method

The most widely used skin testing technique for allergy diagnosis is the prick-puncture method. The skin is pricked or gently punctured, without causing bleeding, to allow allergen extract to penetrate into the epidermal space. Allergen extracts are placed on the volar surface of the arm or the back, and the test always includes histamine (positive control) and allergen extract diluent (negative control). Test for each allergen extract and control solution should be positioned at least 2–2.5 cm apart. The reactions from each allergen are read one by one, usually in 15–20 min, by comparing to the size of wheal in the histamine and diluent control. It is generally accepted that a reaction is considered positive if its wheal diameter is at least 3 mm greater than negative control that should be completely nonreactive. Reaction can be further graded qualitatively (grade 0–4) by comparison to the size of the histamine control (Table 31.1) or semiquantitatively by measuring and recording the diameters of the wheal and flare from each allergen tested that is considered the preferred method. Regardless of which way the reactions are measured or graded, it is crucial that the results be interpreted together with clinical history.

There are several skin testing devices available commercially. Practicing allergists usually consider accuracy, consistency, convenience, perception of pain and discomfort, and cost in selecting their preferred devices. Although a few studies comparing these devices had shown one device may be favorable to others, there was no sufficient data to single out one particular device that was superior to others on all criteria. Regardless of device chosen, what really matters is that allergy skin

Table 31.1 Grading criteria by wheal size for allergy skin testing

Grade	Wheal reaction
0	No significant wheal reaction
1	Wheal size smaller than half of histamine control
2	Wheal size greater than half of histamine but smaller than histamine control
3	Wheal size about the same as histamine control
4	Wheal size greater than histamine control
4p	Pseudopod present

This grading system may be applied when the wheal reaction from histamine is at least 5 mm in diameter, while negative control is completely nonreactive. Note that the histamine control reaction may often peak before the allergen reaction and may need to be read sooner

testing be performed by a well-trained staff under the supervision of an allergist to ensure consistent and reproducible results.

Some of the common errors in allergy skin testing that should be avoided are listed below:

1. False negative from insufficient penetration of allergen extract into the epidermal space or using extracts with insufficient potency.
2. False negative from drugs blocking the immediate wheal-and-flare reactions, including all H1 antihistamines, some tricyclic antidepressants, and ketotifen (not available in the USA). Patients are usually told to stop first-generation H1 antihistamines for 2 days and second-generation H1 antihistamines for 5 days prior to skin testing. H2 antihistamines have minimal inhibitory effects on allergy skin testing. Likewise, leukotriene antagonist, now frequently prescribed for allergy patients, or oral steroid does not interfere immediate reaction on skin testing. Effects of topical antihistamines or other topical allergy medications on skin testing are limited, and stopping these medicines for a day or two before testing should be sufficient. Intermittent use of topical corticosteroid or pimecrolimus does not appear to have a significant effect on skin testing either.
3. Applying allergy testing on patients with certain skin conditions, such as eczema, may reduce skin reactivity. On the contrary, performing skin testing on patients with dermographism is very likely to get false-positive or nonspecific irritating reactions. The testing should always be performed on normal skin.
4. Skin testing should not be performed when history is suggestive of anaphylaxis or any severe systemic reactions from a particular allergen. This is more often in the case of food allergies. A thorough history should always be taken before carrying out skin testing to avoid unnecessary adverse reactions.

Intradermal Testing

When the history indicates allergy as a cause but prick testing is not revealing, further testing by intradermal method may be used. A small volume (about 0.02 ml) of the allergen extract is injected intracutaneously (into the dermis) using a tuberculin syringe with a 26-gauge needle. The starting dose should be at least a 100-fold dilution of the extract used for prick/puncture testing to avoid large local reaction or potential systemic reactions. Intradermal testing has greater sensitivity but less specificity and should be interpreted cautiously with clinical history. It is not recommended for the diagnosis of food allergies as intradermal injection of food allergen extracts has a high false-positive rate and greater risks of systemic reactions. Intradermal testing is performed more often for the diagnosis of bee venoms or drug allergies (penicillin and local anesthetic agents). It is rarely indicated to perform intradermal testing with more than just a few selected allergens and would increase unnecessary risks of systemic reactions to do so.

"Prick-to-Prick" Skin Testing

This modified skin testing is mainly used for evaluation of food allergy. By this method, fresh allergens were used by first pricking raw fruits or vegetables, then pricking the skin immediately with the same needle. The advantage of this approach is based on the assumption that clinically relevant allergen components from these foods may have changed or been lost in the production of commercial food extracts used for conventional skin testing. This test has been applied to the diagnosis of oral allergy syndrome caused by oral contact with fresh or raw vegetable or fruits. Individuals with this condition often have significant pollen allergy that can be diagnosed by conventional skin testing described earlier.

Diagnostic Value of Percutaneous Allergy Testing

It is critical that skin testing demonstrates high sensitivity and specificity in identifying allergens with clinical significance in order to make an effective allergen avoidance plan or formulate an allergen-specific immunotherapy program. Although allergy testing is conducted on the skin for the diagnosis of an allergy condition with symptoms often from different target organ systems, the diagnostic value of allergy skin testing is well established for conditions caused by inhalant allergens. The predictive value is high for a positive prick skin test associated with an inhalant allergen when the history is also suggesting clinical sensitivity related to this allergen. With symptoms suggesting allergies, positive prick skin testing also correlates well with bronchial or nasal challenge. Positive intradermal skin testing and symptoms elicited by allergen challenge, however, are not as well correlated. In the case of food allergy, predictive value of clinical sensitivity with symptoms on positive prick testing is much lower than in the case of inhalant allergens. In general, skin testing with food allergens has higher negative predictive value and is a reliable screening test to rule out IgE-mediated food allergy. Thus when performing allergy testing, it is critical to recognize that a positive reaction does not necessarily identify the allergens causing the symptoms. One should never make the diagnosis of allergy just based on the results of the test alone.

In Vitro Measurement of Allergen-Specific IgE

In vitro testing is used when skin testing is not appropriate for patients under some circumstances previously mentioned, such as (1) those with significant skin condition, (2) those who cannot discontinue antihistamines or other drugs that may interfere reaction to allergens on skin testing, or (3) those with a history of severe reaction to allergens and skin testing with these allergens may be of significant risk or when reagents for skin testing are not available. Since it was introduced in the 1960s, radioallergosorbent test (RAST) has been the major form of in vitro measurement of allergen-specific serum IgE.

This widely used assay is now being replaced by a new fluorescent enzyme immunoassay ImmunoCap. In this system, the sensitivity level is greatly enhanced by using cellulose sponge to increase binding capacity to allergens and fluorescent-labeled anti-IgE antibodies for detection. One of the commonly used score systems for this immunoassay is shown in Table 31.2.

As in the case of skin testing, individuals with a positive in vitro test demonstrating the presence of allergen-specific IgE above normal range may show no clinical sensitivity with no target organ symptoms to these allergens. However, the higher the level of IgE (class 3 or higher), the more likely one finds correlation to clinical symptoms, especially for inhalant allergens. A cutoff IgE level for selected food allergens, including egg, milk, peanut, tree nuts, fish, soy, and wheat, with greater than 95 % correlation to clinical symptoms confirmed by a double-blind food challenge was established in some studies.

ImmunoCap allergy test is now commercially available for a long list of allergens, including indoor allergens, pollens, food, drugs, epidermal and other animal proteins, venoms and other insect allergens, occupational allergens, and others. Tests to measure IgE level to specific native or recombinant allergen components from grasses and other pollens, peanuts and other foods, latex allergens, venoms, animal proteins, and dust mite allergens are also developed that can be used in clinical diagnosis and research.

Most commercial labs report total serum IgE along with individual allergen-specific IgE. Although total serum IgE is generally elevated in patients with allergic condition, it has very limited value in the diagnosis of allergic diseases. In fact, when total IgE is very high (over 1,000 IU/L), the results on individual allergens are more likely to be false positive due to presence of abundant IgE with no defined specificity competing with allergen-specific IgE in the assay. Total serum IgE is needed only in the diagnosis of certain conditions such as allergic bronchopulmonary aspergillosis or hyper-IgE syndrome. It is also required when prescribing anti-IgE therapy for asthma as the initial dosage is calculated according to the body weight and total serum IgE level of the patients.

Allergists tend to advocate skin testing versus laboratory measurement of allergen-specific IgE. When properly performed, skin testing has the advantages of greater sensitivity, ease of performance, and immediate availability of the results.

Table 31.2 Scoring system of Pharmacia CAP system fluorescent immunoassay

Grade	Class	Interpretation
<0.10	0	Negative
0.10–0.34	0/1	Equivocal/borderline
0.35–0.69	1	Low positive
0.7–3.4	2	Moderate positive
3.5–17.4	3	High positive
17.5–49.9	4	Very high positive
50–99.9	5	Very high positive
>100	6	Very high positive

With the improved sensitivity and specificity of the newer fluorescent enzyme immunoassay system that is available for a wider range of allergens, we may see a trend toward increasing usage of these tests, which are actively promoted by commercial labs to primary care physicians, allergists, and other specialists alike. It is critical that all ordering physicians have sufficient knowledge and clinical experience to interpret the results of these tests.

A related issue involves the selection of allergens to be tested. How many allergens should be included when ordering a test panel? Again, the decision is made after a thorough history is taken, and only clinically relevant allergens should be tested. Although the fluorescent enzyme immunoassay may be superior to other allergy tests, it is expensive. Ordering a large number of clinically irrelevant tests not only contributes to unnecessary cost, the information from these tests may be misleading, and the management plans based on the results from these tests may not be warranted. This principle of prudence in allergy testing applies to both inhalant and food allergens, either by skin testing or in vitro IgE measurement. When the history gives an impression of an allergic condition but does not suggest any allergen trigger, a screening test to cover large number of allergens hoping to find something positive is not how allergy should be practiced. Any screening panel should consist of limited tests according to the age and geographic location of the patients and the symptoms they present.

Allergy Testing with No Proven Value

There are many allergy diagnostic tests without scientific basis and no proven diagnostic value. Often, these tests are promoted by the labs or practitioners who have no formal allergy training. In the practice parameters recommended by both American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology, some unproven diagnostic tests for allergy condition are mentioned, including measurement of serum IgG antibodies, mostly to food or mold allergens, food immune complex assay, end-point titration and provocation-neutralization, measurements of changes of skin resistance or muscle strength upon exposure to allergens, and others. Many patients have received unwarranted or inappropriate treatments, or have had unnecessary diet restriction based on the results of these tests. It is the responsibility of the entire medical community to be aware of and prevent the misuse of these scientifically unsound diagnostic tests and treatments.

Newer Trends in Allergy Testing Evidence-Based

As more standardized allergens become available, they should be used in both treatment and diagnostic testing of allergic diseases and in research involving skin testing. The skin reaction from the testing can be better quantified and correlated to

clinical symptoms when standardized reagents are used. Another significant new trend is to use specific native or recombinant allergen components with defined epitopes for allergy testing that may offer higher specificity and sensitivity. For example, high IgE level to peanut component Ara h1, Ara h2, and Ara h3 was found in patients with clinical symptoms of peanut allergy, while individuals sensitized to other components, such as Ara h8, are more likely asymptomatic. Higher specificity in the diagnosis of carrot, egg, and milk allergies by using recombinant peptides was also reported. More efforts should be put into identification and development of clinically relevant allergy components for the diagnosis and treatment of allergic diseases.

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Chapter 32
Primary Immunodeficiencies

Pedro C. Avila and Ramsay L. Fuleihan

Introduction

Deficiencies in the immune system increase susceptibility to infections, autoimmune disorders, and lymphoproliferative diseases. The characteristics of infections provide clues as to what functions of the immune system are defective. Infections in immunodeficient patients can be caused by common or opportunistic organisms and are frequent, severe, recurrent, and difficult to treat. Autoimmune diseases can be of any type, most commonly blood cytopenias, gastroenteropathies, and endocrinopathies. Malignancies are more often hematological or gastrointestinal cancers.

Secondary causes of immunodeficiency occur as a consequence of infection, such as with human immunodeficiency virus (see Chap. 33), in association with lymphoproliferative diseases, are iatrogenic, resulting from medical treatment for cancer with radiation and/or chemotherapy, as well as immunosuppressant therapy for autoimmune diseases. Mild immunodeficiency defects also occur during certain infections (e.g., Epstein-Barr virus, malaria), chronic diseases (e.g., diabetes mellitus, chronic renal insufficiency), nutritional deficiencies (e.g., protein-energy malnutrition, zinc and vitamin deficiencies), protein-losing conditions (e.g., intestinal lymphangiectasia), and autoimmune disorders (autoimmune neutropenia or lymphopenia). These acquired or secondary immunodeficiencies should always be considered in patients suspected of having a primary immunodeficiency.

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In this chapter, we discuss the most common primary immunodeficiency diseases, which result from genetic defects or have unknown etiology. This group of immunodeficiency diseases is rapidly expanding as new specific genetic defects are discovered in the immune system. Although nearly 300 conditions have been characterized, for many only a few cases have been described.

When to Suspect Immunodeficiency and How to Work It Up

The immune system is still developing in infants and children as they face their first antigenic challenges, mount specific adaptive responses, and build immunological memory. Some immunological parameters only achieve adult levels in adolescence. As a result, evaluation of the immune system needs to take into consideration the patient's age. If a local laboratory has not established its own age-specific normal ranges, one needs to consult appropriate references. For example, normal serum immunoglobulin concentration ranges are lower and lymphocyte count higher in newborns and infants compared with older children and adults (see Table 32.1). While IgG levels in the first 6 months of life reflect maternally transferred IgG, serum concentrations of the child's own immunoglobulin levels are low in newborns and slowly rise until adolescence. A blood lymphocyte count of 1500/mm^3 is low normal for adults but is a sign of cellular or severe combined immunodeficiency in neonates. Functional assays of adaptive immunity to antigens depend on previous exposure and sensitization to establish memory response and, thus, are not very helpful in infants. Therefore, the clinician needs to be aware of the patient's age and previous exposures such as vaccinations when functionally assessing the immune system for memory adaptive immunity, particularly in neonates and infants.

The most common manifestations of immunodeficiencies are infections (see Table 32.2). Because of lack of previous exposures and of memory adaptive immunity, healthy infants and children normally suffer infections more frequently than older children and adults. Infants attending day care can develop one acute upper respiratory infection (common cold) per month. Likewise, day care workers and teachers of young children develop respiratory infections more often than adults in jobs without much contact with the public or frequently ill people. Adults usually develop one to two common colds a year. Besides the frequency of infections, how a host handles common infections is important. Immunodeficient patients often have prolonged common colds lasting >10 days and often develop bacterial infections such as otitis media (in children), sinusitis, bronchitis, and even pneumonia. They may present with frequent prolonged infections that require repeated or prolonged courses of oral or intravenous antibiotic therapy. Infections may recur soon after the usual 7–10-day antibiotic courses, needing repeated and prolonged courses for what should be easily treatable common respiratory or mucocutaneous infections. Immunodeficient patients may also have opportunistic infections, deep-seated infections, and/or family history of immunodeficiency or of a relative who died young of an infection. Besides infections, a defective immune system may lead to

Table 32.1 Normal characteristics of the developing immune system

Test	Neonates	Infants			Children		Adults
Age	1–30 days	1–6 months	7–12 months	13–24 months	2–9 years	10–17 years	>18 years
Complete blood count:							
White count (10^3/mm^3)	9.1–34.0	6.0–14.0	6.0–14.0	6.0–14.0	4.0–12.0	4.0–10.5	4.0–10.5
Neutrophils (10^3/mm^3)	6.0–23.5	1.1–6.6	1.1–6.6	1.1–6.6	1.4–6.6	1.5–6.6	1.5–6.6
Segmented (10^3/mm^3)	6.0–20.0	1.0–6.0	1.0–6.0	1.0–6.0	1.2–6.0	1.3—6.0	1.3–6.0
Bands (10^3/mm^3)	<3.5	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Lymphocytes (10^3/mm^3)	3.5–10.5	1.8–9.0	1.8–9.0	1.8–9.0	1.0–5.5	1.0–3.5	1.5–3.5
Eosinophils (10^3/mm^3)	<2.0	<0.7	<0.7	<0.7	<0.7	<0.7	<0.7
Serum:							
IgG (mg/dl)	140–930	250–1190	320–1250	400–1250	560–1380	680–1600	700–1500
IgA (mg/dl)	5–65	10–90	17–95	24–192	26–260	45–380	60–400
IgM (mg/dl)	14–140	14–170	14–170	24–170	35–250	35–250	35–250
IgE (IU/ml)[a]	0.0–6.6	0.0–6.6	0.0–6.6	0.0–20.0	0.0–60.0	3.6–100.0	3.6–100.0

[a]1.0 IU/ml of IgE is equal to 2.4 ng/ml of IgE

Table 32.2 Manifestations of immunodeficiency and laboratory investigation

Manifestations	Immune defects	Laboratory investigation
Antibody deficiencies:		
Recurrent sinopulmonary infections[a]: ≥2 sinusitis or bronchitis per year needing antibiotic therapy Sinusitis needing antibiotics orally for >2 months or intravenously Repeated endoscopic sinus surgery for chronic sinusitis ≥2 pneumonias per year Bronchiectasis Enteroviral gastroenteritis or meningoencephalitis (e.g., polio, echo)	X-linked agammaglobulinemia Common variable immunodeficiency Transient hypogammaglobulinemia of infancy Hyper IgM immunodeficiency IgA deficiency IgM deficiency IgG subclass deficiency Immunodeficiency with thymoma Transcobalamin deficiency Specific antidody deficiency	Components: Serum IgG, IgM, IgA Flow cytometry: B-cell count (CD19 or CD20) CD40L (CD154) on T cells Memory B cells (CD19+CD27+) Switched memory B cells (CD19+CD27+IgD-) Serum IgG subclasse s *Functional*[b]: Isohemagglutinins (IgM response) Antibody response to vaccines (IgG response)
Complement deficiencies:		
Recurrent sinopulmonary infections with encapsulated microbes[c] Recurrent *Neisseria* (gonococcal or meningococcal) invasive diseases	Deficiency of classic pathway proteins Deficiency of alternative pathway proteins.	Components: serum complement proteins Functional: CH50, AH50
T-cell deficiencies:		
Recurrent opportunistic infections with: Herpesvirus infections (CMV, EBV, HSV) Vaccinia, adenovirus, measles Moluscum contagiosum Pyogenic bacteria[a] Mycobacterial infections Fungi: *Candida*, *Aspergillus*, *Pneumocystis jirovecii* Intracellular bacteria[d] Growth failure in infants. Persistent mucocutaneous candidiasis after 1 year of age Protracted diarrhea	Combined T- and B-cell deficiencies: Severe combined immunodeficiencies Wiskott-Aldrich syndrome Ataxia telangiectasia Enzyme deficiencies Bare lymphocyte syndrome Omenn syndrome X-linked lymphoproliferative disease Reticular dysgenesis Isolated T-cell deficiencies: DiGeorge and chromosome 22 anomaly Idiopathic CD4 lymphopenia Chronic mucocutaneous candidiasis Natural killer deficiency	Components: CBC lymphocyte count Flow cytometry: T cells (CD3) T-cell subsets and ratio (CD4/CD8 ratio) Naïve (CD45RA) and memory (CD45RO) B cells (CD20 or CD19) NK cells (CD16 + CD56 double stained) HLA-DR CD40L (CD154) on T cells FISH of chromosome 22 (probe 22q11) Functional: Delayed hypersensitivity testing[e] Lymphocyte proliferation to mitogens[f] Lymphocyte proliferation to antigens[g] Mixed lymphocyte reaction[g] NK-cell cytolytic activity Leukocyte enzyme assays: ADA, PNP

Phagocyte deficiencies:		
Recurrent infections with catalase-positive bacteria and fungi[h] Recurrent skin abscesses Recurrent lymphadenitis Deep-seated abscesses (e.g., lung, liver) Mycobacterial infections Chronic periodontal disease, gingivitis	Neutropenic syndromes Chronic granulomatous deficiency Myeloperoxidase deficiency Leukocyte adhesion molecule deficiencies Leukocyte G6PD deficiency IFN gamma/IL12 axis deficiency	Components: Serial CBC with neutrophil count Flow cytometry: CD18 on PMA-stimulated granulocytes Sialyl-Lewis^X on stimulated granulocytes IFN gamma receptor IL12p70 secretion from stimulated monocytes Anti-neutrophil antibody Functional: Neutrophil oxidative burst[i] Leukocyte G6PD and MPO Staphylococcal killing assay[j] Neutrophil chemotaxis[j]

Abbreviations: *CBC* complete blood count, *CH50* classical complement hemolytic activity 50%, *AH50* alternative complement hemolytic activity 50%, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HSV* herpes simplex virus, *NK* natural killer, *HLA* human leukocyte antigen, *FISH* fluorescent in situ hybridization, *ADA* adenosine deaminase, *PNP* purine nucleoside phosphorylase, *IFN* interferon, *G6PD* glucose-6-phosphate dehydrogenase, *MPO* myeloperoxidase. Sequencing of causative gene variations may be available, particularly in specialized centers

[a]Recurrent sinopulmonary infections due to encapsulated organisms such as pneumococci, streptococci, *Haemophilus influenzae*, and less often staphylococci. These and intestinal gram-negative bacteria are also known as pyogenic bacteria

[b]Isohemagglutinins are IgM antibodies against ABO blood group antigens. Thus, ABO blood typing needs to be performed simultaneously since AB blood type will not develop anti-A or anti-B antibodies. Titers become positive after 1 year of age (>1:4). Specific antibody titers to vaccines include titers to tetanus toxoid, diphtheria toxoid, *Haemophilus influenzae* type B (Hib), and hepatitis B surface antigen, which are all part of the regular immunization schedule in the first 6 months of life in the US. Pneumovax is not very immunogenic in children younger than 2 years. Its immunogenicity improves between ages of 2–5 years and is better after 6 years of age. It contains capsular polysaccharides from 23 *Streptococcus pneumoniae*(pneumococci)serotypes(1,2,3,4,5,6B,7F,8,9N,9V,10A,11A,12F,14,15B,17F,18C,19F,19A,20,22F,23F,33F). Adequate antibody response for a single serotype is when titer improves from non-protective to protective levels (usually >1.3 μg/ml, or based on test manufacturer's instructions) 4–6 weeks after vaccination, or doubling in titer if baseline level was already protective. For children 2–5 years old, it is expected an adequate antibody response for 50% or more serotypes. Those older than 6 years should respond to 70% or more serotypes. Prevnar-13 contains aluminum adjuvant and polysaccharides from 13 pneumococci strains (1 ,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) conjugated with diphtheria CRM_{197} carrier protein, which makes them immunogenic in infants younger than 2 years of age. Because of the protein carrier, it evaluates protein response, not antibody response to polysaccharides alone. Toxoids and other protein vaccines generate a predominantly IgG_1 response, whereas polysaccharides generate predominantly IgG_2 response

[c]Both antibody and complement deficiency are associated with recurrent sinopulmonary infections with encapsulated organisms

[d]Examples of intracellular bacteria are mycobacteria, *Campylobacter*, and *Listeria*

[e]Delayed hypersensitivity testing (DHT) assesses in vivo the specific lymphocyte memory response to antigens to which the patient should have been exposed and sensitized. Antigens are injected intradermally (0.1 ml) and an induration of ≥5 mm is expected in 48–72 h. Antigens commonly used are *Candida*, tetanus toxoid, and mumps. Young children may not have yet acquired the appropriate immunity to respond normally to this test

[f]Mitogens are lectins that bind surface glycoproteins (e.g., receptors) activating leukocytes. They test lymphocyte proliferative capacity in vitro. Phytohemagglutinin (PHA) and concanavalin A (Con A) are T-cell mitogens. They bind to and cross-link T-cell receptors (TCR) inducing T-cell proliferation. Con A stimulation also requires co-stimulatory signal to exert its effect. Pokeweed mitogen (PWM) induces proliferation of both T and B cells. To induce proliferation of B cells only some laboratories use staphylococcal protein A, a B cell superantigen, not a lectin

[g]Specific lymphocyte proliferation to antigens in vitro depends on previous sensitization and memory cellular response to the relevant antigen. Thus, young children may not have yet developed appropriate immunity to respond normally to this test. Antigens commonly used are tetanus toxoid and *Candida*. In mixed lymphocyte reaction, patient's lymphocytes are exposed to irradiated allogenic mononuclear cells and proliferate due to HLA incompatibility

[h]Catalase-positive microbes include staphylococci, *Serratia marcescens*, *Klebsiella*, *Escherichia coli*, *Burkholderia cepacia*, *Candida*, *Aspergillus*, and *Nocardia*. Their catalases catabolize the abnormal small amount of hydrogen peroxide produced by defective neutrophils allowing their replication

[i]Several tests to assess the ability of neutrophils to produce reactive oxygen species, particularly hydrogen peroxide, are available including light microscopy (nitroblue tetrazolium [NBT] oxidation from a yellow to a dark blue color), flow cytometry, chemiluminescence, or superoxide production

[j]Staphylococcal killing assay and neutrophil chemotaxis are very difficult to standardize and are available in only a few laboratories

autoimmune and lymphoproliferative diseases. Lastly, specific immunodeficiencies will have characteristic accompanying disorders and physical signs that may hint to the diagnosis.

An initial workup for primary immunodeficiency can include (1) complete blood count and differential count; (2) quantitative serum immunoglobulins (IgG, IgA, IgM, and IgE); (3) lymphocyte phenotype by flow cytometry including circulating T cells (CD3), T-cell subsets (CD4 and CD8 T cells), B cells (CD20 or CD19), and NK cells (CD3 negative and CD16/CD56 double positive); (4) complement hemolytic activity (CH50); (5) isohemagglutinin titers; and (6) antibody levels to immunizations such as to pneumococcal serotypes and to diphtheria and tetanus toxoids. Other tests can be obtained based on the history and types of infections, which can indicate what component of the immune system is defective as shown in Table 32.2. Additional tests may be appropriate to rule out other diseases. For example, the differential diagnosis for recurrent sinopulmonary infections includes allergic diseases, HIV infection, aspiration (e.g., tracheoesophageal fistula, gastroesophageal reflux, impaired swallowing, and gag reflex), anatomical obstruction (e.g., malformations, foreign body, cancer, nasal polyps, scarring from repeated nasosinus surgeries), and mucociliary dysfunction (e.g., cystic fibrosis, ciliary dyskinesis). Low serum proteins including albumin and IgG, but not the large dimeric IgA and pentameric IgM, occur in nephropathy (nephrotic syndrome). In protein-losing enteropathy (diagnosed by elevated stool alpha1-antitrypsin), all immunoglobulins are low since they are all lost in the stool. Patients with intestinal lymphangiectasia have protein-losing enteropathy and also lose circulating CD4+ T lymphocytes into their stool, resulting in lymphopenia.

Antibody Deficiencies

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) was the first reported primary immunodeficiency (by Ogden Bruton in 1952). Its prevalence is 1:100,000, and it is caused by mutations in the Bruton tyrosine kinase (Btk, located in chromosome Xq22) which leads to an arrest in B-cell development at the pre-B-cell stage. As a result, patients have no B cells, IgG is <200 mg/dl, and the other immunoglobulins are extremely low or absent (IgM, IgA, IgD, and IgE).

Clinical Manifestations

Patients present with recurrent pyogenic infections starting at 5–6 months of age when passively placentally transferred maternal antibodies have waned. These infections include recurrent otitis media, bronchitis, pneumonia, and meningitis. Repeated pneumonias may lead to bronchiectasis. Most common microbes are pneumococcus, *Haemophilus influenzae*, and other streptococci, but gram-negative

bacteria may also be involved. Usually infections recur soon after antibiotic courses are finished with short periods of good health.

These patients are also more susceptible to few virus infections even though they have normal T-cell function. These viruses include wild viruses or live attenuated vaccine viruses related to varicella, measles, paralytic poliomyelitis, and enteroviruses (e.g., echovirus, which can cause meningoencephalitis).

Other manifestations include abnormal dental decay, malabsorption, failure to thrive, chronic conjunctivitis, eczematoid skin infections, and rheumatoid arthritis-like disease. Malabsorption may be due to *Giardia lamblia* infestation. On physical examination, XLA patients lack lymph nodes and tonsils but have a spleen.

Laboratory Diagnosis

Diagnosis is based on extremely low serum IgG, IgA, and IgM and absence of circulating B cells. Functional antibody response (isohemagglutinins and antibody response to vaccines) is also greatly impaired or absent, but it is not necessary for diagnosis when serum immunoglobulins are extremely low. CH50, T cells, and NK cells are all normal. Rarely, intestinal mucosal biopsy has been obtained to demonstrate lack of plasma cells in the lamina propria. In specialized genetic laboratories, analysis of the Btk gene sequence for mutations can be performed to confirm the diagnosis. Diagnosis is particularly difficult in the first 6–9 months of age when maternal antibodies still circulate in the infant. Lack of circulating or tissue B cells can help diagnose XLA. Alternatively, serum immunoglobulins can be checked again in 3 months while infections are treated, antibiotic prophylaxis is given, and live virus vaccines are avoided. In XLA, the antibody levels progressively decline and never rise, whereas in transient hypogammaglobulinemia of infancy, the levels recover by 18–24 months of age. Normal T cells and absence of circulating B cells characterize XLA, whereas B cells are present in transient hypogammaglobulinemia of infancy, congenital HIV infection, early-onset common variable immunodeficiency, and in many forms of severe combined immunodeficiency.

Treatment

XLA patients treated with immunoglobulin replacement therapy (Table 32.3) have excellent lifelong prognosis. In addition, clinicians should be vigilant for infections and comorbidities described above which require specific workup and treatment.

Transient Hypogammaglobulinemia of Infancy

In transient hypogammaglobulinemia of infancy (THI), infants experience a delay in the maturation of their antibody synthesis ability. Its cause is unknown, but it subsides by the end of infancy. Maternal IgG crosses the placenta as early as

Table 32.3 Preparations available for immunoglobulin replacement

Product	Bivigam	Carimune NF	Flebogamma DIF	Gammagard Liquid	Gammagard S/D	Gammaked	Gammaplex	Gamunex C	Hyqvia	Hizentra	Octagam	Privigen
Manufacturer	Biotest	CSL Behring	Grifols	Baxter	Baxter	Kedrion	Bio Products	Grifols	Baxter	CSL Behring	Octapharma	CSL Behring
Form[a]	Liquid 10%	Lyophilized (3–12%)	Liquid 5 or 10%	Liquid 10%	Lyophilized (5 or 10%)	Liquid 10%	Liquid 10%	Liquid 10%	Liquid 10%	Liquid 20%	Liquid 5%	Liquid 10%
Indications[b]	PID	PID, ITP	PID	PID	PID, ITP, CLL, KS.	PID, ITP, CIDP	PID, ITP	PID, ITP, CIDP	PID	PID	PID	PID, ITP
Route[c]	IV	IV	IV	IV,SC	IV	IV,SC	IV,SC	IV,SC	SC	SC	IV	IV
IgA content (μg/ml)	200	720	<50	37	<2.2	46	<4	46	37	<50	<50	<25
Stabilizer[d]	0.29 M glycine,	8.4 mg/ml sucrose	50 mg/ml D-sorbitol	18.8 mg/ml glycine	20–40 mg/ml glucose	0.24M Glycine	0.24M Glycine	0.24M Glycine	0.25M Glycine	0.25M L-proline	100 mg/ml maltose	0.25M L-proline
Sodium content	0.140M	Trace amounts	Trace amounts	Trace amounts	0.145 mEq/ml	Trace amounts	Trace amounts	Trace amounts	8.5 mg/ml	0.045 mEq/ml	30 mM	Trace amounts
Virus inactivation[e]	SD, NF	Low pH pepsin,NF	Low pH, SD, NF, Pas	SD, NF, low pH, Pas	SD	DF, low pH	NF, SD, low pH	DF, low pH	SD, NF, low pH, Pas	NF, DF, low pH	SD, low pH	NF, DF, low pH
TSE reduction label[f]	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No	Yes
pH in liquid form	4.0–4.6	6.4–6.8	5.0–6.0	4.6–5.1	6.4–7.2	4.0–4.5	4.0–4.5	4.0–4.5	4.6–5.1	6.4–7.2	5.1–6.0	4.8

Osmolality (mOsm/kg)[g]	510	384 (at 6 %) 768 (at 12 %)	240–350	240–300	636 (at 5 %) 1250 (at 10 %)	258	258	258	240–300	380	310–380	320
Storage (months)[h]	24 months (2–8 °C)	24 months (2–25 °C)	24 months (2–25 °C)	24 months (2–25 °C)	24 months (2–25 °C)	36 months (2–8 °C)	24 months (2–25 °C)	36 months (2–8 °C)	36 months (2–8 °C)	30 months (2–25 °C)	24 months (2–25 °C)	36 months (2–25 °C)

[a]Lyophilized preparations are best reconstituted in sterile water. Some may also be reconstituted in saline solution (NaCl 0.9 %) or dextrose 5 %, but these solutions will generate higher osmolality. Values in this table relate to reconstitution in sterile water at a final concentration of 5 % or 6 %

[b]Indications: *PID* primary immunodeficiency, *ITP* idiopathic thrombocytopenic purpura, *CLL* chronic lymphocytic leukemia, *KS* Kawasaki syndrome, *CIDP* chronic inflammatory demyelinating polyneuropathy

[c]Route of administration: IV (intravenous). SC (subcutaneous)

[d]Stabilizer keeps IgG in solution preventing formation of aggregates, which may activate complement causing anaphylactoid reactions. Maltose in Octagam may cause spurious elevation of capillary blood glucose readings with certain strips and devices

[e]Virus inactivation processes: the process of purifying IgG from plasma already inactivates many viruses such as HIV. This process involves protein fractionation, precipitation in alcohol, and filtration. In addition, specific steps are added to kill viruses. *SD* solvent-detergent treatment kills enveloped viruses (e.g., HCV, HIV), *NF* nanofiltration eliminates viruses by removing any particles 35 nm or larger, *DF* depth filtration removes viruses and impurities, *Pas* pasteurization (heated at 60 °C for 10 h)

[f]TSE reduction label: processing is proven to reduce the risk for transmissible spongiform encephalopathy (prion disease)

[g]Normal serum osmolality is 285–295 mOsm/kg. Values for lyophilized preparation reflect reconstitution in sterile water

[h]Temperature conversion: 2 °C = 36 °F, 8 °C = 46 °F, 25 °C = 77 °F, 30 °C = 86 °F. Preparations cannot be frozen

Hyqvia contains recombinant human hyaluronidase 160 IU/ml

13 weeks of gestation but in small amounts. Fetal IgG serum levels reach 5–10 % of maternal levels by 17–22 weeks of gestation and 50 % at 28–32 weeks. Only in the last trimester, between 33 and 37 weeks of gestation, the placental transfer increases rapidly reaching 100 % or more of maternal levels. After birth, term infants naturally experience a decline in IgG concentrations with a nadir at 5–6 months at which point maternally transferred IgG has been metabolized, and the infant's own antibody production is developing. The lowest serum IgG levels reach about 350 mg/dl, and normal infants may begin to experience respiratory infections such as otitis media episodes. Premature infants have less maternal IgG at birth and can experience longer and deeper nadir in serum IgG levels until their own IgG synthesis reaches normal levels.

THI infants have persistently low IgG levels whereas IgM and IgA levels are normal, although in some IgA may also be low. They also have circulating B cells. If clinically significant, infants have poor antibody response to vaccines and experience unusually frequent respiratory infections requiring frequent antibiotic courses or continuous prophylactic antibiotics. They rarely need immunoglobulin replacement therapy, which may adversely impair infant's own antibody production (e.g., response to vaccines). THI infants normalize their serum IgG levels and antibody responses by 18–24 months of age.

Common Variable Immunodeficiency

Patients with common variable immunodeficiency (CVID) usually have normal antibody production in their first years or decades of life, but then, for unknown reasons, their antibody production declines and they start experiencing frequent respiratory infections. Several genetic defects have been associated with CVID (e.g., inducible T-cell co-stimulator [ICOS], CD19, CD20, CD21, CD81, TACI, BAFF, PIK3CD, and other genes), but it is unclear why disease starts later in life. Many patients have unknown immunological defects suggesting that many defects in the terminal B-cell differentiation into plasma cells can lead to similar clinical manifestations. Rare cases of CVID have been reported following treatment with sulfasalazine, hydantoin, and carbamazepine. CVID occurs in 1 to 10,000–100,000 individuals.

Clinical Manifestations

Although the onset of CVID can occur at any age, usually patients present between 15 and 35 years of age with recurrent sinopulmonary infections, particularly refractory chronic sinusitis. Infections are caused by common respiratory microbes such as pneumococcus, *Moraxella*, and *Haemophilus influenzae*. Other pyogenic bacteria may also be found. CVID patients may have recurrent bronchitis and pneumonia and may develop bronchiectasis. A noninfectious pulmonary manifestation is

interstitial lung disease (biopsy shows granulomatous-lymphocytic changes, follicular bronchiolitis, lymphocytic interstitial pneumonitis, nodular lymphoid hyperplasia, or organizing pneumonia) which may require immunosuppressant therapy.

CVID patients also have a high prevalence of gastrointestinal and autoimmune diseases, which may precede onset of infections. These include achlorhydria, cholelithiasis, giardiasis, pernicious anemia, malabsorption, autoimmune blood cytopenias (usually thrombocytopenia and hemolytic anemia), rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Graves' diseases, hypothyroidism, inflammatory bowel disease, autoimmune-induced diarrhea with malabsorption, and gastrointestinal bleeding.

Non-caseating granulomas may affect the liver and spleen causing visceromegaly, abdominal lymphadenopathy, and obstructive symptoms. They may also affect the lungs. On examination, patients have mildly enlarged lymph nodes and may have splenomegaly.

Increased incidence of malignancies beyond 40 years of age is also observed. These include gastric carcinoma and an over 100-fold increase in incidence of lymphoma compared with the general population.

Laboratory Diagnosis

Diagnosis is based on clinical manifestations (e.g., infections, autoimmunity, or granulomatous disease), low immunoglobulin levels, and poor antibody response. Diagnosis requires low IgG together with low levels of one or both remainder immunoglobulins (IgA, IgM). Usually IgA is very low or absent, and IgM is low in 50 % of patients. Poor antibody response (see Table 32.2 and footnote) is measured by absent isohemagglutinins (<1:10) and antibody response to polysaccharide vaccine (e.g., Pneumovax). Circulating B-cell number is normal, but circulating Ig-class-switched B memory cells and plasma cells in lymph nodes and lamina propria of the small intestine are decreased. T-cell number and function are usually normal, but eventually many patients may have laboratory evidence of impaired T-cell number and function. However, opportunistic infections associated with T-cell deficiency do not occur, and if they do, the clinician should suspect other diseases such as hyper IgM syndrome or a combined T- and B-cell immunodeficiency. Examples of T-cell abnormalities in CVID include reduced CD4/CD8 ratio, impaired proliferative responses, and impaired delayed hypersensitivity testing. Differential diagnosis includes XLA (in which B cells are absent) and protein-losing enteropathy (low serum albumin and alpha1 trypsin in stools) or nephropathy (proteinuria).

Treatment

CVID patients are treated with immunoglobulin replacement, which leads to excellent prognosis. Manifestations that often occur and need specific management are chronic sinus disease, chronic lung disease (e.g., bronchiectasis, interstitial lung

disease), and gastrointestinal diseases. Surveillance for malignancies is also important. Serology should not be relied upon as a means to diagnose infectious diseases in patients with antibody deficiency and on immunoglobulin replacement. Instead, detection of the infectious agent should be sought (e.g., antigen, PCR, or culture).

Selective IgA Deficiency

The exact cause of selective IgA deficiency (SIgAD) and normal concentrations of other immunoglobulins is unknown despite this being the most common immune defect. It is encountered in about 1:600 Caucasians, but it is 3–30 times less prevalent in Asians. Most patients do not have recurrent infections but may be predisposed to allergic and autoimmune diseases. B cells can switch from IgM to IgG, but not to IgA, whereas T cells are normal and support IgA production in B cells from normal donors. Most cases are sporadic, although there are reports of it occurring in families with other SIgAD and even CVID cases, suggesting shared etiopathogenesis between these deficiencies. SIgAD is also associated with HLA-B8. Some cases of SIgAD have been associated with drugs such as penicillamine, sulfasalazine, anticonvulsants, gold, chloroquine, captopril, and fenclofenac. It may also occur with chronic hepatitis C. When associated with IgG2 deficiency, patients are more susceptible to infections.

In rare cases, patients have deficiency in the secretory component, and thus can produce IgA, but cannot secrete it into the mucosal lumen. In these cases, serum IgA is normal, but salivary IgA is decreased or absent.

Clinical Manifestations

Patients with SIgAD are usually asymptomatic but may have increased susceptibility to infections, allergies, autoimmune diseases, and cancer. If symptomatic, manifestations usually start in the first decade of life.

Infections are usually recurrent and refractory sinusitis, but not pneumonias or bronchiectasis as observed in patients with CVID. However, combination with IgG2 deficiency increases infectious manifestations.

Allergic diseases are increased in patients with SIgAD and are often difficult to treat. SIgAD is twice more prevalent in atopic individuals than in the general population. It is postulated that mucosal IgA prevents absorption of allergens and immune sensitization and that in SIgAD this protective mechanism is absent. Some patients with SIgAD develop allergic reactions to IgA, which are mediated by antibodies against IgA. Many have not received any blood products and it is unclear how they become sensitized. Sensitization may occur through ingestion of breast milk, transplacental maternal IgA transfer, cross-sensitization with cow's milk IgA, or exposure to mucosal IgA from normal individuals. Very rarely, patients with SIgAD will develop anaphylaxis to blood products.

Autoimmune diseases or autoantibodies are present in 37 % of patients with SIgAD. The mechanism for this high prevalence of autoimmunity is unknown. These patients are at risk for developing celiac disease, ulcerative colitis, Crohn's disease, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, Sjögren's syndrome, Coombs-positive autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, autoimmune thyroiditis, Addison's disease, and chronic autoimmune hepatitis.

Some cancers have been reported in association with SIgAD including thymoma, reticulum cell sarcoma, and carcinomas of the lung and esophagus.

Laboratory Diagnosis

Diagnosis is based on very low or absent serum IgA (<15 mg/dl), although in most cases it is absent (<5 mg/dl). Other immunoglobulins are normal or elevated, and plasma cells are present in secondary lymphoid tissues and bone marrow. In infants, diagnosis may be delayed since serum IgA level is low in newborns, rises rapidly in the first 2 years of life, but only reaches adult levels by adolescence. Circulating B-cell numbers are normal, although the number IgA-bearing B cells may be decreased. T-cell numbers and function are normal. Some patients may also have low IgG2. Rare patients may have deficiency in the secretory component, leading to low mucosal IgA, which is diagnosed by detecting normal IgA in serum and its absence in saliva. On occasion, selective IgA deficiency may be the first manifestation of a more severe immunodeficiency such as ataxia telangiectasia or chronic mucocutaneous candidiasis.

Treatment

There is no specific treatment for SIgAD. IgA is the antibody isotype most abundantly produced in the body and a large proportion is secreted in mucosal lumen. Treatment, therefore, is limited to the associated conditions. In those with combined IgG2 deficiency, recurrent infections, and poor antibody response, immunoglobulin therapy to replace IgG can be considered. For patients reacting to blood products who need blood transfusion, washed (3×) packed red blood cells may minimize reactions. Prognosis for SIgAD patients is excellent and mostly determined by associated conditions.

Other Antibody Deficiencies

In *selective IgM deficiency*, patients have absent serum IgM but normal levels of other immunoglobulins. Circulating B-cell number is normal. T-cell number and function are also normal. Patients may or may not have poor antibody response.

They may have recurrent respiratory infections with pneumococci and *Haemophilus influenzae* and may also have autoimmune diseases.

In *selective IgG subclass deficiency*, total IgG may be normal or slightly decreased, but patients lack an individual IgG subclass, usually IgG1, IgG2, or IgG3 since they account for 65 %, 20 %, and 10 % of serum IgG. IgG4 is absent in many normal individuals and it may make up to 5 % of total IgG. Diagnosis of selective IgG deficiency is made if IgG1 is <250 mg/dl, IgG2 <50 mg/dl, or IgG3 <25 mg/dl. Like other antibody deficiencies, they may present with repeated pyogenic sinopulmonary infections and may also develop autoimmune diseases.

In *specific antibody* deficiency, patients have recurrent sinopulmonary infections and normal immunoglobulin levels but have a functional impairment in producing specific antibodies against polysaccharide antigens (e.g., pneumococcal and *H. influenzae* vaccines). Also normal are serum IgG subclasses and antibody responses to protein vaccines (e.g., tetanus and diphtheria toxoids). This immunodeficiency happens in young children with manifestations similar to those of other antibody deficiencies. Many improve their antibody response by 5–10 years of age, but others have persistent deficiency. In addition, adults also developed this disease alone or associated with chronic airway disease such as chronic rhinosinusitis and bronchiectasis.

In *immunodeficiency with thymoma* (*Good's syndrome*), aged adult patients may initially present with recurrent sinopulmonary infections, chronic diarrhea, dermatitis, septicemia, stomatitis, and urinary infections, before a thymoma is discovered by chest X-ray. In 75 % of cases, the thymoma is of the spindle cell type. They are susceptible to development of myasthenia gravis, aplastic anemia, thrombocytopenia, amyloidosis, and chronic hepatitis. They have markedly reduced serum immunoglobulins, may lack circulating B cells, and may have impaired tests of T-cell function. Removal of thymoma does not improve immunodeficiency, but can improve myasthenia gravis and aplastic anemia. Immunoglobulin replacement improves immunodeficiency and chronic diarrhea. Prognosis is poor, and death may occur from infection, aplastic anemia, or thrombocytopenia.

For all these aforementioned other antibody deficiencies, treatment focuses on early diagnosis and treatment of infections, prophylactic antibiotics, and if necessary immunoglobulin replacement therapy.

Immunoglobulin Replacement Therapy

Immunoglobulin preparations replace IgG only. The IgG is purified from serum of thousands of donors obtained by plasmapheresis. These are recurrent donors who are screened negative for blood-borne infectious diseases for at least 6 months

before entering the donor pool. The IgG is purified by alcohol or Cohn fractionation and filtration steps, a process that by itself kills many viruses. Despite that, an outbreak of hepatitis C occurred in the early 1990s due to contaminated intravenous immunoglobulin (IVIG) preparations. As a result, immunoglobulin preparations now undergo additional processes to kill viruses such as solvent-detergent treatment to kill enveloped viruses (e.g., hepatitis B virus and HIV), pasteurization, low pH (pH = 4) together with pepsin treatment, and nanofiltration. There has never been a case of transmissible spongiform encephalopathy (TSE) caused by a contaminated immunoglobulin preparation. Indeed, the alcohol fractionation steps partitions prion proteins, which probably reduces the risk of transmission of prion disease by immunoglobulin products.

The first immunoglobulin preparation was administered intramuscularly because IgG aggregates cause complement activation, leading to anaphylactoid reactions if injected intravenously. In the 1980s, intravenous immunoglobulin preparations became available through the addition of sugars – and later amino acids – which solubilize IgG and prevent aggregation (see Table 32.3). Preparations are also available for subcutaneous (SCIG) infusion which precludes the need for intravenous access, allows easier home self-administration than intravenous infusions, has similar efficacy, results in more stable serum levels, and is safer, causing less severe systemic side effects. Subcutaneous immunoglobulin preparations are infused weekly, but Hyqvia can be infused at the same frequency as intravenous preparations, that is, every 3–4 weeks.

The usual starting dose of intravenous immunoglobulins (IVIG) for primary immunodeficiencies is 400–600 mg/kg infused every 4 weeks. To minimize adverse events, the first infusion should start slowly at 1 mg/kg/min (or 0.01 ml/kg/min or, for adults, 1 ml/kg/h for a 5 % IVIG preparation), and if tolerated, double the infusion rate every 30 min to a maximum of 8 mg/kg/min (or 8 ml/kg/h for a 5 % IVIG). In subsequent infusions, patients usually tolerate starting at faster initial rates, although the maximum rate should be maintained. Dose and interval are adjusted to improve clinical manifestations (e.g., infections and fatigue) and to maintain a trough serum IgG concentration of at least 500 mg/dl after five half-lives (3–4 months). Sometimes dosing at 3-week intervals or more often is necessary for patients who metabolize IgG rapidly.

Mild to moderate adverse events to infusion of immunoglobulin preparations are very common particularly with the first infusions and include headache, nausea, rigors, and back pain. Less often patients experience fever, chest pain, abdominal pain, flushing, vomiting, arthralgia, myalgia, and hives. IVIG is better tolerated in subsequent infusions and eventually many patients tolerate them well without premedications (see below). However, they may recur with switching of immunoglobulin preparations. If adverse events occur during infusion, the infusion rate should be reduced, or even temporarily stopped, depending on the severity of symptoms. Symptoms can be treated with oral acetaminophen 500–650 mg (or 10 mg/kg for children) or oral or parenteral diphenhydramine 25–50 mg (1.25 mg/kg), and rarely

systemic corticosteroids may be necessary (e.g., methylprednisolone 125 mg or 0.5–1 mg/kg IV). To prevent adverse events, one can (1) premedicate patient with acetaminophen and diphenhydramine 30–60 min before infusion. Rarely oral corticosteroids may also be necessary. (2) Infuse at a lower rate. (3) Use a lower IVIG concentration (e.g., 3 % or 5 %). (4) Use a preparation with low osmolality. (5) Switch to a different immunoglobulin brand. (6) Switch from intravenous to subcutaneous immunoglobulin. Extremely rarely anaphylactic reactions may be due to patient's antibodies against IgA, in which case a preparation with low IgA content may help.

Immunoglobulin preparations can also cause severe adverse events. The IVIG preparations have a black box warning on the risk of renal dysfunction, acute renal failure, osmotic nephrosis, and death. The renal damage is caused by hyperosmotic insult. The risk increases in those with preexisting renal insufficiency and diabetes mellitus; aged 65 years or older; with volume depletion, sepsis, and paraproteinemia; and on concomitant nephrotoxic drugs. In addition, rapid infusion, high doses (e.g., 1 g/kg/day × 1–2 days used for autoimmune diseases), hyperosmolar preparations, and IVIG containing sucrose may also increase the risk for renal complications. Thromboembolic events have also been reported particularly with high doses and rapid infusion and in those with preexisting cardiovascular diseases or history of thromboembolic events. Other rare severe adverse events are aseptic meningitis, antibody-mediated (positive direct Coombs test) hemolysis, transfusion-related acute lung injury, cardiac arrest, bullous skin diseases, and anaphylactoid reactions.

Subcutaneous infusion causes lower peak serum levels (minimizes dose-related adverse events) and higher trough serum levels (e.g., around 1000 mg/dl), which may minimize risk of infection. Indeed, serum IgG levels are very stable. Switching routes from intravenous to subcutaneous or vice versa may require dose adjustments according to the preparation insert. Some SCIG doses are about 40 % higher than IVIG dose on a monthly basis. The recommended weekly dose is 100–200 mg/kg, 100 mg/kg per week if starting in immunoglobulin therapy-naïve patients. Systemic adverse events are similar to those of IVIG. In addition, local injection site adverse events occur in 80–85 % of patients but are mild to moderate and wane in intensity and frequency in subsequent infusions, down to 60 % of patients by the tenth infusion, and stabilize at 30–40 % by the 25th infusion. Local reactions included local edema, erythema, and pruritus, which usually disappear the day after the infusion. SCIG can be infused slowly into two to four sites simultaneously at 20 ml/h/site using bifurcated tubing. Sites need to be at least 2 in. apart. Volume infused per site varies among preparations, usually 15–70 ml, although Hyqvia can be infused at 300–600 ml/site because it contains hyaluronidase, which reversibly (lasts 24–48 h) depolymerizes hyaluronan, a polysaccharide in the extracellular matrix of the connective tissue, increasing permeability of the subcutaneous tissue and allowing large volumes to be infused per site. SCIG is infused in rotating sites in the lower abdomen – away from navel and midline – upper thighs, upper arms, and lateral hips.

Complement Deficiencies

Defects in genes involved in the three major complement pathways have been described: classical pathway, alternative pathway, and mannose-binding lectin (MBL). All three pathways converge to activate C3, which then activates the late components that form the membrane attack complex (C5, C6, C7, C8, and C9). The complement system enhances phagocytosis by opsonization and directly kills bacteria and viruses (see Chap. 23).

Except for MBL deficiency, which may affect 5 % of the population, all other complement deficiencies combined account for only 2 % of all primary immunodeficiencies. Defects in all soluble complement components have been described. Most are autosomal recessive deficiencies. Exceptions are properdin deficiency (X-linked) and C1 esterase inhibitor deficiency (see Chap. 11), which is autosomal dominant. MBL deficiency is also autosomal dominant.

Deficiencies in the early components of the classical pathway (C1q, C1r, C1s, C4, and C2) manifest with pyogenic infections caused by encapsulated bacteria (pneumococcus and *Haemophilus influenzae*), but susceptibility to infections is attenuated by the ability to still activate C3 via alternative and MBL pathways. Deficiencies in these early components are also associated with autoimmune collagen vascular diseases (systemic lupus erythematosus) and glomerulonephritis.

C3 deficiency is associated with pyogenic infections, disseminated *Neisseria* infections, and vasculitis. Deficiencies in the late complement components C5, C6, C7, and C8 lead to recurrent disseminated or invasive neisserial infections (mainly *Neisseria meningitides* and to a much lesser extent *N. gonorrhea*). C9 deficiency is associated with pyogenic infections. These distinctions are not strict and deficiency of early components can also be associated with neisserial infections, and late component deficiencies can occur with autoimmune diseases.

Deficiency in components of the alternative pathway can lead to recurrent disseminated or invasive neisserial infections (factor B and properdin deficiencies) or recurrent pyogenic infections (factor D and properdin deficiencies).

Deficiencies in proteins that regulate the complement system also cause disease. Factor H and factor I deficiencies are associated with autoimmune collagen vascular diseases and recurrent pyogenic infections. C4bp deficiency is associated with angioedema and Behçet-like syndrome. These three deficiencies are autosomal recessive. C1 esterase inhibitor deficiency is autosomal dominant and causes hereditary angioedema (see Chap. 11) and is also associated with autoimmune diseases.

Mannan (*or mannose*)*-binding lectin* (*or protein*) (MBL or MBP, chromosome 10q11.2-q21) is a circulating lectin that binds to glycosylated surface components of microbes and activates complement via classical and alternative components leading to opsonization and killing of microbes. It is produced by the liver as part of the acute phase response. MBP activates the complement pathways via its MBL-associated proteases 1 and 2 (MASP-1 and MASP-2). MBL is an important innate defense molecule in the first years of life when maternal antibodies wane and infants start to develop their repertoire of memory antibody responses. Thereafter, it

becomes less clinically relevant. However, few cases of clinically significant MBL deficiency have been described in adults. Median normal plasma levels are 800–1000 μg/l. When deficient, its serum levels are more than tenfold lower than normal (<50 μg/l). MBL-deficient infants present with recurrent respiratory tract infections, otitis media, and chronic diarrhea. This deficiency has been associated with increased susceptibility to HIV infection, systemic lupus erythematosus, arterial thrombosis, and increased morbidity in cystic fibrosis.

Deficiencies in *cell-bound complement proteins* also cause disease. *Complement receptor 1* (CR1) deficiency is probably an acquired disease due to autoimmune complex formation in systemic lupus erythematosus (SLE). CR1 is expressed on erythrocytes and is a cofactor for factor I which cleaves C4b and C3b and inactivates C3 and C5 convertases. On erythrocytes, it binds and captures circulating immune complexes and facilitates their elimination via liver and splenic macrophages. Thus, excessive immune complex formation in SLE due to autoantibodies may consume CR1 causing an acquired, not inherited, deficiency. *Complement receptor 3*(CR3 or CD11b CD18) is an integrin beta 2 and its deficiency is described below (see section "Leukocyte Adhesion Deficiency Type 1"). Mutations in the *phosphatidylinositol glucan A*, an enzyme that forms an anchor for three membrane-bound proteins, causes deficiency of three proteins that regulate complement activation: decay-accelerating factor (DAF), protectin (CD59), and homologous restriction factor (HRF). Other glycosyl phosphatidylinositol-linked proteins are also affected. CD59 deficiency is believed to result in intermittent hemolysis caused by uninhibited membrane attack complexes causing paroxysmal nocturnal hemoglobinuria (PNH).

Laboratory Evaluation of the Complement System

Complement hemolytic activity 50 % (CH50) is a functional test of the complement system that determines the ability of patient's serum complement to lyse 50 % of antibody-sensitized sheep erythrocytes. It is a good screening test for complement deficiency. Patients with severe deficiency of a classical complement component will have a total complement CH50 % of less than 5 % (CH50 <5 %). An exception is C9 deficiency where CH50 is 30–50 % of normal because hemolysis is only partially impaired in this deficiency. Although CH50 is low in deficiencies of components of the classical pathway and of terminal components, deficiency in components of the alternative pathway can also cause low CH50. However, an alternative pathway hemolytic activity test (AH50) is also available in specialized laboratories and tests the ability of serum to lyse rabbit erythrocytes. The AH50 tests the function of alternative pathway components (factors B, H, I, and properdin), C3, and the membrane attack complex (C5 to C9). If CH50 or AH50 is low, the specific complement deficiency may be pursued by quantification and functional assay for individual complement components, which is available in few laboratories.

Two components need careful interpretation of results, C1 esterase inhibitor and C8, because they may be present, but may not be functional. In the case of C1 inhibi-

tor, certain mutations may allow production of nonfunctional molecules. In the case of C8, some of its three chains can be expressed in C8-deficient patients because C8 function is impaired with deficiencies in either C8β alone or both C8α and C8γ.

Lastly, as for any immunodeficiency with known genetic defect, sequencing the affected gene is another option for diagnosis.

Treatment of Complement Deficiencies

There is no specific treatment for complement deficiencies, except for replacement of C1 esterase inhibitor (see below and Chap. 11). Patients with deficiencies in complement components that increase susceptibility to infections should receive vaccines (meningococcal tetravalent vaccine, pneumococcal 23-valent vaccine, and conjugated *H. influenzae* vaccine). During severe infections, transfusion of fresh frozen plasma to attempt replacement of missing component may be beneficial, although in complete deficiencies, patients may develop antibodies to nonself complement proteins after repeated transfusions, reducing efficacy in the long term. Infections should be treated early and aggressively and those with frequent infections may benefit from continuous antibiotic prophylaxis. Treatment of autoimmune diseases is not changed if a patient has concomitant complement deficiency.

Acute angioedema from hereditary C1 esterase inhibitor deficiency can be treated with plasma-derived or recombinant C1 esterase inhibitor, ecallantide (a kallikrein inhibitor), icatibant (a bradykinin B2 receptor antagonist), or fresh frozen plasma. Fresh frozen plasma, however, may adversely worsen angioedema by providing additional complement substrate. Prophylaxis of acute angioedema is based on avoiding triggers (e.g., invasive surgical and dental procedures), plasma-derived or recombinant C1 esterase inhibitor, androgens (e.g., danazol, stanozolol), and antifibrinolytic agents (e.g., aminocaproic acid).

Combined Cellular and Humoral Immunodeficiencies

In these deficiencies, patients have complete or partial defects in T cells (cellular immunity) and in B cells (antibody response).

Severe Combined Immunodeficiencies

Patients with severe combined immunodeficiencies (SCID) have marked impairment of T-cell development and/or function with variable impairment of B cells, which may be primary or secondary to lack of T helper function. The various forms of SCID are characterized by a common clinical presentation in the first months of life, and most require stem cell transplantation therapy.

Clinical Manifestations

Despite the large number of genetic defects causing several types of SCID (Table 32.4), their clinical manifestations are similar and typically start within 3 months of age with persistent infections, failure to thrive, and diarrhea. Infections include persistent oral thrush and *Candida* diaper rash, *Pneumocystis jirovecii* (*carinii*) pneumonia, bacterial pneumonias, protracted diarrhea, and severe infections with common respiratory viruses including respiratory syncytial virus (RSV), Epstein-Barr virus (EBV), and *Cytomegalovirus* (CMV). Live vaccines can also cause clinical infections, particularly *Rotavirus*, which is given routinely in the United States as well as oral polio vaccine and bacillus Calmette-Guerin (BCG), which are administered in the first months of life in some countries, but not in the United States. In addition, patients may have vomiting, fever, or difficult to treat rashes. On examination they have growth failure, have absence of tonsils and of lymph nodes, and may have hepatosplenomegaly. Treatment of infection is difficult. Occasionally, patients may develop graft-versus-host disease (GVHD) from maternal T cells, which is rarely fatal, or from lymphocytes in blood product transfusion, which is usually fatal without immune reconstitution. Use of irradiated blood products helps prevent GVHD and should be routine for young infants and the use of live vaccines is contraindicated.

Laboratory Diagnosis

Early diagnosis of SCID is therefore of paramount importance, which has been aided by the development of newborn screening tests for SCID and other T-cell lymphopenia by quantitative PCR of DNA in newborn dried blood spots to enumerate T-cell receptor excision circles (TREC). TREC levels below the cutoff for the respective State Laboratory should trigger an evaluation for confirmation of T-cell lymphopenia and diagnosis of SCID or other causes of T-cell lymphopenia. The newborn screening test is only a screening test and not a diagnosis of SCID. However, it has allowed the early diagnosis and successful treatment of 90 % of identified newborns with SCID. When newborn screening is not available, laboratory diagnosis starts with identification of lymphopenia in neonates who should have >2500 lymphocytes per mm^3. In addition, they may have hypogammaglobulinemia, although the latter can be masked by maternal IgG. Thymic shadow is absent on chest X-ray. As shown in Table 32.1, flow cytometry enumeration of blood T cells and its subsets, CD4 and CD8 cells including naïve and memory T cells, B cells, and NK cells, is very helpful to identify the type of SCID. CD4 count is usually very low (<200 per mm^3) resulting in impaired lymphocyte proliferation to mitogens and to allogeneic cells (<10 % of control). A high percentage of activated (HLA-DR+) and memory T cells help identify GVHD from maternal engraftment in patients with SCIDs. HLA typing and biopsy of rash can help diagnose GVHD. The

Table 32.4 Phenotypes of combined T- and B-cell immunodeficiencies

Lymphocyte phenotype			Immune defect	Chromosome and inheritance
T	B	NK		
T−	B+	NK−	X-linked SCID (γ_c deficiency) Jak3 deficiency CD45 deficiency IL-2R alpha chain deficiency	Xq13. X-linked 19p13.1. Autosomal recessive 1q31-q32. Autosomal recessive 10p15.1
T−	B+	NK+	IL7R alpha chain deficiency CD3 delta chain deficiency CD3 epsilon chain deficiency	5p13. Autosomal recessive 11q23. Autosomal recessive 11q23. Autosomal recessive
T−	B−	NK−	Adenosine deaminase deficiency	20q13.11. Autosomal recessive
T−	B−	NK+	RAG1 and RAG2 deficiency Artemis deficiency	11p13-p12. Autosomal recessive 10p13. Autosomal recessive
T4+ T8−	B+	NK+	Zap70 deficiency HLA-I deficiency CD3 zeta chain deficiency	2q12. Autosomal recessive 6p21.3. Autosomal recessive 1q22-q23. Autosomal recessive
T4− T8+	B+	NK+	HLA-II deficiency	Four genes in chromosomes 1,13,16, or 19. Autosomal recessive

In T-cell deficiencies total T cells (CD3 cells) are low and both of its subtypes are low (T4 = CD4 helper cells and T8 = CD8 cytotoxic/suppressor cells). In T4+ T8- and T4- T8+ deficiencies, total T-cell number (CD3 cells) is usually normal

Abbreviations: γ_c common gamma chain, *RAG* recombination-activating gene (recombinase), *Zap70* zeta chain-associated protein kinase of 70 kd

presence of maternal cells is diagnostic of SCID as healthy newborns will deplete any maternally engrafted cells. Once lymphocyte phenotyping is available, specific molecular defect can be pursued at the protein and genetic level. Definitive diagnosis is made by demonstrating deficiency of the affected protein and by identifying mutations in the affected gene.

Treatment

The definitive treatment for SCIDs is stem cell transplantation. In addition, patients receive supportive therapy with antibiotic treatment for infections as well as prophylaxis for *Pneumocystis jirovecii*, fungal and sometimes viral infections, immunoglobulin replacement, avoidance of live vaccines, and use of irradiated (2500 rads) blood products (to prevent GVHD). Ideally, an HLA-matched sibling is used for the stem cell transplantation, but transplantation with HLA-matched unrelated donors or HLA haploidentical bone marrow depleted from T cells is more commonly available. Transplantation reconstitutes T-cell number and function in 3–4 months, but B-cell engraftment and function may take longer or may never be fully

reconstituted. Pretransplant conditioning (full or reduced intensity) of the SCID recipient is not necessary because of the severe T-cell defect but may improve T- and B-cell reconstitution. Prophylaxis for GVHD with calcineurin inhibitors (cyclosporine A or FK506) is usually used in the immediate posttransplant period only. Use of CMV- and EBV-negative donors helps prevent fatal systemic viral infections during and immediately after transplantation.

Forms of SCIDs

The most common type of SCID is the *X-linked* form that accounts for about 30 % of cases and is due to lack of the common gamma chain (cγ), a cytokine receptor chain that transduces activation signal into the cytoplasm via phosphorylation of *Janus kinase 3*(Jak3). It is present in the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. IL-7 and its receptor are necessary for T-cell development and IL-15 and its receptor are necessary for NK-cell development. Therefore, this type of SCID is characterized by absent T and NK cells with normal B-cell numbers, which do not function well because of the absence of T-cell help. A similar phenotype ensues with deficiency in Jak3, the fourth most common type of SCID affecting 6 % of cases. Jak3 deficiency is inherited in an autosomal recessive manner and therefore affects males and females equally.

The second most common SCID is *adenosine deaminase* (ADA) deficiency, which accounts for about 17 % of cases. ADA participates in the catabolism of adenosine, as does purine nucleoside phosphorylase (PNP; see Fig. 32.1), which participates in the catabolism of both purines (adenosine and guanosine). Deficiency in PNP also causes SCID. These enzymes similarly transform the deoxy forms of the nitrogen bases (see Fig. 32.1).

ADA deficiency leads to accumulation of purine metabolites, which are toxic for thymocytes (thymic T-lymphocyte precursors) and inhibit T-cell signaling. The high rate of apoptosis of the developing T cells in the thymus due to negative selection and consequent high rate of RNA/DNA catabolism renders this organ more susceptible to this enzymatic defect than other tissues. ADA deficiency leads to accumulation of adenosine (from RNA degradation), deoxyadenosine (from DNA degradation), and methyladenosine. Other nucleotides also accumulate, one being 2′-deoxyadenosine triphosphate (dATP), which is toxic to lymphocytes, particularly T cells. Adenosine inhibits T-cell signaling. dATP inhibits ribonucleotide reductase, which reduces purines and pyrimidines, a necessary step for DNA synthesis. The amount of dATP is increased in erythrocytes 100–2000-fold in this type of SCID. Adenosine and dATP also inhibit S-adenosylhomocysteine hydrolase (SAHH), which is essential for methylation reactions and to maintain cell viability. Lastly, dATP initiates apoptosis by inducing cytochrome c release from mitochondria. ADA deficiency causes the most profound lymphopenia among all SCIDs with counts <500/mm^3 affecting T, B, and NK cells. Diagnosis is confirmed by measuring ADA activity in cell lysates from erythrocytes as a screening tool (<1 % of activity regardless the age of onset symptoms of ADA deficiency) and then con-

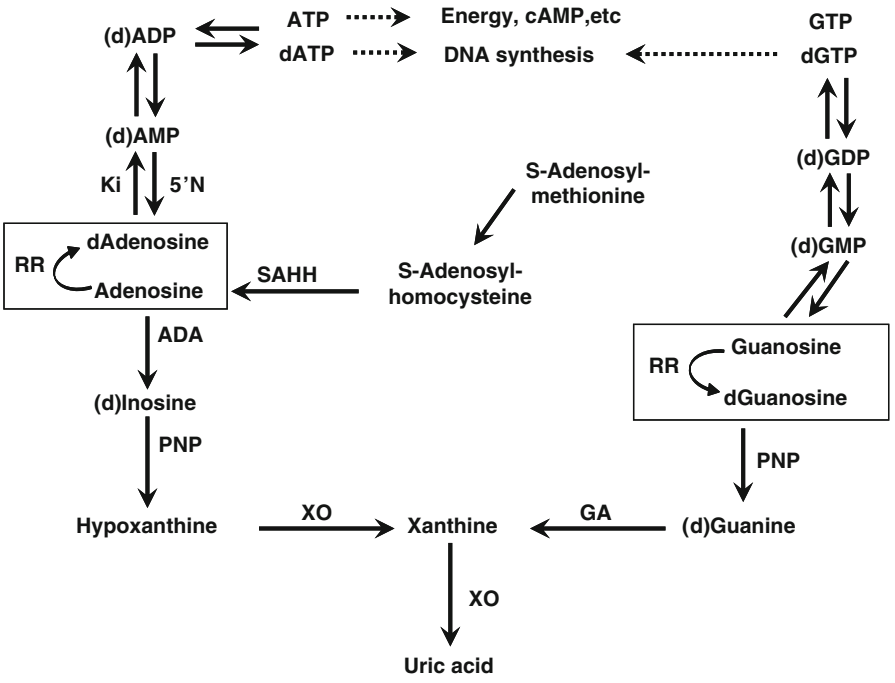

Fig. 32.1 Function of adenosine deaminase (*ADA*) and of purine nucleoside phosphorylase (*PNP*) in the catabolism of purines. Other enzymes in this pathway are adenosine kinase (*Ki*), 5′nucleotidase (5′N), ribonucleotide reductase (*RR*), s-adenosyl homocysteine hydrolase (*SAHH*), xanthine oxidase (*XO*), and guanase (*GA*). "d" denotes deoxy, (*d*) represents either nucleotide or deoxynucleotide forms. For example, (d) adenosine represents both adenosine and deoxyadenosine

firmed in non-erythrocyte cells (blood lymphocytes, EBV-transformed B cells, or fibroblast) and/or by genetic sequencing. Depending on the activity of ADA in lymphocytes, the immunodeficiency may vary in onset. In 85–90 % of ADA-deficient patients, lymphocyte ADA activity is <0.5 %, and clinical manifestations of SCIDs with severe lymphopenia are noticed in the first months of life or may be delayed with onset by 1–2 years of life (delayed-onset form). When lymphocyte ADA activity is 0.5–3 % (still will be <1 % in erythrocytes), the onset of clinical disease is later (late-onset form) by 3–15 years of age, or even in adulthood, when patients present with recurrent sinopulmonary infections, lymphopenia, hyper-IgE, poor antibody response, and autoimmune diseases (thrombocytopenia, hemolysis, hypothyroidism). Partial ADA deficiency (5–80 % of enzyme activity in non-erythrocyte cells) with normal immune function has been detected in population studies. The delay in onset of ADA-SCID also means that it may be missed by newborn screening. Therefore a normal newborn screen in an infant suspected of SCID should not preclude a thorough evaluation for SCID. Besides stem cell transplantation, which is the first choice of therapy for ADA deficiency appearing in infancy, enzyme replacement and gene therapy have been partially successful and are used when an

appropriate stem cell donor is not available. Enzyme replacement therapy can be used until a suitable stem cell donor is found or gene therapy is performed. Enzyme replacement therapy with polyethylene glycol (reduces immunogenicity and prolongs half-life)-conjugated adenosine deaminase (PEG-ADA) derived from calf intestine (ADAGEN®, pegademase bovine) is administered intramuscularly twice weekly at 15–30 U/kg of ideal body weight. Some patients need higher doses of 30–60 U/kg at least initially. PEG-ADA response is monitored by measuring plasma ADA activity, erythrocyte levels of dATP accumulation, and the degree of inhibition of SAH hydrolase activity (<10 % without therapy), which all improve dramatically. SAHH activity is most sensitive marker to monitor therapy efficacy. Recovery of immune function is partial and delayed taking 3–5 months for B- and T-cell numbers to start to increase and longer for antibody response to normalize so that after 12 months 50 % of patients may no longer need immunoglobulin replacement as they develop normal antibody response to bacteriophage. About 50–65 % of patients develop antibodies to ADA, but it becomes a clinically significant problem in only a few patients, who, because of faster elimination of PEG-ADA, experience decreasing plasma ADA levels and clinical deterioration. ADA deficiency was the first disease for which gene therapy was attempted. ADA cDNA was transfected in vitro using retrovirus vectors into expanding patient's own T cells, bone marrow cells, or cord blood CD34+ stem cells (in few patients diagnosed prenatally) and administered back to patients resulting in temporary replacement of ADA in immune cells. Initial attempts were not successful, but modifications of the viral vector have provided improved ADA gene transduction and expression.

Purine nucleoside phosphorylase (PNP, chromosome 14q13.1) deficiency is a rare cause of SCID with similar manifestations as ADA deficiency including severe lymphopenia (<500/mm^3), with infantile and late-onset forms, but usually T cells are more affected than B cells. In PNP deficiency, uric acid is low in the serum (<1 mg/dl) and in the urine. A distinct feature is that half of the patients have neurological symptoms including spastic diplegia or tetraparesis, ataxia, tremor, reduced motor development, hyper- or hypotonia, behavioral difficulties, and varying degrees of mental retardation. Diagnosis is made by measuring enzyme activity in erythrocyte or other cell lysates similarly to ADA deficiency. There is no enzyme replacement available and prognosis is poor even with stem cell transplantation.

Deficiencies in recombinase proteins (RAG1 and RAG2) impair (D) J gene rearrangement of both immunoglobulins and T-cell receptors, thus affecting B and T cells but sparing NK cells. Genetic defects in either RAG1 or RAG2 have been found in an expanding spectrum of immunodeficiency diseases. Null mutations in either gene are associated with a classical SCID phenotype (absent T and B cells but normal NK cells), while hypomorphic mutations in either gene have been associated with Omenn syndrome (see below) or other variable phenotypes including CMV infection with γδT-cell expansion, combined immunodeficiency with granuloma formation, and CD4 lymphopenia. More recent findings suggest that other genetic or environmental factors may affect the clinical phenotype of RAG gene mutations.

In *Artemis* deficiency, also known as Athabascan SCID, the defect is in the gene encoding for the DNA-cross-link repair protein 1C, a nuclease involved in V(D)J gene rearrangement and in DNA repair. Besides defective rearrangement of immunoglobulin and T-cell receptor genes, this deficiency also increases susceptibility to DNA damage from radiation exposure, including X-ray, which should be minimized.

Less common forms of SCID involve molecules involved in the activation or development of lymphocytes. Genetic defects in a number of genes affect T-cell development or function with normal B- and NK-cell numbers. These include defects in the *alpha chain receptor of IL-7*, *CD3 chains*, *calcium*, *and other signaling pathways*. Deficiency in *CD3 zeta chain-associated protein kinase 70* (Zap70) leads to SCID characterized by depletion of CD8 cells (see Table 32.1) with normal numbers but poorly functioning CD4 T cells.

Omenn Syndrome

In Omenn syndrome there is a hypomorphic mutation in RAG1 or RAG2 leading to a partial deficiency of the respective proteins, allowing the development of a limited repertoire of T cells that are poorly regulated and cause a clinical phenotype resembling GVHD. In addition to the immunodeficiency manifestations, these patients present with seborrheic erythroderma, edema, alopecia, eosinophilia (usually >1000 per mm^3), hepatosplenomegaly, lymphadenopathy, and elevated serum IgE. Indeed, patients with SCID who are being engrafted with maternal or blood transfusion-derived lymphocytes may develop overt GVHD and a similar clinical presentation, which is called by some Omenn-like syndrome. Both Omenn syndrome due to deficiency of RAG1 or RAG2 and GVHD must be evaluated with blood lymphocyte phenotyping, HLA typing, and skin biopsy to rule out exogenous lymphocyte engraftment. In Omenn syndrome, starting immunosuppressive therapy prior to transplantation improves the patient's clinical condition as well as the outcome of stem cell transplantation because the recipient's T cells can jeopardize engraftment. Hypomorphic mutations in almost any SCID-causing gene can result in an Omenn syndrome phenotype.

Bare Lymphocyte Syndromes Classes I and II

Deficiencies in HLA class I and II lead to impaired development and function of CD8 and CD4 lymphocytes, respectively. In HLA class I deficiency or *bare lymphocyte syndrome type I*, HLA class I molecules are not expressed on cell surface due to lack of the peptide transporter which is composed of subunits TAP1 and TAP2. These patients cannot be typed for HLA class I. They maybe asymptomatic or may present in late childhood with chronic lung disease.

HLA class II deficiency or *bare lymphocyte syndrome type II* is more frequent than the HLA class I deficiency. It frequently presents in infancy as SCID. It results from defects in factors essential for transcription of MHC class II genes. There are four genetic groups (A, B, C, and D), reflecting defects in four regulators of MHC class II expression: the factor defective in group A is MHC class II transactivator (CIITA, chromosome 16p13); in group B, regulatory factor X ankyrin repeat-containing (RFXANK, chromosome 19p12); in group C, regulatory factor-5 (RFX5, chromosome 1q21.1–q21.3); and in group D, regulatory factor X-associated protein (RFXAP, chromosome 13q14). The prognosis is poor despite stem cell transplantation because the expression of MHC molecules in the thymus is not corrected.

In *reticular dysgenesis*, a very rare form of SCID, patients are born without leukocytes but with normal erythrocytes and platelets. The genetic defect is not known. Most die of overwhelming sepsis in the first days of life or in weeks if kept in isolation in sterile environment. Bone marrow shows no myeloid cells and thymus and spleen have no lymphocytes. Several patients have been transplanted successfully.

Hyper IgM Syndrome

The hyper IgM syndrome (HIM) is a combined primary immunodeficiency caused by defects in the CD40 ligand (CD40L or CD154, in chromosome Xq26.3–27)/CD40 signaling pathway. In this immunodeficiency patients have impaired immunoglobulin class switch from IgM to IgG, IgA, and IgE. As a result, serum IgM is normal or elevated and levels of IgA and IgG are very low. Patients most commonly lack CD40L, a surface molecule transiently expressed on activated T cells that provides the helper signal by binding to CD40 on B cells inducing immunoglobulin class switching, somatic hypermutation, and differentiation into memory B cells. CD40 is also expressed on monocytes, dendritic cells, and some myeloid progenitors and stimulates upregulation of co-stimulatory molecules on antigen-presenting cells. Therefore, defects in CD40L or CD40 also result in a T-cell immunodeficiency, while defects downstream of CD40 result in an antibody deficiency only.

Clinical Manifestations

Male patients with X-linked HIM present early in the first or second year of life with recurrent pyogenic respiratory infections, particularly otitis media, pneumonia, and sepsis. They also have T-cell deficiency and develop *Pneumocystis jirovecii* pneumonia (PJP), which often is the presenting illness and a frequent cause of death. In addition, they have varying degrees of neutropenia and may develop hemolytic or aplastic anemia. If patients survive beyond 20 years of age, they often develop chronic liver disease, sclerosing cholangitis, hepatocellular carcinoma, or a neuroendocrine carcinoma. Some may also develop cryptococcosis and protracted diarrhea due to *Cryptosporidium*.

Laboratory Diagnosis

HIM is suspected in a male patient with normal or elevated (150–1000 mg/dl) IgM and markedly reduced or absent IgG, IgA, and IgE. Isohemagglutinin titers are normal or elevated and antibody response to vaccines is poor with absent isotype switching and memory responses. Diagnosis is confirmed by demonstrating lack of transient expression of CD40L (CD154) on stimulated T cells (mostly CD4 cells) using flow cytometry. However, some mutations in CD40L gene still allow surface expression of nonfunctional CD40L, which can be detected by staining with soluble CD40. Definitive diagnosis is made by identifying mutations in the CD40L gene. Several mutations have been identified in the extracellular, transmembrane, and intracytoplasmic portions of the molecule. Circulating B- and T-cell numbers are normal. T cells proliferate normally to mitogens, but some patients have reduced proliferation to antigens. Neutropenia is present in two-thirds of patients.

Treatment

HIM patients are treated with immunoglobulin replacement therapy and chronic prophylaxis for PJP with sulfamethoxazole-trimethoprim. Granulocyte colony-stimulating factor (G-CSF) may be needed to improve neutropenia. Mortality in early years is caused by infections, particularly PCP, and later due to the liver complications mentioned above. Liver disease tends to recur after liver transplantation. Because of poor prognosis, more aggressive therapy has been attempted. For example, stem cell transplantation has been successful in many patients.

Other Forms of Hyper IgM Syndrome

Besides the X-linked form of HIM (*HIM type 1*), other autosomal recessive defects in molecules involved in immunoglobulin class switch can lead to similar diseases. CD40 (chromosome 20q12-q13.2, *HIM type 3*) deficiency causes disease very similar to CD40L deficiency.

Other forms lead to milder disease than CD40L and CD40 deficiencies. They include deficiencies of enzymes required for immunoglobulin class switch such as activation-induced cytidine deaminase (AID, chromosome 12q13, *HIM type 2*) and uracil N-glycosylase (UNG, chromosome 12q23-q24.1, *HIM type 5*). HIM types 2 and 5 have normal T-cell function (e.g., no susceptibility to PJP) and patients have lymphadenopathy. *HIM type 4* is caused by a defect downstream of AID, although the specific affected gene has not been identified. These enzyme deficiencies have better prognosis and may be diagnosed only in adulthood. Treatment is immunoglobulin replacement.

Another X-linked form of *HIM* is that *associated with ectodermal dysplasia*. In this disease, patients lack IKKγ (chromosome Xq28), also known as NF-κB essential modulator or NEMO. IKKγ binds to two kinases (IKKα and IKKβ) of the NF-κB

inhibitor (IκB), a step required for NF-κB activation and translocation to the nucleus. NF-κB activation occurs after activation of CD40 by CD40L and in other cellular processes such as ectoderma formation in the fetus. Because of the involvement of NF-**κ**B in multiple signaling pathways including antigen receptors, toll-like receptors, the interleukin-1 receptor family, and other members of the TNF-receptor family, the immunodeficiency in this condition affects the innate and adaptive immune systems and is more severe than an antibody deficiency. In addition, it is associated with an enteropathy that can complicate the outcome of stem cell therapy.

Defects in the genes INO80 (INO80 complex subunit A, a DNA helicase involved in chromatin remodeling) and MSH6 (MutS-alpha 160 KDa subunit that selectively repairs GT DNA mispair), can also cause normal or elevated IgM and severe reduction of IgG and IgA.

Other Forms of Combined Cellular and Humoral Deficiencies

In non-severe combined immunodeficiencies, the T-cell defect is milder than in SCIDs. Most are also treated with bone marrow transplantation, but because the partial function of the patient's T cells, these patients require conditioning for ablation of their bone marrow prior to transplantation.

Wiskott-Aldrich Syndrome

The genetic defect in Wiskott-Aldrich syndrome (WAS) is in the WAS protein (WASP, Xp11.22), which participates in signal transduction that regulates cytoskeleton reorganization in hematopoietic cells. It is characterized by the triad of immunodeficiency, thrombocytopenia, and eczema. The first manifestation is bleeding due to thrombocytopenia with low platelet volume in the first year of life. It tends to improve in subsequent years. After 6 months of age, when maternal antibodies wane, patients develop recurrent respiratory infections with common bacterial microbes. Eczema ensues by 1 year of age and typically affects the lower face. Immunological defects include low IgM, high IgA and high IgE, poor antibody response to polysaccharides, decreased T-cell function, and predisposition to develop autoimmune diseases and cancer. Platelet count ranges from 5000 to 100,000 per mm^3, platelets are small, and megakaryocytes are present in the bone marrow. Autoimmune-associated conditions include Coombs-positive autoimmune hemolytic anemia, vasculitis, renal disease, Henoch-Schonlein purpura, and inflammatory bowel disease. Malignancies occur in adolescence or adulthood, most commonly lymphoproliferative cancers, which worsen prognosis even after bone marrow transplant. The best treatment for thrombocytopenia is intravenous immunoglobulin because prednisone and splenectomy increase risk of life-threatening infections. Diagnosis is made in boys with thrombocytopenic purpura and small platelets, together with eczema and

the immune defects mentioned above. Identification of WASP gene mutations confirms that diagnosis. In the absence of any WASP expression, the prognosis is poor without stem cell transplantation, which is curative.

Ataxia Telangiectasia

This multisystem disease is caused by mutations in the ataxia telangiectasia-mutated gene (ATM, chromosome 22q22-q23), which encodes a phosphatidylinositol-3 (PI-3) kinase. This is one of the kinases that respond to DNA damage by phosphorylating key substrates involved in DNA repair and in cell cycle control. This defect makes patients very sensitive to radiation, including X-ray, which leads to chromosome breakage. Eventually, the impaired ability to repair damaged DNA leads to lymphoproliferative and epithelial malignancies. Patients usually present with cerebellar ataxia in the first year of life, followed by telangiectasia in the second and, later, recurrent sinopulmonary infections. However, some present with delayed onset at 4–6 years of age. With time, neurological status deteriorates with choreoathetosis, dysconjugated gaze, and extrapyramidal and posterior column signs. Telangiectasia appears first on the inner scleral conjunctiva (bulbar region) and then affects the nasal bridge, ears, and antecubital fossae. Immunodeficiency is manifested by recurrent sinopulmonary virus and bacterial infections. In puberty, secondary sexual characteristics do not develop and mental retardation may ensue and progress. Laboratory findings include normal or low T- and B-cell function. Patients may have lymphopenia (low CD4 cells, normal B and NK cells), low proliferation to mitogens and allogenic cells, no response to delayed hypersensitivity testing, IgA deficiency (present in 50–80 %), or IgG2 and IgG4 subclass deficiency with poor antibody response. IgE may be absent as well. Patients have elevated alpha-fetoprotein. Definitive diagnosis is made by finding mutations in the ATM gene. No specific therapy exists. Patients may need aggressive antibiotic therapy for infections, antibiotic prophylaxis, immunoglobulin replacement, avoidance of live microbe vaccines, and be cautious to receive only irradiated blood products. Bone marrow transplantation has not been performed and thymus transplantation was not successful. Such approach will likely not reverse neurological changes. Prognosis is poor as immunological and neurological functions deteriorate together with chronic lung disease, but some have lived to the fifth decade. Death results from infections or from malignancies such as non-Hodgkin's lymphoma (45 %), lymphocytic leukemias (14 %), and carcinoma of stomach, liver, and ovaries.

X-Linked Lymphoproliferative Disease or Duncan's Syndrome

Males with X-linked lymphoproliferative disease (XLPD) lack a gene encoding the SH2 domain protein-1A (chromosome Xq25), which leads to lack of NKT cells. They are typically asymptomatic until they develop Epstein-Barr virus (EBV)

infection, to which they are extremely sensitive. EBV causes a severe infectious mononucleosis, which is fatal in 50 % of patients (death from liver failure). If patients survive the acute infection, they evolve with newly acquired hypogammaglobulinemia (~30 %) or Burkitt-type lymphoma (~20 %), usually in the ileocecal region. Some may develop aplastic anemia. Bone marrow transplantation is curative, but prognosis is poor with 75 % mortality by age 10 years and longevity of <40 years.

Another X-linked lymphoproliferative disorder results from defects in the X-linked inhibitor of apoptosis (XIAP) gene, which has been termed XLP-2. Affected patients may present with hemophagocytic lymphohistiocytosis (HLH), which may or may not be triggered by EBV infection, recurrent splenomegaly, and inflammatory bowel disease (IBD) with features similar to Crohn's disease.

Cellular Immunodeficiencies

These are immunodeficiencies affecting cellular immune response, which is mediated by lymphocytes and natural killer (NK) cells.

DiGeorge Syndrome

DiGeorge Syndrome (DGS) is a triad of hypoparathyroidism, thymus hypoplasia, and congenital heart disease. However, this triad and many other manifestations are now recognized as part of a broader disorder called *chromosome 22q11.2 deletion syndrome*. It occurs in 13 per 100,000 live births, usually due to a sporadic deletion. This deletion leads to loss of many genes and abnormal embryonic migration of neural crest cells which form the third and fourth pharyngeal pouches (branchial arches). These branchial arches give rise to the thymus, parathyroid glands, cardiac outflow structures, skull, mesenchyme of face and palate, and neuronal structures of the head and neck. These structures are all formed in the embryo between the fourth and eighth weeks of gestation. The clinical manifestations of this syndrome vary widely both in degree and number of tissues affected. It has also been named CATCH22 (cardiac abnormality/abnormal facies, T-cell deficit due to thymic hypoplasia, cleft palate, hypocalcemia due to hypoparathyroidism resulting from 22q11 deletion) and Shprintzen (or velocardiofacial) syndrome.

Clinical Manifestations

Patients with complete DGS present with hypocalcemia and congenital heart disease, a combination that should lead to diagnostic investigation for chromosome 22q11.2 deletion and for other manifestations including T-cell lymphopenia and facial dysmorphism.

Hypoparathyroidism may manifest in the first day of life as hypocalcemic tetany that is resistant to therapy. Serum phosphorus is high, and parathyroid hormone low. It is usually temporary but may persist into adulthood.

The congenital heart disease in DGS involves conotruncal defects affecting the outflow tract. These include tetralogy of Fallot, type B interrupted aortic arch, truncus arteriosus, right aortic arch, coarctation of aorta, and aberrant right subclavian artery. Ventricular septal defects are also common.

Facial dysmorphism affects face and palate including posteriorly rotated or low-set ears with prominent overfolded helices, hypertelorism, narrow nasal alae with bulbous nasal tip, fish-shaped mouth (small mouth and prominent upper lip), malar flattening, and micrognathia. Palate may contain a submucosal cleft, that is, upon palpation one notices a bone cleft in the distal portion of the hard (bony) palate, although the soft palate and uvula are present. Complete cleft palate or bifida uvula also occurs. The facial features become more prominent as the child grows. They were first described by Shprintzen in 1981 and are called velocardiofacial syndrome (VCFS). Velopharyngeal insufficiency (short palate) may cause feeding difficulty, nasal regurgitation, and hypernasal, among other, speech problems.

Immunodeficiency results from hypoplastic and rarely aplastic thymus. Although thymus is not seen in lateral chest X-rays in newborns, usually there is a small thymus or rests of thymus tissue scattered in submandibular and cervical areas so that the immune defect is mild and transient in most patients (partial DGS).

Other less frequent clinical manifestations in DGS include microcephaly, inguinal and umbilical hernias, esophageal atresia, short stature, slender hands, scoliosis, and neuropsychiatric disorders (e.g., schizophrenia).

Laboratory Diagnosis

DGS is confirmed by detecting the 22q11 deletion by fluorescent in situ hybridization (FISH) and decreased T-cell number. Absence of thymus shadow is noticed in chest X-rays of infants. The 22q11 deletion is detected in 90 % of patients with DGS triad, whereas the remaining DGS cases may be caused by other genetic defects including gestational diabetes and intrauterine exposure to retinoic acid or to alcohol. CD3+ cells may be absent in complete DGS but are decreased in most cases (partial DGS), in the range of 500–1500 cells per mm^3. Both CD4 and CD8 are affected so that the ratio CD4/CD8 is normal or high because CD8 depletion may be more severe than that of CD4. Lymphocyte proliferation to mitogens and allogenic cells is usually normal but is decreased in those with severe T-cell depletion. In severe cases, severe lymphopenia is persistent and can lead to opportunistic infections (Table 32.2). B cells are usually normal, but if CD4 helper function is markedly impaired, poor antibody production may be present and may require immunoglobulin replacement therapy. In some cases, hypogammaglobulinemia or selective IgA or IgM deficiency is also present. It is important to assess patients at regular intervals especially prior to live vaccine administration.

Treatment

DGS management often requires a multidisciplinary team because of the diverse manifestations. From the immunological standpoint, it is important to monitor T-cell deficiency and institute prophylactic measures for T-cell deficiency. These measures include avoidance of live attenuated microbe vaccines (e.g., live virus and BCG vaccines), use of irradiated blood products to prevent graft-versus-host disease, and administration of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis with sulfamethoxazole and trimethoprim. These measures should be started in those with persistent CD4 <400 cells per mm^3 at 2 months of age and should probably be continued until immunodeficiency resolves as determined by normalization of T-cell numbers and function: CD8 >250 per mm^3, CD4 >400 per mm^3, normal T-cell proliferation to mitogens, and antigens or a normal antibody response. Since for most patients the T-cell deficiency is mild and transient resolving in the first year of life, the prognosis of the immunological defect in DGS is good. However, the immunodeficiency can be profound and persistent in a minority of DGS patients (<5 %) and sometimes requires thymus transplantation. In some of these cases, graft-versus-host disease develops due to oligoclonal expansion of patient T cells and transplacental transfer of maternal T cells or because of allogeneic T cells from nonirradiated blood transfusions. The latter is usually fatal and emphasizes the need to irradiate all blood products until immune function can be assessed.

Hypocalcemia may require calcium supplements and 1,25-dihydroxycholecalciferol therapy. Cardiac defects may require surgical repair, as may palate malformations. Some children may also need speech therapy.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis (CMC) refers to chronic or recurrent infections with *Candida spp*. involving skin, nails, oro-esophageal, and vaginal mucosa, but not usually sepsis or deep-seated infections. Skin infection may have "stocking-glove" distribution. CMC can be a manifestation of T-cell immunodeficiency diseases including SCID and idiopathic CD4 lymphopenia, secondary immunodeficiencies including HIV infection, and other primary immunodeficiency diseases affecting the development of Th17 cells or their function, highlighting the role of IL-17-mediated immunity in protection from CMC. Affected patients may present with CMC in the first year of life or in teenage years. Some may have autoimmune disease such as hypoparathyroidism, Addison's disease, and less often, diabetes mellitus, hypogonadism, and adrenocorticotropic hormone (ACTH) deficiency. Other manifestations include pernicious anemia, chronic hepatitis, vitiligo, alopecia, and pulmonary fibrosis. CMC is also a feature of *autoimmune polyendocrinopathy*, *candidiasis*, *and ectodermal dystrophy* (*APECED*), an autosomal recessive disease caused by gene defects in the autoimmune regulator (AIRE) gene (21q22.3). Most APECED patients were found to have autoantibodies to IL-17A, IL-17 F, and IL-22. Other immunodeficiency diseases affecting Th17 development include STAT3 defects in the autosomal dominant

hyper-IgE syndrome, defects in IL-12 p40 or the IL-12R beta subunit, and defects in CARD9.

Diagnosis is ultimately made by identifying the underlying gene defect, but assessment of Th17 T cells and the ability of the patient's cells to secrete IL-17 can help confirm a diagnosis of an immune deficiency underlying CMC. Treatment for CMC often requires systemic rather than topical antifungal antibiotics as well as therapy for associated autoimmune disorders.

Immunodysregulation, Polyendocrinopathy, Enteropathy, X-Linked Syndrome

Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is a rare X-linked deficiency of Foxp3 (chromosome Xp11.23), a member of the forkhead/winged-helix family of transcriptional regulators that is essential for generation of the CD4+CD25+ T regulatory (Treg) cells. These Treg cells inhibit effector T cells and cellular immune responses via both soluble factors (TGFβ and IL10) and via cell-to-cell contact (using inhibitory "co-stimulatory" molecules CTLA4 and GITR). Patients with IPEX lack Treg cells, which leads to exaggerated immune responses and autoimmune diseases.

Clinical Manifestations

Patients present during infancy with various combinations of intractable diarrhea (autoimmune enteropathy with villous atrophy), insulin-dependent diabetes mellitus (IDDM), hemolytic anemia, thrombocytopenia, chronic dermatitis, thyroid autoimmunity, and food allergy. Few survive the first decade of life with death in infancy or early childhood occurring with infections or shortly after immunizations.

Laboratory diagnosis

IPEX is characterized by lack of CD4+CD25+ T cells in the blood and absence of Foxp3 expression by flow cytometry and can be confirmed by identifying defects in the *Foxp3* gene. Total T- and B-cell numbers are normal at birth but seem to expand within weeks, displaying an activated phenotype. Limited information exists on the natural history of immunological markers.

Treatment

Cyclosporine A improves enteropathy temporarily, but prognosis is poor with death before tenth birthday being common. Stem cell transplantation can be curative but IDDM is likely to persist. This disease demonstrates the importance of regulatory T

cells in preventing autoimmune and allergic diseases including food allergy. IPEX-like disease can occur from other gene defects affecting both boys and girls. Patients with defects in the CD25 gene encoding for the alpha chain of the IL-2 receptor, signal transducer and activator of transcription 5b (STAT5b), dominant gain of function mutations in STAT1, and mutations in LPS-responsive beige-like anchor (LRBA) present with an IPEX-like phenotype.

Autoimmune Lymphoproliferative Syndrome

The defect in autoimmune lymphoproliferative syndrome (ALPS) is impaired FAS-induced apoptosis, a major pathway for lymphocyte homeostasis. Apoptosis eliminates harmful lymphocytes such as autoreactive and proliferating effector lymphocytes. In the latter case as a means to terminate immune response once it is no longer necessary. Apoptosis also occurs in other immune cells. ALPS is both genetically and clinically heterogeneous. Both ALPS-0 and ALPS-1a are caused by deficiency in FAS (CD95, chromosome 10q24.1), but the former results from recessive mutations (homozygous), whereas the latter from a dominant mutation. In ALPS-1b, patients lack FAS ligand (CD95L, chromosome 1q23), and in ALPS-2 they lack either caspase 8 or 10 (both in chromosome 2q33-q34). All these molecules participate in the FASL/FAS signaling pathway. The defect in ALPS-3 was recently identified as a defect in protein kinase C delta (PKCδ) gene.

Clinical Manifestations

Because of defective apoptosis, patients with ALPS have signs of excessive lymphoproliferation and autoimmune phenomena. Typically patients present around 24 months of age with a triad of lymphoproliferative disease, autoimmune cytopenias, and susceptibility to malignancies. However, many are diagnosed in adulthood.

Lymphoproliferative disease is characterized by chronic nonmalignant hepatosplenomegaly and lymphadenopathy. Lymph nodes can be normal in size or very prominent forming very large distorting superficial lymph nodes and large thoracic and intra-abdominal adenopathies, which may cause obstructive disease. They may shrink with infections and improve in older patients. Autoimmune disorders affect 50–70 % of patients. More often patients suffer from severe and difficult to treat blood cytopenias including hemolytic anemia, thrombocytopenia, neutropenia, Evans syndrome (a combination of the first two cytopenias). Less often patients may develop glomerulonephritis, optic neuritis, Guillain-Barré syndrome, primary biliary cirrhosis/autoimmune hepatitis, arthritis, vasculitis, childhood linear IgA disease, and factor VIII coagulopathy. Risk of developing autoimmune diseases increases as patients age. Serum autoantibodies are found in up to 92 % of cases.

Malignancies occur in 10 % of ALPS patients. Risk of developing Hodgkin's and non-Hodgkin's lymphomas is 51× and 14× higher than in the general population. Other malignancies may also occur.

Laboratory Diagnosis

Patients have lymphocytosis and hypergammaglobulinemia. Diagnosis is made if patient has three features: nonmalignant lymphadenopathy ± splenomegaly, >1–2.6 % double-negative alpha-beta receptor T cells, and impaired apoptosis of lymphocytes in vitro. Flow cytometry analysis of lymphocytes reveals >1–2.6 % of CD3+CD4-CD8- (double-negative) αβ T cells (range 1–75 %). These double-negative CD3 cells also express CD45RA, CD57, CD27, CD28, perforin, and HLA-DR. Besides these three required features, other characteristics that help in the diagnoses of ALPS are autoimmune disease, family history of ALPS, characteristic pathology of lymph node and spleen (see below), and identifying defective molecule in the apoptosis pathway at the protein and/or genetic level. At the protein level, missing molecules can be measured by flow cytometry or Western blot. At the DNA level, mutations can be identified by sequencing the affected gene.

Pathological examination of lymph nodes reveals prominent paracortical area (T-cell zones) with lymphoblasts. Immunohistochemistry shows that the majority of these cells are CD3+CD4-CD8-T cells. CD4/CD8 ratio is markedly decreased and a polyclonal plasma cell expansion may be present. In the spleen, there are follicular hyperplasia in an expanded white pulp and a massively expanded red pulp containing cells phenotypically identical to those seen in the lymph node paracortical regions.

Treatment

Systemic corticosteroids or immunosuppressants improve lymphoproliferative manifestations, particularly if obstructive disease ensues. Patients should avoid contact sports to prevent splenic rupture. Autoimmune cytopenias also respond well to corticosteroids. If splenectomy becomes necessary, it should be followed by antibiotic prophylaxis until adulthood. Mycophenolate mofetil and rituximab with vincristine have been used with success for severe refractory immune thrombocytopenia. Neutropenia responds to G-CSF therapy. Few patients with severe and progressive disease have benefited from bone marrow transplantation.

Other Cellular Deficiencies

Natural Killer Cell Deficiency

Natural killer (NK) cells are non-T (CD3-) non-B (CD20-)lymphocytes that express CD56 and FcγRIIIA (CD16). They attach to target cells and lyse them by contact. Activation is via IgG and Fc-gamma receptor, or via the absence of MHC-I on the surface of virus-infected or neoplastic cells. Target cell death occurs via perforin or by induction of apoptosis. Few cases have been described of isolated NK-cell deficiency, who presented with Herpesviridae infections (e.g., herpes simplex, varicella, CMV, and EBV viruses). Recently, these patients were found to have defects in the

transcription factor GATA2, which is also associated with monocytopenia; B-cell lymphopenia; mycobacterial, fungal, and viral infections; myelodysplasia; cytogenetic abnormalities; pulmonary alveolar proteinosis; and myeloid leukemias.

Idiopathic CD4 Lymphocytopenia

Several cases of low CD4 count in the absence of HIV infection (based on serology and PCR testing) have been described. Some cases may be normal variants as their T-cell functional tests are normal. Others have impaired T-cell function and develop opportunistic infections, which can be fatal. Most are adults aged 17–70 years and few have spontaneously recovered. In case of T-cell impairment in functional assays and/or history of opportunistic infections, chronic prophylaxis for *Pneumocystis jirovecii* pneumonia and avoidance of live virus vaccines may be considered.

Phagocyte Deficiencies

Neutropenic Syndromes

Neutropenia (less than 1000/mm^3; severe if less than 500/mm^3) increases the risk of pyogenic infections, fever, and sepsis due to bacteria and fungi (see Table 32.2). It may be corrected with administration of granulocyte colony-stimulating factor (G-CSF).

Neutropenia can be secondary to chemotherapeutic agents, glycogen storage disease type 1b, myelokathexis (inability to release neutrophils from the marrow), autoimmune antibodies against neutrophils as in Felty's syndrome with rheumatoid arthritis, bone marrow cancer invasion, myelofibrosis, infections, and deficiencies in vitamin B12 or folate. It also occurs in Shwachman-Bodian-Diamond syndrome, which involves exocrine pancreatic insufficiency, cytopenias, and hematological malignancies caused by defective SBDS gene (chromosome 7q11).

In primary immunodeficiencies, neutropenia can occur as part of other immunological defects such as in X-linked hyper IgM syndrome, X-linked agammaglobulinemia, and Wiskott-Aldrich syndrome (also X-linked) as mentioned above. In addition, as discussed below, neutropenia can be the principal defect in other primary immunodeficiencies such as in congenital and cyclic neutropenia and Chédiak-Higashi syndrome.

Congenital Neutropenia or Kostmann's Syndrome

Mutations in two genes can cause this immune defect. Mutations in neutrophil elastase (ELA2 gene, chromosome 19p13.3) cause sporadic and autosomal dominant cases. Sporadic cases can also result from mutations in the growth

factor-independent 1 (GFI1, chromosome 1p22), a repressor of ELA2 expression and also a transcriptional repressor proto-oncogene that inhibits hematopoiesis. Some patients with GFI1 defects have also developed acute myeloid leukemia.

Mutations in neutrophil elastase gene have also been found in patients with *cyclic neutropenia*. These patients have cyclic inhibition of hematopoiesis and every 21 days develop cyclic fluctuations in the numbers of blood neutrophils, monocytes, eosinophils, lymphocytes, platelets, and reticulocytes. Patients with the disease typically have regularly recurring symptoms of fever, malaise, mucosal ulcers, and, occasionally, life-threatening infections during periods of neutropenia.

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome (CHS) is caused by mutation in the lysosomal trafficking regulator gene (LYST, chromosome 1q42.1-q42.2) which impairs movement of lysosomes in the cytosol. As a result, giant lysosomal granules form in many cells including neutrophils (which allows diagnosis by analysis of blood smear), melanocytes, neural Schwann cells, renal tubular cells, gastric mucosa, pneumatocytes, hepatocytes, Langerhans' cells, and adrenal cells. Large eosinophilic inclusion bodies (peroxidase positive) also form in myeloblasts and promyeloblasts in bone marrow. Clinical manifestations include partial albinism, photophobia, nystagmus, and neutropenia. Neutrophils have impaired chemotaxis and bactericidal activity. Death usually occurs by age 7 years from severe infections or lymphoma. About 85–90% of patients develop a unique lymphoproliferative syndrome called "accelerated phase" of CHS. This disorder is characterized by generalized lymphohistiocytic infiltrates, fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, and bleeding. The prognosis of the accelerated phase is poor with death within 3 years from infection or bleeding unless bone marrow transplantation is performed successfully. Bone marrow transplantation corrects hematological problems, but progressive neurological symptoms ensue in the third decade of life (cerebellar ataxia, peripheral neuropathy, and cognitive abnormalities).

Chronic Granulomatous Disease

Patients with chronic granulomatous disease (CGD) have defective nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which produces superoxide a precursor for other oxygen radicals produced during phagocyte respiratory burst to kill phagocytized bacteria. NADPH oxidase activity is tightly regulated. It becomes active when its four subunits come together. At rest, two subunits of the enzyme are bound to the plasma membrane and form the cytochrome b_{588}: a 91 kilodalton (kd) glycoprotein ($gp91^{phox}$, CYBB gene or beta subunit, chromosome Xp21.2) and a 22 kd protein ($p22^{phox}$, CYBA or alpha subunit, chromosome 16q24). Upon NADPH oxidase activation, two other cytosolic subunits join these two membrane subunits

to form the four-subunit functional enzyme. The cytosolic subunits are the $p47^{phox}$ protein (neutrophil cytosol factor 1 (NCF1), chromosome 7q11.23), and the $p67^{phox}$ protein (neutrophil cytosol factor 2 (NCF2), chromosome 1q25).

Deficiency of either CYBB or CYAA prevents expression of the cytochrome b_{588} and causes the cytochrome-b-negative CGD forms, whereas deficiency of NCFs allows expression of cytochrome b_{588} and causes the cytochrome-b-positive CGD forms (type I due to NCF1/$p47^{phox}$ deficiency and type II due to NCF2/p67-phox deficiency). The most common deficiency is lack of $gp91^{phox}$, an X-linked defect that accounts for 65 % of all CGD cases. Deficiency in any of the other three subunits causes autosomal recessive disease ($p22^{phox}$ deficiency in 5 % of cases, $p47^{phox}$ deficiency in 25 %, and $p67^{phox}$ deficiency in 5 %).

Clinical Manifestations

Clinical manifestations are heterogeneous, varying even between identical twins with the same mutations. Two-thirds of CGD patients present in the first year of life with infections (recurrent suppurative lymphadenitis, pneumonia, impetigo), chronic dermatitis (sometimes since birth), gastrointestinal symptoms (gastric antrum obstruction due to granulomas, bloody diarrhea from CGD colitis, perirectal abscesses with fistulas), and osteomyelitis. Other less common infections are otitis media, conjunctivitis, urinary tract infections, sinusitis, and abscesses in the liver, kidney, and brain. Many have history of chronic diarrhea, gingivitis, and ulcerative stomatitis. On examination, most CGD patients have generalized lymphadenopathy and hepatosplenomegaly, which are enlarged because of non-caseating granulomatosis. Patients also have poor growth (underweight and short stature). Granulomatous disease can lead to obstruction of the gastric antrum, to ileocolic junction, and to hydronephrosis. Some patients manifest disease in adulthood.

Most organisms causing infections in CGD patients produce catalase, an enzyme that catabolizes hydrogen peroxide into water and oxygen. This enzyme eliminates bacterial peroxide, which cannot be used by neutrophils to produce other reactive oxygen species (see Fig. 32.2). As a result, they escape phagocytosis and continue to multiply. The microbes – most catalase positive – that cause infections in CGD patients are *Staphylococcal aureus*, *Aspergillus* spp., enteric gram-negative bacilli (*Escherichia coli*, *Salmonella* spp., *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp.), *Burkholderia cepacia*, *Serratia marcescens*, *Staphylococcus epidermidis*, *Streptococcus* spp., *Candida albicans*, and *Nocardia* spp.

Laboratory Diagnosis

Diagnosis is based on the inability of neutrophils to produce reactive oxygen species (ROS) when stimulated with zymosan or phorbol myristate acetate since NADPH oxidase is inactive in resting phagocytes. In the past, nitro blue tetrazolium (NBT) was used as a substrate. When oxidized by ROS, NBT changes from yellow to a dark

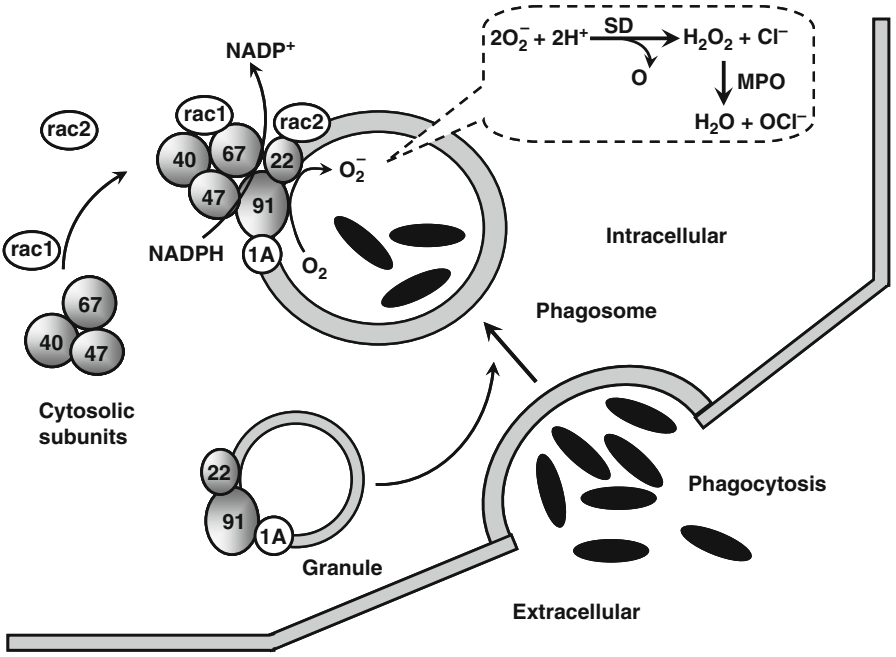

Fig. 32.2 In the respiratory burst of phagocytes, NADPH oxidase initiates formation of reactive oxygen species (ROS) in phagosomes, a process that consumes O_2. NADPH is inactive at rest because its subunits are disassembled. In granules, two membrane-bound subunits (91^{phox} and 22^{phox}) form the cytochrome b_{588} next to the GTP-binding protein rap1A (1A). Upon phagocytosis of microbes, granules fuse with the phagosome, and the cytoplasmic subunits (67^{phox}, 47^{phox}, and 40^{phox}) translocate and bind to cytochrome b_{588} to assemble the active NADPH oxidase. Small cytosolic GTP-binding proteins rac1 and rac2 regulate translocation of 67^{phox} and electron transport in the cytochrome b_{588}, respectively. A case of rac2 deficiency causing CGD has been described. In the phagosome, *superoxide* (O_2^-) produced by NADPH oxidase is transformed by superoxide dismutase (*SD*) into *hydrogen peroxide* (H_2O_2), which is then transformed by myeloperoxidase (*MPO*) into *hypochlorite* (OCl^-). These three ROS kill bacteria

brown-purple color inside neutrophil granules, which is visualized by light microscopy in leukocyte smears. This has been replaced by newer tests using flow cytometry or chemiluminescence. In one flow cytometry assay, normal neutrophils become fluorescent when their hydrogen peroxide reacts with dihydrorhodamine. This is a highly reliable and sensitive assay to detect both disease and maternal X-linked carrier status. Additional tests include flow cytometry or Western blot to identify which of the four subunits is missing and detection of mutations in the gene alleles of the missing subunit. In vitro assays using patient's neutrophils and bacteria can also show that CGD neutrophils have impaired bacterial killing and impaired oxygen consumption.

Other laboratory abnormalities include hypergammaglobulinemia and anemia of chronic disease. Blood leukocytes and sedimentation rate are normal but increase with infections. Granulomatosis in the lungs, liver, and spleen can cause obstructive symptoms and are visualized in CT scan or MRI studies.

Treatment

Prognosis improves with aggressive treatment of infections, aspirating infected lymph nodes, draining abscesses, and identifying infectious etiology by early biopsy of involved organs. Duration of antibiotic therapy is prolonged to 5–6 weeks instead of the usual duration of 1–2 weeks prescribed for immunocompetent hosts. Prophylactic treatment with trimethoprim-sulfamethoxazole reduces mortality due to bacterial infections, and recently, addition of prophylaxis for fungal infections using itraconazole was also beneficial. In addition, CGD patients treated continuously with subcutaneous interferon gamma (IFNγ) at 60 μg/m^2, three times a week, have reduced mortality and morbidity. IFNγ does not increase activity of NADPH oxidase, and it is unclear how it benefits CGD patients.

Glucose-6-Phosphatase Dehydrogenase Deficiency

In glucose-6-phosphatase dehydrogenase (G6PD) deficiency, patients lack G6PD (chromosome Xq28) in leukocytes, which participates in the formation of NADH and NADPH. As a result, they have impaired production of hydrogen peroxide but to a lesser extent than that in CGD. They are predisposed to infections with *S. aureus* and *E. coli*, but clinical manifestations are milder than those in CGD. This deficiency maybe related to G6PD deficiency in red cells, which predisposes to hemolysis with certain drugs such as sulfonamides.

Myeloperoxidase Deficiency

Patients with complete myeloperoxidase (MPO, chromosome 17q23.1) deficiency in leukocytes cannot produce hypochlorite from hydrogen peroxide (see Fig. 32.2) but have normal production of superoxide and hydrogen peroxide and have normal oxygen consumption. Bacterial killing assay shows delayed but eventually even complete bacterial killing. Many patients are asymptomatic, but some may have increased susceptibility to infections with *Candida* and *Staphylococcus*. Diagnosis is made by lack of peroxidase staining in blood neutrophils.

Hyper IgE Syndrome or Job's Syndrome

The hyper-IgE (HIE) syndromes refer to a group of primary immunodeficiency diseases characterized by an elevated IgE level, eosinophilia, recurrent *Staphylococcal* abscesses and skin infections, eczema, and lung infections. Several gene defects have been identified causing autosomal dominant and recessive forms of the disease.

The classical autosomal dominant form (AD-HIE) has been found to result from dominant negative mutations in the signal transducer and activator of transcription 3 (STAT3) gene, while defects in the dedicator of cytokinesis 8 (DOCK8) gene lead to an autosomal recessive form (AR-HIE).

Clinical Manifestations

Typically clinical manifestations of AD-HIE start in childhood with recurrent skin and deep-seated abscesses caused by staphylococci including pneumonia (often with pneumatocele formation) and mastoiditis. The deep-seated infections differentiate HIE from atopic eczema, which can also cause high IgE and staphylococcal impetigo. Less commonly abscesses can affect bones, joints, and viscera. Dermatitis is prominent, but unlike atopic eczema, pruritus is uncommon. In AD-HIE, staphylococcal infections with abscesses stand out, and there is a susceptibility to fungal infections including chronic mucocutaneous candidiasis and invasive aspergillosis. The eczematous rash is not usually related to food allergies. Other abnormalities include a characteristic facies (see below), osteopenia with fractures (osteoporosis) secondary to minor or unrecognized trauma, scoliosis, and hyperextensible joints. Dental abnormalities include the retention of primary teeth, the failure of secondary teeth to erupt, and delayed resorption of the roots of the primary teeth. On examination patients have coarse facial features including frontal bossing; a broad nasal bridge; a wide, fleshy nasal tip; and deep-set eyes. AD-HIE is therefore a multisystem disease affecting the immune system, connective tissues, skeletal system, dentition, and vasculature. The immunological abnormalities are related to a failure of signaling via STAT3 by multiple cytokine receptors including IL-6, IL-10, IL-11, IL-17, IL-22, and IL-23 among other factors. There are a failure to generate Th-17 cells and subsequent failure of IL-17 secretion and function.

While AR-HIE patients have elevated IgE levels, eosinophilia, eczema, recurrent pneumonia and abscesses, and mucocutaneous candidiasis, they do not have the skeletal and connective tissue defects found in AD-HIE. However, they do have an increased susceptibility to viral skin infections, neurological symptoms, hypogammaglobulinemia, and autoimmunity. Defects in DOCK8 have a variety of effects on the immune system including failure of migration of dendritic cells to lymph nodes, defective priming of CD4 T cells, and defects in CD8 and B-cell memory.

Laboratory Diagnosis

There is no specific laboratory test that establishes the diagnosis other than confirmation of a genetic defect in STAT3, DOCK8, or other less common causes of HIE syndrome. Patients have very elevated IgE levels usually >2000 IU/ml and often between 50,000 and 100,000 IU/ml, but levels fluctuate, whereas IgA, IgM, and IgG are normal in AD-HIE. Blood lymphocyte numbers and proliferative responses to mitogens and antigens are normal. Eosinophils are elevated in blood, sputum, and

tissues including in abscesses. Neutrophil respiratory burst and bacterial killing are normal, but they have a chemotactic deficiency probably mediated by T-cell-soluble factors and/or IgE immune complexes. In AR-HIE, patients may have hypogammaglobulinemia, may have lymphopenia, and decreased lymphocyte proliferation.

Treatment

There is no specific treatment. Treatment aims at controlling disease manifestations. Infections are treated with intravenous antibiotics to cover *Staphylococcus*. Deep-seated abscesses need drainage or excision. Early treatment of sinusitis and bronchitis can help prevent pneumonias and onset of chronic lung disease. Prophylaxis with trimethoprim-sulfamethoxazole and antifungals may be beneficial. Topical cutaneous corticosteroids are used for dermatitis and topical mupirocin for skin infections. Osteopenia and dental problems need early surveillance treatment to avoid long-term complications. Interferon gamma and intravenous immunoglobulin have been attempted without clinical benefit. Stem cell transplantation has been successful in patients with AR-HIE, who have a decreased life expectancy and a more severe immune deficiency than patients with AD-HIE.

Leukocyte Adhesion Deficiency Type 1

In leukocyte adhesion deficiency type 1 (LAD-1), an autosomal recessive disease, patients have mutations in the gene encoding CD18 (or integrin beta-2, chromosome 21q22.3), which forms heterodimers with integrins alpha-L (CD11a), alpha-M (CD11b), or alpha-Xto form, respectively, lymphocyte function-associated antigen 1 (LFA-1, CD11aCD18), complement receptor type 3 (Mac-1, CD11bCD18), and leukocyte surface antigen p150, 95 (Leu5, CD11cCD18). LFA-1 is expressed on T, B, and NK cells and Mac-1 on phagocytes and NK cells.

Clinical Manifestations

An initial clinical manifestation is delayed separation of umbilical cord (beyond 3 weeks). In the first weeks of life, they also develop pyogenic infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella*, *Proteus*, and enterococci. Infections are omphalitis and other skin infections, pneumonia, ileocolitis, peritonitis, perineal abscesses, periodontitis, tracheobronchitis, and sepsis. Mortality is high in the first years of life. A milder protracted form with the same genetic defect also exists.

Laboratory Diagnosis

Laboratory findings include leukocytosis, which markedly increases during infections reaching 50,000–100,000 cells per mm^3, but infection sites (e.g., cellulitis) do not accumulate pus. LFA-1 deficiency impairs cellular cytotoxicity from NK and CD8 cells and interaction between antigen-presenting cells and lymphocytes. CR3 deficiency can impair binding to C3b, phagocyte adhesion, chemotaxis, respiratory burst with phagocytosis, and antibody-dependent cellular cytotoxicity. Diagnosis is made by demonstrating lack of expression of CD18 on blood leukocytes stimulated with phorbol myristate acetate or by confirming the genetic defect.

Treatment

Treatment is directed toward infections. Prophylactic antibiotic therapy may be beneficial as well (e.g., for dental procedures). Some have been successfully treated with bone marrow transplantation.

Leukocyte Adhesion Deficiency Type 2

In leukocyte adhesion deficiency type 2 (LAD-2), patients lack the GDP-fucose transporter-1 (chromosome 11p11.2) resulting in lack of expression of sialyl-$Lewis^X$ (CD15s) on the surface of leukocytes. Sialyl-$Lewis^X$ is the ligand for E-selectin and its deficiency on neutrophils impairs their attachment and rolling on activated endothelial cells. As in LAD1, neutrophils also have a chemotactic defect, and patients suffer recurrent pyogenic bacterial infections, periodontitis, and marked neutrophilia with poor pus formation at the infection site. However, unlike LAD1, LAD2 patients have mental retardation.

Deficiency in the IL12/IFNγ Pathway

Macrophages stimulated by microorganisms produce IL12 that binds to IL12 receptor on NK and T cells inducing their production of IFNγ, which in turn acts on macrophages via IFNγ receptor increasing their phagocytic and killing activity. This macrophage-lymphocyte interaction is important in the defense against mycobacteria because several deficiencies in this pathway increase susceptibility to mycobacterial infections.

The active form of IL12 is IL12p70, a heterodimer of IL12p40 (IL12B) and IL12p35 (IL12A). The IL12 receptor (IL12R) is also a heterodimer composed of IL12Rβ1 and IL12Rβ2. Similarly, the IFNγ receptor (IFNγR) is a heterodimer of IFNγR1 and IFNγR2. Stimulation via IFNγR results in activation of the transcription factor STAT1.

Clinical Manifestations

Deficiencies in IL12p40, IL12Rβ1, IFNγR1, IFNγR2, and STAT1 have been described where patients manifest clinically with increased susceptibility to mycobacterial infections caused by usually nonpathogenic bacillus Calmette-Guerin (BCG) and environmental mycobacteria including osteomyelitis, pneumonia, skin infections, and disseminated infection. Deficiencies in IL12p40 and IL12R also increase susceptibility to *Salmonella* and *Nocardia* infections.

Laboratory Diagnosis

Based on the prevalence of IFNγ/IL12 axis defects, laboratory evaluation of patients with nontuberculous mycobacterial infection and without other obvious cellular immunodeficiencies should be performed by flow cytometry for expression of IFNγR1, IFNγR2, and IL12Rβ1, secretion of IL12p40 (or IL12p70) by monocytes stimulated with IFNγ and endotoxin [LPS], and phosphorylation of STAT1 (shows normal function of IFNγR) and of STAT4 (demonstrating functioning IL12R) to identify the specific defect.

Treatment

Besides acute antibiotic treatment for mycobacterial infections, many patients respond well to chronic IFNγ therapy and may need chronic mycobacterial antibiotic prophylaxis. BCG vaccine should be avoided. Because patients with defects in the IFNγR do not respond to therapy with IFNγ, stem cell transplantation has been attempted with variable results.

Defects in Toll-Like Receptor Signaling Pathways

Toll-like receptors (TLR) are pattern recognition receptors found on the surface or inside cells that recognize common patterns of molecules present in pathogens including gram-positive bacteria, gram-negative bacteria, fungi, and DNA or RNA viruses. TLR are present in structural cells, the first responders to pathogens, and also in immune cells. TLR stimulation by pathogens initiates innate immune response. Most TLR signaling pathways activate an inflammatory response characterized by immune defense (e.g., production of reactive oxygen and nitrogen species molecules and interferons), inflammation (e.g., chemokines and cytokines that attract and stimulate antigen-presenting cells and lymphocytes), and engagement of adaptive immunity (e.g., cytokines and expression of co-stimulatory molecules). This response helps control spread of the invading pathogen and clear infection. Genetic defects in several of the TLR molecules or downstream signaling pathway

have been associated with severe or recurrent infections. Surprisingly, each TLR pathway defect is associated with a narrow window of susceptibility. Examples of defects in TLR or their signaling pathway are associated with invasive staphylococcal and streptococcal infections with minimal fever and inflammation (defects in IRAK-4, MyD88) or herpes virus encephalitis (defects in TLR3, UNC93B, and TRAF-3).

Evidence-Based Medicine

Prenatal Diagnosis and Newborn Screening

Since the genetic defects for many primary immunodeficiencies are known, prenatal diagnosis is widely available for inherited diseases. Amniotic fluid cells or fetal blood are used to obtain fetal DNA and check for the gene defect. However, this can only apply to families with a history of a known immunodeficiency. More recently, quantitative PCR for T-cell receptor excision circles (TREC) from newborn dry blood spots has been developed for newborn screening of SCID. The first program started in Wisconsin in 2008. In 2010, newborn screening for SCID was added to the national recommended uniform panel for newborn screened disorders in the USA. The TREC-based assay also identifies patients with other conditions with T-cell lymphopenia such as DiGeorge syndrome and idiopathic T-cell lymphopenia among others. Over the past several years, many states have initiated newborn screening for SCID leading to the early diagnosis and treatment of these patients. Kwan et al. recently reported the outcome of TREC-based newborn screening for SCID and other T-cell lymphopenia from 11 screening programs, 10 states, and the Navajo Nation. They found an incidence of SCID in 1:58,000 patients most of whom were successfully treated by stem cell transplantation, gene therapy, or enzyme replacement.

Definitive Therapy for Primary Immunodeficiency Diseases

Definitive therapy for primary immunodeficiency remains the goal of any treatment plan. Patients with SCID are particularly susceptible to severe and opportunistic infections early in life. Newborn screening described above can make a significant impact on survival and quality of life. To this end, a consortium to study therapy for primary immunodeficiency diseases was developed including more than 25 centers in the United States. Pai et al. recently published the results of a retrospective survey of stem cell transplantation for SCID from 25 centers, comparing the different approaches to transplantation. Irrespective of the approach, transplantation within the first 100 days of life led to an excellent outcome. While stem cell transplantation has made tremendous progress with excellent results, not all patients are able to

undergo stem cell transplantation, and some may fail the treatment. Gene therapy was developed to provide a corrective therapy without the risks of transplantation. Gene therapy was first attempted in adenosine deaminase-deficient SCID in 1990, resulting in temporary success initially but with improved results after recent modifications. In 1999, gene therapy was performed for X-linked SCID where normal common gamma chain (γc) gene was transfected into patients' autologous bone marrow CD34+ stem cells ex vivo using a retrovirus vector. The transfected cells were then transferred back to the patients. Many patients had excellent results including reconstitution of specific antibody response; however, some of the patients developed leukemia because the gene transfection integrated the γc gene next to the proto-oncogene LMO2. Novel approaches are being developed to circumvent this problem. Gene therapy for other immunodeficiency diseases such as WAS and CGD is also under investigation. Mukherjee and Thrasher recently reviewed the progress and pitfalls of gene therapy for primary immunodeficiency diseases. As novel techniques for gene correction are developed, many more immunodeficiency diseases may be amenable to a cure.

Whole Exome and Whole Genome Sequencing

With the advent of next generation sequencing techniques, it has become possible to sequence the whole genome or only the coding exons of patients to identify genetic causes of diseases, including primary immunodeficiency diseases. This technology has allowed the identification of many novel genetic causes of immunodeficiency diseases. In recent review, Platt et al. described the different approaches to identifying the genetic causes of immunodeficiency diseases and the difficulties of each approach. The number of identified gene defects causing primary immunodeficiency diseases is increasing at a rapid rate. As a result, an expert committee of the International Union of Immunological Societies publishes updates on the classification of primary immunodeficiency diseases on a regular basis, containing phenotypes and genetic causes of all immunodeficiencies.

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Web-Based Resources

Diagnosis & management: Searchable database for diagnosis and management of PIDs -http://www.immunodeficiencysearch.com. Immune phenotyping in primary immunodeficiency http://www.ipidnet.org.

National Institutes of Health: National Institute of Allergy and Infectious Diseases resources on primary immunodeficiencies. https://www.niaid.nih.gov/topics/immunedeficiency.

Patient Organizations: Immune Deficiency Foundation. http://primaryimmune.org/. Jeffrey Modell Foundation. http://www.info4pi.org/. International Patient Organization for Primary Immunodeficiencies. http://www.ipopi.org.

Societies: American Academy of Allergy, Asthma & Immunology. http://www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease.aspx. European Society for Immunodeficiencies. http://www.esid.org.

Chapter 33
HIV Infection

Philip M. Grant and Andrew R. Zolopa

Introduction

Untreated infection with human immunodeficiency virus (HIV) causes progressive immunodeficiency, resulting in opportunistic infections and cancers. Treatment focuses on inhibiting viral replication and, for those patients with immune dysfunction, administering prophylactic treatment to prevent serious infections. In this chapter, we review the pathophysiology, the immunologic consequences, the treatment, and the management of two common inflammatory/allergic conditions associated with HIV infection: hypersensitivity reactions and immune reconstitution inflammatory syndrome (IRIS).

Pathophysiology of HIV

HIV-1 is a single-stranded RNA retrovirus that infects humans. The virus envelope attaches itself to the human cell, binding CD4 receptors of T lymphocytes and monocytes and a co-receptor (either CCR5 or CXCR4). Once attached to the receptors, the virus enters the cell. Replication of the virus depends on a reverse transcriptase (RNA-dependent DNA polymerase) to make a DNA copy of the viral RNA. A

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second strand of DNA is synthesized making a double-stranded DNA replica of the viral RNA. The DNA strand is integrated into the host cellular DNA using the viral enzyme integrase. The viral building blocks (HIV-1 RNA, gag proteins, and various enzymes) are synthesized and assembled inside the cell and then bud through the plasma membrane of the cell, creating mature viral particles that can infect other cells.

Immunologic Consequences of HIV Infection

Because HIV has a high affinity for the CD4 receptor, helper T cells are the major target of HIV. The number of CD4 T cells is the primary laboratory parameter used for assessing the severity of immunodeficiency as well as the immunologic response to treatment. Viral replication results in progressive depletion of CD4 cells. There is preferential loss of naive CD4 cells over memory CD4 cells early in infection. In addition to the loss of CD4 cells, HIV infection also impairs the function of remaining CD4 cells.

Although HIV causes CD4 cell loss, it simultaneously leads to a state of immune activation of CD4 and CD8 cells and monocytes. Activation enhances the ability of HIV to infect additional CD4 cells. Monocyte activation results in elevated production of multiple cytokines including tumor necrosis factor alpha and interleukin 6. Overall, immune activation likely contributes to the dysfunctional immune response against opportunistic infections. Although circulating CD8 cells expand initially with infection, with progressive infection, there is loss of CD8 cells, B lymphocytes, and natural killer cells.

In the absence of treatment, HIV infection results in susceptibility to serious opportunistic infections and cancers. The average time between infection and serious immunodeficiency (i.e., a CD4 count below 200 cells/μL) or an opportunistic infection is approximately 10 years, but can range from "rapid progressors" (1–2 years from infection to serious immune deficiency) to so-called nonprogressors (persons who have been infected for longer than 15 years without treatment but who maintain relatively preserved immune function).

With potent antiretroviral therapy (ART), there is a rapid increase (first few months after starting therapy) in circulating naive and memory CD4 and CD8 cells. This is followed by a slower increase (first year and beyond) in circulating naive CD4 and CD8 cells and a decrease in circulating memory cells. It is thought that the ability of T cells to respond to a variety of antigens improves during this second phase. Immune activation also decreases—although never returns to levels seen in uninfected individuals. With these immunologic improvements, marked reductions in the appearance of opportunistic infections and malignancies have occurred.

Treatment of HIV Infection

Antiretroviral Therapy

Treatment of HIV infection focuses on suppressing viral replication. HIV viral replication is measured by real-time polymerase chain reaction or less commonly a branched DNA assay, producing a result commonly referred to as a "viral load." The optimal timing for the initiation of antiretroviral treatment is not entirely known and considers the benefits of viral suppression and reduced immune activation and infectivity vs. the costs of medications and the potential for side effects. With the improved tolerability of current antiretroviral medications and an evolving recognition of the adverse consequences of immune activation, current guidelines recommend all individuals infected with HIV-1 should be treated with antiretrovirals, regardless of CD4 count and viral load. An ongoing large randomized study, the START study, hopes to provide more definitive evidence on the optimal timing of antiretroviral therapy.

Once a decision to initiate therapy has been made, several important principles should guide therapy. First, because HIV-infected patients can develop drug resistance to antiretroviral agents, a major goal of therapy should be full suppression of viral replication as measured by the plasma viral load. Therapy that fully suppresses plasma viral load also correlates with antiviral effect in other compartments. To achieve and maintain virologic control over time, combination therapy is essential.

The current standard of care for treatment-naive individuals is to use at least three agents in combination. Several well-tolerated single-tablet regimens that combine multiple antiretroviral agents are now available and have been shown to be potent and well tolerated. Despite this simplicity, some patients still have challenges with adherence. Adherence can be promoted through the use of medication boxes with compartments (e.g., MediSets), supportive counseling, or daily supervised therapy.

Monitoring of antiretroviral therapy has two goals. Laboratory evaluation for toxicity depends on the specific medications used and generally is performed approximately every 3–6 months once a patient is on stable therapy. Efficacy is determined by monitoring the CD4 cell count and the HIV viral load. These tests of efficacy should be performed 1–2 months after the initiation or change of antiretroviral regimen and every 3–6 months thereafter in clinically stable patients. Reasons for changing antiretroviral regimens include adverse reactions, a desire for a more compact antiretroviral regimen, and rising or persistently detectable viral loads (generally above 200 copies/mL). When therapy is modified due to virologic failure, clinicians should initiate at least two agents to which an individual has not been exposed or to which there is minimal or no resistance. In addition, other medications that may remain partially active against the patient's virus are frequently continued. With currently available therapy, a fully active regimen can be constructed for nearly every patient.

Although the ideal combination of drugs has not yet been defined for all clinical scenarios, possible choices can be better understood after a review of the six major classes of medications: nucleoside/tide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs). Table 33.1 shows the dose and potential side effects of antiretroviral agents in common usage.

Nucleoside/Tide Reverse Transcriptase Inhibitors

There are currently seven available NRTIs: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, and zidovudine. Didanosine, stavudine, and zidovudine have been phased out in the developed world due to their poor side effect profiles. Emtricitabine and lamivudine are essentially interchangeable, and one of these agents is included in most antiretroviral regimens given their excellent tolerability and antiviral efficacy. Abacavir and tenofovir disoproxil fumarate are also frequently used and are generally well tolerated. Several combination NRTI tablets have been formulated, but the ones still in common usage are Epzicom (abacavir and lamivudine) and Truvada (emtricitabine and tenofovir disoproxil fumarate). Combination medications decrease pill burden and improve adherence to therapy. Emtricitabine, lamivudine, and tenofovir disoproxil fumarate also have activity against hepatitis B and are generally used in patients coinfected with HIV and hepatitis B.

Nonnucleoside Reverse Transcriptase Inhibitors

There are five FDA-approved NNRTIs: delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Delavirdine is rarely used because of a high pill burden and a relative scarcity of clinical data to support its efficacy. Nevirapine is also not frequently used due to a worse adverse effect profile than comparators. Efavirenz has been one of the most commonly used first-line agents since its approval in 1998. However, with the availability of better-tolerated agents, efavirenz is no longer recommended as first-line treatment for treatment-naive individuals, according to the Department of Health and Human Services. Rilpivirine is a well-tolerated agent, but is less effective than efavirenz in individuals with high viral loads (>100,000 or >500,000 copies/mL, depending on the study). Resistance to an NNRTI generally leads to resistance to the other drugs in the class, although etravirine often maintains at least partial activity in the presence of NNRTI-associated resistance.

Protease Inhibitors

Nine PIs, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir, are currently available. Fosamprenavir, indinavir, nelfinavir, saquinavir, and tipranavir are rarely used due to increased pill burden,

Table 33.1 Characteristics of antiretroviral agents in common usage

Drug	Dose	Adverse effects	Special monitoring	Notes
Nucleoside/tide reverse transcriptase inhibitors				
Abacavir	600 mg daily or 300 mg twice daily	Hypersensitivity reaction (fever, rash, influenza-like illness); potential increased MI risk	HLA-B*5701 allele screening prior to initiation of therapy; do not administer to those who test positive	Reduced efficacy in patients with high baseline viral load in one study; similar activity at high viral loads when paired with lamivudine and integrase inhibitors vs. emtricitabine/ tenofovir disoproxil fumarate
Emtricitabine	200 mg daily	Well tolerated	None	Very similar to lamivudine; active against HBV
Lamivudine	300 mg daily or 150 mg twice daily	Well tolerated	None	Active against HBV
Tenofovir disoproxil fumarate	300 mg daily	Progressive diminution in kidney function, decrease in bone mineral density, rarely can cause acute renal failure and proximal tubulopathy	Serum creatinine, eGFR, urinalysis	Active against HBV; dose adjustment required with renal dysfunction
Nonnucleoside reverse transcriptase inhibitors				
Efavirenz	600 mg daily	Central nervous system effects, rash, potentially teratogenic and increased suicidality	Pregnancy testing	Take on empty stomach to decrease adverse neuropsychiatric effects; should not be administered in first trimester of pregnancy
Etravirine	200 mg twice daily	Rash and hypersensitivity reactions	None	Active against many NNRTI-resistant variants
Nevirapine	200 mg daily (extended release) or 200 mg twice daily (immediate release)	Rash, hepatotoxicity, hypersensitivity reaction	Liver function tests	Avoid in women with pretreatment CD4 counts >250 and in men with pretreatment CD4 counts >400; need dose escalation at initiation

(continued)

Table 33.1 (continued)

Drug	Dose	Adverse effects	Special monitoring	Notes
Rilpivirine	25 mg orally once daily	Depression, insomnia, headache, rash	None	Must be taken with a meal (≥400 kcals); avoid in patients with HIV-1 RNA >100,000 copies/mL; should not be combined with a proton pump inhibitor
Protease inhibitors				
Atazanavir	400 or 300 mg with ritonavir 100 mg or cobicistat 150 mg daily	Jaundice, nephrolithiasis, nephrotoxicity, cholelithiasis, decline in bone mineral density, GI adverse effects	Cholesterol, triglycerides if boosted, bilirubin	Taken with light meal; avoid with proton pump inhibitors; requires dosing separation with H_2 blockers, antacids
Darunavir	Treatment naive: 800 mg with ritonavir 100 mg or cobicistat 150 mg daily Treatment experienced: 600 mg with ritonavir 100 mg twice daily or 800 mg with ritonavir 100 mg (or cobicistat 150 mg) daily	Rash	Cholesterol, triglycerides	Must be administered with pharmacologic booster
Lopinavir	400/100 mg twice daily or 800/200 mg once daily	GI adverse effects, hypertriglyceridemia, potential increased MI risk	Cholesterol, triglycerides, fasting glucose	Adverse effects and pill burden have made other PIs more attractive for first-line therapy
CCR5 antagonists				
Maraviroc	300 mg orally twice daily	Well tolerated	Assess HIV co-receptor usage prior to therapy	Adjust dose when given with inducers/inhibitors of cytochrome P450 3A4
Integrase strand transfer inhibitors				

Drug	Dose	Adverse effects	Special monitoring	Notes
Dolutegravir	50 mg daily (integrase inhibitor-naive patients); 50 mg twice daily (integrase inhibitor-experienced patients with suspected resistance)	Well tolerated	None	Active against many raltegravir-/elvitegravir-resistant variants; separate dosing from antacid
Elvitegravir	150 mg daily (as part of a co-formulated tablet); 85 mg daily (to be used with ritonavir-boosted atazanavir or lopinavir); 150 mg daily (to be used with ritonavir-boosted darunavir, fosamprenavir, or tipranavir)	Well tolerated	None	Resistance develops rapidly at virologic failure; administered with a pharmacologic booster; separate dosing from antacid
Raltegravir	400 mg twice daily	Well tolerated	None	Resistance develops rapidly at virologic failure; cross-resistance to elvitegravir

suboptimal efficacy, problematic drug–drug interactions, and/or side effect profile. Pharmacologic boosting by inhibition of the cytochrome P450 system with either ritonavir or cobicistat is now generally the standard when using PIs and allows for a reduction in pill burden, but does lead to many potential drug–drug interactions. Clinicians should consult the product inserts before prescribing PIs with other medications. Drugs such as rifampin that are known to induce the P450 system should be avoided. Darunavir is the most commonly used PI due to excellent antiviral activity in treatment-naive and treatment-experienced individuals and best-in-class tolerability and is now available co-formulated with cobicistat. Atazanavir (with cobicistat) and lopinavir (with ritonavir) also have co-formulations available.

Fusion Inhibitors

Enfuvirtide blocks the entry of HIV into cells and remains an option for patients harboring multi-class-resistant virus. However, it must be administered subcutaneously, resulting in painful injection site reactions. Given the availability of newer medications that are active against highly resistant HIV strains, enfuvirtide is rarely used.

CCR5 Antagonist

Maraviroc is an active drug in individuals harboring only CCR5-using virus (approximately 90 % of treatment-naive and 50 % of treatment-experienced individuals). Both genotypic and phenotypic assays are available to determine the "tropism" of a patient's virus. Maraviroc is well tolerated, but due to its required twice-daily usage, it is generally only used in treatment-experienced individuals.

Integrase Strand Transfer Inhibitors

There are three currently available INSTIs: dolutegravir, elvitegravir, and raltegravir. Pharmacologic boosting is required with elvitegravir. INSTI-containing regimens have rapidly become the most commonly prescribed first-line regimens due to their excellent tolerability and antiviral activity. Dolutegravir has the benefit of once-daily dosing and activity against some viral strains resistant to elvitegravir and raltegravir.

Constructing Combination Regimens

Combinations including two NRTIs (referred to commonly as the "nuc backbone") and a third agent (an NNRTI, PI, or INSTI) remain the standard of care for initial treatment. Because approximately 10 % of newly infected persons will have some

degree of transmitted drug resistance, resistance testing should be performed before initiation of therapy. Current regimens are highly effective and durable with clinical trial data showing up to 90 % of patients with undetectable viral loads after 1 year of therapy. Given the high potency of multiple different regimens, convenience and tolerability have become the driving factors in the selection of an initial regimen for most patients. Single-tablet regimens combining two NRTIs with an NNRTI (efavirenz/tenofovir disoproxil fumarate/emtricitabine and rilpivirine/tenofovir disoproxil fumarate/emtricitabine) or an INSTI (dolutegravir/abacavir/lamivudine and elvitegravir/cobicistat/ tenofovir disoproxil fumarate/emtricitabine) are now available and have greatly simplified therapy. As discussed above, INSTI-based regimens are increasingly selected for initial therapy given their excellent tolerability and antiviral activity.

In the absence of head-to-head comparisons of different regimens in different scenarios, several general principles should guide the choice of combinations. The most important determinant of treatment efficacy is adherence to the regimen. Therefore, it is vitally important that the regimen chosen be one to which the patient can easily adhere. In general, patients are more compliant with medication regimens that are once or twice a day only, do not require special timing with regard to meals, can be taken at the same time as other medications, do not require refrigeration or special preparation, and do not have bothersome side effects. Second, it is desirable to prescribe combinations that have been demonstrated effective in clinical studies. To the extent possible, agents to which the patient has not been exposed are preferable to drugs for which resistance mutations may have already occurred. Toxicities should ideally be nonoverlapping. Interactions between drugs that result in potentially toxic levels should be avoided. An individual's relative contraindications to a given drug or drugs should be considered. The regimen should not include agents that are either virologically antagonistic or incompatible in terms of drug–drug interactions. Compatible dosing schedules—prescribing medications that can be taken at the same time—improve adherence to treatment. Finally, highly complex therapeutic regimens should be reserved for individuals who are capable of adhering to the rigorous demands of taking multiple medications and having this therapy closely monitored. Conversely, simplified regimens that deliver the lowest number of pills given at the longest possible dosing intervals are desirable for patients who have difficulty taking multiple medications.

Drug Resistance

HIV-1 drug resistance limits the ability to fully control HIV replication and is a leading cause for antiretroviral regimen failure. Resistance has been documented for all currently available antiretrovirals but is significantly more common with some antiretrovirals than others. The problem of drug resistance is widespread in HIV-infected patients undergoing treatment in countries where antiretroviral therapy is widely available. However, the development of multiple new antiretrovirals, easier dosing schedules including single-table regimens, efforts to improve

adherence, and more common usage of certain antiretrovirals with "high barriers to resistance" (i.e., pharmacologically boosted PIs and dolutegravir) have made resistance of declining concern in the clinic. Despite this welcome occurrence, drug resistance remains a problem because of cross-resistance between drugs within a class. For example, the resistance patterns of elvitegravir and raltegravir are overlapping, and patients with virus resistant to elvitegravir are unlikely to respond to raltegravir even though they have never received treatment with this agent. Similarly, the resistance patterns of nevirapine and efavirenz are overlapping.

Additionally, the issue of resistant virus does not just concern the treatment-experienced patient. Resistance is not uncommonly documented in patients who are treatment naive but who have been infected with a drug-resistant strain—"primary resistance." Cohort studies of treatment-naive patients entering care in North America and Western Europe show that 10 % or more of recently infected individuals have been infected with a drug-resistant strain of HIV-1. As such, current expert guidelines recommend genotypic resistance testing for all patients at diagnosis. Resistance testing is also recommended for patients who are on an antiretroviral regimen and have suboptimal viral suppression (i.e., viral loads above 200–1000 copies/mL). Both genotypic and phenotypic tests are commercially available, and in randomized controlled studies, their use resulted in improved short-term virologic outcomes compared to making treatment choices without resistance testing. Furthermore, multiple retrospective studies have conclusively demonstrated that resistance tests provide prognostic information about virologic response to newly initiated therapy that cannot be gleaned from standard clinical information (i.e., treatment history, examination, CD4 count, and viral load tests).

Because of the complexity of resistance tests, many clinicians require expert interpretation of results. In the case of genotypic assays, results may show that the mutations selected for during antiretroviral therapy are drug specific or contribute to broad cross-resistance to multiple drugs within a therapeutic class. An example of a drug-specific mutation for the reverse transcriptase inhibitors would be the M184V mutation that is selected for by lamivudine or emtricitabine therapy—this mutation causes resistance only to those two drugs. Conversely, the thymidine analog mutations ("TAMs") of M41L, D67N, K70R, L210W, T215Y/F, and T219Q/K/E are selected for by either zidovudine or stavudine therapy but contribute to resistance to all the drugs in the NRTI class. Further complicating the interpretation of genotypic tests is the fact that some mutations that cause resistance to one drug can actually make the virus that contains this mutation more susceptible to another drug. The M184V mutation, for example, is associated with increased sensitivity to zidovudine, stavudine, and tenofovir. Phenotypic tests also require interpretation in that the distinction between a resistant virus and sensitive one is not fully defined for all available drugs. Both methods of resistance testing are limited by the fact that they may measure resistance in only some of the viral strains present in an individual. Resistance results may also be misleading if a patient is not taking antiretroviral medications at the time of testing. Thus resistance results must be viewed cumulatively; that is, if resistance is reported to an agent on one test, it should be presumed to be present thereafter even if subsequent tests do not give the same result.

Prophylaxis for Opportunistic Infections

All HIV-infected patients with positive purified protein derivative (PPD) reactions (defined in HIV-infected patients as 5 mm or greater of induration) or a positive interferon-gamma release assay (IGRA) should receive treatment for latent tuberculosis infection. A chest radiograph should be performed first to exclude active tuberculosis. In individuals with severe immune immunosuppression from endemic areas, a sputum AFB stain and culture should be performed to rule out active tuberculosis prior to initiation of treatment for latent tuberculosis.

For patients with severe immune suppression, prophylaxis for other opportunistic infections is also needed. In the era prior to ART, patients started on prophylactic regimens were maintained on them indefinitely. However, studies have shown that in patients with an adequate response to ART—as measured by increases in CD4 counts at or above the levels that are used to initiate treatment—prophylactic regimens can safely be discontinued.

Primary prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP) should be prescribed to patients with a CD4 count below 200 cells/μL, a CD4 lymphocyte percentage below 14 %, another AIDS-defining illness, or oral candidiasis (Table 33.2). Patients with a history of PCP should receive secondary prophylaxis until they maintain a CD4 count above 200 cells/μL in response to ART for at least 3 months. More recent data also suggest that those with a CD4 count between 100 and 200 cells/μL and a suppressed viral load are also at low risk for PCP and do not require prophylaxis.

The four regimens for prophylaxis of PCP are trimethoprim–sulfamethoxazole, dapsone, atovaquone, and aerosolized pentamidine. Trimethoprim–sulfamethoxazole is inexpensive, widely available, and the most effective agent for prophylaxis. However, hypersensitivity reactions are common (see later). Dapsone is a second-line prophylactic agent with minimal side effects. Before prescribing dapsone, clinicians should make certain that the patient is not glucose-6-phosphate dehydrogenase deficient because such patients are at high risk of developing hemolytic anemia with

Table 33.2 Infection prophylaxis for HIV-infected individuals

Infection	Indication	Treatment
Tuberculosis	PPD >5 cm or + IGRA	Isoniazid 300 mg daily + pyridoxine 50 mg daily × 9 months
Pneumocystis jiroveci pneumonia	CD4 count <200 cells/μL, CD4 percentage <14 %, AIDS-defining illness, or oral candidiasis	Trimethoprim–sulfamethoxazole one double-strength tablet daily or dapsone 100 mg daily
Toxoplasmosis	CD4 count <100 cells/μL and positive toxoplasma IgG	Trimethoprim–sulfamethoxazole one double-strength tablet daily or dapsone 50 mg daily + (pyrimethamine 50 mg + leucovorin 25 mg) weekly
Mycobacterium avium complex infection	CD4 count <50 cells/μL	Azithromycin 1200 mg weekly or clarithromycin 500 mg twice daily

dapsone therapy. For patients unable to take trimethoprim–sulfamethoxazole or dapsone, atovaquone and aerosolized pentamidine are third- and fourth-line treatment options, respectively.

Prophylaxis against *Mycobacterium avium* complex (MAC) infection should be given to patients with a CD4 count below 50 cells/μL. The preferred regimen is azithromycin (1200 mg orally weekly). Before initiating prophylaxis, clinicians should establish with a blood culture that the patient does not have disseminated MAC infection. Prophylaxis against MAC infection may be discontinued among patients whose CD4 counts rise above 100 cells/μL in response to ART.

Toxoplasmosis prophylaxis is desirable in individuals with a positive toxoplasma IgG serology and CD4 counts below 100 cells/μL.

Cytomegalovirus (CMV) infection is also common in advanced HIV disease, but prophylaxis is not recommended due to the toxicity of ganciclovir/valganciclovir and conflicting results from clinical trials regarding its efficacy.

Cryptococcosis, candidiasis, and endemic fungal diseases are also candidates for prophylaxis. One prophylactic trial from the pre-ART era showed a decreased incidence of cryptococcal disease with the use of fluconazole, 200 mg orally daily, but the treated group had no benefit in terms of mortality. Fluconazole (200 mg orally once a week) was found to prevent oral and vaginal candidiasis in women with a CD4 count below 300 cells/μL.

Because individuals with advanced HIV infection are susceptible to a number of opportunistic pathogens, the use of agents with activity against more than one pathogen is preferable. It has been shown, for example, that trimethoprim–sulfamethoxazole confers protection against PCP and toxoplasmosis.

Treatment of HIV Manifestations

HIV can affect every organ system in the body. For references on the diagnosis and treatment of HIV-related infections and malignancies, see the evidence-based medicine section and the reference list at the end of the chapter.

Hypersensitivity Reactions

Hypersensitivity reactions are drug-specific immune responses (production of a specific antibody or reaction of sensitized T cells) that are independent of drug dose. HIV-infected individuals are more likely to develop hypersensitivity reactions than uninfected individuals.

Severity of the reaction can vary from mild to life-threatening with a wide variety of manifestations, including rash, fever, hepatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis (TEN), hypotension, anaphylaxis, and death. Typically symp-

toms occur within a few weeks of starting the medication. They can begin almost immediately in the case of rechallenge.

Among medications used in the treatment of HIV, hypersensitivity reactions are particularly common with abacavir, nevirapine, and trimethoprim–sulfamethoxazole, which commonly are used in both the treatment and the prophylaxis of PCP. For abacavir, the negative predictive value of a negative screen for HLA-B*5701 has been shown to be 100 % in whites and blacks. In those positive for HLA-B*5701, abacavir should be avoided. There is a genetic test available that can predict an increased risk for nevirapine hypersensitivity reactions, but the test does not have as favorable test characteristics as the screen for abacavir hypersensitivity so it is not routinely used.

With mild hypersensitivity reactions (e.g., a morbilliform rash not involving mucosal structures occurring 7–14 days after starting trimethoprim–sulfamethoxazole), it is sometimes possible to continue treatment with supportive care (e.g., antihistamines). Severe reactions should prompt immediate discontinuation of treatment.

For patients in whom treatment is stopped due to hypersensitivity, it is best to switch them to an alternative agent. Sometimes, however, this is not possible. In such cases, patients can sometimes be successfully desensitized to a particular drug. Experiences with desensitization protocols have been published for sulfonamides, efavirenz, nevirapine, and enfuvirtide. Rechallenge should never be attempted with abacavir because of life-threatening reactions to this medication after rechallenge.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a local or systemic inflammatory response to a specific preexisting organism that occurs following rapid immune recovery as a result of ART. These inflammatory reactions may present with generalized signs of fevers, sweats, and malaise with or without more localized manifestations that usually represent unusual presentations of opportunistic infections. For example, patients with CMV retinitis have developed vitritis after initiation of ART. MAC can present as focal lymphadenitis or granulomatous masses in patients receiving ART. Tuberculosis may paradoxically worsen with new or evolving pulmonary infiltrates and lymphadenopathy. Progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis may also behave atypically.

The diagnosis of IRIS is one of exclusion and can be made only after a recurrence or the development of a new opportunistic infection has been ruled out as the cause of the clinical deterioration. A prospective study of 180 HIV-infected patients with preexisting *M. tuberculosis*, MAC, or *Cryptococcus neoformans* begun on ART found that 32 % developed IRIS. The median time between start of therapy and diagnosing IRIS was 46 days. Individuals with a more rapid initial fall in HIV-1 RNA level in response to therapy were more likely to develop IRIS.

Management of IRIS is conservative and supportive with use of steroids only for severe reactions. Generally, ART should be continued unless the reaction is life-threatening.

Evidence-Based Medicine

A central question facing clinicians is choosing the best available antiretroviral regimen. While the first studies of ART in the mid-1990s showed dramatic differences in hard clinical outcomes such as death and new opportunistic infections, subsequent studies have used the surrogate outcome of virologic suppression to determine efficacy.

The Department of Health and Human Services (DHHS) provides frequent updates evaluating the clinical trial evidence supporting the use of different regimens. Currently first-line DHHS-recommended regimens include dolutegravir/abacavir/lamivudine, elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine, raltegravir/tenofovir disoproxil fumarate, and darunavir/ritonavir/tenofovir disoproxil fumarate/emtricitabine.

As discussed above, recent studies have supported integrase inhibitor-containing regimens as preferred therapy in treatment-naive individuals. The SINGLE study compared dolutegravir/abacavir/lamivudine to the previous gold standard of efavirenz/tenofovir disoproxil fumarate/emtricitabine. At week 48, the proportion of participants with an HIV-1 RNA level of less than 50 copies per milliliter was significantly greater in the dolutegravir/abacavir/lamivudine group than in the efavirenz/tenofovir disoproxil fumarate/emtricitabine group (88 % vs. 81 %, $P = 0.003$). The difference was driven primarily by reduced side effects with the dolutegravir-containing regimen.

AIDS Clinical Trials Group Study A5257 was a three-arm study comparing raltegravir vs. darunavir/ritonavir vs. atazanavir/ritonavir, all paired with tenofovir disoproxil fumarate and emtricitabine. For the combined virologic failure/tolerability endpoint, raltegravir was superior to atazanavir (difference 15 %, 95 % CI 10–20 %) and to darunavir (difference 7.5 %, 95 % CI 3.2–12 %). Again, the improved tolerability of the integrase inhibitor (raltegravir in this case) was the primary reason for the superiority of the integrase inhibitor containing in the study.

Unfortunately, the best regimen for antiretroviral-experienced patients has not been fully determined and needs to be individualized based on history of response and side effects to prior medications and resistance patterns.

Resources

HIV treatment continues to evolve. Therefore, the best sources of information are regularly updated websites. A useful website is AIDSinfo (www.aidsinfo.nih.gov). This site, provided as a service of the US Department of Health and Human Services,

has a database of medications and clinical trials, as well as multiple up-to-date guidelines including those for antiretroviral treatment of adults, children, and pregnant women. UCSF maintains an excellent website (http://hivinsite.ucsf.edu/) which includes an excellent online textbook as well as information on medications. Clinical Care Options (www.clinicaloptions.com) has become a leading provider of content including cases and conference summaries. Clinical Care Options also produces an online textbook focused on contemporary issues in HIV (https://www.inpractice.com).

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Chapter 34
Complementary and Alternative Medicine in the Treatment of Allergic and Asthmatic Disease

Leonard Bielory

What Is Complementary and Alternative Medicine (CAM)

Complementary and alternative medicine, as defined by the National Center for Complementary and Alternative Medicine (NCCAM), is a group of diverse medical and health-care systems, practices, and products that are not presently considered to be part of conventional medicine. "Conventional medicine" is medicine as practiced by holders of MD (medical doctor) or DO (doctor of osteopathy) degrees and by their allied health professionals, such as physical therapists, psychologists, and registered nurses. Other terms for conventional medicine include allopathy; Western, mainstream, orthodox, and regular medicine; and biomedicine. Some conventional medical practitioners are also practitioners of CAM, for example, osteopathic manipulation. Other terms for complementary and alternative medicine include unconventional, nonconventional, unproven, and irregular medicine or health care.

Complementary and alternative medicine involves the use of various modalities in a variety of domains (Fig. 34.1) to relieve symptoms and treat various diseases. Some of the most commonly used CAM modalities include herbal therapy, homeopathy, acupuncture, Ayurveda, and behavior modification techniques. CAM has its roots in many different cultures, western and eastern. It should be remembered that many medications used today in traditional medicine for allergic, asthmatic, and immunologic disorder disease found their origin in herbs and other alternative medicines of the past. As examples, corticosteroids, which are prominently used in the treatment of both asthma and atopic disease, have their origin in ground placenta

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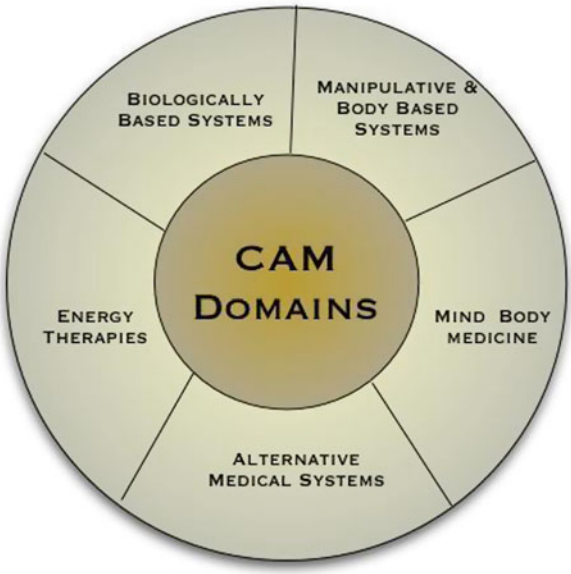

Fig. 34.1 CAM domains – the five CAM domain alternative medical systems that include traditional oriental medicine/acupuncture, homeopathy and naturopathy medicine, and Ayurvedic medicine; energy therapies that include bioelectromagnetic applications, Reiki, and qigong; biologically based systems that include diet, nutrition, lifestyle changes, herbal agents, and pharmacological and biological treatments; manipulative and body-based systems that include chiropractic and massage; and mind-body medicine that includes meditation, yoga, imagery, prayer, hypnosis, music therapy, and biofeedback

and the urine of pubescent boys, and the mast cell stabilizer cromolyn is historically derived from the Middle Eastern khella plant.

Definitions and Descriptions of Commonly Used Modalities

Herbal Therapies

Several herbal remedies have been noted in the literature to have efficacy in the treatment of allergies. A diverse sampling of various anti-inflammatory plants has been described, as have been a variety of plants and herbals that provide solely symptomatic relief (Fig. 34.2).

Homeopathy

Homeopathy works on the principle of treatment with "similars." The remedies prescribed by homeopathic practitioners are essentially very dilute solutions of drugs known to cause the very symptoms that are to be treated. According to the literature

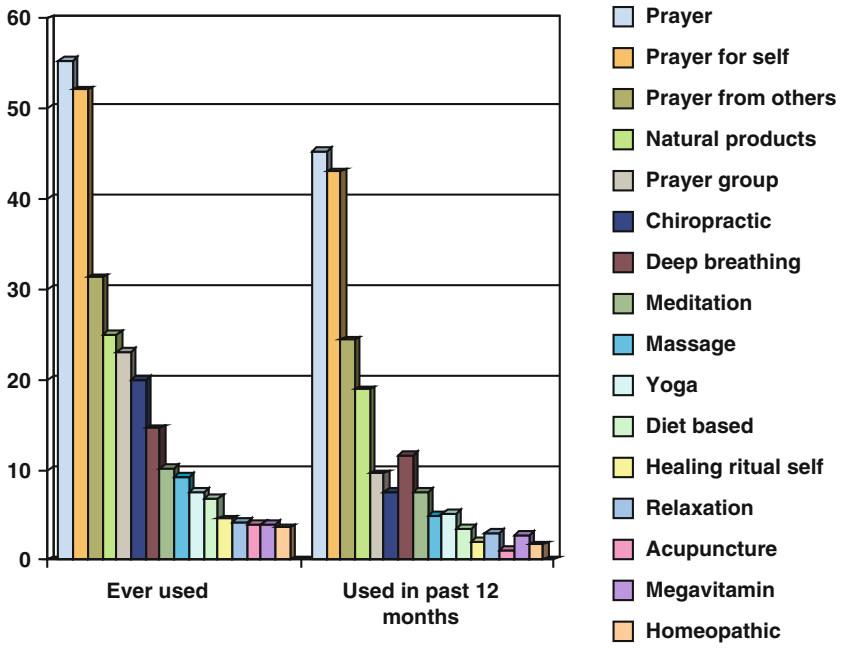

Fig. 34.2 Commonly used herbal remedies in CAM

reviewed, 3–4 % of CAM users use homeopathy, and about 75 % of patients seen by a homeopathic practitioners report symptomatic improvement. Homeopathic remedies are determined by "provings" and are listed in the *Homeopathic Materia Medica*.

Acupuncture

Acupuncture is a form of traditional Chinese medicine that was originally thought to work on the principle of redistribution of qi, the life energy. In traditional Chinese medicine, it is believed than an imbalance of qi or poor flow of qi is the origin of disease. By placing needles at specific points along meridians, qi can be redirected into better balance. NIHCDP (NIH Acupuncture Consensus Development Panel) within the Office of Alternative Medicine (now the NIH National Center for Complementary and Alternative Medicine) has already been working to prove the efficacy of acupuncture in the treatment of specific conditions; the most notable are nausea, pain, and addictions.

Ayurveda

Very little disease-specific research appears to have been completed in Ayurveda, a medical tradition originating from India. Ayurvedic medicine is derived from the

teachings of ancient Hindu healers and first appeared in text between 1500 and 1000 BC. Ayurvedic therapeutic interventions include yoga, meditation, breathing exercises, and herbal preparations. In its truest form, Ayurveda exists for the *promotion of health* rather than the prevention of specific disease states which have already begun to affect the body.

Behavior Modification Techniques

Behavior modification techniques include yoga and breathing retraining utilized by some asthmatic patients and teaching patients to respond differently or avoid allergic stimuli.

How Modalities Have Been Studied to Date

The integration of CAM interventions into the conventional day-to-day care of patients recommended by health-care providers is limited by the lack of acceptance due to an inadequate randomized placebo-controlled studies used to prove their efficacy. Although there is a paucity of data detailing the mechanisms or even the efficacy of many modalities, one must start to carefully review the literature for CAM interventions that have undergone randomized clinical studies with scientific scrutiny. The design of randomized placebo-controlled studies in CAM is complicated by difficulties in blinding, difficulties in creating an appropriate placebo (particularly for acupuncture), and difficulties in designing a control treatment when the mechanisms of actions of the modality to be tested are poorly delineated. Additionally, the difference in philosophy of CAM interventions from conventional health care allows for significant variation in the way CAM modalities are practiced. Therapies are often individualized for a particular patient and their particular disease state, and results can vary with patient's perception of their interaction with the CAM provider, which is often more personal than the interaction between patients and traditional health-care providers. Thus, study results may easily vary between CAM providers. Although one recent study showed no link between a patient's positive or negative attitude regarding a homeopathy remedy and outcomes in the treatment versus placebo groups, in studying the efficacy of CAM interventions, one must also appreciate and assess the importance of placebo effect due to the relationship that patients have with CAM providers.

As difficult as the design will be, the effort needs to be made to ensure patient safety and to prove efficacy of these modalities. By establishing mechanisms and efficacy of CAM intervention modalities currently in use, new options for traditional intervention may be discovered, and currently used medications may be improved.

Identifying Patients Most Likely to Use CAM

Epidemiology of CAM Use

The use of CAM has increased markedly in the worldwide population and specifically in the US population. Recent research continues to reflect that a majority of people worldwide use CAM interventions in some form for either the prevention or the treatment of disease with estimates of 80 % noted by the World Health Organization. In the USA, one third of the population has tried some form of complementary/alternative medicine. It is thought that perhaps two thirds (40–67 %) of the population with chronic disorders imparting devastating mortality such as immunodeficiency associated with HIV have used CAM interventions. Other studies have shown that between 20 and 55 % of pediatric patients have used some form of CAM interventions in the past year. This is particularly important for allergists as children suffer disproportionately from atopic disease.

Why Patients May Use CAM

CAM interventions are most commonly used for chronic conditions. Although the most common conditions associated with CAM interventions are either neuropsychiatric or musculoskeletal, atopic and immunologic disorders such as asthma, allergies, or immunodeficiencies are also common problems for which people use CAM. Asthma and atopic diseases are frustrating to patients because of the lack of a permanent and reliable cure or even a predictable remission. Patients generally understand that CAM intervention is not curative, but in some instances, it has been reported to provide some form of benefit in terms of symptom relief and improvement in quality of life issues. In regard to CAM interventions for the treatment of allergic disorders, most have concentrated on the use of herbal remedies derived from medicinal plants, homeopathy, acupuncture, and Ayurvedic interventions. In recent data published, 55 % of adults said they were most likely to use CAM because they believed that it would help them when combined with conventional medical treatments. Additionally, 28 % of adults used CAM because they believed conventional medical treatments would not help them with their health problem. Thirteen percent used CAM because they felt that conventional medicine was too expensive.

Identifying Populations Likely to Use CAM

One study in California focusing on patients with the diagnosis of asthma or rhinosinusitis revealed that 42 % of all patients surveyed had used CAM interventions; 24 % of all patients had used herbs. Forty-two percent of the herb users

used ephedra-containing products. The majority (>75 %) of all patients were college educated. Although earlier studies have shown education to be a factor in herbal use, no statistically significant link was found between level of education and the use of CAM interventions. Considering issues of health disparities, Hispanic patients and those with incomes less than $20,000 annually were less likely to have used CAM interventions. Women were found to be more likely to have used homeopathy, acupuncture, and massage; younger age was associated with medicinal caffeine use. Finally, self-assessed disease severity did not have an impact on herb use, but patients who felt they had more severe disease used homeopathy. This data reemphasizes the importance of discussing CAM interventions with all patients.

Screening for CAM Use by Patients

Many patients and patients' parents are reluctant to discuss their use of CAM interventions with their physician, so it is important that the physicians ask their patients about CAM intervention use. In order to better assist their patients, physicians should be prepared to discuss some of the benefits and risks associated with various CAM modalities so that patients will feel open to share their CAM experiences with the physician. The importance of inquiring about CAM intervention is exemplified in a survey of 142 pediatric patients seen in the ER; 45 % of parents reported giving their child an herbal supplement. The most commonly used supplements were aloe, echinacea, sweet oil, eucalyptus, gingko, ginseng, and goldenseal. One parent reported the concomitant administration of albuterol and ephedra. Many of these patients did not share their use of these therapies with their physicians. This lack of open communication puts the patient at risk of drug interactions, leading to therapeutic toxicity or inefficacy of traditional therapies.

Modalities Commonly Used in the Treatment of Asthma

Herbals

There are a wide variety of herbs used in the treatment of asthma. Particularly common is the use of ma huang, a traditional Chinese medicine, the main active ingredient of which is ephedrine. Methylxanthines, an established asthma treatment that includes theophyllin are found in tea leaves, regular black tea and coffee have also been used for the therapeutic effects of their methylxanthine component, caffeine in the treatment of asthma. In a study of 601 adult asthmatics comparing the use of CAM agents, 8 % reported the use of herbal remedies, and 37 % of herb users used ephedrine-containing products. Six percent of all patients used

ephedrine alone, and 6 % used coffee or black tea. This study found that while coffee, black tea, or other herb use was associated with an increased risk of ER visits and hospitalization related to asthma, the ephedrine-containing herbs and ephedrine supplementation were not. These agents did have cardiac and neurological adverse effects.

Traditional Chinese medicine remedies often involve the use of several herbs, but they most commonly include ma huang (ephedra). Ginkgo biloba has been used, and although the mechanism of efficacy is often questioned, several platelet-activating factor antagonist effects have been identified. Licorice has been used for its anti-inflammatory properties, while various other herbs have anticholinergic actions such as the smoke of henbane leaves and stramonium cigarettes.

Herbal combinations used in traditional Japanese medicine are similar to those in traditional Chinese medicine, and these agents are commonly known as saiboku-to/sho-saiko-to. Some of these agents have been shown to have a downregulating effect on lipoxygenase and cyclooxygenase activity. There have been numerous citations of the adverse effects including hepatotoxicity and pneumonitis regarding these agents. Other common plants that are known to have active ingredients include the Ayurvedic datura plants as a source of atropine and Coleus forskohlii plants that produce a beta-sympathomimetic effect.

Mucokinetic drugs used in Europe include mustard and horseradish. The North American derived echinacea has been used for the prevention and treatment of common cold for hundreds of years. However, recent evidence using various echinacea preparations showed no effect over that of a placebo. There may be an effect when *Echinacea purpurea* is used for treatment of colds, but no definitive evidence was found for this. There have been recent reports of complications of the use of echinacea including anaphylaxis, bronchospasm, urticaria, and angioedema that are more commonly reported in individuals with atopy.

Studies such as using a mixture of camphor, eucalyptus, and menthol have demonstrated the potential improvement on nasal resistance to airflow and general improved nasal sensation.

Acupuncture

Acupuncture's common use for asthma treatment may stem from its non-pharmacologic nature, low cost, and ready accessibility in many urban centers. There is a paucity of reliable date to support its use. Even in studies with sham acupuncture used as a control, the data has not been reliable in supporting the efficacy of acupuncture. In studies where acupuncture and beta-agonists were compared, the beta-agonists have proven superior therapeutic benefits for patients. There are case reports of mechanical side effects from the needles including contact dermatitis and pneumothorax. As in any practice involving sharp metal piercing of the skin, there is a risk for infectious disease transmission (hepatitis B and C, HIV) with this modality.

Homeopathy

It is estimated that 3–4 % of patients who utilize CAM use homeopathic therapy. There have been several reviews of the use of homeopathy in the treatment of both adult and pediatric patients with chronic stable asthma. This modality is tailored to the individual needs of each patient, which lead to difficulties in standardization of the studies. However, in all cases, the studies were placebo controlled. While several meta-analyses on the efficacy of homeopathy have found no difference from placebo, 75 % of patients utilizing homeopathy report subjective improvement. However, none of the studies were able to demonstrate an objective improvement in patient's disease status, pulmonary function, or quality of life scores. A Cochrane Database review concluded that there is not enough evidence to reliably assess the possible role of homeopathy in asthma.

Behavioral Techniques and Behavior Modification

Many patients have reported benefits from disciplined breathing exercises, including yoga and relaxation exercises, for control of their asthmatic symptoms. There have been some studies that demonstrate superior benefits when compared to traditional pharmacological therapy alone. When yoga is compared to a control of a stretching program, these benefits are lost. However, there are many different forms of yoga, and these differences will need to be carefully studied before it will be possible to recommend for or against yoga in the treatment of asthma.

Modalities Commonly Used in the Treatment of Allergic Rhinoconjunctivitis

Apitherapy

Apitherapy is the use of intentional bee stings on a weekly schedule to treat specific inflammatory disorders based on anecdotal observations of treatments for bronchitis and arthritis. Some of the reports use the meridian acupuncture lines. Animal models have demonstrated changes from bee stings associated with metalloproteinases, melittin (melittinin) in the bee venom. The beneficial effects of bee stings have been ascribed to melittin (melittinin), an anti-inflammatory agent, known to be hundred times stronger than cortisone demonstrating suppression of cytokine production. However, bee venom proteins such as melittin are associated with anaphylaxis as well as hepatotoxicity and intracerebral hemorrhages. This is not to be equated with insect venom desensitization as that utilizes bee venom that is specifically associated with the induction of anaphylaxis in sensitive individuals.

Herbals

Many studies of herbs in the treatment of allergic disease can be found; the following are examples of herbal remedies for rhinitis, dermatitis, and conjunctivitis. Butterbur, a petasine (*Petasites hybridus*), is an herbaceous plant native to Europe, Northern Africa, and Southwest Asia in the petasine family. The petasines have been shown in vitro to cause their effects by the inhibition of leukotriene synthesis, inhibition of histamine binding to H1 receptors, and blockage of degranulation of inflammatory cells. In a randomized double-blind parallel-group comparison study, the effects of butterbur were compared with the effects of commonly used oral antihistamine, cetirizine. The 125 study participants scored their allergic symptoms; global functioning was assessed by questionnaire. The "overall" outcome was that butterbur's effects compared to with cetirizine were similar. Symptom-specific outcomes were not individually evaluated. It was noted that there was no pattern of side effects noted with butterbur, while drowsiness was noted with cetirizine. Honey has anecdotally been reported to modulate the allergic response of seasonal allergy sufferers. In a randomized double-blind placebo-controlled study comparing the effects of pasteurized honey, unpasteurized honey, and placebo, 36 subjects ingested one tablespoon of honey/day for 195 days during peak allergy seasons (May–August). The patients rated the severity of the following symptoms: sore eyes, swollen eyes, watery eyes, itchy eyes, headache, runny nose, sneezing, itchy nose, postnasal drip, and stuffy blocked nose. No change in symptoms was noted consistently when honey users were compared to the placebo-controlled group. Eight weeks of daily treatment with a Chinese herbal remedy (extract of 18 herbs) reduced the severity of nasal symptoms and nonnasal symptoms and improved measures of quality of life in a randomized, double-blind, placebo-controlled study of 55 patients with seasonal allergic rhinitis seen in a Chinese medicine clinic in Australia.

One of the first studies of herbal therapy in atopic dermatitis involved 47 children with severe eczema treated with Zemaphyte™ (active ingredients *Ledebouriella seseloides*, *Potentilla chinensis*, *Anebia clematidis*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris*, *Glycyrrhiza uralensis*, and *Schizonepeta tenuifolia*). After an 8-week treatment period, the study group demonstrated a 91 % decrease in erythema compared to 10 % decrease observed in the placebo group. A similar study was conducted in adults with similar results. These herbs have been theorized to work by several mechanisms, including stimulation of the adrenal cortex leading to increased endogenous cortisone and cortisol release, potentiation of endogenous corticosteroids by slowing metabolic degradation, corticosteroid activity of the plants themselves, decreased production of inflammatory compounds (leukotrienes, prostaglandins, and arachidonic acid), antipruritic effects (possibly via vasoconstriction), and antibacterial action. More recently, 2 weeks of topical treatment with a licorice extract gel (made with 2 % licorice extract; 19.6 % glycyrrhizinic acid in gel) reduced erythema, edema, and itching in a double-blind study of 60 patients with atopic dermatitis.

Euphrasia drops (from the *Euphrasia rostkoviana officinalis*) were studied in a prospective cohort trial for their efficacy in the symptomatic treatment of conjunctivitis of any etiology (allergic, irritative, infectious). Eighty patients were enrolled in the study, and 65 patients completed the study in which patients used were permitted to use one drop of Euphrasia eye drops up to five times daily as needed for symptoms: reddening, burning, and veiling of vision. At the conclusion of the study, it was reported that >95 % of patients experienced a complete disappearance of their symptoms within 3–17 days of starting the Euphrasia drops, with optimal results from the administration of one drop three times a day.

Flavonoids have been shown to have inhibitory activity on mast cells and thus can decrease allergic symptoms. This activity appears to be enhanced by combining these compounds with sulfated proteoglycans.

Acupuncture

Acupuncture has also been studied in the treatment of allergic rhinitis. In a small randomized and controlled study ($n=30$) of patients suffering from seasonal allergic rhinitis, efficacy of treatment with acupuncture was assessed. The group was divided into two and treated with acupuncture or a sham control, each performed three times a week for 4 weeks. After the initial 4 weeks, the groups were crossed so that the original placebo group became the treatment group and vice versa. In both cases, the subjects treated with acupuncture, when compared to a control group receiving sham acupuncture, had a 70 % relief of their nonnasal (itching eyes and eye watering) and nasal seasonal allergy symptoms. The sham control group had a 30 % relief of their symptoms. The participants used no antihistamines, although they were available if the individual were to have deemed them necessary. Acupuncture has also been reported to have a limited but appreciable effect in the treatment of severely dry eyes.

Homeopathy

In a study designed to determine if homeopathy was primarily a placebo response, a 30c (1 part in 10^{60}) solution of grass pollen extract was given to 70 patients, and a placebo remedy was given to an additional 70 patients. When patients' symptom scores (based on symptoms of sneezing, blocked and runny nose, and watery, red, irritated eyes) were compared between the two groups, there was a significant improvement in the homeopathically treated group. However, some members of this group also suffered from exacerbation of their symptoms, leaving the author of the study to recommend that homeopathy may be more useful as a preventative measure than for acute symptomatic relief. In a retrospective study assessing systemic medication use in allergy sufferers, those patients who had used homeopathy in addition to traditional medication for allergy had an average reduction of their use of antihistamines by 70 % due to symptomatic relief from homeopathy treatment.

Nontraditional Immunotherapy

Also important in the prevention of allergic response is immunotherapy. There has been some interesting research into the feasibility of sublingual and direct conjunctival immunotherapy for the prevention of allergic rhinitis. In a double-blind placebo-controlled study, an accelerated course of sublingual immunotherapy (SLIT) was used in the prevention of seasonal rhinoconjunctivitis due to grass pollen. A statistically significant change was found in the study group, who received two sublingual grass pollen extracts daily for 15 days. The dose was scaled upward in the induction period and was readministered three times a week during the allergy season. A similarly efficacious use of sublingual immunotherapy was demonstrated in a double-blind placebo-controlled study of children allergic to *Parietaria judaica*. This study also noted that children who utilized this modality tolerated it well and demonstrated good compliance with the administration schedule. Finally, in a double-blind study comparing efficacy of sublingual immunotherapy to traditional injection therapy, the subjective efficacy noted by the patient in daily symptom diaries was equitable. When IgG levels and skin reactivity were analyzed, only the injective therapy was of benefit. Overall, the subjective patient response to sublingual immunotherapy seems to be comparable to more traditional injection therapy and has been recognized by WHO (World Health Organization) as a reasonable alternative means of administration of immunotherapy in the prevention of allergic rhinoconjunctivitis.

Local conjunctival immunotherapy entails instilling antigen drops in the eyes of patients known to suffer from allergic conjunctivitis. In a double-blind, placebo-controlled study, 24 subjects were divided into two groups. An increasingly concentrated dose of antigen was administered to each eye daily. At the conclusion of the 6-month trial, the antigen-specific conjunctival provocation test score was significantly lower in the study than placebo populations. This may represent, in addition to the previously described sublingual immunotherapy, a viable alternative to injected immunotherapy.

Halotherapy

Halotherapy (HT, Greek halos = salt) is a "physical therapy" modality that uses dry aerosol microparticles of salt and other minerals to treat a variety of "chronic" respiratory diseases that are known to be associated with inflamed mucosal surfaces, e.g., asthma, sinusitis, and rhinitis. The various designs of halotherapy rooms are an attempt to duplicate an ancient practice of speleotherapy (Greek speleos = cave) that has been practiced in the northern Mediterranean and Aegean Sea cultures, in which patients enter old salt mines. This may include just increasing breathing within those environments or actually performing particular physical or breathing exercises. The benefits of this are not known. The majority of the clinical trials are mainly reported in Russian-language journals due the extensive geographical distribution of caves in Eastern Europe, while there is a growing industry associated with halotherapy along the Dead Sea in Israel. No evidence from randomized controlled trials has been found.

Laser Therapy

Laser light therapy utilizes laser light energy to specific targets that have been related to asthma and allergy, including the endobronchial tissue, tympanic membrane, blood, and skin. The terms found in the literature reflecting this form of therapy include laser ablation, photodynamic therapy (PDT) of bronchial tissue, endobronchial helium-neon laser irradiation (ELI), noninvasive hemolaserotherapy in asthma and rhinosinusitis, low-intensity laser radiation (LILR), intravenous laser irradiation of blood, intravenous He-Ne laser (wavelength 0.63 μm) radiation of the blood, pulsed and continuous-wave low-energy infrared laser radiations, and low-energy laser radiation (Uzor unit). Laseropuncture (laser acupuncture) has been reported for the use in the treatment of asthma and allergies. This is not to be confused with bronchial thermoplasty.

Probiotics

The mechanism of allergy development has been fodder for medical science for many years. Hygiene hypothesis is one of the popular theories of how allergic disease develops in some individuals and basically relates that as the developing immune system has had to fend off fewer pathologic antigens, it has become reactive to benign and common environmental allergens. It is with this theory in mind that probiotics have been used in an effort to minimize the development of allergic disease. In probiotics, *Lactobacillus rhamnosus* is purposely given to infants and young children with the intention to reduce their development of allergic disease. *Lactobacillus rhamnosus* taken orally can lead to late induction of IL-10. This response has been found to vary with the immunologic status of the patient. When IL-4 is absent or at low levels, IL-10 diminishes eosinophilic inflammation and IgE responses. While this has led to a decrease in atopic eczema and cow's milk allergies, benefits for adults and older children have not yet been definitively demonstrated.

Behavioral Techniques and Behavior Modification

It has been shown that eye rubbing worsens the symptoms of ocular allergies. In a study of 33 pts with cat allergy with were exposed to cat dander for 75 min; 15 min after exposure, one of their eyes was rubbed for 15–20 s; the rubbed eyes experienced increased itching and hyperemia when compared with the non-rubbed eye. Teaching patients to modify their response to allergic symptoms (i.e., avoiding rubbing itchy eyes) may effectively decrease the severity of symptoms experienced.

Ethical-Legal Issues Raised by Patient's Use of CAM

Risks associated with CAM interventions include direct toxicities of the therapies themselves, the lack of conventionally tested medical interventions, and the liability risk for physicians who provide or counsel patients in the use of complementary and alternative medicines.

Side Effects of CAM

The majority of adverse effects reported have been associated with herbal formulations similar to the risks associated with conventional pharmaceutical agents and have included hepatic and renal toxicities and hypersensitivity reactions (see Summary Table 34.1). Hepatotoxicity has previously been reported with Kinshi-gan and Sho-saiko-to. Both formulations contain Ginseng Radix, Scutellariae Radix, and Glycyrrhizae Radix. Liver injuries generally peaked within 3–4 days of challenge and resolved within 2 weeks; challenge testing may induce severe allergic reactions in addition to hepatic injury, particularly in patients with known allergic disease. However, more serious adverse effects have also been reported such as fatal cases of liver failure associated with restarting Kinshi-gan and Sho-saiko-to and acute pneumonitis with Sho-saiko-to.

Renotoxicity examples include hypokalemia, water retention and sodium retention associated with licorice ingestion, and nephrolithiasis associated with ephedra. The widely used ephedra has also been linked with severe cardiovascular and neurological side effects, including ten fatalities. Ephedra has recently come under even more scrutiny for its use in diet and performance enhancement. In the doses required to effect weight loss, side effects are commonly observed. California banned the distribution and sale of ephedra alkaloid-containing products effective January 1, 2004. Under the law, licensed health-care practitioners may prescribe or dispense ephedra-containing products only for purposes other than weight loss, bodybuilding, or athletic performance enhancement.

As with any unregulated substance, one must also be concerned about the amount of pharmacologically active drug in any given preparation and any contaminants. Traditional Chinese medications have been linked with both dosage toxicities and contamination. Many of the remedies may be safe at low doses but at higher doses become markedly toxic. However, without studies to establish the therapeutic index, it is difficult, if not impossible, to advise patients on the use of CAM interventions. Contaminants that have been found range from NSAIDs, steroids, and benzodiazepines to heavy metals (e.g., lead) (see Summary Table 34.2). The wealth of misleading anecdotal and poorly obtained scientific evidence is dangerous for patients who expect "natural" complementary/alternative medications to be naturally safe.

There have also been adverse effects reported with acupuncture (see Summary Table 34.3). Side effects reported include vasovagal effects, earaches, gastrointestinal

Table 34.1 Herbs in allergy and asthma: mechanisms of action/symptoms treated and observed adverse effects

Herb	Mechanism of action/symptom treated	Adverse effect
Allium cepa (onion)	Inhibits mast cell degranulation	Strong odor
Aloe arborescens	Bronchodilation	Electrolyte imbalances, abdominal cramps, pseudomelanosis coli
Atropa belladonna	Anticholinergic and bronchodilating properties	Ataxia, hallucinations, extrapyramidal reactions, decreased bowel sounds, photophobia, sinus tachycardia, thirst, and urinary retention
Bu-zhong-yi-qi-tang (traditional Chinese medicine)	Decreased capillary permeability; decreased eosinophils, CD4 cells, IL-4, and IL-5; inhibited Th2 cell responses	None reported
Caffeine	Bronchodilator	Insomnia, GERD, hypertension
Coleus forskohlii	Bronchodilator; possibly due to intracellular stimulation of adenylate cyclase to produce cAMP; high doses required to produce effect	Tremor and hypokalemia, although proportionally less than effect of beta-agonist in study
Datura stramonium (jimsonweed)	Tropane alkaloids (atropine, hyoscyamine, hyoscine, scopolamine); bronchodilator	Ataxia, hallucinations, extrapyramidal reactions, decreased bowel sounds, photophobia, sinus tachycardia, thirst, and urinary retention
Echinacea	In vitro antiviral effects vs. influenza; limited effect in recent studies	Anaphylaxis, bronchospasm, urticaria, angioedema, hepatitis, hypertension, A-fib, acute renal failure, and vasculitis
Eucalyptus	Cold/influenza remedy; mucokinetic/decongestant; cockroach repellant	Allergic reactions
Chamazulene (chamomile)	Leukotriene inhibitor	Rarely, anaphylaxis in patients allergic to ragweed/chrysanthemum; botulism
Goldenseal (hydrazine)	Treatment of URI, diarrhea, conjunctivitis, acute otitis media, eczema	Peripheral vasoconstriction/hypertension; irritation of the oropharynx; nausea, vomiting, diarrhea
Hi chun (Korean)	Stabilizes mast cell membrane; inhibits histamine release	None reported
Jisil (Korean)	Stabilizes mast cell membrane; inhibits cAMP and decreased IgE production	None reported
Kutki/kurro (Indian Ayurvedic)	Stabilizes mast cell membrane	None reported

Table 34.1 (continued)

Herb	Mechanism of action/symptom treated	Adverse effect
Licorice	Slows the change of cortisol to cortisone, blocks histamine induced capillary permeability, inhibits PAF, and has antitussive activities	Hypokalemia; hyperaldosteronism
Ma huang (ephedra) Wu-hu-tang	Oral adrenergic agonist, it inhibits mast cell degranulation and has sympathomimetic activity; for treatment of asthma/allergic rhinitis, doses are usually 15, 25, or 30 mg three times a day	Concern of safety when used in high doses, particularly for weight loss (100 mg two times a day); common side effects include hypertension, tachycardia, palpitations, nervousness, headache, insomnia, dizziness, euphoria, nephrolithiasis, seizure, stroke, and myocardial infarction; has caused sudden death
Menthol (mint)	Decongestant action	Ingestion may be fatal (mechanism of death not reported)
Minor Blue Dragon	Stabilizes mast cell membranes	None reported
Peppermint oil (mint)	Decongestant action/stabilizes mast cell membranes	Cardiac arrhythmias
Sho-seiryu-to (Japanese)	Decreased IgE-mediated cutaneous reactions; complement inhibition; anticholinergic effect leads to drying of secretions and decreased inflammation	None reported
Urtica dioica (nettle)	Stem nettles contain histamine, serotonin, and choline; used in the treatment of allergic rhinitis	Contact urticaria with natural plant leaves; diarrhea; gastric irritation; edema; decreased urinary volume
Tylophora indica (India)	Alkaloid derivative plant which acts as a bronchodilator; induced PEF improvement in one study	Nausea, vomiting, and sore mouth; worse when plant is chewed
Saiboku-to (Japanese) Chaipo-tang (Chinese)	Inhibition of 11-beta-dehydrogenase leads to increased endogenous cortisol levels; in studies patients dropped their steroid doses. Did not induce downregulation of glucocorticoid or beta-2-adrenergic receptors	Pneumonia/pneumonitis

Table 34.2 Adverse effects reported from contaminants of herbs and homeopathic remedies

Contaminant	Number of reports	Adverse effect noted
Mercury	4	Motor and vocal tics
Lead	111	Anemia/encephalopathy
Steroids	2	None
Arsenic	75	

Table 34.3 Acupuncture and other physical modalities: observed adverse effects

Modality	Sample size	Adverse effect
Acupuncture	Unknown	Hepatitis B
Acupuncture	1	Cardiac tamponade
Acupuncture	1	Septic sacroiliitis
Acupuncture	1	Septic arthritis
Acupuncture	1	HIV
Acupuncture	1	Pneumothorax
Spinal manipulation	Unknown	CVA
Spinal manipulation	1	Holocord astrocytoma
Massage	1	Large hematoma
Cupping	1	Sepsis

complaints, five reports of pneumothorax, one case of cardiac tamponade, and one documented case of hepatitis B, among others.

Significant Interactions with Western Therapies

Aside from CAM modalities taken for the control of asthma or allergic disease, physicians must also remember to ask about remedies taken for other conditions. As noted earlier, echinacea is often taken as prophylaxis for the common cold. It has been associated with anaphylaxis, bronchospasm, urticaria, angioedema, hepatitis, hypertension, atrial fibrillation, acute renal failure, and vasculitis. One case report describes a middle-aged woman who developed anaphylaxis within a few minutes of ingesting a solution of echinacea. She had been taking the supplement for several years prior to the event without incident; she had a history of atopy, oral allergy syndrome, and urticaria/angioedema associated with bananas. After the incident, allergy was confirmed with skin prick and intradermal testing to the same solution the patient had ingested. Findings were further confirmed by RAST. Further investigation of other patients in the practice found that even among those who had not been using echinacea, but were sensitive to grass pollen, 94 % had positive immediate skin tests to echinacea. As such, patients with atopy may be at higher risk than the general population of developing serious adverse reactions to herbal modalities. Green tea has been shown to have antioxidant, antibacterial, antiviral activity, and it

is taken by many patients as a preventative measure. In one case report, 11 patients developed occupational asthma associated with the inhalation of green tea dust; 5 of the 11 had symptoms after drinking green tea as well. The allergen association was confirmed with intradermal tests and challenge inhalation. Another commonly used herb, ginseng, has also been associated with adverse effects. Ginseng is often used for weakness and fatigue, additionally it is thought to have efficacy in boosting immune system function. Adverse effects reported include nausea, diarrhea, euphoria, insomnia, headaches, hypertension, hypotension, mastalgia, and vaginal bleeding. Due to liver effects, it may lower blood alcohol concentration and decrease warfarin efficacy. Interactions with caffeine may lead to hypertension. Ginseng may lead to hypoglycemic episodes in patients taking insulin or oral hypoglycemic agents. It is contraindicated in hypertension, acute asthma, acute nosebleeds, acute infections, or menorrhagia. Garlic has been used for its cardiovascular benefits and for relief of cold, colds, and rhinitis. However, it has been associated with gastrointestinal disturbances, change in body odor, hypoglycemia, and allergic reactions. St. John's wort is commonly used for the treatment of depression. It has been found to induce cytochrome 3A4. This action can decrease levels of conventional medications including cyclosporine (commonly used as an immunomodulator in transplantation), indinavir (commonly used in the treatment of HIV), and oral contraceptive pills. Decreased levels and the resultant diminished therapeutic effect of any of these medications can lead to significant complications.

Risks Associated with Lack of Western Therapeutic Involvement

Traditional physicians are not needed to refer patients for complementary/alternative modalities. As such, traditional therapies may be delayed or omitted for these patients. In one study of adherence to allopathic treatment among asthmatics in India, CAM interventions, particularly yoga, Ayurveda, and homeopathy, were seen as barriers to achieving adherence with beta-agonist or other traditional interventions. Twenty-six percent of individuals using CAM interventions were not concomitantly using traditional treatment for asthma/rhinitis, and there is concern that use of CAM interventions may delay use of specific anti-inflammatory therapy, leading to increased ER visits or hospitalizations. Additionally, some patients may be swayed by CAM practitioners regarding immunization. Only 30 % of chiropractors, homeopaths, and naturopaths recommend immunization, while 7 % of American naturopaths actively oppose immunization.

Liability Risks for Physicians

Some patients may seek the advice or referral from their physician before seeing the care of a CAM provider. This discussion is more likely when CAM use has been discussed in the past, so that the patient feels comfortable discussing alternative

treatment options with the primary physician. In this role, it must be remembered that the physician is still responsible for the coordination of overall care of the patient. Physician liability may stem from recommendations to pursue CAM interventions or from failing to actively discourage the use of certain CAM interventions.

There are essentially four categories under which the risks fall (from low to high):

(A) Evidence supports both efficacy and safety (e.g., acupuncture for chemotherapy-induced nausea).
(B) Evidence supports safety, but evidence regarding efficacy is inconclusive (e.g., homeopathy for rhinitis).
(C) Evidence supports efficacy, but evidence regarding safety is inconclusive (e.g., ginkgo for dementia).
(D) Evidence indicates serious risk or inefficacy (e.g., injections of unapproved substances; inattention to known herb-drug interactions).

The liability risk associated with a particular modality increases as less is known about positive efficacy or safety. In determining the category a particular CAM intervention falls within, the physician must document the literature supporting a particular therapeutic choice and document that the risks and benefits of a given CAM intervention were discussed with a patient, and if possible the patient should sign documentation of their assumption of risk. This is particularly advisable if the patient will be replacing traditional treatment with CAM interventions. One method of dividing modalities into risk groups for patients uses three categories: sufficient evidence to view the therapy as reasonable and sometimes recommend, reasonable with caveats, and clearly unwise. These categories were originally developed for the use of oncologists to use when discussing treatment options with their patients but can be effectively used for any patient considering CAM interventions. When referring a patient, it is also prudent to confirm the competency/certification of the practitioner to whom your patient is referred.

Conclusions

CAM interventions are continuing to grow in popularity among patients in the USA and abroad for the treatment of a myriad of conditions. Asthma and allergic disease are among the conditions most commonly treated with complementary/alternative medicine. These modalities may offer exciting opportunities for patients who respond poorly to or have difficulty tolerating traditional treatment, but it is advisable to discourage patients from abandoning conventional therapy completely.

Herbs are among the CAM modalities most commonly used and unfortunately also appear to most commonly cause adverse effects. Adverse effects associated with CAM use may be due to toxicity of the intervention itself or contaminants of the intervention. For these reasons, and because atopic patients may be more susceptible to adverse reactions from these modalities, it is important that allergists and clinical immunologist are well versed in the benefits and risk associated with CAM use. Since patients may not volunteer their experiences with CAM interventions,

physicians must routinely screen all patients. Furthermore, well-designed, randomized, and placebo-controlled studies are needed to clearly establish the efficacy and safety of these modalities so that patients and physicians can reasonably establish the risk to benefit ratio associated with various modalities.

Evidence-Based Medicine

There have been several recent publications advancing the assessment of several herbal remedies in the treatment of allergic disorders. It is important to appreciate that although negative studies are rarely published, they are finding a role in the assessment of CAM therapy as it is just as important to know what does not work as to what does potentially work in the treatment of allergies.

An update on an interesting herbal, Tinofend (*Tinospora cordifolia*), an extract derived from the stem of *Tinospora cordifolia* that had been studied in a double-blind randomized allergic rhinitis trial over the course of 8 weeks ($n=75$ patients), noted statistically significant improvement in sneezing, nasal discharge, nasal obstruction, and nasal pruritus, compared with those receiving placebo. They reported 71 % patients of TC group had 100 % improvement, whereas in placebo group 88 % had no relief from this symptom. A major adverse effect was reported as an increase in total blood leukocyte count in 69 % of patients (compared to 11 % in placebo group). In a limited murine model of asthma, there was also noted antioxidant activity that may warrant further investigation. There have also been limited reports of hepatotoxicity, but more recent reports suggest a positive role of *Tinospora* in alcoholic liver disease.

Bioflavonoids have been a unique focus of one of the pillars of allergy, Dr. Elliot Middleton, who studied its antiallergic properties in the 1980s. Quercetin was one of the original agents investigated in the treatment of allergic diseases based upon original studies demonstrating a mast-cell-stabilizing effect and dose-dependent inhibition of various allergic inflammatory mediators including the release of histamine, interleukin-8 (IL-8), tumor necrosis factor (TNF), and formation of prostaglandin D_2. Quercetin as a component of an *Artemisia abrotanum* intranasal was evaluated in an uncontrolled study of allergic rhinitis patients ($n=12$) who reported an effect within 5 min that lasted for hours. Ocular symptoms also improved with intranasal application. Interestingly it has demonstrated to decrease the "flushing" syndrome seen in patients that are using niacin for cholesterol control.

Final Point

The development of high-quality research will advance the integration of complementary techniques into the "standard of care" in Western medicine, but one must remember that the plural of anecdote is anecdotes – not evidence – and we must wait for the studies to provide guidance to maximize the health outcomes of our patients suffering from asthma and allergies.

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Chapter 35
Nutrition, Diet, and Allergic Diseases

Sarah J. Kuhl

Introduction

Most physicians have little medical education or formal training in nutrition, and there is much conflicting information available in the popular press. In addition, the national dietary guidelines continue to evolve with ongoing research and information, which is not without controversy. This may result in confusion and uncertainty about diet in both patients and physicians.

Dietary Reference Intake

The Dietary Reference Intake (DRI) delineates the nutrition recommendations from the Institute of Medicine (IOM) of the National Academies (United States). The nutrient content is often expressed in terms of daily value or %DV in a given food amount (such as one serving, 100 g, cup, tablespoon, etc.).

The recommended dietary allowance (RDA) was developed during the World War II in order to investigate issues of nutrition in the interests of national defense. They were intended to provide better nutrition to both civilians and military. In the early 1950s, US Department of Agriculture (USDA) nutritionists made recommendations regarding the number of servings of each food group in order to make it easier for people to receive their RDAs of each nutrient. The RDAs have subsequently been revised every 5–10 years.

Manufactured foods are typically labeled with Reference Daily Intake (RDI) values, which are originally based on the highest 1968 recommended dietary allowances

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(RDA) for each nutrient. Food is labeled with % daily values of calories, total fat, saturated fat, cholesterol, sodium, total carbohydrate, dietary fiber, sugars, and protein based on a 2000 cal diet. Beginning in 2006, trans fats also appeared on the label. As of 2010, only the micronutrients vitamin A, vitamin C, calcium, and iron are required to be listed. Ingredients must be listed by order of quantity and by weight. Nutritional needs also vary between growing children, pregnant women, active and sedentary adults, and the elderly.

The USDA dietary guidelines change with time. The 2006 recommendation to avoid trans fats is an example. If the 2015 guidelines are accepted, there is an increased emphasis on vegetables and fruits, whole grains, low-fat and nonfat dairy, seafood, and legumes and nuts. The recommendations are to lower sugar intake, as well as processed and red meat intake, and a shift from saturated fat to polyunsaturated fatty acids.

The US Department of Agriculture recommends 50 % fruits and vegetables in MyPlate, which has replaced the food pyramids which were previously recommended. There is criticism that even MyPlate continues to combine science with the interests of the food industry.

Marion Nestle has documented considerable concern that since food and nutrition research in the United States is often funded by corporations and negative results may not be reported, so it can be difficult to sort fact from fiction. Former FDA commissioner David Kessler has written about how the food industry has found combinations of salt, fat, and sugar that lend themselves to overeating and obesity, rather than satisfaction.

Optimal Nutrition

In part because the national recommendations change over time and are different from some recommendations in other countries, there is some research and opinion regarding what constitutes optimal nutrition, particularly for the prevention and treatment of diseases.

A systematic review and meta-analysis of nutrients and foods for the primary prevention of asthma and allergy noted that serum vitamin A was lower in children with asthma compared with controls, that high maternal dietary vitamin D and E intakes during pregnancy were protective for the development of wheezing outcomes, that adherence to a Mediterranean diet was protective for persistent wheeze and atopy, and that 17 of 22 fruit and vegetable studies reported beneficial associations with asthma and allergic outcomes.

Certain fruits and vegetables appear to affect asthma, and in some studies the consumption of vegetables alone was inversely associated with risk of asthma. There also appears to be an inverse association between the incidence of asthma and the consumption of apples. In other studies, a control diet restricted in the vegetables and fruits enhanced asthma symptoms, while supplementation with tomato juice improved asthma symptoms. The incorporation of omega-3 fatty acid-containing

foods such as fish has been shown to decrease the incidence of childhood asthma by 30–50 %. Prebiotics and probiotics may affect the microbiome.

Recent work has implicated the gut microbiota and its response to diet. It appears that disturbing the gut microbiome early in life is associated with a greater risk of developing allergic disorders. Probiotics also likely affect the microbiome, and evidence suggests they are helpful in the prevention of atopic dermatitis and asthma.

Food Avoidance in Specific Allergy Syndromes

Allergic Rhinitis Patients with ragweed allergy will often react to chamomile, a close relative of ragweed and a popular tea.

Oral Allergy Syndrome The oral allergy syndrome (OAS) or pollen-food allergy syndrome is a relatively common form of food allergy, which occurs in people who have pollen allergy. The major symptoms are itching and sometimes swelling of the oropharynx following the ingestion of some raw fruits, vegetables, or nuts. The patient's pollen allergies cross-react with antigens on the ingested food.

Food Allergy Patients with food allergy typically need to eliminate the offending foods and any close relatives. They need to be highly aware of food labels in processed foods and ingredients in restaurant foods. This is covered in detail in the food allergy chapter.

Primary Prevention of Allergic Disease Through Nutritional Interventions

The Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology recently published recommendations for the primary prevention of allergic disease through nutritional interventions, according to currently available literature and expert opinion. Avoidance of diets during pregnancy and lactation were not recommended, although more research is recommended for peanuts. Exclusive breast-feeding for 4–6 months is recommended. For high-risk infants who cannot be exclusively breast-fed, hydrolyzed formula appears to help prevent cow's milk allergy and other allergic diseases such as atopic dermatitis, allergic rhinitis, asthma, and food allergy. Previous recommendation from the American Academy of Pediatrics (2000) is delaying the introduction of highly allergenic foods such as cow's milk, peanuts, tree nuts, and fish until age 1–3 years. However, this did not appear to prevent food allergies, so the general recommendation appears to be that these foods can be introduced after the age of 6 months. One possible exception is a child who has an increased risk of peanut allergy due to having a sibling with peanut allergy; referral to an allergist for testing and

counseling is recommended. Typically single-ingredient complementary foods are introduced between 4 and 6 months of age at a rate not faster than one new food every 3–5 days. Once a few typical complementary foods such as rice and oat cereal, yellow/orange vegetables, fruits, and green vegetables are tolerated, highly allergenic foods may be introduced. The initial taste of the highly allergenic foods can be given at home recognizing that most reactions occurred during the first congestion. The food can then be increased gradually, particularly if the infant has atopic dermatitis. If the child develops a single-food allergy, their risk for developing other allergies increases, so referral to an allergist is recommended.

Nutritional Supplements or Nutraceuticals

Nutritional supplements or nutraceuticals are sometimes thought of as alternatives to pharmaceuticals and are sold as dietary supplements in the United States. Other countries vary in the regulation of herbal medications and other nutraceuticals. The German Commission E, a scientific advisory board of the German equivalent of the Food and Drug Administration (FDA), reviews the scientific evidence for the approval of substances and products previously used in traditional, folk, and herbal medicine. In contrast, herbal medications from China have been found to be adulterated and contain ingredients not on the label, as well as heavy metals such as lead.

Chang and Gershwin reviewed complementary and alternative medicine in allergy and immunology. Ayurvedic medicines such as *Tinosporacordifolia* and a mixture called Aller-7 have improved symptoms of allergic rhinitis. The herb *Urtica dioica* or stinging nettle has also been shown to relieve symptoms of allergic rhinitis in many patients. Butterbur (*Petasites* species) appears to help some symptoms of allergic rhinitis and asthma.

The first physicians were likely herbalists, who noted the effects of food and herbs over time in their local populations. We still use drugs that were originally derived from plants. However, the evidence for effectiveness is limited to few studies, dosing may differ between different batches of herbs, and there may be unrecognized toxicities or additives in the herbal preparations, as well as interactions with standard pharmaceuticals. Some of these herbs may be helpful in low concentrations from reliable companies, particularly in mild disease, but should be used with caution until there is more evidence supporting their use.

Evidence-Based Medicine

The Dietary Reference Intake, the American reference for recommended food and nutrient intake from the Institute of Medicine, is constantly evolving in the face of evidence from new information and research, some of which is influenced by food corporations. Optimal nutrition may be different for different disease states, as well

as different for different ethnicities, which may have adapted to local foods over centuries.

Recent work has implicated the gut microbiota and its response to diet. Trompette and colleagues recently reported that dietary fermentable fiber content changed the composition of gut and lung microbiota in mice, particularly by altering the ratio of Firmicutes to Bacteroidetes. Due to the change in the gut microbiota, the concentration of short-chain fatty acids including propionate increases with increased metabolism of fiber. Propionate treatment enhanced the numbers of dendritic cell precursors, but the dendritic cells that seeded the lungs were ineffective at promoting TH2 (allergic) responses.

A recent study by Kim and colleagues showed that mice fed with a high-fat diet had increased levels of IL-17 in obesity-associated airway disease, associated with increased levels of innate lymphoid cells (ILC3) producing IL-17A. In addition, they showed that in ten human patients with pulmonary disease, BAL fluid samples contained substantial levels of IL-17-expressing cells that appeared to be comparable to the mouse ILC3 cells. An increased amount of these cells in patients with severe asthma suggests that these cells may have a pathological role in human asthma.

Asthma is a heterogeneous disease with phenotypes that appear to be driven by distinct immunologic pathways. This research suggests that diet may help prevent or modulate asthma.

Conclusion

The short answer to the complex question of what to eat for optimal health has been summarized by Michael Pollen: "Eat food. Not too much. Mostly plants." His book, *Food Rules*, further clarifies healthy recommendations for the general population and includes such recommendations as "Don't eat anything that your great-grandmother wouldn't recognize as food."

For allergic diseases, certain diets such as the Mediterranean diet appear to be helpful. For patients with pollen allergies, it is important to avoid foods that cross-react with pollens.

For patients with food allergies, the Food Allergy and Asthma Network is often an indispensable resource for helping patients avoid foods and recognize cross-reacting foods.

The field of nutritional supplementation or dietary supplements remains controversial, but the wisdom of traditional cultures in many cases appears to be better than embracing "better living through chemistry" of the 1950s. Foods that are easily grown in a specific region often became part of the local diet, and over time, people who thrived on that diet may have been selected to survive. So although further epidemiologic studies will likely be helpful, the diet and nutrients that may be needed by an individual patient are more elusive and in some cases may be related to their genetic heritage. We are learning more about how a change in diet can change the microbiome and may be able to change diet or supplements to alleviate the burden of allergic disease, in individuals and populations.

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Chapter 36
Prevention and Control Measures in Management of Allergic Diseases

Shuba Rajashri Iyengar

Introduction

The causal relationship between allergic disease and allergen exposure has been well documented throughout the literature. Therefore, measures to reduce allergen exposure have been fundamental in the treatment of all types of allergic disease, including asthma and allergic rhinitis. The significance of this can be seen in studies conducted over 80 years ago, in which patients with asthma and atopic dermatitis were successfully treated by living in a climate chamber. Comparable studies have been performed more recently and have demonstrated that changing asthmatic patients from their domestic environment to a hospital room for several months resulted in significantly decreased airway hyperresponsiveness from bronchial provocation studies.

Although these measures are impractical in outpatient medicine, they demonstrate the importance of allergen exposure and sensitization in the pathogenesis of allergic disease. Sensitization to one or more of the major indoor allergens has been consistently found to be the strongest risk factor for asthma. In addition, studies examining the reunification of East Germany with the more industrialized West Germany demonstrated the effects of environmental exposure on the development of asthma and allergic disease in two genetically similar populations. The prevalence of asthma (and bronchial hyperresponsiveness) as well as atopy was greater in West German than East German children. West German children had significantly greater rates of sensitization to mite, cat, and pollen allergens.

Therefore, identifying pertinent indoor and outdoor allergens (through skin and serum IgE testing) is essential in the management of asthma and atopic disease.

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Further steps include the determining and reducing allergen reservoirs (through barrier methods, air filtration, etc.) and long-term strategies to maintain allergen reduction and control.

Indoor Allergens

Dust Mite

Background

Household dust can contain many different species of mites; however, in most countries, the pyroglyphid mites are the majority. This includes *D. pteronyssinus* and *D. farinae*. These mites are eight-legged microscopic creatures that are invisible to the naked eye. They live on skin scales and other debris. In addition, they are not capable of drinking liquids and so must absorb water through a substance extruded from their leg joints. This makes them entirely dependent on the humidity of the ambient environment. In addition to humidity, they have strict temperature requirements and can only grow between temperatures of 65 °F and 80 °F.

Ideal areas for mites to live include carpets, mattresses, pillows, sofas, and clothing as these can be very humid environments. However, even with reductions in the ambient humidity, it may take several months for mites to die and even longer for allergen levels to decrease in carpets, pillows, mattresses, and sofas. This is because, as the moisture level drops, mites will withdraw from the surface to deeper layers of carpet and upholstery, making them difficult to eradicate.

The largest quantity of the mite allergen is found in its fecal particles. This is the major particulate source of dust allergen in house dust. Many of these allergens have now been characterized and are referred to as *group 1* (Der p 1 and Der f 1) and *group 2* (Der p 2 and Der f 2).

Control Strategies

Key principles in reducing dust mite exposure include identifying and reducing dust mite reservoirs. These are objects that harbor large amounts of the specific allergen. For instance, dust mite reservoirs include bedding, carpets, furniture, and other upholstered items (please see Table 36.1). Measures to reduce reservoir carriage of dust mite include obtaining dust mite impermeable covers, washing bedding in hot water, and carpet removal. The next step in reducing dust mite exposure involves strategies to change the ambient environment. This includes measures to decrease humidity (like a dehumidifier) as well as changing of the bedroom or entire home. Most strategies target the former, as these measures are relatively simple and inexpensive and have been shown to have a greater impact (See Table 36.1).

Table 36.1 Dust mite avoidance measures

Reservoir reduction
1. Bedding
(a) Impermeable zippered covers for pillows and mattresses (on all beds that patient sleeps on)
(b) Washing all bedding (pillowcases, sheets, blankets) at 130 °F weekly
(c) Removing blankets/comforters that are not washable or using with an impermeable zippered cover
(d) Removing all upholstered toys on bed (unless washed at 130 °F or placed in freezer overnight weekly)
2. Carpets
(a) Vacuum weekly with a filtration system (i.e., HEPA filter) or cleaner
(b) If possible, replace carpets with linoleum or wood flooring in the bedroom (first priority) and other living spaces
(c) Remove carpets on concrete slabs
(d) Clean and wash area rugs
3. Furniture (sofa, draperies, throw pillows, and other upholstered items)
(a) Reduce upholstered items, especially old sofas and draperies. If necessary, consider plastic covers for old sofas/chairs
(b) Clean and dust items often, especially those in the bedroom (household member rather than patient should do this)
Ambient environmental changes
1. Humidity: reduce humidity to <50 % of the relative humidity
(a) If possible, avoid living in the basement or overly humid environments
(b) Consider second floor bedroom of house or apartment
2. Air filtration systems: generally not thought to be very effective for mite control

Reservoir Reduction

These methods are aimed at finding those items that harbor dust mites and eliminating or reducing the amount of mites and mite antigen in them. They mainly consist of pillows, mattresses, bedding, sofas, and other upholstered items. Examples are provided in Table 36.1.

Impermeable zippered covers to reduce dust mite and mite allergen exposure are widely used. Traditionally used items were entirely plastic, but now tightly woven synthetic fibers or nonwoven synthetics that allow vapor to pass through (but not allergen) are available. Dust mite allergens (Der f 1 and Der p 1) were blocked below detectable limits by fabrics of less than 10 μm in pore size. Fabrics with an average pore size of 6 μm or less blocked cat allergen (Fel d 1). The effect of dust mite impermeable covers on reducing clinical symptoms is under debate, but most studies show that these measures should not be performed in isolation. Most practitioners recommend these methods be performed in combination with the washing of bedding, the avoidance of stuffed animals, and the frequent vacuuming/removal of carpets (see Table 36.1).

Many investigators have studied the use of chemicals to kill mites or denature allergens, but there is modest data favoring of this approach. Only benzyl benzoate

and tannic acid have been marketed in the USA and have had minimal mite reduction when applied to carpets.

Lastly, those studies been successful in demonstrating a clinical benefit from allergen avoidance measures have ensured sustained use for greater than 6 months. Therefore, patient education and follow-up to ensure compliance are extremely important.

Ambient Environmental Changes

As dust mites thrive in humidity, decreasing the humidity to below 50 % of the relative humidity can decrease mite growth. However, this can be difficult to accomplish in humid geographical areas (Southeastern states, areas along the Pacific coast). General recommendations include not living in basement areas and, if living in an apartment, to live on the second floor or above. Air filtration units are not helpful for dust mite reduction. This is because most of the airborne mite allergen is carried on large particles (larger than 10 μm) that fall rapidly after disturbance. Therefore, after several minutes little mite allergen is detectable.

Animal Dander

Background

The domestic animals that are most commonly encountered in the USA include cats, dogs, and rodents. Since prolonged rodent exposure most often occurs in the occupational setting, this topic will be addressed in the Chap. 17.

Cats

The main cat allergen is Fel d 1, although other characterized proteins produced by cats have been found to be allergenic for patients (i.e., Fel d 2, Fel d 3). The most important sources of the allergen are the sebaceous, salivary, and perianal glands, with the skin and fur being the principal reservoirs. There are several properties of the Fel d 1 protein that contribute to its high allergenicity. First, it is very heat stable. For example, exposure at 140 °C for 60 min resulted in only 30 % denaturation of the molecule. Next, it is easily airborne. Both Fel d 1 and Can f 1 (main dog antigen) are carried by small particles (5–10 μm in diameter) that are light and are readily airborne for long periods of time after minimal disturbance. Lastly, cat dander particles can stick to all available surfaces such as furniture, clothing, and walls. Therefore, they frequently travel to indoor environments which should theoretically be cat-free (like houses, schools, and other types of public buildings). Many studies have shown that the clothes of cat owners represent the main source for the dispersal of cat allergens in cat-free environments. Because of these properties of the Fel d 1 antigen, the allergen can persist for many months even when cats are removed from the house.

Cat allergen is a major risk factor for asthma. Asthma has been found to be strongly associated with sensitization (assessed by skin testing) to cat allergens. It has also been found that cat allergen exposure was associated with both sensitization and persistent wheezing at age 4 years.

Dogs

Can f 1 is the major allergen found in dogs. Similar to Fel d 1, it can accumulate in house dust and is easily airborne. In addition, it can also collect in public areas, like schools. However, Can f 1 allergy is less common than Fel d 1 allergy as a cause of asthma. Like Fel d 1, it was associated with both sensitization and persistent wheezing at 4 years of age, but only in a subgroup of patients with maternal atopy.

Control Strategies

Source and Reservoir Reduction

The same principles that have been applied to dust mite exposure reduction can be applied to animal dander. This includes reservoir identification and reduction as well as long-term strategies to maintain allergen reduction (please see Table 36.2). Most practitioners agree that an atopic patient who is sensitized to cat or dog allergen should not live with a pet in their home. However, because most families are reluctant to part with the pet, eliminating the source of allergen in sensitized individuals becomes difficult. Because pets are quite mobile and pet allergen particles are very sticky, these antigens become widely distributed across a home, as discussed previously.

Like dust mite allergen, pet allergen reservoirs in the home include all upholstered items (bedding, sofas, carpet, chairs, draperies, etc.). Measures to reduce allergen are similar to those discussed above, but these measures are frequently ineffective if the source (i.e., the pet) is not removed from the home. Pet allergen concentrations are 10–1000 times higher in homes with a pet than without.

Cockroach

Background

Although several species of cockroaches are found in North American homes, the best known are the German cockroach (*Blattella germanica*) as well as the American cockroach (*Periplaneta americana*). These insects are common in inner-city apartments in the USA. Aerosolized proteins from secretions, fecal material, saliva, debris, and dead bodies of cockroaches induce IgE-mediated hypersensitivity. The characterization of allergens derived from German and American cockroaches (Bla g 1–5) has been reported.

Table 36.2 Animal dander avoidance measures

Reservoir reduction
1. Pet removal
(a) The most effective strategy is to remove the pet from the house
(b) After removal, vacuum clean and wash all surfaces (including walls) on which Fel d 1 or Can f 1 may have accumulated. Carpets and upholstery must be cleaned. Bedding and clothing must be washed
(c) Restricting animals to areas of the house has not been shown to be effective
(d) Cats should be washed twice weekly to obtain a significant reduction of Fel d 1 shedding; however, protein reaccumulates quickly
2. Clothing (this is especially important for cat owners)
(a) Washing (water superior to dry cleaning) the clothes and avoiding use of allergen-contaminated clothes outdoors
3. Carpet
(a) Remove carpeting from all environments and replace with linoleum or wood flooring, if possible. Alternatively, use vacuum cleaner with a HEPA (or polyethylene) filter and double-thickness bags
4. Bedding
(a) Wash bedding in water weekly. Using detergent solutions at 25 °C for at least 5 min is recommended
5. Furniture
(a) Remove or limit all upholstered furniture (sofas, draperies, chairs, etc.)
(b) Clean and dust items often
Ambient environment
1. Air filtration systems: recommended in combination with above methods; HEPA or electrostatic units

Cockroach allergy has been found to be an important risk factor for emergency department visits for asthma and hospital admissions. This association was restricted to urban areas, where cockroach allergens were found in the houses.

Control Strategies

Reservoir Reduction

Attempts at reducing exposure to cockroach allergen with the goal of improving clinical outcome in inner-city patients with asthma have been generally unsuccessful. One of the most well known of these attempts was the National Cooperative Inner-City Asthma Study in which 265 inner-city families with asthmatic children underwent several different interventions, including insecticide application and directed education. Approximately 20 % of the families were randomly selected to have Bla g 1 measured in settled dust from the kitchen, bedroom, and TV/living

room. After 1 year, no significant changes were seen from preextermination levels and only 50 % of families had been compliant with cleaning instructions.

Major reservoirs for cockroaches are areas where food waste is available. These are usually areas of the kitchen/dining room and are usually used dishes and cooking utensils, garbage, and open food containers.

Therefore, recommendations include:

- Using multiple baited traps or poisons. This ranges from boric acid, which can kill roaches by destroying their foregut, to a range of chemicals, including hydramethylnon, abamectin, and fipronil.
- Washing dishes and cooking utensils immediately after use.
- Disposing of domestic garbage and food waste quickly.
- Removing cockroach debris promptly.

Outdoor Allergens

Background

The most widely recognized and abundant sources for outdoor allergens are pollen grains and fungal spores. As this topic is discussed in detail in Chap. 5, please refer to this chapter for information regarding pollen distribution and seasonal patterns.

Pollen allergens were believed to play a role in allergic rhinitis, but the particle size of pollen was considered too large to penetrate the lower airways and therefore too large to lead to asthma. However, there is increasing evidence for a relationship between exposure to pollen, fungal, and other airborne allergens and the exacerbation of asthma and other forms of allergic disease. For example, studies examining data from the second National Health and Nutrition Surveys have demonstrated an association between increased skin test reactivity to several different outdoor pollens and significant decrements in FEV1 in symptomatic asthmatic children. In addition, asthma and allergic rhinitis were associated with skin test reactivity to specific outdoor allergens, like *Alternaria*. In addition, allergic rhinitis alone (without the presence of asthma) was associated with skin test reactivity to ryegrass and ragweed.

Plant Pollens

Pollen allergen exposure depends on the pollination process occurring in wind-pollinated (anemophilous) plants, including trees, grasses, and weeds, rather than insect-pollinated plants. This is because, in wind-pollinated plants, pollen grains are released into the atmosphere and must passively find their way onto an appropriate receptive female. Because this process is very inefficient, these plants produce large

amounts of pollen to ensure successful fertilizations. Therefore, pollen from these types of plants is the most abundant and the most significant in regard to human exposure.

Pollen grains are usually spherical with a rigid cell wall formed of a complex polysaccharide-based substance. They are identified using light microscopy by the size and shape of the grain as well as wall structure. Most airborne pollen grains are 15–50 μm in diameter, although the overall range is broad (10–100 μm).

The potency of pollen allergens is not just a matter of protein abundance. Comparable amounts of two allergens in rye grass pollen, for instance, can produce widely different allergenicities based on radioallergosorbent test (RAST) inhibition. Therefore, there are differences in structure and composition that confer allergenicity.

Up to this point, most attention has been directed at allergens contained within pollens as primary sources of allergen. However, attention is now being focused on small particle fractions and their association with pollen allergens. Grass allergens measured in fine-particle aerosols have been found joined to diesel exhaust particles and starch grains. The role of pollen-derived allergens being associated with these small particle fractions is still unclear. However, because of the microscopic size of these particles, they could easily enter the lower airways. Therefore, they may play a role in asthma exacerbations. In addition, there is a potential increased risk of exposure because of longer amounts of time spent airborne.

Fungal Spores

Fungal spores are released from either by active or passive mechanisms. The active mechanisms all depend on changes in moisture conditions. Ascospores and basidiospores are released as the spore-bearing cell absorbs water, either during rainfall or as humidity increases. Some dry-weather spores (e.g., *Cladosporium*) are shaken loose as the spore-bearing cell twists as it dries. In other cases, air movements alone are sufficient to cause release of spores. Rainfall is well known to cause release of spores. Because rainfall both disperses and removes spores, it is difficult to predict airborne spore concentrations during rainfall. However, during long gentle rains, there is thought to be much higher spore concentrations than on sunny days without rain.

Control Strategies

1. Keep windows and doors closed to prevent outdoor allergens from coming into the home.
2. Remove indoor sources that can collect pollen and support fungal growth.
   (a) Dust all surfaces frequently.
   (b) Eliminate/reduce the number of indoor plants.

(c) Clean moldy surfaces.
(d) Keep the house well ventilated and free of dampness.
(e) Avoid basements.
(f) Do not use window fans.

3. Stay indoors during the times when the allergen is abundant outdoors.

(a) Learn about the prevalence patterns of each relevant allergen, including seasonal, geographic, and daily variation patterns (please see Chap. 5).

Evidence-Based Home/School

Intervention Methods

Because children with asthma who live in the inner city are exposed to multiple indoor allergens, several recent studies have looked at the impact of different environmental intervention methods on asthma symptomatology and morbidity. Lai et al. evaluated endotoxin exposure in inner-city schools, as this is associated with airway inflammation in children. After studying 248 students with asthma from 38 inner-city schools, they found that the children with asthma were exposed to high levels of airborne endotoxin at school and that there were increased asthma symptoms in non-atopic children. Therefore, school-related exposures may represent a strategy to decrease asthma morbidity in this population. Other relevant environmental exposures include exposure to mouse allergen, which may even be more of an impact than cockroach allergen exposure, as well as tobacco smoke. This study demonstrates that a tailored, multifaceted environmental treatment can decrease indoor allergen levels in inner-city homes and schools, as well as symptomatology.

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Chapter 37
Antihistamines and Mast Cell Stabilizers

Christopher D. Codispoti, Timothy J. Craig, and Giselle S. Mosnaim

Mechanism of Allergic Disease

The allergic response is comprised of an early phase and a late phase. The early phase, which occurs within minutes of allergen exposure in sensitized individuals, is characterized by the release of preformed mediators including histamine and proteases. The late phase, which tends to occur within 3–12 h after antigen exposure, involves the recruitment of additional cells to augment the inflammation. These cells may include eosinophils, basophils, monocytes, and lymphocytes (Fig. 37.1).

Histamine is a key mediator in allergic disease and primarily produced in mast cells and circulating basophils. In response to antigen exposure in an appropriately sensitized atopic individual, IgE antibodies are produced and bind to high-affinity receptors on mast cells and basophils by the Fc portion of the IgE antibody. Subsequent cross-linking of these bound IgE antibodies by antigen begins a series of events that leads to the extracellular release of histamine, other proteins, and cytokines. Histamine may cause a variety of physiologic effects depending on its target cell. Binding to smooth muscle may cause bronchoconstriction and

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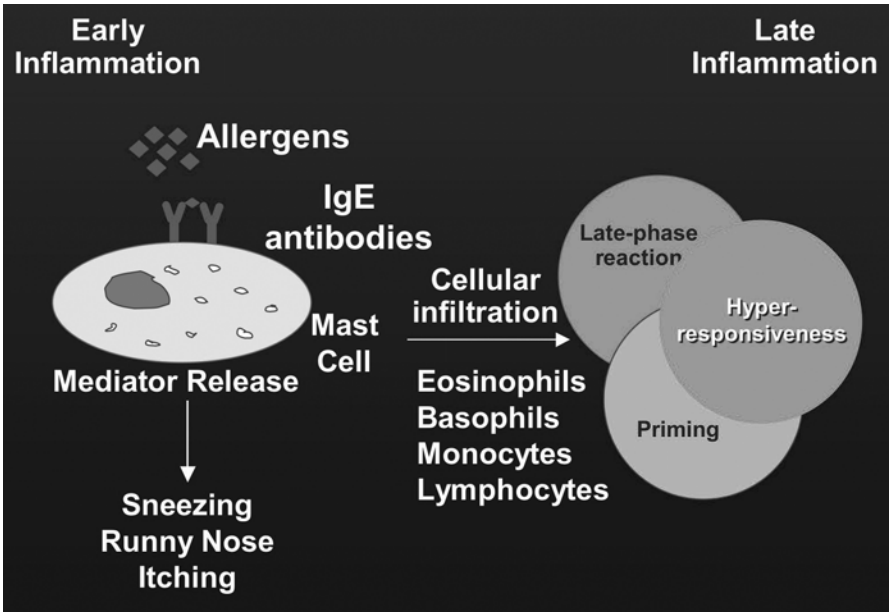

Fig. 37.1 Early- and late-phase response of allergic inflammation. The early-phase response (early inflammation) is characterized by the cross-linking of IgE antibodies on the surface of the mast cell by the allergen, releasing preformed mediators such as histamine. The late-phase response (late inflammation) occurs several hours later due to cellular infiltration by eosinophils, basophils, monocytes, and lymphocytes (Adapted with permission 2015. Copyright © 1991 Massachusetts Medical Society. All rights reserved. Naclerio)

vasodilation, binding to endothelial cells can lead to increased vascular permeability, and binding to sensory nerves may lead to a burning sensation as well as itching. These physiologic effects may translate clinically into symptoms of sneezing, rhinorrhea, pruritus, and urticaria.

Antihistamine Mechanism of Action

Four distinct histamine receptor subtypes have been identified, designated as H_1, H_2, H_3, and H_4. In allergic disease, the focus is on the H_1 receptor. H_1-antihistamines function as inverse agonists at the histamine H_1 receptor, stabilizing the receptor in the inactive conformational state (Fig. 37.2).

The clinical efficacy of H_1-antihistamines is mainly due to this inverse agonist activity at the H_1-histamine receptor. Independent of their histamine-blocking action, antihistamines also exert anti-inflammatory effects, including downregulation of mediator release, intracellular adhesion molecule expression, superoxide generation, chemotaxis, and cytokine expression, and upregulation of neutrophil

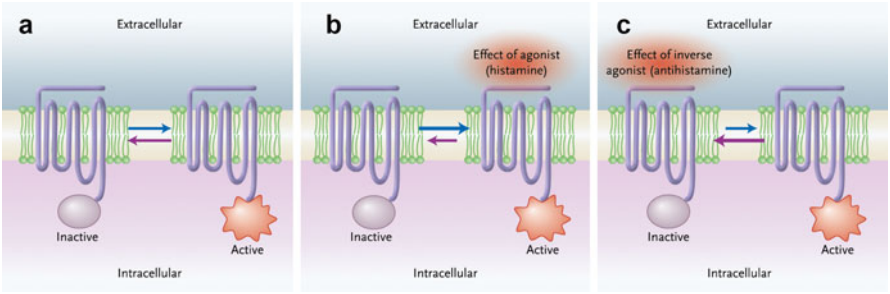

Fig. 37.2 The H_1-histamine receptor. This figure panel (**a**) shows the histamine H_1 receptor active state in equilibrium with the inactive state. In panel (**b**) a histamine H_1 receptor agonist, histamine, as it preferentially binds the active state, stabilizes the receptor in the active conformation and thus causes a shift in the equilibrium toward the active state. In panel (**c**) a histamine H_1 receptor inverse agonist, an H_1-antihistamine, preferentially binds the inactive state, stabilizing the receptor in the inactive conformation, and thus causes a shift in the equilibrium toward the inactive state (Adapted with permission 2015. Copyright © 2004 Massachusetts Medical Society. All rights reserved. Simons)

and epithelial cell immunoreactivity and number and function of β-adrenergic receptors. The clinical significance of these anti-inflammatory effects still requires further investigation, and this research is leading to new understanding of the mechanisms for allergic disease and the development of new drugs to treat the clinical symptoms.

Antihistamines

Antihistamines currently available on the market in the United States include oral first-generation, oral second-generation, topical intranasal, topical skin, and topical ophthalmic formulations.

Oral First-Generation Antihistamines

Oral first-generation antihistamines include diphenhydramine, clemastine, tripelennamine, pyrilamine, brompheniramine, chlorpheniramine, triprolidine, hydroxyzine, promethazine, and cyproheptadine. Hydroxyzine is available by prescription, and some of the other agents, such as diphenhydramine and chlorpheniramine, are available over the counter. They are nonselective receptor antagonists and exert antiserotonergic, anticholinergic, antidopaminergic, and anti-α-adrenergic effects. Due to their blockage of muscarinic receptors, they may cause significant anticholinergic effects, including dry mouth, constipation, urinary retention, and sinus tachycardia. The lipophilic properties of oral first-generation antihistamines allow them to cross

the blood-brain barrier and interact with central nervous system H_1 receptors. Because histamine controls vigilance during the waking state, this blockade of the effects of endogenous histamine in the central nervous system may lead to sedative effects. As a class, they are also often referred to as *sedating* antihistamines, a term which has been operationalized to indicate both drowsiness and impairment in motor and cognitive abilities. Studies have also demonstrated discrepancies between patient self-reported and objective measures of drowsiness and impairment due to these medications. Further corroborating these findings, oral first-generation antihistamines cause significant loss of productivity at school and at work and impair driving performance. In the elderly, they may worsen dementia and induce delirium. Optimal dosing for oral first-generation antihistamines is several times a day. As the terminal elimination half-life of these drugs varies from 9.2 to 27.9 h, even if taken only at bedtime, there may be potential sedation the following day. In general, their rate of sedation is twice that of placebo, and 25–50 % of patients are affected.

Oral Second-Generation Antihistamines

Oral second-generation antihistamines currently available in the United States include cetirizine, levocetirizine, loratadine, desloratadine, and fexofenadine. These drugs are referred to by a variety of different names, including "nonsedating," "low-sedating," "new-generation," "next-generation," and "third-generation" antihistamines, for which there are no universally accepted definitions. This terminology should be avoided as it may cause confusion among clinicians and patients.

In contrast to the oral first-generation antihistamines, the oral second-generation antihistamines have more specific peripheral H_1 receptor selectivity and are thus less likely to cause antiserotonergic, anticholinergic, antidopaminergic, and anti-α-adrenergic effects. Furthermore, they are lipophobic, and therefore, the possibility of their penetration of the blood-brain barrier to act on central H_1 receptors to cause sedative effects is diminished. Overall, they also have a quicker onset of action, longer duration of action, increased potency, and reduced adverse events.

The second-generation antihistamines have been well studied in clinical trials, and their clinical efficacy, safety profiles, significant drug interactions, use during pregnancy and lactation, clinical indications, dosage and administration, as well as comparative efficacy with respect to other agents used to treat allergic diseases have been clearly established.

Clinical Efficacy

All five oral second-generation antihistamines have shown efficacy in controlling symptoms of allergic rhinitis, 24-h symptom control, and anti-inflammatory potential. Pollen challenge studies conducted in an Environmental Exposure Unit (EEU)

are often used to characterize the time to onset of clinically important relief with oral second-generation antihistamines.

Safety Profile

Central Nervous System Effects

Undesirable effects of antihistamines are related to their ability to cross the blood-brain barrier and function as inverse agonists at H_1 receptors in the brain, causing sedation. The oral second-generation antihistamines, due to their lipophobic properties, are less likely than their lipophilic first-generation counterparts to exert these effects. Cetirizine has demonstrated sedative properties even at recommended doses in patients aged 12 or older (11–14 % versus 6 % receiving placebo). Levocetirizine dihydrochloride, the active R-enantiomer of cetirizine, has also been associated with somnolence in patients aged 12 or older. Sedative properties have been observed with desloratadine and loratadine at two to four times higher than recommended doses, but not at therapeutic doses. At clinically indicated doses, or higher than therapeutic doses, fexofenadine has not been shown to cause sedation.

Cardiotoxicity

Antihistamines are more likely to cause cardiotoxicity when plasma concentrations are elevated. Thus, it is important to consider overdose and drug-drug interactions when discussing cardiotoxicity.

The first oral second-generation antihistamines approved for use in the United States, terfenadine and astemizole, were removed from the market in the late 1990s due to their association with rare but serious adverse cardiac events, including ventricular arrhythmias, cardiac arrest, and death. In 20 of the first 25 cases of proarrhythmic effects related to terfenadine reported to the United States Food and Drug Administration (FDA), patients had at least one documented risk factor causing elevation of blood concentrations of terfenadine and predisposing them to these adverse reactions: 11 patients were taking concomitant drugs known to inhibit hepatic terfenadine metabolism, 3 had taken an intentional overdose, and 6 likely had hepatic cirrhosis.

In summary, first-generation oral antihistamines, including diphenhydramine and hydroxyzine, have demonstrated QT_c prolongation at higher than recommended doses. Terfenadine and astemizole were withdrawn from the market due to their cardiotoxicity. Even at higher than therapeutic doses, cetirizine, levocetirizine, desloratadine, fexofenadine, and loratadine have not demonstrated clinically significant cardiac effects. It is important to underscore that fexofenadine, although it is the primary metabolite of terfenadine, does not exhibit cardiotoxicity.

Drug Interactions

Terfenadine, astemizole, and loratadine are substrates of the hepatic cytochrome P450 isoenzymes, which can be found in the liver and small intestine. Specifically, loratadine is a substrate for cytochrome P450 isoenzymes 3A4 and 2D6. Other drugs which inhibit the cytochrome P450 isoenzymes 3A4 and/or 2D6, including ketoconazole, erythromycin, cimetidine, and clarithromycin, may elevate the plasma concentrations of loratadine, terfenadine, and astemizole. With both terfenadine and astemizole, this elevation resulted in torsades de pointes, but there does not appear to be any clinical significance of this elevation with loratadine. Cetirizine, levocetirizine, fexofenadine, and desloratadine do not undergo cytochrome P450 metabolism.

Fexofenadine and desloratadine interact with the efflux transporter P-glycoprotein, and fexofenadine interacts with the uptake transporter organic anion-transporting peptide (OATP). Due to P-glycoprotein, ketoconazole taken concomitantly with desloratadine and fexofenadine may increase the plasma concentration of these antihistamines by 40 % and 135 %, respectively. However, adverse effects associated with this elevation have not been reported. Coadministration of 1.2 L of grapefruit juice decreased plasma levels of fexofenadine likely due to the saturation of OATP carrier proteins with grapefruit juice. The effectiveness of fexofenadine should also be monitored when taken concurrently with antacids. Antacids may bind fexofenadine and thus decrease its absorption.

Sedation and driving impairment due to cetirizine may be augmented by the concomitant use of alcohol (Table 37.1). Cetirizine, levocetirizine, loratadine, desloratadine, and fexofenadine all accumulate with renal impairment. The doses of these medications should be adjusted accordingly. Cetirizine, desloratadine, and loratadine undergo significant liver metabolism to varying degrees, 30 %, more than 90 %, and more than 98 %, respectively. These three drugs require dose reduction in patients with hepatic impairment. Levocetirizine is excreted primarily by the urine (85.4 %) and in the feces (12.9 %). Fexofenadine undergoes less than 4 % liver metabolism. It does not accumulate in patients with hepatic dysfunction, nor does it require dose adjustment.

Pregnancy and Lactation

Some consider oral first-generation antihistamines, except brompheniramine, as first-line therapy for allergic diseases during pregnancy. Chlorpheniramine, tripelennamine, and diphenhydramine are all category B. Brompheniramine should be avoided during pregnancy and is a Pregnancy Category C. Others consider the second-generation antihistamines as first-line therapy during pregnancy. This is especially true for women that have not responded to or had significant side effects upon taking oral first-generation antihistamines. Testing in animal models and postmarketing reporting have led the United States FDA to label cetirizine, levocetirizine, and loratadine as Pregnancy Category B and fexofenadine and desloratadine as Pregnancy Category C.

Table 37.1 Comparison of FDA-approved second-generation oral antihistamines

	Cetirizine	Levocetirizine	Fexofenadine	Loratadine	Desloratadine
Age indication	≥6 months	≥6 months	≥6 months	≥2 years	≥6 months
Pregnancy	B	B	C	B	C
Sedation	Yes (14 %)	No (2–6 %)	No (1–3 %)	No (8 %)	No (5 %)
Performance impairment	Yes	Yes	No	No	No
QTc prolongation with increased drug levels	No	No	No	No	No
Substantial effect of macrolides on bioavailability	No	No	Yes	Yes	No
Accumulation in renal or hepatic dysfunction	Both hepatic and renal	Renal only	Renal only	Both hepatic and renal	Both hepatic and renal

Cetirizine, levocetirizine, desloratadine, and fexofenadine are indicated down to ≥6 months of age. Loratadine is indicated down to ≥2 years of age. Cetirizine, levocetirizine, and loratadine are Pregnancy Category B, whereas desloratadine and fexofenadine are category C. Cetirizine and levocetirizine may cause sedation and performance impairment at recommended doses. Clinical trials do not show sedation or performance impairment with the use of recommended doses of desloratadine, fexofenadine, and loratadine. None of these agents cause clinically significant QT_c prolongation with increased drug levels. Macrolides may have a substantial effect on the bioavailability of fexofenadine and loratadine, but not on the bioavailability of cetirizine, levocetirizine, or desloratadine. Whereas cetirizine, desloratadine, and loratadine may accumulate in both renal and hepatic impairment, levocetirizine and fexofenadine accumulate only with renal impairment

Based on animal and human studies in nursing mothers taking oral second-generation antihistamines that examine the amount of drug secreted into breast milk, cetirizine, levocetirizine, and desloratadine are not recommended for nursing mothers. Caution should be exercised when prescribing fexofenadine and loratadine to a nursing mother. As there is no Category A medication in pregnancy, and by extension during lactation, a rational approach is to optimize allergen avoidance, followed by initiating non-pharmacologic therapies (e.g., saline irrigation, nasal strips) and if necessary selective use of Category B medications. Most consider nonsedating antihistamines and topical nasal corticosteroids as safe to use during pregnancy.

Clinical Indications

Oral second-generation antihistamines are indicated for the treatment of seasonal and perennial allergic rhinitis, as well as chronic idiopathic urticaria.

Allergic Rhinitis

Allergic rhinitis is a chronic condition affecting 10 % to more than 40 % of the population worldwide. It is one of the top ten reasons for patients to visit their primary care physicians. Clinical symptoms include pruritus, sneezing, rhinorrhea, and nasal congestion. Allergic rhinitis is part of a systemic inflammatory process and is often associated with other inflammatory conditions such as asthma, rhinosinusitis, allergic conjunctivitis, and otitis media with effusion. It has traditionally been classified as either seasonal or perennial, depending on whether the patient is sensitized to cyclical pollens or year-round allergens such as in door mold, pets, dust mites, and cockroaches. More recently, a new classification system, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, has been developed by the World Health Organization. Under this new system, allergic rhinitis is defined as intermittent or persistent and mild or moderate to severe. Intermittent symptoms are present less than 4 days per week or less than 4 weeks per year. Persistent symptoms are present more than 4 days per week and more than 4 weeks per year. Mild symptoms do not interfere with sleep, do not impair daily activities, do not affect work and school, and do not cause troublesome symptoms. A patient is considered to have moderate to severe disease if one or more of the following symptoms are present: abnormal sleep, impairment of daily activities, impairment of work and school activities, and troublesome symptoms.

The ARIA guidelines outline a stepwise approach to treatment of allergic rhinitis. Initial pharmacotherapy for mild intermittent allergic rhinitis consists of an oral antihistamine, an intranasal antihistamine, or an oral decongestant. For persistent and moderate to severe symptoms, intranasal steroids are first-line recommended treatment. Appropriate follow-up care accompanied by step-up or step-down therapy is the cornerstone for long-term management of this chronic disease.

Oral second-generation antihistamines, including cetirizine, desloratadine, loratadine, and fexofenadine, have been studied in patients with allergic rhinitis and concomitant asthma. These studies have led to several clinical findings regarding oral second-generation antihistamines, including the following: whereas the oral first-generation antihistamines were thought, but never documented, to exacerbate asthma because of their anticholinergic effects, the oral second-generation antihistamines, with their lack of anticholinergic effects, do not pose this problem. In addition, by ameliorating allergic rhinitis, they may indirectly improve symptoms of asthma; and they may serve as a useful adjunctive therapy in patients with allergic rhinitis and concomitant asthma.

Other Treatment Options for Allergic Rhinitis in Addition to Antihistamines

There are a variety of other options for the treatment of allergic rhinitis in addition to oral and intranasal antihistamines (Table 37.2). These medications include intranasal steroids, intranasal chromones/mast cell stabilizers, oral and topical

Table 37.2 Therapeutic options in the treatment of allergic rhinitis*

	Sneezing	Rhinorrhea	Nasal congestion	Nasal pruritus	Ocular symptoms
Intranasal steroids	3+	3+	3+	2+	2+
Intranasal chromones	1+	1+	1+	1+	Ø
Oral decongestants	Ø	Ø	3+	Ø	Ø
Intranasal anticholinergics	Ø	2+	Ø	Ø	Ø
Antileukotrienes	Ø	1+	2+	Ø	2+

*Medications used in the treatment of allergic rhinitis have different degrees of effectiveness in targeting specific symptoms

decongestants, oral decongestant-antihistamine combinations, topical anticholinergics, and antileukotrienes.

Intranasal Steroids

Intranasal steroids are currently the most effective class of medications for the treatment of allergic rhinitis and improve all nasal symptoms, including rhinorrhea, pruritus, congestion, and sneezing. They are first-line treatment for patients with persistent moderate to severe symptoms or whose main complaint is nasal congestion. Nasal steroids are superior to antihistamines for nasal congestion. In contrast, antihistamines appear to be superior for ocular symptoms. Intranasal steroids are superior to intranasal chromones for overall symptom reduction. The main adverse effect of intranasal steroids is mucosa irritation and nasal bleeding, and additionally, when used in children, there may be some, but minimal, effects on growth.

Oral Decongestants and Oral Decongestant-Antihistamine Combinations

Antihistamines are frequently combined with oral decongestants to offer better symptom control of nasal congestion. Oral decongestants, such as pseudoephedrine, are currently available in the United States. These medications produce vasoconstriction in the nasal mucosa via stimulation of alpha-2 adrenergic receptors and can ameliorate nasal congestion by vasoconstriction. They do not improve any of the other symptoms of allergic rhinitis. Side effects of oral decongestants include insomnia, irritability, palpitations, and tachycardia. Oral decongestants are contraindicated in patients with severe or uncontrolled hypertension, severe cardiovascular disease, narrow-angle glaucoma, urinary retention, and during or within 14 days of use of monoamine oxidase inhibitors. Pseudoephedrine is available in 30-mg tablets, 120-mg sustained-release tablets, 15-mg chewable tablets, and 15-mg/5-mL and 30-mg/5-mL liquid. Multiple

over-the-counter first-generation antihistamine plus decongestant combination products are available. The second-generation antihistamine plus decongestant products include loratadine 10 mg and pseudoephedrine 240 mg, combination; loratadine 5 mg and pseudoephedrine 120 mg, combination; desloratadine 5 mg and pseudoephedrine 240 mg, combination; cetirizine 5 mg and pseudoephedrine 120 mg, combination; fexofenadine 60 mg and pseudoephedrine 120 mg, combination; and fexofenadine 180 mg and pseudoephedrine 240 mg, combination.

Topical Intranasal Antihistamines

With respect to intranasal antihistamines, there are only two agents available in the United States, azelastine and olopatadine. Azelastine is available by prescription only, and it is approved for use in adults as well as children down to 5 years of age. Olopatadine is also available by prescription only and is approved for adults and children down to 6 years of age. Azelastine is indicated for perennial allergic rhinitis, seasonal allergic rhinitis, and vasomotor rhinitis at the recommended dose of two sprays per nostril twice daily. Olopatadine is indicated for seasonal allergic rhinitis. Studies of azelastine have shown an onset of action within 3 h after initial dosing and sustained efficacy over the following 12-h interval. The most common side effects reported are bitter taste (19.7 % versus 0.6 % placebo) and sedation (11.5 % versus 5.4 % placebo). Azelastine is labeled Pregnancy Category C. Studies of olopatadine have shown an onset of action within 30 min after initial dosing and sustained efficacy over the following 12-h interval. The most common side effects of olopatadine reported are bitter taste, headache, epistaxis, pharyngolaryngeal pain, postnasal drip, cough, and urinary tract infections in adults and adolescents down to 12 years of age (>1 %). In children 6–11 years of age, the most common side effects are epistaxis, headache, upper respiratory tract infection, bitter taste, pyrexia, and rash. Olopatadine is labeled Pregnancy Category C.

Topical Anticholinergics Compared to Antihistamines

A topical intranasal anticholinergic agent, ipratropium bromide, is available in 0.03 and 0.06 % concentrations. Ipratropium 0.03 % is indicated for the perennial allergic rhinitis and nonallergic rhinitis at doses of two sprays in each nostril two to three times per day. Ipratropium 0.06 % is indicated for seasonal allergic rhinitis at doses of two sprays in each nostril four times a day. The main indication for ipratropium is in the treatment of rhinorrhea. When intranasal ipratropium was added to oral terfenadine, there was significant improvement in total severity and duration of rhinorrhea when compared to vehicle and terfenadine.

Antileukotrienes Compared to Antihistamines

The antileukotriene montelukast is indicated for the treatment of allergic rhinitis. As summarized in the ARIA guidelines and AAAAI Practice Parameter, antileukotrienes are equivalent to antihistamines, but are less efficacious than intranasal corticosteroids. The combination of montelukast and antihistamines is superior to monotherapy of either agent alone.

Urticaria

Chronic idiopathic urticaria is characterized by the appearance of transient pruritic erythematous wheals. Individual lesions resolve within 24 h, and then new ones appear. Chronic urticaria is defined as recurring episodes of hives lasting more than 6 weeks. Oral second-generation antihistamines are first-line therapy as well as the mainstay of treatment. Both first- and second-generation antihistamines are used for acute urticaria, although neither is FDA approved for this indication; however, due to adverse effects, guidelines suggest that the first and second stage of therapy include FDA-approved doses of second-generation antihistamines and double the dose for those that fail to respond.

Allergic Conjunctivitis

Ocular allergy symptoms may present alone, and this condition is termed allergic conjunctivitis. The symptoms often present in combination with allergic rhinitis, and this is then termed allergic rhinoconjunctivitis. Topical ophthalmic antihistamines and oral antihistamines are the cornerstone of treatment for allergic conjunctivitis and allergic rhinoconjunctivitis, respectively.

Atopic Dermatitis

It is controversial whether antihistamines are effective for the relief of pruritus associated with atopic dermatitis. Although not FDA indicated, in practice, antihistamines are often used to treat itching associated with these conditions. Sedative effects of first-generation antihistamines are frequently utilized to induce sleep at night in those with sleep disturbance from pruritus.

Other Uses of Antihistamines in Nonallergic Diseases

Meclizine is an antihistamine used for the treatment of motion sickness prophylaxis as well as vertigo of vestibular origin. A combination tablet, acetaminophen plus diphenhydramine, is available over the counter as a pain reliever/sleep aid.

Dosage, Administration, FDA Indications, and Dosage Adjustment in Hepatic or Renal Impairment

The second-generation oral antihistamines come in a variety of formulations and dosages appropriate for children and adults. Levocetirizine and desloratadine are available by prescription only. Cetirizine, loratadine, and fexofenadine are available over the counter. Cetirizine, loratadine, desloratadine, and fexofenadine are also available with pseudoephedrine as antihistamine-decongestant combination tablets.

Cetirizine

Cetirizine is available as 5-mg and 10-mg tablets, 5-mg and 10-mg chewable tablets, and 1-mg/mL syrup. It is indicated for seasonal allergic rhinitis in patients older than 2 years, perennial allergic rhinitis in patients older than 6 months, and chronic idiopathic urticaria in patients older than 6 months. For patients 6–23 months of age, the recommended dose is 2.5 mg daily; for patients 12–23 months of age, the recommended starting dose is 2.5 mg daily, and the maximum recommended dose is 2.5 mg every 12 h; for patients 2–5 years of age, the recommended starting dose is 2.5 mg daily, and the maximum recommended dose is 2.5 mg every 12 h to 5 mg daily; for patients older than 6 years, the recommended dose is 5–10 mg daily. For patients with renal or hepatic impairment older than 6 years or the elderly (older than 77 years old), the recommended dose is 5 mg daily. Cetirizine is not recommended in patients with renal or hepatic impairment younger than 6 years.

Levocetirizine

Levocetirizine is available as 5-mg tablets and 2.5-mg/5-mL oral solution. It is indicated for seasonal or perennial allergic rhinitis and chronic idiopathic urticaria.

For patients 6 months to 5 years of age, the recommended starting dose is 1.25 mg daily; for patients 6–11 years of age, the recommended starting dose is 2.5 mg daily; for patients 12 years and older, the recommended starting dose is 5 mg daily. For patients 12 years and older with renal impairment (with or without hepatic impairment), the dose of levocetirizine should be reduced, and the dose reduction is dependent on the degree of renal impairment. For mild renal impairment (creatinine clearance 50–80 mL/min), the levocetirizine dose should start at 2.5 mg daily; for moderate impairment (creatinine clearance 30–50 mL/min), the levocetirizine dose should start at 2.5 mg every other day; for severe impairment (creatinine clearance 10–30 mL/min), the levocetirizine dose should start at 2.5 mg every 3 days.

Loratadine

Loratadine is available as 10-mg tablets, 10-mg orally disintegrating tablets, and 1-mg/1-mL syrup. It is indicated for seasonal allergic rhinitis in patients older than 2 years of age and chronic idiopathic urticaria in patients older than 2 years of age. For patients 2–5 years of age, the recommended dose is 5 mg daily; for patients older than 6 years of age, the recommended dose is 10 mg daily. For patients 2–5 years of age with renal or hepatic impairment, the recommended starting dose is 5 mg every other day. For patients older than 6 years of age with renal or hepatic impairment, the recommended starting dose is 10 mg every other day.

Desloratadine

Desloratadine is available as 5-mg tablets, 5- and 2.5-mg orally disintegrating tablets, and 0.5-mg/mL syrup. It is indicated for seasonal allergic rhinitis in patients older than 2 years, perennial allergic rhinitis in patients older than 6 months, and chronic idiopathic urticaria in patients older than 6 months. For patients 6–11 months of age, the recommended dose is 1 mg; for patients 1–5 years of age, the recommended dose is 1.25 mg; for patients 6–11 years of age, the recommended dose is 2.5 mg daily; and for patients older than 12 years, the recommended dose is 5 mg daily. For patients older than 12 years with renal or hepatic impairment, the recommended starting dose is 5 mg every other day.

Fexofenadine

Fexofenadine is available as 30-, 60-, and 180-mg tablets, as well as a 30-mg/5-mL oral suspension. It is indicated for seasonal allergic rhinitis in patients $\geq$2 years of age and for chronic idiopathic urticaria in patients $\geq$6 months of age. For patients 6–24 months of age, the recommended dose is 15 mg twice daily; for patients 2–11 years of age, the recommended dose is 30 mg twice daily; for patients $\geq$12 years of age, the recommended dose is 180 mg daily or 60 mg twice daily. For patients 6–24 months of age with renal impairment, the recommended starting dose is 15 mg once daily; for patients 2–11 years of age with renal impairment, the recommended starting dose is 30 mg once daily. For patients $\geq$12 years of age with renal impairment, the recommended starting dose is 60 mg once daily.

Topical Intranasal Corticosteroid-Antihistamine Combinations

There is one intranasal antihistamine and corticosteroid combination, azelastine and fluticasone. The azelastine-fluticasone combination is indicated for seasonal allergic rhinitis. The azelastine-fluticasone combination is available by prescription only

and is approved for use in adults as well as adolescents down to 12 years of age. The azelastine-fluticasone combination is labeled Pregnancy Category C.

Topical Skin Antihistamines

The topical skin antihistamines include over-the-counter diphenhydramine, but its use has been associated with a high rate of contact dermatitis. For this reason, allergy specialists generally recommend oral antihistamines over topical skin agents.

Ocular Antihistamines and Antihistamine-Mast Cell Stabilizer Combination Products

A variety of topical ophthalmic antihistamine and antihistamine-mast cell stabilizer combination products are available on the market in the United States. Two ophthalmic H_1-antihistamines and their dosages include emedastine difumarate 0.05 % one drop in each eye up to four times daily and levocabastine hydrochloride 0.05 % one drop in each eye four times daily. Emedastine difumarate and azelastine hydrochloride are indicated for the treatment of patients with allergic conjunctivitis older than 3 years of age, and levocabastine hydrochloride is indicated for the treatment of seasonal allergic rhinitis in patients older than 12 years of age. Mast cell stabilizer plus antihistamine intraocular combination products include olopatadine hydrochloride 0.1, 0.2, and 0.7 %, azelastine hydrochloride 0.05 %, bepotastine besilate 1.5 %, and ketotifen fumarate 0.025 %. Bepotastine besilate 1.5 % is indicated in patients older than 2 years, and the recommended dose is one drop in each affected eye twice a day. Olopatadine hydrochloride 0.1 and 0.2 % are indicated for the treatment of allergic conjunctivitis in patients older than 3 years of age. Olopatadine hydrochloride 0.1 % is dosed at one drop in each affected eye twice a day allowing 6–8 h between doses. Olopatadine hydrochloride 0.2 % and 0.7 % are dosed at one drop in each affected eye once daily. Azelastine hydrochloride 0.05 % and ketotifen fumarate 0.025%are indicated for the treatment of allergic conjunctivitis in patients older than 3 years. Azelastine hydrochloride 0.05 % is dosed at one drop in each affected eye twice daily. Ketotifen fumarate 0.025 % is dosed at one drop to each affected eye every 8–12 h.

Mast Cell Stabilizers

Intranasal Chromones/Mast Cell Stabilizers

Intranasal mast cell stabilizers currently available include cromolyn sodium and nedocromil sodium. By inhibiting the degranulation of sensitized mast cells, cromolyn sodium blocks the release of inflammatory mediators involved in causing the symptoms of allergic disease. Clinical trials have shown cromolyn sodium to be effective in ameliorating both the early- and late-phase reaction in participants with

allergic rhinitis. The drug is indicated for use in both seasonal and perennial allergic rhinitis. Patients usually get symptom relief within the first week of treatment, and there is enhanced symptom improvement over the following weeks with continued use. The four times daily dosing may impede adherence initially. Once desired symptom control has been achieved, a less frequent dosing schedule may suffice to maintain control. As local adverse effects are uncommon, and they have poor systemic absorption, mast cell stabilizers have an excellent safety profile. The 4 % intranasal solution is indicated for adults as well as children down to 2 years of age.

Topical Ophthalmic Mast Cell Stabilizers

Some examples of topical ophthalmic mast cell stabilizers and their dosage indications include pemirolast potassium, 0.1 % one to two drops in each eye four times daily for up to 4 weeks; nedocromil sodium 2 %, one to two drops in each eye twice daily; cromolyn sodium 4 %, one to two drops in each eye four to six times daily at regular intervals; and lodoxamide tromethamine 0.1 %, one to two drops in each eye four times daily for a maximum of 3 months. Cromolyn sodium is indicated for allergic conjunctivitis for patients older than 4 years of age, pemirolast potassium and nedocromil sodium are indicated for allergic conjunctivitis for patients older than 3 years of age, and lodoxamide tromethamine is indicated for the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis in patients older than 2 years of age.

The adverse effect profile of this class of medications is minimal, and it is unlikely that adverse effects will interfere with adherence to therapy; however, the need for frequent dosing may interfere with compliance to therapy.

Conclusion

Oral second-generation antihistamines are the cornerstone of treatment for allergic rhinitis and chronic idiopathic urticaria. Extensive clinical studies attest to their safety and efficacy in both adult and pediatric populations. The variety of formulations, including tablet, chewable tablet, rapidly disintegrating tablet, and liquid preparations, once-a-day dosing, and onset of action within a few hours and 24 h duration of action, enhance their widespread use.

Evidence-Based Medicine

New antihistamines have been tested to determine if there is added benefit in allergic rhinitis and urticaria. As reported by Stokes et al., a new histamine receptor 3 antagonist in combination with 60 mg of fexofenadine demonstrated improvement in nasal congestion, pruritus, rhinorrhea, and sneezing. In a separate phase 2 trial, Barchuk

et al. showed that treatment with another histamine receptor 3 antagonist reduced the increase in nasal cavity cross-sectional area measured by acoustic rhinometry following ragweed challenge in an environmental exposure chamber in comparison to placebo, but this effect was not significant ($P=0.06$). In further exploratory analyses, there was a significant improvement in total nasal symptom score and the individual components of the symptom score including nasal congestion ($P=0.007$), runny nose ($P=0.016$), itchy nose ($P=0.007$), and sneezing ($P<0.0001$) when compared to placebo. Further research is needed to support these findings.

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Chapter 38
Bronchodilators

Jennifer S. Kim and Rachel E. Story

Bronchodilators are an essential component of asthma treatment, especially in acute exacerbations. In this chapter, we review pharmacology, methods of delivery, and clinical indications for the use of various bronchodilators.

Pharmacology of Bronchodilators

β-Agonists

β-Agonists are the most effective agents to produce bronchodilation. Inhalation of β-agonists is the preferred mode of administration. Proper drug delivery device selection and education are key aspects for maximal efficacy.

β-Adrenoreceptors

β-Adrenergic agonists exert their effects through transmembrane G protein-coupled receptors. There are three types of β-adrenergic receptors: β1, β2, and β3. β1 receptors exist predominantly in the heart, whereas β3 receptors are found in adipose tissue. β2 receptors, however, are ubiquitous and can be found in the lung, liver, kidney, and gastrointestinal smooth muscle. In the lung, they are widely distributed in smooth muscle, submucosal glands, epithelium, alveoli, and the arterial system.

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They also are found on inflammatory cells that are associated with asthma. These include macrophages, mast cells, neutrophils, eosinophils, and lymphocytes.

Mechanism of Action and Cellular Effects

The active site of the β2 receptor is located within the transmembrane region consisting of seven β-helices. Once the β-agonist attaches to its receptor, signal transduction occurs. Adenylate cyclase is activated, increasing the cyclic adenosine monophosphate (cAMP). cAMP then is believed to activate protein kinase A, which causes phosphorylation, thereby leading to cellular effects, such as relaxation of bronchial smooth muscle.

Important nonbronchodilator actions of β-agonists include increased mucociliary clearance, protection of respiratory epithelium against bacteria, inhibition of cholinergic neurotransmission, and priming of the glucocorticoid response.

Structure and Development of β-Adrenergic Agents

Epinephrine

The first catecholamine introduced for the treatment of asthma was epinephrine by injection in 1903. Epinephrine has both α- and β-adrenergic effects. It acts rapidly but for a short time. Epinephrine remains the drug of choice for anaphylaxis but has diminished important for asthma.

Ephedrine

In the late 1930s, another catecholamine, ephedrine, became widely used as the first effective oral adrenergic bronchodilator. Although employed for several decades, ephedrine is a relatively weak bronchodilator that is no longer being used for asthma.

Isoproterenol

Introduced in 1941, isoproterenol was the first β-specific (but non-β2-selective) adrenergic agonist developed. It has a very short duration of action and is not useful as an oral medication because of gastrointestinal inactivation. For decades, however, it was the preferred drug for aerosol administration. Modifications made to isoproterenol have produced improved medications so the progenitor is no longer recommended for use.

Short-Acting Nonselective β2-Agonists

Metaproterenol

Metaproterenol is a noncatecholamine bronchodilator that can be administered by aerosol and is also active orally due to its resistance to gastrointestinal activation. Its structure and clinical activity is otherwise similar to isoproterenol. At high doses, it loses β2-adrenergic specificity and is no longer useful clinically.

Fenoterol

Fenoterol has never been approved for use in the United States. Its unique characteristic is that is a complete agonist for the β-adrenergic receptor. At high doses, therefore, its potency induces more cardiac stimulation and extrapulmonary side effects compared to other β2-agonists.

Short-Acting Selective β2-Agonists

Once the differentiation between β1- and β2-adrenergic receptors was made, efforts were directed toward the development of β2-selective agonists. More selectivity for the β2 receptor and longer duration of action can be achieved structurally by increasing the bulk of the side chain (Fig. 38.1).

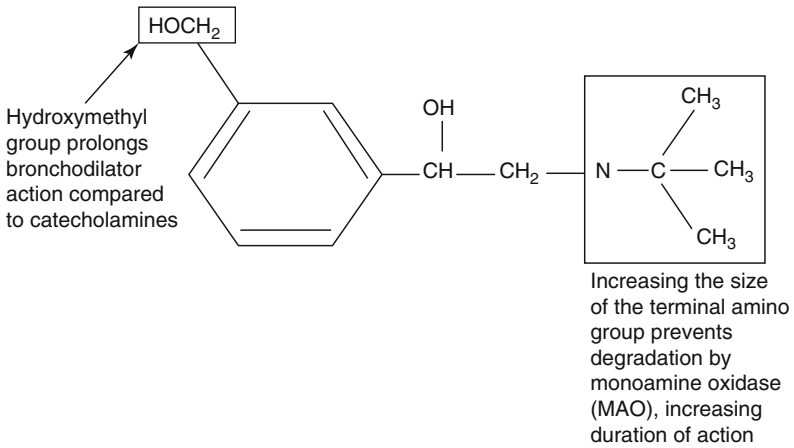

Fig. 38.1 Structure of albuterol

Albuterol, Levalbuterol, and Terbutaline

These selective β2-agonists produce bronchodilation but with decreased cardiac stimulation.

Albuterol (also called salbutamol) is available as a metered-dose inhaler, nebulized solution, and in 2015 approved by the Food and Drug Administration (FDA) as a dry-powder breath-actuated inhaler. Oral dosage forms are available but have limited efficacy and greater risk for significant side effects.

Levalbuterol is a single isomer of albuterol and is available also as an inhaler and a nebulized solution. Some studies suggest fewer adverse effects compared with albuterol.

Terbutaline is a noncatecholamine β2-agonist.

Pirbuterol has equivalent bronchodilation and cardiac stimulation to albuterol but was phased out in 2008 when chlorofluorocarbon propellant use was made illegal.

Long-Acting Selective β2-Agonists

Two β2-agonists were developed in the early 1990s that provide more than 12 h of bronchodilation: salmeterol and formoterol. Structurally, increasing the size of the terminal amino group protects against monoamine oxidase (MAO) degradation, thereby prolonging the duration of action.

Salmeterol

Salmeterol has a long lipophilic side chain that interacts with the "exosite" (an auxiliary binding site) of the receptor. This interaction prevents dissociation from the β2 receptor and results in repeated stimulation of the active site of the receptor, thereby producing prolonged bronchodilation.

Formoterol

Formoterol, due to its more moderate lipophilicity, penetrates the plasma membrane and gradually escapes out to interact with the β2 receptor. Formoterol has a faster onset of action compared to salmeterol. However, they are equally β2 selective.

Ultra-long-Acting Selective β2-Agonists

Effects of newer long-acting β-agonists (LABAs) last at least 24 h. COPD is the primary indication in the United States; data are lacking on its use in asthma. Currently FDA-approved in the United States include:

- *Arformoterol* (FDA-approved in 2006): a single-isomer version of formoterol available as a nebulized solution.
- *Indacaterol* (2011): a dry-powder inhaler with rapid onset of action; studies have shown improvements in FEV1 after only 5 min.
- *Vilanterol* (2013): available in combination with fluticasone furoate and separately in combination with umeclidinium (see section "Anticholinergics") and not available as monotherapy.
- *Olodaterol* (2014): available as monotherapy and in combination with tiotropium bromide (see section "Anticholinergics").

Anticholinergics

Anticholinergics are second-line bronchodilators behind β2-agonists. There are five muscarinic receptor subtypes, but M1, M2, and M3 receptors predominate in the lung. M2 receptors are the most abundant type in the airway; their activation results in decreased acetylcholine release, thereby inducing bronchoconstriction, mucus secretion, and vasodilation. M3 receptors are the primary mediator of smooth muscle bronchoconstriction. All muscarinic receptors can be blocked by atropine.

Ipratropium bromide is widely used and effective in treatment of asthma as well as COPD and rhinitis. Use is limited by frequent dosing (every 6 h). Meta-analyses show modest improvement in airflow obstruction with ipratropium is used as an adjunct with b2-agonists for treatment of acute asthma exacerbations in adults. Moreover, in pediatric studies, ipratropium use decreases hospitalization rates. There is rare potential for paradoxical bronchoconstriction. Ipratropium binds M2 and M3 receptors equally, but blocking M2 receptors can lead to increased acetylcholine release from the vagus nerve, which may induce bronchoconstriction.

Tiotropium bromide has a slower onset of action compared with ipratropium and is dosed once daily. Tiotropium also binds M2 and M3 receptors equally, but unlike ipratropium, tiotropium disassociates from M2 receptors ten times faster than from M3 receptors. Moreover, tiotropium dissociates from M3 receptors 100 times more slowly than ipratropium. Tiotropium has been shown to improve asthma control when added to an inhaled corticosteroid or a combination of ICS/LABA (see section "Long-Term Control Medication Use in Asthma"). Also available as of 2014 is a combination of anticholinergic and LABA inhaler (*umeclidinium* and vilanterol) used once daily as maintenance treatment of COPD.

Xanthines

Theophylline is a phosphodiesterase (PDE) inhibitor metabolized by ccP450 (primarily CYP1A2). Several anti-inflammatory and immunomodulatory mechanisms have been proposed, but the nonspecific inhibition of PDE appears to be the most important. Plasma concentrations must be monitored due to the risk of toxicity, thus limiting its use.

Factors that contribute to decreased clearance include liver disease, heart failure, pneumonia, age >60 years, fever above 102F for >24 h, hypothyroidism, and certain medications (e.g., cimetidine, ciprofloxacin, erythromycin, allopurinol, serotonin reuptake inhibitors). High concentrations can induce seizures, arrhythmias, and even death.

Roflumilast is an oral PDE4 inhibitor approved by the FDA for COPD. PDE4 inhibition decreases inflammation, promotes airway smooth muscle relaxation, and attenuates late (but not early) response to inhaled allergen. The use is limited by side effects, particularly nausea and vomiting.

Magnesium Sulfate

The mechanism of action of magnesium sulfate is not clearly defined. Magnesium ion decreases the uptake of calcium by bronchial smooth muscle cells, which in turn leads to bronchodilator. Magnesium may also have a role in inhibiting mast cell degranulation, thus reducing inflammatory mediators. In addition, magnesium inhibits the release of acetylcholine from motor nerve terminals and depresses the excitability of muscle fibers.

Routes of Administration for β-Agonists

Inhalation of aerosolized medication is the preferred route of administration for short-acting β-agonists. Seventy-five percent of maximum bronchodilation is noted after 5 min with a peak in 30–90 min. Significant bronchodilation is maintained for 4 h after a single treatment. The same degree of bronchodilation is achieved with systemic administration of β-agonists, but there are far fewer side effects with aerosolized administration. There is no role for oral β-agonists in the treatment of asthma because side effects are dose limiting and there is an equivalent degree of bronchodilation in both oral and inhaled formulations.

Devices for Aerosolized Administration of β-Agonists

Table 38.1 outlines details of available devices.

Nebulizers

Nebulizers are drug delivery devices used to administer medication in the form of a mist inhaled into the lungs. Nebulizers use oxygen, compressed air, or ultrasonic power to break up medical solutions and suspensions into small aerosol droplets. Delivery of the

Table 38.1 Devices for aerosolized administration of β2-agonists

Device	Age	Technique
Nebulizer		
With face mask	Infants and young children	Tidal breathing with good seal (mask or mouthpiece)
With mouthpiece	Older children and adults	
HFA-MDI and VHC		
With face mask	Infants and young children	Tidal breathing for six respiratory cycles per actuation
With mouthpiece	Older children and adults	Slow inhalation (3–5 s) with 10-s breath hold
DPI	Older children and adults	Rapid (1–2) deep inhalation with 10-s breath hold

medication does not require coordination and therefore may be used for any age group. Often this is the method of medication delivery in moderate to severe exacerbations in an immediate or urgent care setting although the available evidence suggests there is no difference in pulmonary function response between using a nebulizer vs. MDI with VHC/spacer when properly used and with equivalent dosing.

Metered-Dose Inhalers

Metered-dose inhalers (MDIs) are pressurized canisters that use propellants to generate particles. Chlorofluorocarbons (CFCs) were previously used as propellants but have been found to decrease the protective ozone layer. Thus, as of 2009, manufacturers of inhalational aerosols were required to utilize a different propellant called hydrofluoroalkane (HFA).

Technique is commonly incorrect, thereby providing suboptimal medication delivery. Even with proper technique, only a small percentage of the dose is inhaled into the lungs. Valved holding chambers (VHC) or spacers are recommended for use with MDIs. For younger children (<5 years), a VHC/spacer with mask is recommended.

Dry-Powder Inhalers

Dry-powder inhalers (DPIs) do not use propellants and are breath actuated. The medication in DPIs is inhaled in a dry form, requiring a tight seal around the mouthpiece and a rapid, deep inspiration. An inspiratory flow rate of up to 60 L per minute is required for proper delivery. Thus, DPIs are not appropriate for young children.

There are a variety of devices, but DPIs generally require some procedure to allow a measured dose of powder to be ready for the patient to take. The medication is commonly held either in a proprietary form inside the inhaler or in a capsule for manual loading. Once actuated or loaded, the operator places the mouthpiece of the

inhaler into their mouth and takes a deep inhalation, followed by a 10-s breath hold. DPI medications must be stored in sealed packaging in a dry place at room temperature and humidity between 40% and 50%. Exposure of the powder to moisture degrades the ability of the device to disperse its medication as a fine powder upon inhalation.

Clinical Use of Bronchodilators for Acute Severe Asthma

Selective Short-Acting: β-Agonists

Selective short-acting β-agonists are the mainstay of treatment in acute severe asthma. Less β2-selective medications, such as isoproterenol, metaproterenol, and epinephrine, are not recommended because of increased cardiac stimulation.

In most cases airway obstruction is secondary to both inflammation and smooth muscle contraction. Thus therapy with bronchodilators does not completely reverse obstruction, and treatment with systemic steroids is usually required in moderate to severe exacerbations. Because systemic steroids require at least 4 h to improve asthma symptoms, they should be given promptly. However, acute therapy focuses on inhaled β-agonists.

Inhaled preparations of β-agonists are strongly preferred over oral preparations because side effects are dose limiting in the oral preparations. For moderate to severe exacerbations, continuous or repetitive administration of inhaled β-agonists is recommended. Racemic albuterol (R- and S-albuterol) is the most commonly used β-agonist in the United States. The pure (R)-enantiomer of albuterol, called levalbuterol, produces comparable bronchodilation to racemic albuterol. When given in equivalent dose with proper technique administered via nebulizer or MDI, racemic albuterol and the pure (R)-enantiomer produce equal results.

Second: Line Agents for Acute Severe Asthma

Bronchodilators other than short-acting β-selective agonists, such as methylxanthines, anticholinergics, epinephrine, and magnesium, can be used as adjuvant therapy in acute asthma.

Epinephrine

The use of subcutaneous epinephrine is beneficial in some patients who fail to improve with inhaled therapy with short-acting β-agonists; however, there is no proven benefit of systemic therapy with epinephrine over aerosolized albuterol.

Anticholinergics

The anticholinergic medication ipratropium bromide may increase the degree of bronchodilation when used in conjunction with β-agonists, especially in children. In addition, anticholinergics are the recommended treatment for β-blocker-included bronchospasm.

Methylxanthines

Studies show no additional benefit to treatment with methylxanthines (aminophylline, theophylline) in acute asthma if a patient receives optimal treatment with inhaled β-agonists. Furthermore, the short-acting β-agonists produce three to four more times more bronchodilation than methylxanthines.

Magnesium

A recent meta-analysis shows that treatment with intravenous magnesium sulfate in addition to β2-agonists and systemic steroids produced benefit in both adults and children. Adults were found to have improved pulmonary function, and children had improved pulmonary function and a 30 % reduction in hospital admissions. The 2007 EPR3 guidelines recommend consideration of IV magnesium in patients with lifethreatening exacerbations and in those whose exacerbations remain severe after 1 h of intensive conventional therapy. Routine use is not recommended. Additional data is needed to establish a clearer role for magnesium in the management of acute asthma.

Long-Acting β2-Agonists

There is no role for the use of long-acting β2-agonists in the treatment of acute asthma.

Long-Term Control Medication Use in Asthma

Short-Acting β-Agonists

National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend the use of short-acting β-agonists as "quick relief" medications. Daily scheduled use of β-agonists is not recommended because it shows no benefit in mild asthma and may

cause worsening of asthma symptoms in moderate asthma. There are genetic polymorphisms in the β-receptor such that some genotypes will have improved lung function with daily β-agonist administration, whereas others will have significant deterioration in lung function with regular use. The use of more than one canister of a short-acting β2-agonist per month or increase in use is associated with life-threatening asthma, and daily anti-inflammatory treatment should be instituted or increased in these situations.

Long-Acting β-Agonists

Long-acting β-agonists (LABAs) can be used as adjuvant therapy with inhaled corticosteroids in moderate and severe persistent asthma. Because LABAs are not anti-inflammatory, the NHLBI recommends their use only as an adjunct to inhaled corticosteroids and not for use as monotherapy. Studies suggest that the addition of a LABA is superior to increasing the dose of inhaled corticosteroids in asthma control, and the addition of a LABA is superior to the addition of theophylline or a leukotriene pathway-modifying agent in improving asthma. LABAs should not be used for quick relief for acute symptoms. LABAs have a black box warning because some studies report an increase in asthma-related deaths in parties on LABAs. This is discussed further in the evidence-based medicine section of this chapter.

Methylxanthines

Sustained-release theophylline is primarily a bronchodilator and is not a NHLBI-preferred medication for persistent asthma because its anti-inflammatory activity is modest. Its use may benefit a subset of severe persistent asthmatics when used as an adjunctive controller medication. Common side effects include headache, nausea, vomiting, abdominal discomfort, and restlessness. Serum concentrations of 10–15 ug/mL indicate therapeutic levels for asthma. Regular monitoring of serum levels is recommended to prevent toxic side effects, which include seizures and cardiac arrhythmias. There is a narrow therapeutic index, and many commonly used medications, such as erythromycin and cimetidine, affect theophylline blood levels.

Anticholinergics

The addition of tiotropium to inhaled glucocorticoids and LABAs has been studied in patients with poorly controlled asthma. Studies found that the addition of tiotropium to inhaled glucocorticoids and LABAs resulted in a significant increase in time to first exacerbation and provided sustained bronchodilation. While systematic

reviews suggest that tiotropium may have a beneficial role in moderate to severe persistent asthma, it has not yet been included in NHLBI recommendations.

Exercise-Induced Bronchospasm

Exercise-induced bronchospasm (EIB) occurs secondary to loss of heat and water from the lung during exercise. The use of short-acting β-agonists prior to exercise prevents EIB in more than 80 % of patients and is effective for 2–3 h. A single dose of LABA prevents EIB for up to 12 h but, as discussed earlier, should only be used in conjunction with daily anti-inflammatory therapy, primarily inhaled corticosteroids.

Adverse Effects and Safety of β-Agonists

Adverse Effects of β-Agonists

Because β2 receptors are found in many organ systems, including the skeletal muscle, lung, liver, kidney, and gastrointestinal smooth muscle, there is a wide variety of adverse effects. Tolerance to nonbronchodilatory effects of β-agonists often occurs within 2 weeks. The use of short-acting β-selective agonists decreases side effects. Administration via inhalation also decreases side effects.

The most common side effect of β-agonists is tremor caused by activation of β2 receptors of skeletal muscle. Tolerance to tremor often develops in 2 weeks. Palpitations and tachycardia occur less often with the use of selective β-agonists but is still present. Myocardial ischemia can occur, and isoproterenol is particularly noted for altering coronary blood flow with resultant subendocardial ischemia. Prolonged QTc occurs with both selective and nonselective β-agonists and can lead to arrhythmias. Metabolic effects of β-agonists include hyperglycemia, hypokalemia, and hypomagnesemia. Table 38.2 offers a more complete list of potential side effects.

Safety of β-Agonists

The safety of both short- and long-acting β-agonists has been debated since the introduction of MDI β-agonists. In the 1960s, a significant increase in asthma mortality occurred in the United Kingdom and six other countries, coinciding with the introduction of MDI β-agonists. The increased mortality occurred only in countries using high-dose inhaled isoproterenol, and many deaths were attributed to the medication. In the 1970s, a similar epidemic occurred in New Zealand that some studies attributed to the use of fenoterol. Fenoterol produces a significant decrease in pulmonary function and asthma control when used regularly in moderate asthma. However, a subsequent study in New Zealand found that fenoterol was used more

Table 38.2 Adverse effects of inhaled β-agonists

Tremor
Restlessness
Hyperactivity
Insomnia
Palpitations
Prolonged QTc
Arrhythmia
Myocardial ischemia
Seizures
Transient decrease in PaO2
Abdominal discomfort
Nausea
Hyperglycemia
Hypomagnesemia
Paradoxical bronchospasm

often in patients with severe asthma. After adjusting for asthma severity, the use of fenoterol did not increase the risk of life-threatening asthma.

Studies do not agree on whether an indicated risk of life-threatening asthma is associated only with specific β-agonists or such as fenoterol and high-dose isoproterenol or whether increased risk for life-threatening asthma is a class effect of β-agonists. In a study that reviewed the health insurance database of more that 12,301 patients who were prescribed asthma medications in Saskatchewan Canada, increased asthma mortality occurred only when β-agonists were used in excess of 1.4 canisters per month. The investigators argued that increased use of β-agonists was not responsible for increased mortality but was simply a marker of increased asthma severity, which is itself a risk factor for fatal asthma.

Safety questions around the use of long-acting β-agonists are currently under scrutiny. On March 2, 2006, the FDA approved labeling changes with new black box safety warnings for asthma LABAs, namely, medications containing salmeterol xinafoate. These warnings were issued due to concerns that regular treatment with LABAs may be associated with an increased risk of severe exacerbations and even death from asthma in a small subset of patients.

Because of early safety concerns after the introduction of LABAs, the manufacturer of salmeterol, GlaxoSmithKline, on the FDA's request designed a study called the Salmeterol Multicenter Asthma Research Trial (SMART), which was initiated in June 1996. The outcomes measured included respiratory-related deaths and life-threatening experiences (intubation or mechanical ventilation). Approximately 26,000 patients were enrolled and randomized to receive either salmeterol or placebo for 28 weeks in addition to their usual therapy. Compliance was not reinforced, and the use of inhaled corticosteroids (ICS) was not a prerequisite to participation in the study. The study was stopped due to findings of a small but significant increase in combined respiratory-related deaths or life-threatening experiences in subjects receiving salmeterol as opposed to placebo.

Evidence-Based Medicine

Studies including several meta-analysis and systematic reviews have had conflicting results regarding the safety of LABAs. There is controversy over whether the use of LABAs is associated with an increase in severe asthma exacerbations and increased asthma and cardiac mortality in a small subgroup of patients.

In February 2010 the FDA issued requirements for manufacturers of all products containing LABAs to make changes regarding their use in asthma treatment. Changes included the contraindication of LABAs without the use of an inhaled corticosteroid and recommended that LABAs only be used when needed to achieve or maintain asthma control.

In contrast to studies raising concerns about LABA safety, multiple well-designed clinical studies have confirmed the superiority of combination therapy (LABA + ICS) over monotherapy with a higher dose of ICS. How can we reconcile these findings? The NHBLI recommends that the established benefits of LABA for the vast majority of patients who require more than low-dose ICS alone should be weighed against the increased risk for severe exacerbations, though uncommon, associated with the daily use of LABAs.

On April 14, 2011, the FDA required all manufacturers of LABAs that are marketed for asthma in the United States to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus ICS as compared with ICS alone. A total of 5 multinational, randomized, double-blinded clinical trials will be conducted with four in adults and children 12 years or older and one in children 4–11 years of age. Medications studied will include budesonide with formoterol fumarate (Symbicort), fluticasone propionate with salmeterol (Advair), and mometasone furoate with formoterol fumarate (Dulera).

In March of 2016 the results of the first trail were published in the New England Journal of Medicine. Patients aged 12 years and older (N=11,679) were enrolled in a randomized, double-blind trial to receive either fluticasone with salmeterol or fluticasone alone for 26 weeks. Patients who received fluticasone with salmeterol did not have significantly higher risk of serious asthma related events (death, endotracheal intubation, or hospitalization) than those who received fluticasone alone. In addition, patients who received fluticasone with salmeterol had a 21% lower risk of severe asthma exacerbation than those treated with fluticasone alone.

While results of the initial trial are reassuring, until we have more data from the additional trials, reserving combination therapy for more severe disease (as per NHBLI guidelines) seems prudent. Prior to the addition of LABAs, consider the lack of patient adherence or presence of other concomitant medical conditions when a patient fails to respond appropriately to ICS therapy. Patients, once prescribed LABAs, would benefit from close medical monitoring, particularly if symptoms become difficult to control.

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Chapter 39
Glucocorticoids

Joseph D. Spahn

Introduction

Glucocorticoid (GC) therapy remains one of the most valuable treatment modalities in the management of asthma and allergic rhinitis. GCs have been used in the treatment of allergic diseases for over 50 years. Pioneering studies performed in the 1950s found cortisone, the first synthetic GC, to result in significant improvements in asthma symptoms and pulmonary function. Unfortunately, reports describing the multitude of adverse effects associated with chronic cortisone began to appear, and much of the early enthusiasm of chronic oral GC treatment for asthma waned. Over the next couple of decades, attempts to deliver GCs topically were a major focus of research and development. By the mid-1970s the first inhaled GC was approved for use in the treatment of asthma. The development of highly effective inhaled GC preparations has revolutionized how we care for patients with asthma. By virtue of their high topical-to-systemic potency, inhaled GC therapy has proven to be both safe and effective in the treatment of asthma. This chapter will provide a broad overview of the structure, mechanisms of action, pharmacokinetics, efficacy, adverse effects, and current issues associated with both systemic and inhaled GC therapy in asthma, in addition to a brief discussion of intranasal GC therapy for the treatment of allergic rhinitis.

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Chemistry

Synthetic GCs are cortisone-based molecules that have undergone structural modifications designed to enhance their potencies and prolong their durations of action. Anti-inflammatory GCs have a 17-hydroxyl group and methyl groups at carbons 18 and 19 (Fig. 39.1). Further modifications to the basic steroid structure have increased the anti-inflammatory effects while decreasing mineralocorticoid effects. Unfortunately, it has not been possible to separate the unwanted metabolic effects from the desired anti-inflammatory properties of GCs.

Mechanisms of Action

Both asthma and allergic rhinitis are immune-mediated diseases in which a specific inflammatory reaction involving T_{H2} lymphocytes, eosinophils, and IgE occurs. GCs have broad anti-inflammatory effects, so it should come as no surprise that GCs are among the most effective classes of medications available for use in allergic disease. GCs act at several levels of the inflammatory response (Table 39.1), with their primary effect coming mainly from their ability to inhibit the expression and/or production of molecules involved in the initiation and maintenance of the inflammatory response. Specifically, they inhibit the upregulation of adhesion molecules on endothelial cells that are required for the adhesion and subsequent migration of inflammatory cells to sites of inflammation. They also inhibit the production of cytokines involved in inflammatory cell recruitment, activation, and proliferation. GCs also have potent vasoconstrictive properties. By decreasing capillary permeability at sites of inflammation, plasma exudation is inhibited which results in a reduction of tissue edema, as well as reductions in the concentration of inflammatory and chemotactic factors and ultimately in a decrease in the inflammatory response. Lastly, GCs upregulate β-adrenergic receptors on airway smooth muscle cells, thereby rendering these cells more responsive to beta-agonist therapy.

Systemic Glucocorticoid Therapy

Pharmacokinetics

Prednisone, prednisolone, and methylprednisolone are all rapidly and nearly completely absorbed following oral administration with peak plasma concentrations occurring within 1–2 h. Prednisone is an inactive prodrug that requires biotransformation of the 11-ketone group to an 11-hydroxyl group (see Fig. 39.1a). This conversion to prednisolone (its active form) occurs via first-pass hepatic metabolism.

Once absorbed, GCs bind to serum proteins and are metabolized in the liver by the cytochrome P450 isoform 3A4 (CYP3A4) into inactive compounds. The rate

of metabolism or clearance of GCs can be altered by drug interactions and disease states. Cystic fibrosis and hyperthyroidism are diseases where higher GC doses may be required due to intrinsically enhanced clearance and metabolism. GC elimination may also be altered by numerous concomitant medications (Table 39.2). Drug interactions may result in either reduced or enhanced clearance and consequently an increased risk for adverse effects or a diminished therapeutic response, respectively. The anticonvulsants, phenytoin, phenobarbital, and carbamazepine, and the antimicrobial, rifampin, are potent inducers of CYP3A4 and when used concurrently with systemic glucocorticoids can significantly increase the metabolism of all systemic GCs with methylprednisolone especially vulnerable to enhanced clearance. Case reports have described breakthrough symptoms

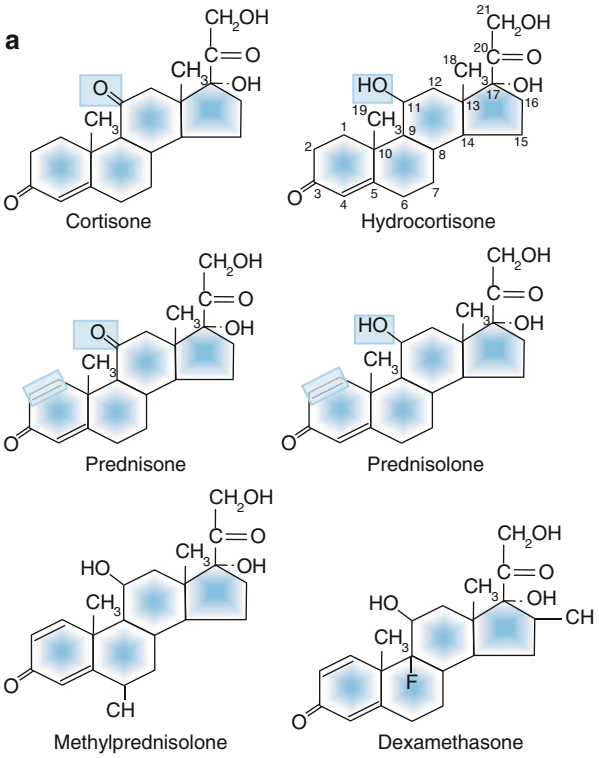

Fig. 39.1 (**a**) Molecular structures of commonly administered systemic glucocorticoids used in the treatment of asthma. Carbon and ring nomenclature is noted for cortisone. Note that cortisone and prednisone are prodrugs that require the ketone group on carbon 11 must be converted to a hydroxyl group. The addition of a double bond between carbons 1 and 2 provides greater glucocorticoid and less mineralocorticoid effects. (**b**) Molecular structures of the available inhaled glucocorticoids used in the treatment of asthma. All of the currently available inhaled glucocorticoids (beclomethasone dipropionate [*BDP*], ciclesonide [*CIC*], flunisolide [*FN*], budesonide [*BUD*], fluticasone propionate [*FP*], fluticasone furoate [*FF*], and mometasone furoate [*MF*]) have further alterations at the 17 and 21 carbon positions that result in further increases in anti-inflammatory effects and subsequent metabolism to inactive or nearly inactive metabolites. All of the inhaled GC preparations are halogenated except for budesonide and ciclesonide

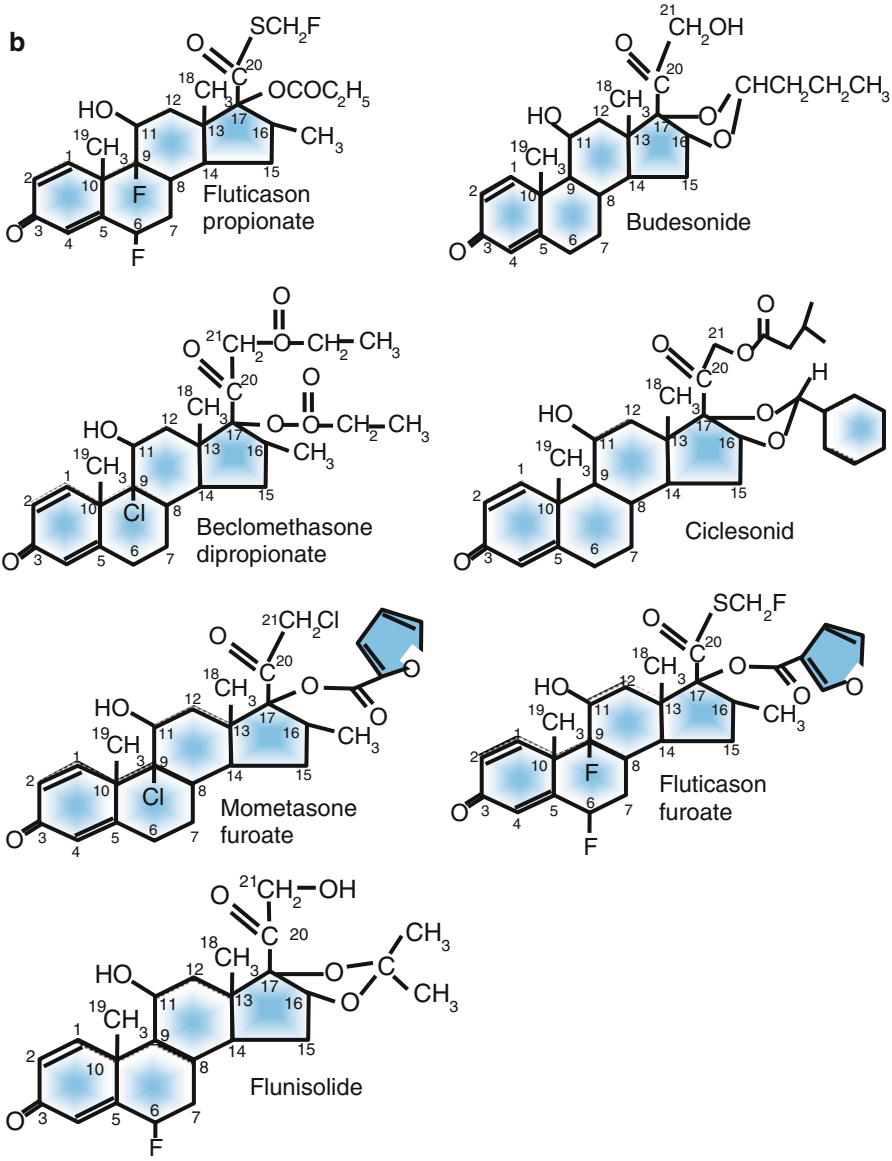

Fig. 39.1 (continued)

and worsening asthma control in steroid-dependent asthmatics that were subsequently placed on rifampin. In this scenario, one may require higher doses of prednisone or more frequently administered doses to maintain adequate asthma control.

Other medications can delay GC elimination by inhibiting CYP3A4. Significant reductions of GC clearance have been noted with concomitant ketoconazole and oral contraceptives containing estrogen. Methylprednisolone clearance can be reduced

Table 39.1 Mechanisms of glucocorticoid action in asthma

I. *Inhibitory effects*
A. Inhibition of leukocyte activation, function, and survival
1. T lymphocytes
2. Eosinophils
3. Monocyte/macrophages
B. Inhibition of leukocyte adhesion/migration
C. Inhibition of the production of cytokines important in the differentiation, proliferation, and activation of inflammatory cells
1. IL-2, IL-3, IL-4, IL-5, IL-13, GMCSF
D. Inhibition of the production and/or release of inflammatory mediators
1. Lipid mediators (platelet-activating factor, leukotrienes, prostaglandins)
2. Cytokines (IL-1, IL-6, TNFα)
3. Eosinophil-derived cytotoxic proteins (eosinophil cationic protein [ECP], major basic protein [MBP])
E. Inhibition of transcription factor function
II. *Positive effects*
A. Vasoconstrictive properties
B. Potentiation of β-adrenergic receptor
C. Stimulation of anti-inflammatory proteins
1. IκB-β
2. GILZ (GC-induced leucine zipper)
3. MKP-1 (MAP kinase phosphatase-1)
4. IL-1 receptor antagonist
III. *Effects on gene transcription by altering chromatin structure*
A. Inhibition of HAT (histone acetyltransferases)
B. Upregulation of HDAC (histone deacetylases)

Table 39.2 Potential drug interactions with systemic glucocorticoids

Glucocorticoid	Drugs which increase clearance	Drugs which decrease clearance
Methylprednisolone	Carbamazepine	Ketoconazole
	Phenobarbital	Troleandomycin
	Phenytoin	Erythromycin
		Clarithromycin
	Rifampin	Oral contraceptives
Prednisolone	Antacids (decrease absorption)	Ketoconazole
	Carbamazepine	Oral contraceptives
	Phenobarbital	
	Phenytoin	
	Rifampin	

from 50 % to 70 % by the coadministration of clarithromycin and erythromycin. If a drug interaction that increases clearance is identified, one can simply increase the GC dose. Alternatively, a "split" dosing regimen may be considered with two-third of the total daily GC dose administered in the morning and the remaining one-third

administered in the afternoon. This strategy may provide for a more normal plasma concentration vs. time curve and could result in better responsiveness. If these changes offer no benefit, a change to a GC with a longer half-life, such as dexamethasone, could be another option.

Efficacy of Oral Glucocorticoid Therapy in Asthma

Glucocorticoid Therapy for Acute Asthma in Adults

Systemic GC therapy is considered first-line therapy for the treatment of acute severe asthma. Over the past 50 years, numerous studies have demonstrated the efficacy of systemic GC therapy in the outpatient clinic, the emergency room, and hospitalized patients. Short courses of GC administered in the outpatient department have been shown to decrease the rate of asthma relapse, while intravenous methylprednisolone administered in the emergency room can decrease the need for subsequent hospitalization. In studies evaluating the effectiveness of intravenous GC therapy in hospitalized patients, GC therapy is superior to placebo with respect to multiple clinical outcomes. Despite their widespread use, the optimal dose of GC in the acute setting has not been firmly established. In one of the few studies which have attempted to determine a dose response, 40 mg of methylprednisolone was found to be as effective as 125 mg administered every 6 h in patients admitted with status asthmaticus. In contrast, a study which evaluated three doses of prednisolone (0.2, 0.4, and 0.6 mg/kg/day) for 2 weeks in asthmatics requiring a prednisolone burst due to worsening asthma symptoms found the highest dose to be the most effective. There is also no consensus regarding the duration of GC treatment for acute asthma. Since duration of treatment is in part related to the severity of the initial episode, recommendations for the length of treatment must be tailored to the individual case. With that in mind, it has recently been recommended to treat patients admitted in status asthmaticus with at least 36–48 h of IV therapy with a transition to oral GC therapy when tolerated. The duration of the oral GC taper will depend on the individual's response but should span 4–12 days. A number of protocols outlining systemic GC therapy in acute asthma have been published, but therapy should always be tailored to the individual patient's condition. The National Heart, Lung, and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma recommends either prednisolone, prednisone, or methylprednisolone 120–180 mg/day in three or four doses for 48 h and then 60–80 mg/day until predicted or personal best peak expiratory flow (PEF) for adults reaches 70 %.

Glucocorticoid Therapy for Acute Asthma in Children

Systemic GC therapy has also been shown to improve multiple outcomes in children with acute asthma. Studies performed over the past several decades have shown improvements in PEFR, FEV_1, and PaO_2 and reductions in the rate of asthma relapse. In addition, studies evaluating a single dose of GC, administered either parenterally or

orally, in the emergency department setting have demonstrated reductions in subsequent hospitalization. Lastly, studies comparing the effectiveness of oral prednisone to intravenous (IV) methylprednisolone in the treatment of acute asthma have shown both modalities to be equally effective. Liquid formulations of prednisone (Prelone®, Pediapred®, Orapred®) can be administered to infants and young children who cannot swallow pills. Liquid preparations are more completely and more rapidly absorbed with peak serum levels occurring within 1 h compared to 2 h with tablets.

A classic study published over two decades ago found that early oral GC use during an acute asthma exacerbation significantly reduces the progression of asthma symptoms. In this placebo-controlled study of children presenting to the clinic with acute asthma, all patients who received prednisone improved, with only one relapse noted following discontinuation of therapy. In contrast, 42 % of the placebo-treated patients developed worsening asthma symptoms requiring rescue intervention. As continued asthma symptoms often lead to emergency care and/or hospitalization, this study was the basis for the recommendation of early institution of prednisone during acute exacerbations.

Issues such as the optimal dose, duration of treatment, and route of administration remain largely empirical and depend largely on the severity of the acute exacerbation. A recent study in children with acute asthma found no difference in efficacy when prednisolone was administered in doses of 0.5, 1, or 2 mg/kg/day. As mentioned previously, oral GCs can be used in many cases, although hospitalized children requiring high flow rates of oxygen to adequately treat hypoxemia are obvious candidates for intravenous GC therapy. In this situation, methylprednisolone sodium succinate (Solu-Medrol®) 1–2 mg/kg as a loading dose followed by 0.5–1 mg/kg every 6 h is recommended. Once oral medications are tolerated, a switch to oral prednisone can be made at a dose of 2 mg/kg/day (maximum dose 60 mg/day) in two divided doses for an additional 2–4 days followed by a taper to 1 mg/kg/day administered in a single morning dose for an additional 2–4 days prior to stopping. For outpatient management of acute exacerbations, a short course of prednisone is administered with a starting dose of 2 mg/kg/day (maximum dose 60 mg/day) in two divided doses for 2–3 days followed by a reduction to 1 mg/kg in a single morning dose for an additional 2–3 days. The NHLBI guidelines recommend administering either prednisone, prednisolone, or methylprednisolone, 1 mg/kg/dose every 6 h for 48 h and then 1–2 mg/kg/day (maximum dose 60 mg/day) in two divided doses until predicted or personal best PEF is 70 %. Whether oral GC therapy is effective in the treatment of preschool-aged children with viral-induced wheezing is controversial and is discussed further in the "Evidence-Based Medicine" section at the conclusion of the chapter.

Chronic Oral Glucocorticoid Therapy in the Management of Severe Persistent Asthma

With the advent of combination second-generation inhaled GC/long-acting beta-agonist (LABA) therapy, the number of patients who require chronically administered oral steroid therapy has declined substantially, especially in children with severe asthma. Unfortunately, a small number of patients continue to require

regular oral GC use despite optimal therapy with combination high-dose inhaled GC/LABA therapy to maintain adequate asthma control. Studies performed three decades ago found that the therapeutic effects of steroids persisted longer than their metabolic effects. Consequently, investigators began to evaluate several dosage schedules and found that AM dosing of prednisone on alternate days resulted in the greatest improvement in asthma control while minimizing its adverse effects. Thus, the goal is to taper their oral GC dosing to alternate-day therapy, if at all possible.

Adverse Effects of Chronically Administered Systemic Glucocorticoids

As all nucleated cells in the body have a common GC receptor, all are potentially affected and thus susceptible to adverse effects. These effects can occur immediately (i.e., metabolic effects) or can develop insidiously over several months to years (i.e., osteoporosis and cataracts). In addition, some adverse effects are limited to children (growth suppression), while others appear to require interaction with other drugs (nonsteroidal anti-inflammatory agents and peptic ulcer disease). Most adverse effects occur in both a dose-dependent and duration of treatment manner. Table 39.3 lists many of the common adverse effects associated with chronic GC use.

Osteoporosis

Osteoporosis, a significant and common adverse effect, is often overlooked secondary to its insidious onset. All patients who require high-dose inhaled GC therapy or patients who have received >7.5 mg prednisone (or equivalent) daily for at least 6 months are at risk for developing osteoporosis. Risk factors for steroid-induced osteoporosis include inactivity, sex hormone deficiency, a diet deficient in calcium, and concurrent use of drugs such as furosemide, anticonvulsants, and excessive thyroid hormone replacement. Because demineralization of bone is not detectable on conventional radiographs until a significant degree of bone mineral density is lost, the diagnosis of osteoporosis is best made using bone mineral densitometry.

Treatment of osteoporosis consists of attempting to decrease either the inhaled or the oral GC dose, increasing calcium intake to 1000–1500 mg of elemental calcium per day supplemented with at least 400 IU/day of vitamin D and increasing weight-bearing physical activities such as walking. Activities such as heavy lifting, high-impact aerobics, and contact sports are not recommended as these activities can result in compression fractures of the vertebral bodies in addition to fractures of the long bones. Patients with severe osteoporosis may require treatment with a remittive medication (e.g., bisphosphonate therapy) and a referral to an endocrinologist.

Table 39.3 Adverse effects associated with systemic glucocorticoid use

1. Dermatologic effects:
Dermal thinning/increased skin fragility
Acne
Striae
Hirsutism
2. Endocrinologic effects:
Adrenal suppression
Growth suppression
Delayed sexual maturation in children
Weight gain
Cushingoid habitus
Diabetes mellitus
3. Musculoskeletal effects:
Osteoporosis/vertebral compression fractures
Aseptic necrosis of bone (hips, shoulders, knees)
Myopathy (acute and chronic forms)
4. Metabolic effects:
Hypokalemia
Hyperglycemia
Hyperlipidemia
5. Ophthalmologic effects:
Cataracts (posterior subcapsular)
Glaucoma
6. Immunologic effects:
Diminished immunoglobulin G (IgG) levels
Loss of delayed-type hypersensitivity (DTH)
Potential for increased risk of opportunistic infection/severe varicella infection
7. Psychological/neurologic effects:
Mood swings, depression, psychosis
Steroid withdrawal syndrome
Pseudotumor cerebri
8. Hematologic effects:
Lymphopenia
Eosinopenia
Neutrophilia
9. Cardiovascular effects:
Hypertension
Atherosclerosis

Myopathy

Two distinct types of myopathy can occur with systemic GC therapy. An acute, severe myopathy can occur in patients hospitalized with severe asthma exacerbations. These patients have often required intubation/mechanical ventilation and have received paralytic agents in addition to high-dose parenteral GC therapy. They

will have markedly elevated serum creatine phosphokinase (CPK) levels and diffuse necrosis of skeletal muscle on biopsy. Recovery begins after GC withdrawal but more than 6 months may be required for complete recovery. The more commonly encountered form is the insidious development of proximal muscle atrophy in patients receiving chronically administered GCs. Isokinetic muscle testing (Cybex®) of hip flexor strength appears to be the most sensitive and objective measure of proximal muscle weakness. Enzymes of muscle origin such as CPK, aldolase, and lactate dehydrogenase (LDH) are not typically elevated, and biopsy of affected muscle reveals atrophy, rather than necrosis.

Cataracts

Posterior subcapsular cataracts (PSCs) are a well-described complication of chronic GC use with a prevalence rate of up to 29 %. GC-induced cataracts are often small but can significantly affect visual acuity and require surgical intervention. Although the development of cataracts appears to be related to the cumulative dose and the duration of treatment, there is a significant degree of variability with respect to individual susceptibility to cataract formation. It is unknown whether GC dose reduction or discontinuation will result in regression or disappearance of the cataract, although some studies suggest that if recognized early, regression can occur. A yearly ophthalmologic exam to evaluate for the presence of cataracts and glaucoma is recommended for all patients receiving high-dose inhaled GC therapy, patients who require frequent courses of oral GCs, and patients requiring chronically administered oral GC therapy.

Growth Suppression

Growth suppression continues to be the GC-associated adverse effect that causes the most concern among parents of patients who require oral or inhaled GC therapy. Regular daily therapy, frequent short courses, or high-dose alternate-day GC therapy can cause suppression of linear growth. Doses of prednisone as small as 0.1 mg/kg administered daily for as short a period as 3 months have resulted in significant suppression of linear growth. When GCs are administered on alternate days, the degree of suppression may be less, but significant growth suppression can still occur. Complicating the issue of GC-induced growth suppression is the finding that poorly controlled asthma can also impair growth. This is a significant issue especially as it pertains to whether chronic inhaled GC therapy is associated with growth suppression (see below). As daily or high-dose alternate-day GC therapy for extended periods of time can result in permanent growth retardation, every effort should be made to decrease the amount of oral GC to less than 20 mg on alternate days. If the child's oral GC dose cannot be tapered to $\leq$20 mg on alternate days, treatment with recombinant growth hormone can be considered. Growth hormone therapy can increase linear growth in children on chronic GC therapy, but the response is dependent on the dose of GC administered; the higher the daily dose of prednisone, the less effective GH therapy is.

Adrenal Insufficiency

Patients who are adrenally suppressed as a consequence of oral chronic GC therapy are at risk of developing acute adrenal insufficiency at times of stress such as surgical procedures, gastroenteritis resulting in dehydration, or trauma. Patients who develop acute adrenal insufficiency can present with dehydration, shock, electrolyte abnormalities, severe abdominal pain, and lethargy out of proportion to the severity of the presenting illness. This is a medical emergency requiring prompt diagnosis and rapid treatment with intravenous hydrocortisone (2 mg/kg initially followed by 1.5 mg/kg every 6 h until stabilization is achieved and oral therapy is tolerated) and vigorous fluid replacement if dehydration and hypotension are present. All patients on chronic oral GC therapy should be considered adrenally suppressed and should wear a medical alert bracelet, which identifies them as being at risk for acute adrenal insufficiency. All adrenally suppressed individuals should be given hydrocortisone at the time of any surgical procedure (1–2 mg/kg) and every 6 h thereafter for the next 24–48 h with a switch to their usual oral GC dose when oral medications are tolerated. The same recommendations are to be followed at other times of acute stress. Complete recovery from adrenal suppression can take from 6 months to 1 year after cessation of long-term GC use. Thus, all patients with a history of chronic GC use should be considered adrenally suppressed and should be managed as such for up to 1 year following cessation or significant reduction of oral GC therapy.

Other Adverse Effects

Other common adverse effects of chronic oral GC therapy include increased appetite with weight gain and the development of a Cushingoid habitus consisting of moon facies, buffalo hump, central obesity with wasting of the extremities, atrophy of the skin with the development of striae, and hirsutism. Psychological disturbances from increased emotional lability to frank psychosis can occur, as well as hypertension, peptic ulcer disease, atherosclerosis, aseptic necrosis of bone, and diabetes mellitus. Chronic GC use can also result in immunologic attenuation with loss of delayed-type hypersensitivity, diminished IgG levels without change in functional antibody response, potential for reactivation of latent tuberculosis infection, and possible increased risk for infection especially the development of severe varicella in patients who have not been vaccinated.

Inhaled Glucocorticoid Therapy

The first inhaled GC was approved in the mid-1970s. It took several modifications to the basic structure of hydrocortisone to make a GC that was potent enough to suppress airway inflammation when delivered in microgram quantities. The addition of one or more halogens (fluorine or chlorine) to the structure and/or modifications to carbon 17 and/or carbon 21 have resulted in GCs with increasing potency

and less potential for adverse effects (Fig. 39.1b). By effectively delivering small quantities of a potent GC directly into the airways, inhaled GC therapy maximizes the beneficial effects while minimizing the systemic effects of GCs. In other words, inhaled GCs have a superior therapeutic index compared to oral GCs. Although inhaled GCs had been available for decades, their use, especially in pediatric patients, had been limited to those patients with severe asthma. As our understanding of asthma changed, with the demonstration of airway inflammation even in mild asthma, and with long-term studies demonstrating both the safety and effectiveness of inhaled GCs in children with mild asthma, inhaled GCs have become first-line therapy in all patients with persistent asthma.

Efficacy of Inhaled Glucocorticoid Therapy

Bronchial hyperreactivity (BHR) is an essential component of asthma that describes the enhanced twitchiness of the airway. Medications that can attenuate the level of BHR have proven to be the most effective in the treatment of persistent asthma. To this day, no other class of asthma controller medications has been shown to be as effective as inhaled GCs with respect to influencing BHR. Reductions in BHR from two- to sevenfold have been reported within 6 weeks of instituting inhaled GC therapy. Associated with improvements in BHR come reductions in asthma symptoms, the need for short-acting beta-agonist use, and improved baseline pulmonary function, in addition to reductions in acute exacerbations. Studies evaluating the effect of inhaled GC therapy on airway inflammation have consistently demonstrated significant reductions in airway eosinophils and T helper type 2 lymphocytes (TH2 cells). In addition, a few studies have demonstrated a positive effect on airway remodeling with decreased angiogenesis and modest reductions in the thickness of the basement membrane following inhaled GC therapy. In summary, inhaled GC therapy results in improvement in lung function, reductions in BHR and asthma symptoms, and need for supplemental β-agonist use, in addition to suppression of airway inflammation and possibly effects on airway remodeling.

Several studies have also demonstrated inhaled GCs to reduce asthma morbidity and mortality. Patients on inhaled GC therapy are less prone to require prednisone and have fewer ER visits and hospitalizations with reductions of up to 50%. In patients with severe and/or poorly controlled asthma, the reduction in hospitalizations can approach 70%. An important epidemiologic study from Canada found inhaled GCs, in a dose-dependent manner, to significantly reduce the risk of death from asthma. Specifically, low-dose beclomethasone dipropionate (200 mcg/day) therapy reduced the risk of a fatal asthma attack by 50% compared to age- and severity-matched asthmatics not on regular inhaled GC therapy. No other class of asthma medication has shown as great an effect on reducing asthma morbidity and mortality as inhaled GCs.

Inhaled Glucocorticoids as First-Line Therapy

Inhaled GCs are now recommended as the preferred controller agent in all patients with persistent asthma including children. This recommendation was made in the 2002 update to the NHLBI guidelines and was based on a comprehensive review of both the efficacy and safety of long-term inhaled GC use in both adults and children with asthma. This review found inhaled GCs not only to be the most extensively studied but also the most effective class of controller medications. Lastly, two large studies that evaluated the safety and effectiveness of over 1000 children with mild to moderate asthma followed for at least 5 years were published in 2000. Both studies demonstrated that long-term inhaled GC therapy was safe and effective.

Further support of using inhaled GCs earlier in the course of the disease comes from studies that found inhaled GC therapy to be the most effective when begun soon after the onset of the disease. These studies found inhaled GC therapy to be effective in decreasing asthma symptoms, supplemental β-agonist use, and improving pulmonary function with the largest improvements noted in new-onset asthmatics who had been diagnosed within 2 years.

Available Inhaled Glucocorticoids

There are currently seven inhaled GCs available for use in the United States (see Fig. 39.1b). Some are administered by metered-dose inhalers (MDIs) using hydrofluoroalkane (HFA) as their propellant, while others utilize dry powder inhalers (DPIs). Beclomethasone dipropionate (BDP) is marketed as Qvar® and is available in two strengths, 40 and 80 μg per actuation; flunisolide (FLN) is now marketed as Aerospan® and delivers 80 μg per actuation; fluticasone propionate (FP) marketed as Flovent is available in two delivery devices: a DPI called the Diskus and an MDI. Each delivery device comes in three doses: 44, 110, and 220 μg/actuation for the MDI and 50, 100, and 250 μg/actuation for the DPI. Budesonide (BUD) is marketed as Pulmicort® and comes in a DPI called the Flexhaler (90, 180 μg/actuation) and as a suspension for nebulization (Respules) and is available in three doses: 0.25, 0.5, and 1.0 mg. Budesonide is the only GC available for use by nebulization. Mometasone furoate (MF) marketed as Asmanex® comes in a DPI called the Twisthaler (110, 220 μg/actuation) and an MDI (100, 200 μg/actuation). Ciclesonide (CIC) marketed as Alvesco® is available in an MDI with two doses: 80 and 160 μg/actuation. Lastly, fluticasone furoate (FF) is the latest inhaled GC available for use in asthma. It is marketed as Arnuity® and is delivered via a DPI called the Ellipta in two doses (100, 200 μg/actuation). The recommended dosages for both adults and children for all of the inhaled GCs are listed in Table 39.4.

Table 39.4 Dosage guidelines for inhaled glucocorticoids

Glucocorticoid	Low daily dose	Medium daily dose	High daily dose
A. *Adults*			
Beclomethasone (Qvar®)	80–240 mcg	240–480 mcg	>480
MDI: 40 or 80 mcg			
Budesonide (Pulmicort Flexhaler®)	200–400 mcg	400–600 mcg	>600 mcg
DPI: 90, 180 mcg			
Ciclesonide (Alvesco®)	160–320 mcg	160–640 mcg	640 mcg
MDI: 80, 160 mcg			
Flunisolide (Aerospan®)	160 mcg	160–320 mcg	320 mcg
MDI: 80 mcg/puff			
Fluticasone propionate (Flovent®, Flovent Diskus®)	88–264 mcg	264–660 mcg	>660 mcg
	100–250 mcg	250–500 mcg	750 mcg
MDI: 44, 110, 220 mcg			
DPI: 50, 100, 250 mcg			
Fluticasone furoate (Arnuity Ellipta®)	100 mcg	100–200 mcg	200 mcg
DPI: 100, 200 mcg			
Mometasone furoate (Asmanex HFA®, Twisthaler®)	220 mcg	220–440 mcg	440–880 mcg
DPI: 110, 220 mcg			
MDI: 100, 200			
B. *Children*			
Beclomethasone (Qvar®)	80–160 mcg	160–320 mcg	>320 mcg
MDI: 40 or 80 mcg (approved for children ≥5 years old)			
Budesonide (Pulmicort Flexhaler®)	200 mcg	200–400 mcg	>400 mcg
DPI: 90, 180 mcg (approved for children ≥6 years old)			
Budesonide suspension for nebulization (Pulmicort Respules®)	0.5 mg	1.0 mg	2.0 mg
0.25 mg, 0.5 mg, 1 mg (approved for children 1–8 years old)			
Ciclesonide (Alvesco®)	80 mcg	80–160 mcg	160 mcg
MDI: 80, 160 mcg (approved for children ≥12 years old)			
Flunisolide (Aerospan®)	80 mcg	80–160 mcg	160 mcg
MDI: 80 mcg/puff (approved for children ≥6 years old)			
Fluticasone propionate (Flovent®, Flovent Diskus®)	88–176 mcg	176–440 mcg	>440 mcg
	100–200 mcg	200–500 mcg	>500 mcg
MDI: 44, 110, 220 mcg			
DPI: 50, 100, 250 mcg (44 and 50 mcg approved for children ≥4 years old)			
Fluticasone furoate (Arnuity Ellipta®)	100 mcg	100–200 mcg	200 mcg
DPI: 100, 200 mcg (approved for children ≥12 years old)			

Table 39.4 (continued)

Glucocorticoid	Low daily dose	Medium daily dose	High daily dose
Mometasone furoate (Asmanex®, Asmanex Twisthaler®)	110 mcg	110 mcg	110 mcg
MDI: 100, 200 mcg	100 mcg	(100 mcg	100 mcg
DPI: 110, 220 mcg (approved for children ≥4 years old)			

Pharmacokinetics and Pharmacodynamics of Inhaled Glucocorticoids

BUD, FP, MF, and FF are often called "second"-generation inhaled GCs in that they have greater topical-to-systemic potencies than the older inhaled GCs including triamcinolone acetonide, flunisolide, and beclomethasone dipropionate. CIC is unique in that it has been dubbed a 2.5 generation inhaled GC because in addition to it being a potent GC, it is thought to have the least potential for adverse effects. In theory, it has the best topical-to-systemic ratio of all the available inhaled GCs, although this has not been conclusively confirmed in comparative clinical research studies.

BDP and CIC are prodrugs that are converted to BMP and des-CIC by esterases in the lung tissue. Oropharyngeal adverse effects are less common with these two drugs as they are not activated until they reach the airway epithelium. CIC and BUD are unique among the inhaled GCs in that they become conjugated to fatty acids within the airway tissue. For lipid conjugation to occur, there must be no steric hindrance of the hydroxyl group at carbon 21. Fatty acid conjugation of the GC renders it more lipophilic which allows it to remain in the lung tissue for a greater period of time than the native inhaled GC. In addition, these fatty acid conjugates serve as a depot for the active drug. This has important implications as inhaled GCs with the longest lung retention times not only have a greater ability to suppress airway inflammation but also minimize the absorption of the drug from the lung to the systemic circulation. As a result, they have less bioavailability and less potential for adverse effects. In addition BUD, FP, and MF have all been shown to have oral GC-sparing effects in adults with steroid-dependent asthma. Few studies have attempted to compare the clinical efficacy of the available inhaled GCs. FP and MF are thought to be roughly twice as potent as the other available inhaled GCs. Because a greater percentage of BDP is delivered to the lung due to its smaller particle size, than FP, it is considered to be as equally effective as FP on a microgram per microgram basis. High-dose FP therapy (≥1000 μg/day) has been shown to result in two to four times greater suppression of adrenal function than equivalent doses of BUD. Thus, FP may have a greater potential for systemic effects at high doses compared to the other inhaled GCs.

Qvar® and Alvesco® are unique, in that both drugs dissolve in the ozone-friendly propellant, HFA, as opposed to CFC. Dissolved drugs result in finer particle sizes compared to drugs that remain in a suspension with HFA such as FP, MF,

and BUD. Particle sizes of a mean diameter size of 1.1 μm are seen with BDP and CIC compared to particle sizes of 3.5–4.0 μm for most other inhaled GCs. The smaller particle size results in enhanced lung deposition and greater drug delivery to the distal portions of the lung. As a result, lower doses of BDP provide superior efficacy compared to BDP delivered using the traditional CFC propellants.

Dose/Frequency of Use

Asmanex® and Arnuity® are recommended as once-daily inhaled GCs. Pulmicort® can also be used once daily, once a patient's asthma is controlled. The remaining products recommend twice-daily administration. With respect to dosage, the more severe or poorly controlled the asthma, the higher the initial dose (see Table 39.4 for recommended doses). High-dose inhaled GC therapy is often used in an attempt to rapidly optimize pulmonary function and clinical symptoms. Once asthma control is optimized, the dose is tapered following clinical symptoms and pulmonary function closely. Whether starting with high-dose inhaled GC results in more rapid or greater initial improvement in asthma control remains debatable. At least two studies have shown low-dose therapy to be as effective as high-dose therapy as initial treatment. In any case, the ideal inhaled steroid dose should be large enough to control asthma symptoms, yet small enough to avoid the potential for adverse systemic effects.

Adverse Effects of Inhaled GC Therapy

Adrenal Suppression

Inhaled GC therapy can result in suppression of the hypothalamic-pituitary-adrenal (HPA) axis with the degree of suppression dependent on the dose of the inhaled GC delivered and the duration of treatment. The preponderance of data would suggest doses of ≤400 μg/day of budesonide (or equivalent) are not associated with changes in the HPA axis, but as the inhaled dose is increased to above 1000 μg/day, significant suppression of the HPA axis can occur. Although FP is thought to have comparable systemic effects to the other inhaled GCs at doses recommended for the treatment of mild and moderate asthma (176–440 μg/day), the same cannot be said regarding high-dose FP therapy (≥1000 μg/day). A number of studies have demonstrated significantly greater HPA axis suppression with FP compared to equivalent doses of BUD. In addition, there have been a few case reports of children who developed acute adrenal insufficiency while on high-dose FP therapy (≥1000 mcg/day). Because FP is twice as potent as many of the other inhaled GCs, one should only use high-dose FP in patients with severe, poorly controlled asthma or in patients with steroid-dependent asthma in an attempt to lessen their oral GC requirement.

Growth Suppression

Growth suppression is the steroid-associated adverse effect that causes the most concern for parents and clinicians who care for children. In the late 1990s, several studies suggested that BDP, in doses as little as 400 μg/day, could result in suppression of linear growth. Unfortunately, these studies were limited by the short duration of the study (1 year or less). In addition, the pubertal status of the children was not always ascertained, baseline growth velocity data was lacking, or there were significant differences in baseline height and/or age between the different treatment groups at entry into the study. Complicating this issue further was the long-known, but often overlooked, observation that asthma, especially poorly controlled asthma, could adversely affect growth.

Two long-term studies published in 2000 helped to clarify the effect of inhaled GCs on growth. The Childhood Asthma Management Program (CAMP) study enrolled over 1000 children to receive BUD, nedocromil, or placebo for 5 years. The children who had received BUD (200 mcg twice daily) were 1.1 cm shorter than those who received placebo or nedocromil at the end of the study. Of significance, the loss of growth velocity occurred primarily in the first year of therapy, and using the Tanner equation to calculate anticipated adult height, the adult was calculated to be 174.8 cm for both the BUD- and placebo-treated groups.

This point strengthened by a longitudinal study of 211 asthmatic children who had regular assessment of linear growth to adulthood. One hundred forty-two children who had been treated with a mean daily dose of 412 mcg of BUD for a mean of 9.2 years were compared to 18 asthmatics not treated with inhaled GCs and 52 healthy controls. The investigators found no difference in the measured vs. the expected adult heights in any of the groups studied. In addition, no correlations were found between duration of treatment and cumulative dose of BUD. Of interest, they too noted a transient suppression of growth during the first few years of therapy, but it did not adversely impact adult attained height.

Children from the CAMP study had their heights measured serially over the next decade so that all participants had reached their adult heights. Children who had received long-term BUD therapy were 1 cm shorter than the children who had received placebo, suggesting that the 1 cm loss of growth that occurred early after starting inhaled steroid therapy was never made up during adolescence as was originally hypothesized. Thus, a child placed on long-term inhaled GC therapy is likely to be 1 cm shorter than expected as an adult. As 1 cm is just over a third of an inch, this adverse effect on growth has little clinical meaning.

Osteoporosis

Osteoporosis can be a debilitating complication of oral GC therapy, but whether inhaled GC therapy can cause osteopenia or osteoporosis over time is less clear. Some studies have found significant reductions in BMD of the femoral neck of asthmatics treated with inhaled GCs compared to age-matched controls, with significant inverse correlations found between bone mineral density and the dose

duration (product of the average daily dose of inhaled GC in grams and the duration of therapy in months). In contrast, other studies have failed to demonstrate any deleterious effect on bone mineral density.

Given the discrepancy in results among the above studies, Toogood et al. sought to differentiate between the effect of inhaled GCs compared to the effect of other important variables including past or current oral GC use, age, physical activity level, and postmenopausal state. The investigators found inhaled GC therapy to result in a dose-dependent reduction of BMD with a decrease of approximately 0.5 standard deviations for each increment of inhaled GC dose of 1000 mcg/day, yet a larger lifetime exposure to inhaled GCs was associated with a greater BMD. The authors speculated that this "protective effect" was due to reconstitution of BMD following conversion from oral to inhaled GC therapy.

The CAMP study remains the largest study to evaluate the effect of inhaled GCs on BMD in children with asthma. Yearly BMD determinations were performed on all children, and at no point during the study did the BMD differ between budesonide- (400 mcg/day) and placebo-treated children. In addition, there was no difference in the bone age among the three groups studied at the conclusion of the 5-year study. The CAMP study strongly suggested that long-term low-dose inhaled GC therapy has no adverse effect on bone growth or BMD in children with mild to moderate asthma.

Cataracts/Glaucoma

Epidemiologic studies have found weak, but statistically significant, associations between inhaled GC therapy and either cataracts or glaucoma. Limitations of the studies include the population studied (mean age of 65 years) and failure of the studies to provide any indication of clinical significance or visual impairment. Agertoft and Pedersen performed slit lamp evaluations on 157 asthmatic children on BUD an average of 4.5 years and on 111 age-matched, asthmatic controls. One child on BUD was found to have a posterior subcapsular cataract, but this was a known cataract with the diagnosis made 2 years before the child began BUD therapy. Upon completion of the CAMP study, all children underwent eye exams for cataracts with one possible cataract identified. Thus, long-term treatment with low- to mid-dose inhaled GCs in children which are unlikely to cause cataracts and ophthalmologic surveillance is probably not warranted.

Other Adverse Effects

There have been a number of other adverse effects associated with inhaled GC therapy including hypoglycemia, the development of Cushingoid features, opportunistic infections, dermal thinning, and psychosis. Most of these adverse effects have been reported as case reports, with few controlled studies performed to objectively evaluate the potential for and significance of these complications.

Intranasal Glucocorticoids for the Treatment of Allergic Rhinitis

Anti-inflammatory Effects

Intranasal GCs are first-line therapy for patients with moderate to severe seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Allergic inflammation plays a prominent role in the pathogenesis of allergic rhinitis with activation of T_{H2} cells and subsequent influx of eosinophils into the nasal mucosa following inhalation of allergen. No other therapy is as effective as GC therapy in terms of reducing nasal inflammation. Nasal GCs have been shown to inhibit the influx and activation of inflammatory cells, inhibit the expression of pro-inflammatory cytokines, and inhibit the production of nasal nitric oxide and can attenuate the production of allergen-specific IgE. In addition, nasal GCs, when chronically administered, can block the development of both the immediate- and late-phase allergic responses.

Clinical Efficacy

There are presently five nasal GC products available including beclomethasone dipropionate (Qnasl®), triamcinolone (Nasacort®), budesonide (Rhinocort®), fluticasone propionate (Flonase®), fluticasone furoate (Veramyst®), mometasone furoate (Nasonex®), and ciclesonide (Omnaris®). All of the products are available in aqueous suspensions except Qnasl® which is available in an MDI. Multiple studies over the past couple of decades have demonstrated this class of medications to result in reduced nasal secretions, sneezing, and decreased nasal congestion. For this reason they are the most effective therapy for patients with allergic rhinitis. As noted with oral and inhaled GC therapy for the treatment of asthma, clear dose-response relationships are difficult to demonstrate with intranasal GC therapy. Low-dose (32 mcg/day) aqueous budesonide therapy has been shown to be as effective as a dose eightfold larger (256 mcg/day) in reducing nasal blockage, runny nose, and sneezing while significantly improving the quality of life in patients with PAR. These findings suggest that the lowest dose studied was already at the plateau of the dose-response curve. Studies evaluating the onset of effect of intranasal glucocorticoids in PAR found improvements in runny nose and nasal congestion within 36–60 h. Nasal GCs have also been shown to be effective in patients with SAR. Intranasal glucocorticoids have been compared to oral and intranasal antihistamines and have been shown to result in a greater reduction in nasal symptom scores in addition to significant reductions in nasal inflammation (Fig. 39.2).

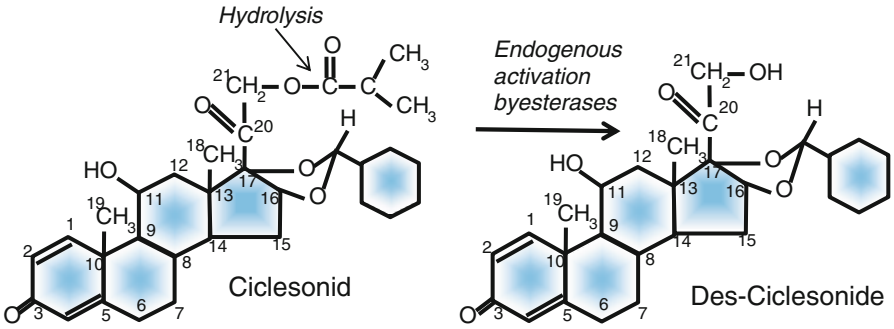

Fig. 39.2 Bio-activation of ciclesonide. The *arrow* indicates the ester bond that is hydrolyzed by cellular esterases to concert the parent compound, ciclesonide, into the active metabolite, desisobutyryl-ciclesonide (des-CIC)

Adverse Effects of Nasal Glucocorticoid Therapy

Local Effects

Reported adverse effects of nasal GC therapy from controlled clinical trials in seasonal and perennial rhinitis include headache, nasal dryness, nasal irritation or burning sensation, epistaxis, nausea/vomiting, cough, asthma symptoms, viral infection, upper respiratory infection, pharyngitis, otitis, sinusitis, conjunctivitis, tinnitus, dyspepsia, and, rarely, septal perforation. Constitutional complaints such as abdominal pain, diarrhea, fever, aches and pains, dysmenorrhea, dizziness, flu-like symptoms, and bronchitis have also been reported. Whether intranasal GC results in atrophy of the nasal epithelium has been evaluated in patients with perennial allergic rhinitis compared to healthy control subjects before and after long-term mometasone therapy. No significant changes in the nasal mucosa were noted the in pre- and posttreatment specimens in both normal subjects and subjects with perennial rhinitis. In addition, complete resolution of inflammatory changes was seen in about a third of the mometasone-treated patients.

Adrenal Suppression

Although the potential for systemic absorption through the nasal route is far less than that via the systemic route, recent studies indicate that intranasal GC can have effects on HPA axis and growth. Wilson et al. evaluated the systemic HPA axis activity of triamcinolone acetonide (220 mcg/day), beclomethasone dipropionate (336 mcg/day), and fluticasone propionate (200 mcg/day), using overnight urinary cortisol excretion and low-dose ACTH stimulation test in a single-blind, randomized, four-way, crossover, placebo-controlled study of 16 healthy subjects. Suppression of overnight urinary cortisol was found with fluticasone (43 %), triamcinolone (23 %), and beclomethasone (21 %), although, compared to placebo, the only statistically significant difference was seen with fluticasone. In addition, no

significant differences between placebo and the three active drugs were seen with regard to suppression of morning serum cortisol and ACTH-stimulated response.

The same group of investigators using a single-blind, randomized, four-way, crossover, placebo-controlled design separated by a 7-day washout period compared the systemic activity of triamcinolone acetonide (220 mcg/day), budesonide (200 mcg/day), and mometasone (200 mcg/day) given for 5 days in patients with allergic rhinitis. No significant difference between the placebo and any of the active treatments was found for fractionated or 24 h plasma cortisol levels, fractionated and 24 h uncorrected urinary-free cortisol or cortisol/creatinine levels, osteocalcin levels, and blood eosinophil count. These findings are suggestive of the lack of significant bioactivity in markers of adrenal function, bone metabolism, and blood eosinophils from currently available nasal GC at the specified doses.

Growth Suppression

Few studies have investigated the long-term effects of nasal GC therapy on linear growth in children. In a double-blind, randomized, parallel group study by Skoner et al., prepubertal children with perennial allergic rhinitis aged 6–9 years were treated for 1 year with either aqueous beclomethasone dipropionate 168 mcg twice daily or placebo. The growth velocity in the beclomethasone-treated group (0.013 cm/day) was significantly slower than the placebo-treated children (0.017 cm/day, $p<0.01$). After 1 year, the change in standing height was 5.0 cm for the beclomethasone-treated patients and 5.9 cm for the placebo-treated patients ($p<0.01$), with significant differences in mean height change between the two groups detected as early as 1 month into the study that persisted throughout the study. There were no significant differences between treatment groups in baseline morning plasma cortisol or response to 0.25 mg cosyntropin stimulation at baseline, 6 months, and 12 months into the study.

In contrast, a study that evaluated the linear growth of children who received intranasal mometasone furoate (100 mcg once daily) vs. placebo showed no differences in heights at all time points for both mometasone- and placebo-treated groups. In addition, at weeks 8 and 52, the mean increase in height from baseline in the nasal GC-treated group was actually higher than the placebo group (at week 52, 6.95 vs. 6.35 cm, $p=0.02$). However, no significant difference in the rate of growth was found between the two treatment groups (mean growth 0.018 cm/day for both groups). As in the case of oral-inhaled GC, whether short-term effects of nasal GC therapy on growth suppression reflect long-term changes and ultimately final adult height is not yet determined.

Summary

GCs are an important pharmacologic modality in the treatment of the two most common allergic diseases – asthma and allergic rhinitis. Systemically administered GCs are first-line agents for acute severe asthma, while inhaled GCs are first-line agents

for the long-term management of all patients with persistent asthma. In addition, intranasal GCs are first-line agents for the treatment of moderate to severe SAR and PAR. It is a well-established fact that long-term systemic GC therapy can result in serious adverse effects. Fortunately, topically applied GC preparations have been developed which greatly minimize the systemic adverse effects while achieving beneficial airway effects. Many previously steroid-dependent asthmatics have been tapered off oral GC following institution of inhaled GC therapy. As with oral GC therapy, high-dose inhaled GC therapy can result in systemic adverse effects. Of importance, studies have shown low-dose inhaled GC therapy, even when administered long term, is unlikely to result in any clinically meaningful adverse effects. By using the lowest possible effective GC doses, as well as maximizing other therapeutic modalities, adverse systemic effects from GCs can be greatly minimized.

Evidence-Based Medicine

Despite many advances in our understanding of the pathogenesis and treatment of asthma in both adults and children, many questions regarding how to best treat preschool-aged children with recurrent wheeze remain. Complicating the issue is the observation that approximately two-thirds of preschool children with recurrent wheeze will "outgrow" their wheezing illness by grade school. Those who continue to wheeze and who will eventually be diagnosed with asthma by grade school are likely to be atopic. A number of studies have demonstrated the effectiveness of chronic inhaled steroid therapy in preschool-aged children, but in nearly every study, the populations studied were atopic children at greatest risk for subsequent asthma. In fact, one of the predictors of inhaled GC response in a post hoc analysis of the Prevention of Early Asthma in Kids (PEAK) study, where approximately 300 2–3-year-old children received low-dose FP vs. placebo over a 2-year period, was aeroallergen sensitivity. Atopic preschool children treated with FP with fluticasone were less likely to require oral GCs, have fewer ED visits, and were less likely to require supplementary controller medications. As this group constitutes a minority (one-third) of all children who wheeze early in life, it remains to be determined if inhaled steroid therapy is as effective in nonatopic preschool-aged children with recurrent wheeze. This same issue holds true regarding whether there is a differential response to oral glucocorticoid therapy during acute episodes. As discussed below, a couple of recently published studies attempted to address this issue. Unfortunately, flaws in their study design prevent us from knowing for sure if oral GCs are only useful for a specific phenotype of (atopic vs. nonatopic) viral-induced wheezers.

Two recent studies published in *The New England Journal of Medicine* sought to evaluate the effectiveness of either very high-dose inhaled GC or oral GC therapy in preschool-aged children presenting to an ED with viral-induced wheeze. In the first study, Panickar et al. enrolled 700 children 10 months to 6 years of age who presented to the ED with viral-induced wheezing who remained symptomatic after

albuterol therapy. Half of the participants received prednisone, the other half a matching placebo with the primary outcome being length of hospital admission. The authors found no difference in the length of hospitalization between the children who received prednisone and those who received placebo. They concluded that in children presenting to a hospital with mild to moderate wheezing associated with a viral infection, oral prednisolone was no better than placebo.

As ambitious as this study was, it fails to answer several fundamental questions about preschool-aged children who have recurrent wheezing. We know that systemic GCs are very effective in the treatment of older children and adults with acute asthma exacerbations, with many virally induced. This begs the question, what is different about preschool-aged wheezers? This question could easily have been addressed had the investigators determined how many of the children actually had a viral infection and what type of infection they had. It is possible that certain viruses, especially rhinovirus, are more likely to respond to oral GCs as it triggers an eosinophilic inflammatory response (steroid responsive), whereas other viruses trigger neutrophilic responses (steroid unresponsive). In addition, the investigators failed to determine what percentage of these children were atopic as defined by positive skin tests or specific IgE to a panel of aeroallergens. This is an important omission, in that atopic preschool-aged children with an acute wheezing illness associated with a viral respiratory tract infection may be more responsive to oral GCs than nonatopic preschool-aged children. Another limitation of the study comes from the relatively low dose of prednisolone used (10 mg for 10–24-month-old children and 20 mg for 2–6-year-old children). These doses are smaller than those recommended by the NHLBI asthma guidelines. Lastly, the length of admission for both placebo- and prednisone-treated children was far less than 24 h! In my experience, a preschool-aged child with an acute wheezing illness who requires admission to the hospital often spends in excess of 48 h, while some will require several days before they are well enough to go home. This suggests to me that the exacerbations these investigators studied were mild or moderate at worst and may not have required treatment with prednisone at all.

The second study evaluated the effectiveness of high-dose inhaled FP therapy in a similar population of preschool-aged children with viral-induced wheezing. In this study, 129 children 1–6 years of age received either FP 750 mcg twice daily or matching placebo at the beginning of an upper respiratory tract infection and continuing for a maximum of 10 days over a 6–12-month period of time. The primary outcome was number of oral GC courses. To be eligible, children had to have had one course of prednisone in the past 6 months or two courses in the past year and to be nonatopic. Children who received fluticasone at the first sign of a respiratory tract infection required 50 % fewer courses of prednisone, had shorter durations of each illness, and required less beta-agonist therapy, but their gain in both height and weight was significantly lower than those who received placebo.

This study also has a number of limitations. First, no attempt was made to verify if the wheezing episodes were truly the result of a viral infection. Second, of over 2000 potential study participants screened, only 129 children were randomized to receive treatment. This would suggest that the children they evaluated make up a

very small subgroup of preschool-aged children with viral-induced wheeze making the results unlikely to be generalized to the larger population of preschool-aged children with recurrent wheeze. Third, the dose of inhaled fluticasone chosen for use was very high and would be considered high-dose inhaled GC therapy for adults with severe persistent asthma. It is doubtful that many clinicians would use such high doses of FP to treat acute wheezing illnesses. Lastly, this form of therapy was associated with growth suppression, an adverse effect that most clinicians and parents would attempt to avoid.

So how does one reconcile the differences between the two above studies? For one, the study designs were quite different, the Panickar study involved giving a single course of prednisone in patients presenting to the ED, while the Ducharme study evaluated the preemptive use of high-dose fluticasone during viral respiratory tract infections over a period of 6 months to 1 year. Second, the populations studied were different from each other. The children in the Ducharme study had more severe disease as manifested by 50 % having required hospitalization in the past vs. 20 % in the Panickar study. In addition, to be eligible for the Ducharme study, children had to have had frequent exacerbations requiring prednisone in the past. Lastly, only nonatopic children were studied in the Ducharme study, whereas Panickar et al. made no attempt to identify atopy in their study.

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Chapter 40
Anti-immunoglobulin E (IgE) Therapy

Jeffrey R. Stokes and Thomas B. Casale

Introduction

In 1967 Ishizaka originally described IgE. Subsequently, elevated total serum IgE was found in many atopic patients and has been associated with multiple disease states. In predisposed individuals, allergen-specific IgE is produced subsequent to exposure to relevant allergens. After production, IgE is bound to the high-affinity IgE receptor, FcεRI, on the surface of mast cells, basophils, and dendritic cells. Relevant allergen binds to the Fab portion of the IgE molecule. In type I hypersensitivity reactions, cross-linking of two adjacent IgE molecules on the surface of mast cells and basophils initiates intracellular signaling pathways that result in the release of preformed and rapidly synthesized mediators followed by the synthesis and release of many cytokines important for allergic inflammation. The availability of humanized monoclonal antibodies against IgE has provided a therapeutic option to explore the role of IgE in allergic diseases.

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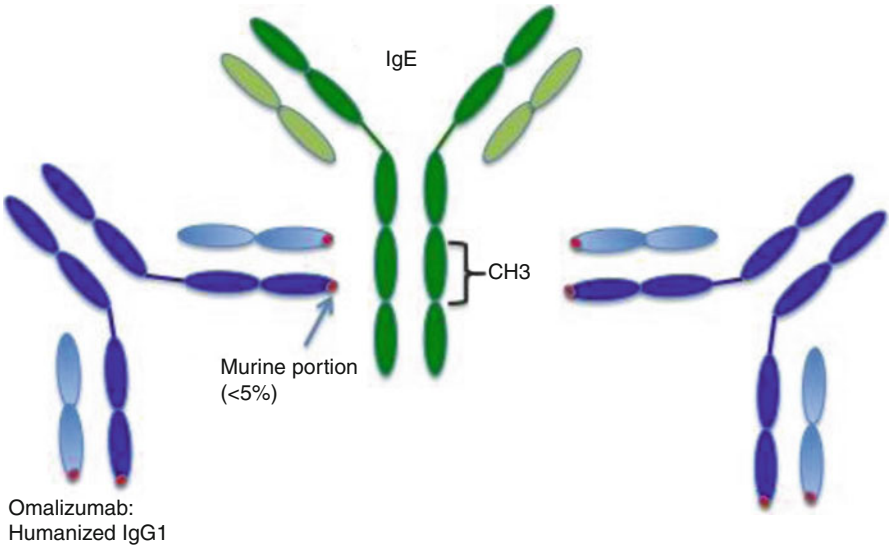

Fig. 40.1 Omalizumab binding with IgE to form trimer

Background

Omalizumab is a humanized, monoclonal antibody that recognizes and binds to the Fc portion of the IgE molecule typically forming a trimer (Fig. 40.1). The binding of omalizumab to IgE results in the formation of soluble immune complexes that are cleared by the reticuloendothelial system. This binding of omalizumab to free IgE prevents the binding of IgE to FcεRI and the subsequent expression of IgE on the cell surface. Omalizumab binds to the same site that IgE molecules use to attach to FcεRI (CH3 domain); thus it cannot cross-link cell surface-expressed IgE. Since omalizumab can bind only to soluble IgE, it should not cause degranulation of mast cells and basophils, but cases of hypersensitivity reactions to omalizumab have been reported.

Mechanism of Action

Administration of omalizumab results in a 99 % reduction in free serum IgE levels within 2 h of omalizumab dosing. Within 7 days, omalizumab administration results in reductions of expression of FcεRI on basophils and dendritic cells. Omalizumab had no effect on cutaneous mast cell FcεRI expression by skin biopsy within 7 days, but by day 70, the expression was reduced by 90 %. Within 3 months of therapy, human basophil responsiveness (histamine release ability) is reduced by 90 %. Omalizumab has a weak and delayed effect on allergen-induced immediate skin test responses, although the inhibitory effects of omalizumab on late-phase skin responses are more rapid and profound. In asthmatics, omalizumab has been shown

to decrease inflammation as measured by exhaled nitric oxide (NO) and blood and sputum eosinophils.

In bronchial biopsies, treatment with omalizumab resulted in a significant decrease in the mean percentage of sputum eosinophils from 6.6 % to 1.7 % and was associated with a significant reduction in tissue eosinophils; cells positive for FcεR1; CD3+, CD4+, and CD8+ T lymphocytes; B lymphocytes; and cells staining positive for IL-4. The addition of omalizumab to baseline combination asthma therapy significantly decreases circulating IL-13 levels. In addition, omalizumab treatment has been shown to induce human eosinophil apoptosis in patients with allergic asthma and decreases in blood eosinophils.

Omalizumab Disease-Specific Effects (Table 40.1)

Allergic Asthma

A number of studies have established the efficacy and safety of omalizumab for the treatment of patients with asthma leading to the US Food and Drug Administration's (FDA) approval of omalizumab in 2003 for the treatment of moderate to severe persistent allergic asthma in patients 12 or older.

An early phase II study examined asthma symptom scores in 317 moderate to severe allergic asthmatics on inhaled and/or oral corticosteroids. Two active treatment protocols were used, low- and high-dose omalizumab. Symptom scores improved in both groups after 12 weeks. In addition, subjects in the omalizumab treatment groups had fewer asthma exacerbations and were able to reduce or discontinue corticosteroids to a greater extent than those on the placebo arm.

Three phase III trials were conducted on a total of 1,405 patients with moderate to severe allergic asthma. Two trials were conducted in subjects 12 years of age and older treated with inhaled corticosteroids, while the other trial treated children aged 6–12 years old receiving inhaled corticosteroids. In these studies,

Table 40.1 Omalizumab treatment options

Current indications for use:
Allergic asthma
Chronic spontaneous urticaria
Effective therapy:
Allergic rhinitis
Nonallergic asthma
Adjuvant with immunotherapy
Potential therapy:
Atopic dermatitis
Mast cell disorders
Oral desensitization
Food allergy

omalizumab was administered subcutaneously every 2–4 weeks in doses ranging from 150 to 375 mg. During the initial 16 weeks, omalizumab was added onto a stable dose of inhaled corticosteroids. After 16 weeks, patients underwent a steroid reduction phase lasting an additional 12 weeks. The primary end point in all three studies was a reduction in asthma exacerbations. Omalizumab treatment led to a significant reduction in asthma exacerbations when compared with placebo. In addition, omalizumab was corticosteroid sparing in all three studies. There were twice as many subjects in the omalizumab group who successfully discontinued corticosteroids compared with placebo treatment. Patients on omalizumab experienced fewer asthma symptoms, less rescue medication usage, and improved quality of life scores. In the two adolescent and adult studies, omalizumab resulted in significant, albeit small, improvements in lung function. The data from these three studies were pooled to determine the effect of omalizumab on serious asthma exacerbations. Omalizumab-treated patients had significantly fewer unscheduled outpatient visits and emergency room visits and fewer hospitalizations.

Data from 1,070 adolescents and adults from two of these phase III trials were pooled to determine characteristics of patients who respond to omalizumab treatment. The greatest benefits were noted in patients who had two or more of the following characteristics: a history of emergency treatment of asthma in the last year, patients on $\geq$800 μg inhaled beclomethasone per day, or patients with an FEV1 $\leq$65 % of predicted peak expiratory flow.

Of 1,412 patients in phase III trials, 254 patients were identified as high risk (required intubation, visited an emergency room, required overnight hospitalization, or received treatment in an ICU during the last year). In these patients on the steroid-stable phase of the studies, omalizumab treatment resulted in a reduction in significant asthma exacerbation episodes by over 50 % and a lower likelihood of rehospitalization due to asthma.

In clinical practice, omalizumab is typically added to the therapeutic regimen in patients who remain poorly controlled despite maximal medical therapy. In a 52-week trial in patients with moderate to severe allergic asthma who were symptomatic, despite treatment with high doses of inhaled corticosteroids plus long-acting β_2-agonists, antileukotrienes, or oral steroids, the addition of omalizumab was evaluated. Those patients treated with omalizumab showed a greater reduction of asthma exacerbations (60 %), unscheduled physician visits, and days missed from work or school compared to placebo. A review of 8 clinical trials and nearly 3,500 patients with asthma demonstrated that the addition of omalizumab reduced exacerbations, asthma hospitalizations, and rescue medication use and improved symptom scores and quality of life, independent of patient's age, duration of treatment, or severity of asthma. In addition, there was no difference in adverse events or serious adverse events between omalizumab and placebo treatment. Overall, these studies suggest that omalizumab is effective as an add-on therapy in asthmatics that are poorly controlled despite maximal medical therapy.

Omalizumab treatment is beneficial for adolescents and children with persistent allergic asthma. Omalizumab decreased the number of exacerbations in inner city children and adolescents who had a history of one or more exacerbations from

48.8 % to 30.3 %. This reduction was especially demonstrated for seasonal exacerbations (fall/spring). In these patients, both daily symptoms and daily ICS dose were significantly reduced with omalizumab.

In 2014, a Cochrane meta-analysis consisting of 25 studies, involving 6,382 people, concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to inhaled steroids and was significantly more effective than placebo in increasing the number of participants who were able to reduce or withdraw their inhaled steroids.

More recently, analysis of data from several previous studies suggests that the reduction of asthma exacerbations due to omalizumab was most prominent in patients with elevated blood eosinophils and exhaled FeNO.

Nonallergic Asthma

Case studies have also found omalizumab improved asthma control in patients with allergic asthma but baseline IgE levels less than 17 kU/l and in a patient with no evidence of specific allergen sensitization but elevated total IgE levels. A study comparing 29 severe, nonatopic asthmatics with 266 severe, atopic asthmatics all treated with omalizumab showed similar improvements in symptoms. A randomized, placebo-controlled, double-blind study evaluated omalizumab treatment in 41 severe refractory nonatopic asthmatics on high-dose ICS/LABA medications (33 % taking oral corticosteroids). Omalizumab significantly decreased expression of high-affinity IgE receptor (FcεRI) on basophils and plasmacytoid dendritic cells and improved lung functions.

Allergic Rhinitis

The effect of omalizumab was evaluated in 536 patients with ragweed-sensitive allergic rhinitis. Omalizumab or placebo was administered prior to the onset of the ragweed season and every 3–4 weeks throughout the ragweed season. Subjects treated with 300 mg omalizumab demonstrated significantly lower nasal symptom scores, improved Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores, and less days missed from work/school when compared with placebo. Another seasonal allergic rhinitis study examined the therapeutic benefits of omalizumab in 251 patients with allergic rhinitis symptoms to birch. Patients treated with omalizumab showed significant improvement compared to placebo in average daily symptom scores, usage of rescue antihistamines, and quality of life measures. Omalizumab has also been shown to be effective in the treatment of perennial allergic rhinitis in nearly 300 patients with moderate to severe disease. Both mean daily nasal severity scores and rescue antihistamine use were significantly lower in omalizumab-treated patients when compared with placebo. Over 400 patients with asthma and allergic

rhinitis were treated with omalizumab or placebo for 28 weeks. More patients in the omalizumab group demonstrated improvement in both asthma and rhinitis quality of life indices (57.7 % vs. 40.6 %). A recent meta-analysis published in 2014 reviewed 11 studies with a total of 2,870 patients randomized. In the nine studies that measured daily nasal symptom scores, omalizumab significantly reduced symptoms. Rescue medication use was also decreased in the nine studies that evaluated that end point. No significant differences in adverse events were reported vs. placebo.

Omalizumab plus Immunotherapy

Since omalizumab decreases serum IgE and the expression of FcεRI on key immune effector cells, this could enhance the immune tolerance to allergens delivered by immunotherapy. Thus, combining omalizumab with allergen immunotherapy should improve clinical benefits and safety.

The addition of omalizumab to standard maintenance dose subcutaneous immunotherapy (SCIT) was evaluated in 221 children and adolescents with birch- and grass-induced allergic rhinitis. Compared to birch SCIT, omalizumab plus SCIT during birch season decreased symptoms by 57 %. During grass season combination therapy improved symptoms by 71 %, while grass immunotherapy alone had only a 32 % reduction in rhinitis symptoms. When these findings were further analyzed for the grass pollen-allergic children, omalizumab plus immunotherapy treated groups had significantly diminished rescue medication usage and symptomatic days when compared to immunotherapy alone.

The use of omalizumab prior to rush SCIT, followed by 12 weeks of dual omalizumab and immunotherapy, is more effective than rush SCIT followed by immunotherapy alone in ragweed-allergic patients in reducing rhinitis symptoms. In addition, those patients receiving omalizumab plus immunotherapy had fewer adverse events than those receiving immunotherapy alone with a reduction of anaphylaxis attributed to immunotherapy of 80 %. In patients with persistent asthma, the use of omalizumab in conjunction with cluster SCIT resulted in less systemic reactions, 13.5 %, compared to placebo at 26.2 %. Omalizumab patients also were more likely to achieve maintenance dosing, 87 %, compared to 72 % of the patients on placebo.

The concurrent use of omalizumab in a few cases of venom SCIT demonstrated conflicting results in preventing systemic reactions due to immunotherapy. Finally, omalizumab pretreatment of 11 children with cow's milk allergy has been demonstrated to safely allow oral desensitization to milk powder.

Food Allergy

Food allergies affect about 6 % of children under the age of 3 and 2 % of adults, with 1.5 million suffering from peanut allergy in the United States. Another humanized IgG1 monoclonal IgE antibody, TNX-901, was evaluated in 84 peanut-allergic

patients. Patients were dosed every 4 weeks for four doses with an oral challenge performed within 2–4 weeks after the final dose. By the end of treatment, all three verum groups and the placebo group had a greater threshold of peanut tolerability. However, only the high-dose (450 mg) TNX-901 group had a significant improvement from a threshold dose of 178 mg (one-half peanut) to 2,805 mg (nearly nine peanuts), but 25 % of the patients had no improvement. In a small study of 14 peanut-allergic patients treated with omalizumab or placebo, 44 % of patients treated with omalizumab vs. 20 % of placebo-treated patients were able to tolerate ≥1,000 mg peanut flour. This study was terminated early and most subjects treated with omalizumab were not able to tolerate >1,000 mg peanut flour.

Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory disease of the skin that affects 10–20 % of children and 1–3 % of adults. The use of omalizumab in atopic dermatitis has been limited to case studies and small trials. In the allergic form of atopic dermatitis, serum total IgE is elevated. Conflicting data on the effectiveness may be due to the exceptionally high level of IgE in atopic dermatitis patients making it difficult to reduce the levels significantly. A small trial in seven pediatric patients with severe atopic dermatitis demonstrated that omalizumab was effective in reducing atopic dermatitis symptoms even in a patient with a baseline IgE level as high as 17,190 IU/L. Atopic dermatitis patients without filaggrin mutations have shown greater response to omalizumab treatment. This may indicate that those patients with skin barrier alterations, such as filaggrin mutations, as a key component of their atopic dermatitis may be less likely to respond to treatment than patients with more of an immunodysregulation profile.

Urticaria

In chronic urticaria, approximately 40–50 % of the patients have an autoimmune component. This may be due to the presence of IgG antibody directed to the α-subunit of the IgE receptor or IgG directly against IgE. These autoantibodies lead to degranulation of basophils and cutaneous mast cells triggering the urticarial reaction. Because omalizumab decreases both cell-surface IgE levels and the number of high-affinity IgE receptors, the patients having these autoantibodies would be expected to see symptom improvement.

In an initial proof of concept study of 12 patients with chronic urticaria, omalizumab demonstrated a significant response in 11 out of 12 patients with 7 patients achieving complete symptom resolution. This eventually led to three large, phase III, randomized, double-blind, placebo-controlled studies, Asteria I, Asteria II, and Glacial. All three studies evaluated patients 12–75 years old with refractory chronic spontaneous urticaria.

In the Asteria I study, 318 symptomatic patients despite licensed doses of H1 antihistamine therapy were randomized to one of three different doses of omalizumab (300 mg, 150 mg, 75 mg) or placebo every 4 weeks for 24 weeks. The 300 mg dose improved urticaria symptoms by the first week of treatment compared to placebo, and all three doses significantly reduced urticarial symptoms by 12 weeks. At 12 weeks, 52 % of the high-dose omalizumab patients had their urticaria symptoms well controlled, and 36 % were completely controlled.

The Asteria II trial was similar in design with 323 patients with chronic urticaria who remained symptomatic despite H1 antihistamine therapy at licensed doses. After 12 weeks of treatment, the patients on 150 mg and 300 mg doses of omalizumab demonstrated significant improvements in symptom scores and number of urticarial lesions compared to placebo. Of those patients on 300 mg of omalizumab, 53 % were without lesions and 44 % had no rash or itching.

The Glacial trial was different from the Asteria trials in that patients were symptomatic despite using H1 antihistamines up to 4× licensed doses plus H2 blocker and/or leukotriene antagonist. Three hundred thirty-five patients were randomized to either 300 mg of omalizumab or placebo every 4 weeks for 24 weeks of treatment and 16 weeks follow-up. Symptoms were decreased by 12 weeks and remained low for the 24 weeks of omalizumab treatment.

In a review of over 900 patients with chronic urticaria, the response rate to omalizumab in symptomatic patients despite standard therapy was 65 % with complete resolution in 40 %, and improvement was noted in just a few days in a subset of patients. Physical urticarias that have been reported to respond to omalizumab include cholinergic, solar, cold-induced, delayed pressure, dermatographic, and localized heat urticaria.

Current urticaria guidelines of the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO); American Academy of Allergy, Asthma, and Immunology (AAAAI); and the American College of Allergy, Asthma, and Immunology (ACAAI) recommend the use of omalizumab in treating chronic urticaria after failure of high-dose (two to fourfold licensed) antihistamines with or without the addition of leukotriene-modifying agents.

Other Allergic Diseases

Case reports and small case series have demonstrated the benefit of omalizumab in other disease states such as ABPA, mastocytosis, nasal polyposis/sinusitis, eosinophilic gastrointestinal diseases, latex allergy, drug allergy, and idiopathic anaphylaxis.

Dosing

The only FDA-approved anti-IgE therapy available is omalizumab (Xolair®). This is supplied as a lyophilized powder, 150 or 75 mg on reconstitution with sterile water for subcutaneous injection. The recommended dose is 0.016 mg per

kilogram of body weight per international unit of IgE every 4 weeks, administered subcutaneously at either 2- or 4-week intervals for adults and adolescents (persons 12 years of age and older) with moderate to severe perennial allergic asthma. Since omalizumab is currently available in 75 or 150 mg vials, dosing charts are used to calculate the dose based on multiples of 75 (Table 40.2). In March of 2014, the US FDA approved the use of omalizumab 150 or 300 mg every 4 weeks for chronic urticaria for patients 12 years and older who remain symptomatic despite H1 antihistamines.

Cost

The cost of omalizumab is substantially higher than other available asthma and urticaria medications. One 150 mg vial costs approximately $1,000. However, despite its high cost, it may still be cost-effective when its use is limited to those asthmatic patients with more severe disease. This includes patients with frequent exacerbations and those requiring emergency care or hospitalization. Furthermore, the improvements noted in patients with severe chronic urticaria including resolution of symptoms and better quality of life support its use for this disease.

Pharmacokinetics

Omalizumab is absorbed slowly, reaching peak serum concentrations after a week with an average absolute bioavailability of 62 %. In asthma patients, omalizumab serum elimination half-life averaged 26 days. Serum total IgE levels (i.e., bound and

Pre-treatment Serum IgE	Body weight			
	30–60 kg	***> 60–70 kg***	***> 70–90 kg***	***> 90–150 kg***
≥ 30–100 IU/ml	150 mg every 4 weeks	150 mg every 4 weeks	150 mg every 4 weeks	300 mg every 4 weeks
> 100–200 IU/ml	300 mg every 4 weeks	300 mg every 4 weeks	300 mg every 4 weeks	225 mg every 2 weeks
> 200–300 IU/ml	300 mg every 4 weeks	225 mg every 2 weeks	225 mg every 2 weeks	300 mg every 2 weeks
> 300–400 IU/ml	225 mg every 2 weeks	225 mg every 2 weeks	300 mg every 2 weeks	No effective dosing reported
> 400–500 IU/ml	300 mg every 2 weeks	300 mg every 2 weeks	375 mg every 2 weeks	
> 500–600 IU/ml	300 mg every 2 weeks	375 mg every 2 weeks		
> 600–700 IU/ml	375 mg every 2 weeks			

Table 40.2 Omalizumab dosing for asthma patients 12 years and older

unbound) increase after the first dose due to the formation of omalizumab-IgE complexes, which have a slower elimination rate compared with free IgE. Total IgE levels increased with omalizumab therapy up to fivefold after 1 month and more than eight times pre-omalizumab levels after 3 months of therapy, while free IgE levels decreased. Total IgE levels may take up to a year to achieve pretreatment levels after discontinuation of omalizumab. Measurement of total IgE is difficult due to omalizumab: IgE complexes interfering with the accuracy of standard testing for both serum IgE levels and allergen-specific IgE antibody levels.

Safety

Omalizumab has proven to be a generally well-tolerated medication with few adverse reactions. The most common adverse event is a local reaction at the injection site that may include burning, pruritus, hives, pain, redness, induration, swelling, warmth, and bruising.

In the clinical trials, there were no differences noted in urticarial reactions between the omalizumab group (1.2 %, 39/3,224) and placebo group (1.1 %, 24/2,019). There are rare cases of anaphylaxis occurring after omalizumab treatment. A task force was assembled in 2007 to review anaphylactic events associated with omalizumab administration. Omalizumab was administered to 39,510 patients with an anaphylaxis-reporting rate of 0.09 %. A total of 35 patients had 41 episodes of anaphylaxis associated with Xolair (omalizumab) administration. Of those 36 events for which the time of reaction was known, 22 (61 %) reactions occurred in the first 2 h after one of the first three doses, and 5 (14 %) of the events after the fourth or later doses occurred within 30 min. In 2011 the task force reviewed additional cases and confirmed the original recommendations made in 2007 as regards administration and monitoring of treated patients (Table 40.3).

Pooled data from phase I to III studies of omalizumab showed an increase in malignancies in omalizumab patients (0.46 %) compared with control subjects (0.22 %). All tumors but one (a recurrent non-Hodgkin's lymphoma) were solid tumors. An independent panel of oncologists compared the cancer rates for those reported in the omalizumab studies to this population age range and concluded that there was no increased relative risk associated with omalizumab therapy.

An Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma (EXCELS) assessed the long-term safety of omalizumab in a clinical practice setting as part of a phase IV US Food and Drug Administration post-marketing commitment. A total of 7,857 patients were enrolled in the study from 445 sites (5,007 omalizumab treated; 2,829 controls). Crude rates of malignancies were 16.0/1,000 patient-years in the omalizumab group, while the control group rates were 19.1/1,000 patient-years. Crude rates of malignancies excluding nonmelanoma skin cancer were 6.2/1,000 in the omalizumab cohort and 6.3/1,000 person-years in the non-omalizumab cohorts. These results from EXCELS and data from pooled studies suggest that omalizumab is not associated with an increased risk of malignancy.

Table 40.3 Omalizumab patient checklist

Informed consent:
Should be obtained from the patient after discussing the risks, benefits, and alternatives to omalizumab (Xolair)
Anaphylaxis education:
Educate the patient on the signs, symptoms, and treatment of anaphylaxis
Epinephrine auto-injector:
Prescribe and educate the patient on the proper use of auto-injectors and advise patients to carry an epinephrine auto-injector before and for 24 h after omalizumab (Xolair) injection
Preinjection health assessment:
Assess health status, including vital signs and some measure of lung function for patients with asthma as necessary (e.g., peak expiratory flow or FEV1)
Wait period after injection:
Patients should be kept under observation for 2 h after the each of the first 3 injections
This time can be reduced to 30 min after each injection after the first 3 doses
This time may be modified based on a physician's clinical judgment after discussing the risks with the patient

During interim analyses of EXCELS, an increase of arterial thrombotic events (ATEs) including stroke, transient ischemic attack, myocardial infarction, unstable angina, pulmonary hypertension, and cardiovascular death was observed. In the final analysis the rate of ATE per 1,000 patient-years was 7.52 (115/15,286 patient-years) for omalizumab-treated patients and 5.12 (51/9,963 patient-years) for control patients with a hazard ratio of 1.32 (95 % confidence interval 0.91, 1.91). In analyzing pooled randomized double-blind, placebo-controlled clinical trials lasting eight or more weeks, the rate of ATE per 1,000 patient-years was 2.69 (5/1,856 patient-years) for omalizumab-treated patients and 2.38 (4/1,680 patient-years) for placebo patients (rate ratio 1.13, 95 % confidence interval 0.24 5.71).

Post-marketing reports of possible side effects have arisen since omalizumab was approved. One case of severe thrombocytopenia was noted. Thrombocytopenia has been added to potential adverse events associated with omalizumab even though no causal relationship was established, and routine platelet monitoring is not required. In addition, rare cases of alopecia have been reported (<0.1 %), but no causal relationship to omalizumab has been established.

Conclusion

The development of a selective anti-IgE humanized monoclonal antibody represents a novel and important therapeutic option for severe asthma, chronic urticaria, and other allergic diseases. The data suggest omalizumab inhibits activation of mast cells and basophils and decreases the effects of other inflammatory cells such as eosinophils through a variety of mechanisms. This has resulted in clinical improvements in patients with moderate to severe allergic asthma, including significant reductions in exacerbations. Patients with chronic urticaria unresponsive to

antihistamines also have a good therapeutic effect with omalizumab. Omalizumab appears to be a relatively safe, well-tolerated medication. In years to come, the role of omalizumab or other anti-IgE antibody strategies in pediatric asthma, nonallergic asthma, food allergy, atopic dermatitis, ABPA, and chronic hyperplastic sinusitis and as an adjuvant to allergen immunotherapy will evolve. In this regard, second-generation anti-IgE therapies are currently being evaluated for patients with moderate to severe asthma and urticaria. These may prove to be improvements on omalizumab including the ability to dose regardless of IgE levels or body weight.

Evidence-Based Medicine

- Urgert MC, van den Elzen MT, Knulst AC, Fedorowicz Z, van Zuuren EJ. Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment. Br J Dermatol. 2015 Apr 18. doi: 10.1111/bjd.13845. [Epub ahead of print]
  - This systematic review assessed the quality of the evidence for the effects of omalizumab as treatment in patients with CSU by searching PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials. Five randomized controlled trials (RCTs) which included 1,116 participants were evaluated. Three phase III studies (Asteria I, Asteria II, and Glacial) and two phase II studies (MYSTIQUE and X-QUISITE) were included. There was a statistically significant improvement in measures of disease activity and quality of life following treatment with omalizumab 300 mg per month for up to 6 months when compared to placebo (mean difference (MD) −11.58, 95 % CI −13.39 to −9.77 and MD −13.12, 95 % CI −16.30 to −9.95, respectively). Complete response was achieved in 38.1 % of the patients treated with omalizumab compared to 5.6 % of the patients treated with placebo, while 55 % of omalizumab patients and 14 % of placebo patients noted partial response. There was no difference in the proportion of participants reporting adverse events between the omalizumab and placebo treatment.
- Busse W, Buhl R, Vidaurre CF, Blogg M, Zhu J, Eisner MD, Canvin J. Omalizumab and the risk of malignancy: Results from a pooled analysis. J Allergy Clin Immunol. 2012;129:983–9.e6.
  - Data from 67 completed phase I–IV trials were included in a pooled analysis to evaluate cancer risk. Overall there were 11,459 unique patients with 7,789 patients treated with omalizumab and 4,252 control patients. In 32 randomized double-blind, placebo-controlled trials, 25 patients were noted to have malignancies: 14 in 4,254 omalizumab-treated patients and 11 in 3,178 placebo-treated patients. The incidence rate of malignancies per 1,000 patient-years of observation time for omalizumab patients was 4.14 and in patients treated with placebo was 4.45. No association was noted between omalizumab treatment and malignancy.

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Chapter 41
Allergy Immunotherapy

Jeffrey R. Stokes and Thomas B. Casale

Introduction

Allergic diseases have increased in prevalence over the last 30 years, affecting as many as 40–50 million people in the United States. Allergen immunotherapy has been a therapeutic option for over 100 years and its use is supported by multiple placebo-controlled trials. Allergen immunotherapy alters the course of allergic diseases through either a series of injections of extracts composed of clinically relevant allergens or sublingual tablets containing clinically relevant allergens The term "allergen extract" has been replaced by "allergen vaccine" by the World Health Organization to reflect that allergen vaccines are used in medicine as immune modifiers. The preferred term for therapy is allergen immunotherapy.

Indications

Allergen immunotherapy is used in the treatment of allergic rhinitis, allergic asthma, atopic dermatitis (with aeroallergen sensitization), and stinging insect venom hypersensitivity. The diagnosis of these diseases is made by history and physical exam supported by testing to confirm IgE sensitization. Skin testing by prick or

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Table 41.1 Immunotherapy

Currently indicated	Allergic rhinitis
	Allergic asthma
	Venom allergy
	Atopic dermatitis with aeroallergen sensitization
Not indicated	Food allergy
	Chronic urticaria/angioedema
Relative contraindications	Unstable asthma (absolute contraindication)
	Concurrent use of beta-blockers or ACE inhibitors
	Severe coronary artery disease
	Malignancy
	Unable to cooperate/communicate clearly (very young children

intradermal method is the preferred objective assessment, but in vitro tests are an alternative, especially when skin testing is unable to be performed.

Candidates for venom or Hymenoptera immunotherapy include all patients who have experienced life-threatening allergic reactions or non-life-threatening systemic reactions to Hymenoptera stings. The risk of anaphylaxis for a venom-allergy patient from an insect sting is greater than the risk of anaphylaxis from immunotherapy. In patients younger than 16 years of age with only urticaria to Hymenoptera stings, immunotherapy is not generally recommended. However, in patients older than 16 years of age with only cutaneous reactions, immunotherapy is a recommended option. Venom immunotherapy is also indicated for patients who have recurrent bothersome large local reactions especially those with occupational exposure.

Immunotherapy is also effective for pollen, mold, animal dander, dust mite, and cockroach allergies. Symptomatic patients with allergic rhinitis and asthma despite allergen avoidance and pharmacotherapy are candidates for immunotherapy (Table 41.1). Other candidates include allergic rhinitis or asthma patients having undesirable adverse reactions to medications or those wishing to reduce or eliminate long-term pharmacotherapy. In addition to reducing symptoms to current allergens, immunotherapy may prevent the development of sensitization to new allergens or progression of allergic rhinitis to asthma, especially in children.

Mechanism

The exact mechanism of how subcutaneous immunotherapy works is not fully understood, but involves shifting a patient's immune response to allergen from a predominately allergic T-lymphocyte (TH2) response to a "non-allergic" T-lymphocyte (TH1) response. Lymphocytes of a TH2 phenotype typically produce

IL-4 and IL-5, cytokines needed for IgE production and eosinophil survival. Findings of increased production of IFN-γ and a decreased production of IL-4 and IL-5 have not, however, been consistently demonstrated after immunotherapy. What has been consistent is the increased production of allergen-specific IL-10. IL-10 causes a shift in allergen-specific IgE to allergen-specific IgG4. This change is orchestrated by regulatory T-cells which downregulate allergic immune responses in part through the release of IL-10 and TGF-β. With allergen immunotherapy, the seasonal increase in allergen-specific IgE is blunted, while protective allergen-specific IgG4 production is increased. However, these changes in IgE and IgG may not correlate with clinical efficacy, so periodic skin testing or in vitro IgE antibody measurements are not always useful in evaluating responses to immunotherapy. Sublingual immunotherapy also induces regulatory T-cells via cytokines released from Langerhans cells, myeloid dendritic cells, and macrophages.

Contraindications

Relative contraindications for immunotherapy include medical conditions that reduce patients' ability to survive a serious systemic allergic reaction, such as coronary artery disease or the concurrent use of β-blockers (including eye drops) or angiotensin-converting enzyme inhibitors (Table 41.1). Beta-adrenergic blocking agents may make the treatment of immunotherapy-related systemic reactions more difficult. Despite this, immunotherapy is indicated for patients with life-threatening stinging insect hypersensitivity receiving β-blockers. Allergen immunotherapy should not be initiated in asthmatic patients unless the patient's asthma is relatively stable with pharmacotherapy. Patients who are mentally or physically unable to communicate clearly, such as very young children, are not good candidates for immunotherapy as it may be difficult for them to report early symptoms of a systemic reaction. Pregnancy is not a contraindication for immunotherapy, but by custom immunotherapy is not initiated during pregnancy. If a patient becomes pregnant while already on immunotherapy, the dose is not increased during the pregnancy but maintained at the current level in an attempt to avoid anaphylactic reactions.

Dosing

Standard allergen immunotherapy is administered as a subcutaneous injection. The appropriate allergen extracts (vaccines) are selected based on the patient's clinical history, allergen exposure history, and the results of tests for allergen-specific IgE antibodies. The immunotherapy vaccine should contain only clinically relevant allergens. When preparing mixtures of allergen vaccines, the prescribing physician must take into account the cross-reactivity of allergens, the optimal dose of each constituent, and the potential for allergen degradation caused by proteolytic enzymes

Table 41.2 Conventional subcutaneous allergen immunotherapy

Buildup
1000–10,000-fold dilution starting dose (depending upon sensitivity)
Increase dose once to twice a week with at least 2 days in between injections
Maintenance achieved after 4–6 months
Maintenance
Therapeutic dose administered every 2–6 weeks
Therapy continued for 3–5 years

in the mixture. The efficacy of immunotherapy depends upon achieving an optimal therapeutic dose of each allergen in the vaccine.

Subcutaneous allergen immunotherapy dosing consists of two treatment phases: the buildup phase and the maintenance phase. The prescribing physician must specify the starting immunotherapy dose, the target maintenance dose, and the immunotherapy buildup schedule. The highest concentration of vaccine that is projected to provide the therapeutically effective dose is called the "maintenance" dose or concentrate. In general, the starting immunotherapy dose is 1000- to10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose may be even lower. Dilute concentrations are more sensitive to degradation and lose potency more rapidly than the more concentrated preparations. Thus, their expiration dates are much shorter and must be closely monitored.

The buildup phase involves injections with increasing amounts of allergens. The frequency of the injections can vary depending upon the protocol. The most common or "conventional" protocol recommends dosing once to twice a week with at least 2 days between injections (Table 41.2). It is customary to repeat or reduce the dose if there has been a substantial time interval between injections. Patients with greater sensitivity may require a slower buildup phase to prevent systemic reactions. With this schedule, maintenance is usually achieved after 3–6 months (Table 41.3). Alternative schedules such as "rush" or "cluster" immunotherapy rapidly achieve maintenance dosing and should preferably be administered by an allergist/immunologist because of an increased risk for systemic reactions. Allergen immunotherapy dosing schedules should be written by appropriately trained physicians, and primary care physicians should seek their advice if questions or issues arise during administration.

The maintenance phase begins when the effective therapeutic dose is achieved. This final dose is based on several factors including the specific allergen, the concentration of the extract, and how sensitive a patient is to the extract. Once maintenance is achieved, the intervals for injections range from every 2 to 6 weeks, but are individualized for each patient. Clinical improvement can be demonstrated shortly after the patient reaches their maintenance dose. If no improvement is noted after 1 year of maintenance therapy, a reassessment should be done. Possible

Table 41.3 Typical buildup schedule for conventional subcutaneous allergen immunotherapy

1:1000 (v/v)	0.05
	010
	0.20
	0.40
1:100 (v/v)	0.05
	0.10
	0.20
	0.30
	0.40
	0.50
1:10 (v/v)	0.05
	0.07
	0.10
	0.15
	0.25
	0.35
	0.40
	0.45
	0.50
Maintenance concentrate	0.05
	0.07
	0.10
	0.15
	0.20
	0.25
	0.30
	0.35
	0.40
	0.45
	0.50

reasons for lack of efficacy need to be evaluated, and if none are found, discontinuation of immunotherapy should be considered. Patients should be evaluated at least every 6–12 months while on immunotherapy by the prescribing physician. Duration of maintenance therapy is generally 3–5 years. Treatment may lead to prolonged clinical remission and persistent alterations in immunologic reactivity. The severity of disease, benefits from sustained treatment, and the convenience of treatment are all factors that are considered when deciding the length of therapy for each individual patient.

Many studies, from Europe, have shown that high-dose sublingual allergen immunotherapy (SLIT) is effective for certain patients. Some of the earlier studies suffered from inconsistencies including varying doses of allergen and multiple dosing regimens. More recently, several double-blind, placebo-controlled, randomized

control trials with standard dosing and time frames conducted in North America and Europe have demonstrated the effectiveness of SLIT in patients with allergic rhinitis. The positive results from these studies have led to the US Food and Drug Administration approval of two grass and one ragweed SLIT tablets in 2014 (Table 41.5). Dosing should be initiated 12–16 weeks prior to the allergen season and continued throughout the season (pre-seasonal/coseasonal) or continuously for a minimum of 2–3 years. Dosing is daily during the treatment phase with local side effects such as oral pruritis and throat irritation commonly noted especially early (during the first week) during treatment. The five-grass product (Oralair)® is available in two strengths (100 IR and 300 IR). For children and adolescents ages 10–17, the dose is increased over the first 3 days: on day 1, a 100 IR tablet is given; on day 2, two 100 IR tablets are given; on day 3 and following, the 300 IR tablet (same as for adults) is given. For the ragweed and timothy grass products, Ragwitek™ and Grastek®, children and adults take the same dose, a single tablet daily over the prescribed time period, with no buildup.

Recently, several studies have demonstrated the effectiveness of oral immunotherapy for food allergy (peanut, milk, egg) in children. In general, patients after therapy are able to tolerate higher levels of allergen without serious adverse reactions. It has been noted that with the daily treatment some patients develop eosinophilic esophagitis to the specific food that resolves with the discontinuation of the offending food. Several questions such as appropriate dosing and duration of treatment need to be answered before this therapy can be considered anything but experimental.

Safety

The greatest concern with allergen immunotherapy is safety. Local reactions at the injection site, such as redness, swelling, and warmth, are common. These reactions can be lessened with H1 antagonists prior to injections. Local reactions can be managed with treatments such as cold compresses or topical corticosteroids. Large, local, delayed reactions ($\geq$25 mm) do not appear to be predictors of developing severe systemic reactions and generally do not require adjustment of dosing schedules. However, some patients with a greater frequency of large local reactions (>10 % of injections) may be at increased risk for future systemic reactions and dosing adjustments may be necessary.

The incidence of systemic reactions, such as urticaria, angioedema, increased respiratory symptoms (nasal, pulmonary, ocular), or hypotension, ranges from 0.05 to 3.2 % per injection or 0.84–46.7 % of patients. Risk factors for systemic reactions include errors in dosing, symptomatic asthma, a high degree of allergen hypersensitivity, concomitant use of β-blocker medications, injections from new vial, and injections given during periods when allergic symptoms are active, especially during the allergy season. A recent survey of 1700 allergists reported that 58 % of responders had an event in which a patient received an injection meant for another patient and 74 % reported that patients had received an incorrect amount of vaccine.

These errors resulted in a multitude of adverse events including local reactions, systemic reactions, and even one fatality. Thus, it is extremely important to make sure patients are questioned about potential risk factors and the correct vials are used to administer immunotherapy injections.

It is unclear if premedication with antihistamines can reduce the frequency of systemic reactions in conventional immunotherapy, but in cluster or rush immunotherapy, premedication can reduce the rate of systemic reactions.

The incidence of fatalities due to immunotherapy is extremely low and appears to be lessening. From 1990 to 2001, fatal reactions occurred at a rate of 1 per 2.5 million injections, with an average of 3.4 deaths per year. Most fatal reactions occurred with maintenance doses of immunotherapy. Between 2008 and 2012, only one fatal reaction was noted with 23.3 million injection visits. The patient population at greatest risk was poorly controlled asthmatics. In many of the fatalities, there was either a substantial delay in giving epinephrine or epinephrine was not administered at all. The incidence of near-fatal reactions (respiratory compromise, hypotension, or both requiring epinephrine) is 2.5 times more frequent than fatal reactions. Overall systemic allergic reactions of any severity (grades 1–4) occurred at a rate of 8.0 reactions per 10,000 injection visits. Severe (grade 4) reactions were reported at a rate of 0.01 per 10,000 injections, or 35 reactions documented in 2012.

Adverse reactions associated with SLIT may be local or systemic. Local reactions are fairly common, affecting up to 75 % of SLIT patients. Isolated gastrointestinal symptoms associated with SLIT, e.g., nausea or gastrointestinal pain, may be considered local reactions due to swallowing the tablet. If gastrointestinal symptoms occur in conjunction with other systemic symptoms, they would be considered systemic reactions. Most SLIT local reactions occur shortly after treatment initiation and cease within 2 weeks without any medical intervention. The use of antihistamines in the treatment of a local reaction should be considered. Since SLIT generally is administered in a setting without direct medical supervision after the initial dose, patients should be given instructions regarding recognition and management of adverse reactions and when SLIT should be withheld (e.g., asthma exacerbation). Also, prescribing information for the three FDA-approved SLIT products recommends that patients have an epinephrine auto-injector.

Treatment of Anaphylaxis

Systemic allergic reactions can be life threatening and need to be treated rapidly. Most systemic reactions are limited to the skin, such as urticaria. Respiratory symptoms are seen alone or with skin manifestations in 42 % of systemic reactions. Epinephrine is the standard of care for severe systemic or anaphylactic reactions. Treatment of anaphylactic reactions includes placing a tourniquet above the injection sites and immediately injecting epinephrine 1:1000 intramuscularly, preferably into the anterolateral thigh. For adults, the dose is typically 0.2–0.5 cc, and for children, 0.01 mL/kg (max 0.3 mg dose) every 5–10 min as needed. For

convenience, subcutaneous injection at the arm (deltoid) is frequently used, but intramuscular injection into the anterolateral thigh produces higher and more rapid peak levels of epinephrine.

Subcutaneous Allergen Immunotherapy in General Practice

According to practice guidelines, subcutaneous allergen immunotherapy should be administered in a setting that permits the prompt recognition and management of adverse reactions. The preferred setting is the prescribing physician's office, especially for high-risk patients. However, patients may receive immunotherapy injections at another health-care facility if the physician and staff at that location are equipped to recognize and manage systemic reactions, in particular anaphylaxis. Informed consent should be obtained prior to administering allergen immunotherapy. A full, clear, and detailed documentation of the patient's immunotherapy schedule must accompany the patient when receiving injections at another health-care facility. Use of a constant uniform labeling system for dilutions may reduce errors in administration. The maintenance concentration and serial dilutions should be prepared and labeled for each individual patient. The American Academy of Allergy, Asthma and Immunology's recommended nomenclature and color-coded system is contained in Table 41.4.

Table 41.4 Subcutaneous allergen immunotherapy vaccine labeling

Dilution from maintenance	Dilution designation in volume per volume (V/V)	Color	Number
Maintenance	1:1	Red	1
10-fold	1:10	Yellow	2
100-fold	1:100	Blue	3
1000-fold	1:1000	Green	4
10,000-fold	1:10,000	Silver	5

Table 41.5 SLIT products

Product	Components	Regimens	Updose	Children
Oralair	Sweet vernal, orchard, perennial rye, Timothy, Kentucky blue grass	Pre-seasonal/coseasonal (start 4 months before onset of season)	First 3 doses	10–17
Grastek	Timothy grass	Pre-seasonal/coseasonal (start 3 months before season) or year-round	No	5–17
Ragwitek	Short ragweed	Pre-seasonal/coseasonal (start 3 months before season)	No	No

All three products are daily tablets indicated for allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens

A brief review of a patient's current health status is recommended prior to administration. It is important to assess any current asthma symptoms, increased allergic symptoms, any new medications, or any delayed reactions to the previous injection. In patients with asthma, peak expiratory flow rate measurements should be obtained prior to each injection. In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation or if peak flow measurements are below 20 % of the patient's baseline values. Immunotherapy may need to be decreased or held if significant allergic symptoms are present prior to an injection.

Most severe reactions develop within 20–30 min after the immunotherapy injection, but reactions can occur after this time. Patients should wait at the physician's office for at least 20–30 min after the immunotherapy injection. In some cases, the wait may need to be longer depending upon the patient's history of previous reactions.

It is usual practice to reduce the dose of vaccine when the interval between injections is longer than prescribed. This reduction in dose should be clearly stated on the patient's immunotherapy schedule. Because of the potential of extract degradation over time, when new vials are started, the initial dose is decreased and then built back up to maintenance. When a systemic reaction occurs, the physician needs to decide if immunotherapy should be continued. This should be done in consultation with the physician who prescribed the immunotherapy. If the decision is to continue, the dose of the vaccine needs to be appropriately reduced to reduce the risk of a subsequent systemic reaction.

Efficacy and Outcomes

Once maintenance dosing is achieved for venom immunotherapy, 80–98 % of individuals will be protected from systemic symptoms upon sting challenges. Maintenance therapy is generally recommended for 3–5 years, with growing evidence that 5 years of treatment provides more lasting benefit. A low risk of systemic reactions to stings (approximately 10 %) appears to remain for many years after discontinuing venom immunotherapy. In children who have received venom immunotherapy, the chance of systemic reaction to a sting after discontinuation of immunotherapy is even lower.

The efficacy of subcutaneous and sublingual allergen immunotherapy for allergic rhinitis has been clearly demonstrated in a number of clinical trials and meta-analyses. These studies have shown significant improvements in symptoms, quality of life, medication use, and immunologic parameters. Subcutaneous allergen immunotherapy for allergic rhinitis has been shown to be beneficial for at least 3–6 years after completion of a 3-year course of treatment. Data from Oralair® clinical trials also showed sustained clinical benefits for at least 2 more years after 3 years of preseasonal/coseasonal therapy course.

The efficacy of immunotherapy for asthma has been assessed in many trials, but some studies have been difficult to interpret either because of the use of poor-quality allergen extracts or suboptimal study design. The risk/benefit ratio of

immunotherapy for asthma must always be considered. Currently, professional societies recommend that patients with asthma and FEV1 values less than 70 % should not receive immunotherapy. A Cochrane review in 2004 examined the role of subcutaneous allergen immunotherapy for asthma. This review of 75 trials with 3100 patients found a significant reduction in asthma symptoms and medication use and improvement in bronchial hyperreactivity associated with the administration of allergen-specific immunotherapy. The reviewers concluded that immunotherapy was effective in asthma and commented that one trial found that the size of the benefit was possibly comparable to inhaled corticosteroids. Because SLIT pivotal studies were not designed to study asthma, none of the 3 FDA-approved tablets list asthma as an indication. However, the pivotal SLIT tablet trials did include patients with controlled asthma, and beneficial effects on asthma symptoms were demonstrated in those studies.

Summary

Allergen immunotherapy has been a valuable tool in treating allergic rhinitis, asthma, and stinging insect hypersensitivity for decades. Although newer pharmacological agents continue to become available, immunotherapy is still the only available treatment that alters the natural course of allergic diseases. Even though there are some risks, these can be minimized when immunotherapy is given in an appropriate environment to carefully selected patients. Guidelines have been established to further reduce the risks by establishing a universal system of reporting dilutions and establishing appropriate dosing for subcutaneous allergen immunotherapy. Despite a large body of evidence demonstrating the positive therapeutic benefits of immunotherapy, only 3 million patients in the United States are receiving immunotherapy out of a potential 40–50 million allergic patients, many of whom could benefit from this therapy. Newer therapies, such as anti-IgE (omalizumab), when used with immunotherapy may improve the efficacy and safety profile of immunotherapy in the future. In addition, newer forms of immunotherapy such as T-cell peptides, epicutaneous immunotherapy, or adjuvants combined with allergens are currently under investigation.

Evidence-Based Medicine

Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol*. 2011;127(1):64–71. This study evaluates the use of sublingual allergen immunotherapy versus placebo in 345 children, 5–17 years of age, with allergic rhinitis to grass. The children were treated with once-daily grass AIT (2800 bioequivalent allergen units, 75,000 standardized

quality tablet, approximately 15 mg of Phl p 5) or placebo starting 16 weeks before the 2009 grass pollen season. Treatment was well tolerated with no systemic reactions noted, while mild transient reactions such as oral pruritis and throat irritation were common. Even though 89 % of the patients were polysensitized, treatment with only grass SLIT improved symptom scores, medication use, and quality of life by 26 %.

Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, Melac M, Zeldin RK. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol*. 2012 Dec;130(6):1327–34.e1. doi: 10.1016/j.jaci.2012.08.032. Epub 2012 Oct 31

- Four hundred seventy-three adults with grass-induced allergic rhinitis were randomized in a double-blind, placebo-controlled study to receive 300IR five-grass pollen sublingual tablet or placebo starting 4 months before and continuing through the pollen season. A combination of symptom and medication use was reduced 28 % in the treatment group compared to the placebo group during this time. In those patients with a higher baseline grass-specific IgE level of ≥0.1 kU/L, the improvement was 30 % as they made up the bulk of the patients. This study also had no anaphylactic events and oral pruritis and throat irritation were common.

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Chapter 42
Anaphylaxis and Its Management

Brant R. Ward and Lawrence B. Schwartz

Definition

Paul Ehrlich identified mast cells in tissues as a graduate student by the end of the nineteenth century, speculating on their nutritive functions for surrounding cells and receiving the Nobel Prize in 1906 for contributions to immunology. Charles Richet and Paul Portier in 1902 coined the term *anaphylaxis* after observing experimental dogs die after repeated injections with sea anemone toxin, leading to Richet receiving the Nobel Prize in 1913 for discovering anaphylaxis. They were attempting to induce protection from the toxin (prophylaxis) but paradoxically produced the opposite effect. However, the connection between mast cells and anaphylaxis only occurred decades later, as pathophysiologic mechanisms and therapeutic regimens became increasingly better understood. Nevertheless, more precise diagnostic tools along with interventions that reduce risk and treat serious manifestations are still needed for anaphylaxis.

Because anaphylaxis comprises a constellation of signs and symptoms and has multiple causes, a precise and universally accepted definition has been elusive. Confusion arises because systemic reactions can be mild, moderate, or severe, and some clinicians reserve the term for severe reactions, whereas others use it to include milder cases. Furthermore, anaphylaxis can be localized or isolated to a particular organ system (e.g., the skin, the latter referred to as cutaneous anaphylaxis). Most authorities agree that a good working definition of systemic anaphylaxis should include the acute onset of significant symptoms and signs of either respiratory difficulty, hemodynamic changes, or both that may occur in conjunction with involvement of skin (urticaria and angioedema) and other mucosal sites (e.g., gastrointestinal). In terms of pathophysiology, anaphylaxis can be defined as a form

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of immediate hypersensitivity arising when mast cells and/or basophils are provoked to secrete mediators with potent vasoactive and smooth muscle contractile activities that evoke a systemic response. The systemic response can involve one or more principal targets, including the cardiovascular, cutaneous, respiratory, and gastrointestinal systems, tissue sites where mast cells are most abundant.

The terms *anaphylactic* and *anaphylactoid* were previously used in an attempt to distinguish between mast cell activation initiated by allergen and IgE versus those that initiate mast cell activation by alternative pathways. However, the current recommendation is to use the term *anaphylaxis* to describe any clinical scenario which results from mast cell or basophil activation. Anaphylactic reactions should be further subdivided into *immunologic* and *non-immunologic* reactions. For example, foods and venoms are common causes of allergen/IgE/FcεRI-mediated mast cell activation, and anaphylaxis as a result of exposure to these allergens would thus be considered an immunologic reaction. Reactions to radiocontrast media, vancomycin, aspirin, and certain endogenous products, including C3a, C5a, and substance P, are considered non-immunologic, as these compounds directly activate mast cells and basophils through G protein-coupled receptors, independent of the FcεRI pathway. Furthermore, immunologic anaphylaxis requires a prior exposure to that allergen, leading to IgE production and then mast cell sensitization, whereas non-immunologic reactions can occur on the first exposure to an offending agent. The manifestations are clinically indistinguishable because the mediators elicited from the mast cells by these two pathways overlap extensively, and thus acute therapies are similar. However, understanding differences in causation will impact therapeutic interventions aimed at preventing future attacks.

Pathophysiology

Cells

Mast cells and basophils are the principal effector cells involved in anaphylactic reactions, although other cells, including eosinophils, T cells, monocytes, and epithelial cells, may also participate and thereby affect the intensity, duration, or character of the reaction. In classic anaphylaxis, an allergen exposure must lead to sensitization before an immediate hypersensitivity reaction can occur. This process, which takes at least 5–7 days, involves antigen processing by antigen-presenting cells, which then present peptide antigens to TH2 cells that, in turn, nurture and instruct allergen-specific B cells to switch from production of IgM or IgG to IgE. Consequently, immunologic anaphylaxis does not occur on first exposure to an allergen but may occur after subsequent exposures.

Sensitized mast cells and basophils are armed with allergen-specific IgE that binds to its high-affinity cell-surface receptor, FcεRI. Activation occurs after multivalent allergens cross-link IgE and thereby aggregates FcεRI, resulting in mediator release from the mast cell. Monovalent antigens fail to elicit mediator release because they bind IgE molecules without cross-linking them.

Mediators

Mediators released by mast cells and basophils include preformed mediators stored in secretory granules, newly generated products of arachidonic acid, and an array of cytokines and chemokines. Histamine is the sole biogenic amine stored in all granules of human mast cells and human basophils and is responsible for many of the signs and symptoms associated with systemic anaphylaxis. When released, it diffuses freely and interacts with H1, H2, H3, and H4 receptors. Stimulation of H1 receptors, found on endothelial cells, smooth muscle cells, and sensory nerves, leads to contraction of bronchial and gastrointestinal smooth muscle, relaxation of vascular smooth muscle, permeability of postcapillary venules, vasoconstriction of coronary arteries, and pruritus. In the central nervous system (CNS), blocking H1 receptors appears to cause drowsiness. H2 receptors reside on gastric parietal cells and at lower levels on inflammatory cells, bronchial epithelium, and endothelium and in the CNS. H2 receptor-mediated increased acid production in the stomach, albeit transient, may occur during systemic anaphylaxis, but it is more likely to become clinically significant when histamine levels are chronically elevated, as observed in patients with systemic mastocytosis. H3 receptors are found primarily on cells in the CNS. H4 receptors are found on hematopoietic cells, such as mast cells, basophils, and eosinophils, and they may modulate certain aspects of inflammation, such as eosinophil recruitment. H4 receptors also reside on sensory neurons and may modulate pruritus.

Prostaglandin D_2 (PGD_2) is the principal cyclooxygenase (COX)-catalyzed product of arachidonic acid secreted by activated mast cells, but not activated basophils. Both COX-1 and COX-2 are involved in PGD_2 production by mast cells. Consequently, a nonselective COX inhibitor might be better than a selective one at blocking PGD_2-mediated responses during anaphylaxis. Furthermore, the leukotriene C_4 (LTC_4) is the principal 5-lipoxygenase-catalyzed product released by both mast cells and basophils after its formation from arachidonic acid. LTC_4 and its bioactive metabolites, LTD_4 and LTE_4, bind to CysLT1 (bronchial smooth muscle, epithelial and endothelial cells, leukocytes) and CysLT2 (vascular smooth muscle, endothelial and epithelial cells, leukocytes, heart muscle), both G-protein-coupled receptors, causing bronchoconstriction, mucus secretion, eosinophil recruitment, vasopermeability, diminished cardiac contractility, vasoconstriction of coronary and peripheral arteries, and vasodilation of venules. Antagonists of CysLT1 (montelukast, zafirlukast) and a 5-lipoxygenase inhibitor (zileuton) are currently available on the market.

Platelet-activating factor (PAF) is another lipid mediator, reportedly produced by mast cells and basophils, whose role in anaphylaxis is becoming better appreciated. It is rapidly formed during immunologic and non-immunologic reactions from arachidonic acid in a pathway requiring phospholipase A, though it can also be synthesized de novo in a reaction catalyzed by cholinephosphotransferase. The physiologic effects of PAF overlap significantly with those of the leukotrienes and include bronchoconstriction, eosinophil recruitment, increased vasopermeability,

reduced cardiac contractility, and platelet aggregation. Importantly, levels of PAF in the blood correlate with the severity of an anaphylactic reaction. Moreover, PAF in the circulation is rapidly inactivated by PAF acetylhydrolase (PAF-AH), and individuals with low levels of PAF-AH appear to be at increased risk for severe anaphylaxis compared to those with higher levels.

Mast cells also are the principal source of heparin proteoglycan and certain proteases. Heparin, a negatively charged polysaccharide, can trigger activation of factor XII and the contact pathway after release from mast cells. This ultimately results in the activation of plasma kallikrein, which cleaves high molecular weight kininogen (HK), generating bradykinin, a potent inducer of vascular dilation and permeability. Increased contact pathway activation and decreased plasma HK levels may affect the severity of anaphylactic episodes. All mast cells possess the mature form of tryptase in their secretory granules. One subset, called MC_{TC} cells, also stores chymase, mast cell carboxypeptidase A3, and cathepsin G in their secretory granules and expresses CD88 (C5aR) on their surface. The other subset has no chymase or CD88 and is called MC_T cells. Mature tryptases are released from secretory granules by activated mast cells, levels in serum serving as a clinical marker for mast cell activation. In contrast, a portion of the precursor forms of tryptases (protryptases) are spontaneously secreted by mast cells at rest, levels in serum serving as a clinical marker of the total body burden of mast cells. Current immunoassays for tryptase measure either the mature tryptase or total tryptase (mature + pro forms of tryptase). Basophils express small amounts of tryptase and are deficient in the other proteases, but they also express CD88.

Cytokines (tumor necrosis factor alpha [TNF-α], interleukin [IL]-5, IL-6, IL-13, IL-16, granulocyte-macrophage colony-stimulating factor [GM-CSF], basic fibroblast growth factor [bFGF], vascular endothelial growth factor [VEGF]) and chemokines (IL-8, monocyte chemotactic protein [MCP]-1, monocyte inflammatory protein [MIP]-1α) represent another dimension of the mediators secreted by activated mast cells. The same cytokines and chemokines are produced, though to a lesser extent, by activated basophils that furthermore are potent sources of IL-4. Although these mediators are produced by other cell types, their delayed secretion after mast cell and basophil activation (hours to days) augments and extends the vasoactive and inflammatory potential of such cells and may impact the severity and duration of anaphylaxis. As selective antagonists of the relevant cytokines and chemokines become available and are tested for therapeutic benefits, their roles in the pathogenesis of anaphylaxis will be better understood.

Etiology

The most common allergens causing systemic anaphylactic reactions include drugs, insect venoms, foods, radiocontrast media, allergen immunotherapy injections, and latex. Although known causes can be identified in the majority of cases, between 25 % and 35 % are idiopathic. Most allergens are typically proteins or glycoproteins that serve as complete antigens, capable of eliciting immediate hypersensitivity

reactions in a sensitized subject without further processing. The lipid-binding properties of some allergens provide adjuvant activity. The protease activity of other allergens may facilitate their penetration at mucosal sites. In contrast to complete antigens, most drugs act as haptens. They become covalently linked to self-proteins in the circulation, in tissues, or on cells, emerging as multivalent allergens.

Drugs

A myriad of drugs are known to be responsible for anaphylaxis. Most drugs act as haptens and become covalently linked to self-proteins in the circulation, in tissues, or on cells, emerging as multivalent allergens. Penicillin allergy is reported in 10 % of the population, but in actuality up to 90 % of those patients do not have specific IgE and could use penicillin as safely as the general population. Approximately 1–8 % of patients with penicillin-specific IgE antibodies are thought to develop an immediate-type hypersensitivity to cephalosporins. Aztreonam, in contrast, lacks these cross-reactive epitopes and may be safely used in penicillin-allergic patients.

Immunologic and non-immunologic reactions have been reported for a number of biologic response modifiers, especially chimeric or humanized antibodies that still retain peptide sequences from the species of origin such as abciximab, basiliximab, infliximab, rituximab, omalizumab, and cetuximab. Reactions to omalizumab are somewhat unusual, in that symptoms are most likely to occur with the first three injections and may be delayed, developing hours or days after exposure. Up to 5 % of persons receiving cetuximab have had an anaphylactic reaction on the first exposure to the medication. The cause for this appears to be due to preexisting IgE antibodies to alpha-gal moieties, which are present on the Fab heavy chain portions of the antibody.

Radiocontrast media (RCM), narcotics, neuromuscular-blocking agents, and vancomycin are common causes of non-immunologic reactions. Such reactions may result from binding of these drugs to the G protein-coupled receptor, MrgprX2, whose analog in mice was recently shown to mediate mast cell activation by neuromuscular-blocking agents and fluoroquinolone antibiotics. Low-ionic strength radiocontrast media are less likely than high-ionic strength varieties to elicit a systemic reaction. Vancomycin produces a mast cell activation event known as red man syndrome, typically involving flushing without cardiovascular compromise, though hypotensive anaphylaxis may occur with an extremely rapid infusion. Reactions to vancomycin usually can be avoided by reducing the rate of administration of the antibiotic. In patients with systemic mastocytosis, these agents must be used cautiously, if at all, because their increased mast cell burden can result in increased mediator release.

Aspirin hypersensitivity typically manifests as either a respiratory or a cardiovascular reaction, although sometimes overlap is observed. Respiratory reactions include bronchospasm, nasal congestion, and rhinorrhea and may extend beyond the respiratory tract to include abdominal cramping, watery diarrhea,

and urticaria. Cardiovascular reactions, identical clinically to allergen-induced systemic anaphylaxis and shock, also can occur. In most cases such reactions appear to be pharmacologically (not IgE) mediated, and in sensitive subjects they can occur to any of the COX-1 inhibitors. Although COX inhibitors may shunt arachidonic acid metabolism to the lipoxygenase pathway, a mechanism to explain mast cell activation has not yet emerged. COX-2-selective inhibitors appear to be relatively safe in aspirin-sensitive asthmatics. However, they may cause cardiovascular collapse in those with a history of cardiovascular reactions and thus are contraindicated in this subgroup of patients. Less commonly, sensitivity occurs to only one of the drugs within this class and is due to IgE against an associated unique chemical moiety.

Foods

Foods are also a leading cause of anaphylactic reactions. Most cases of food-induced anaphylaxis in children occur to egg, peanut, cow's milk, wheat, or soy, whereas peanuts, tree nuts, and seafood account for most reactions in adults. Peanut allergy has doubled in prevalence over the past two decades in the United States and Europe but is uncommon in Asia. Apparently, the roasted forms used in the United States and topical ointments containing peanut oil used in Europe increase sensitization. Reactions to allergens in seeds such as sesame seem to be growing in importance, and a variety of different foods have proven to be important allergens in specific individuals. Food-induced reactions typically occur after a sensitive individual ingests that food, but they may also occur when a sensitive subject is kissed by someone who has recently ingested the food allergen.

Hypersensitivity to fresh fruit most commonly manifests as oral allergy syndrome (OAS), a form of contact urticaria that occurs within minutes of ingestion and presents as itching, burning, and swelling of lips, tongue, roof of the mouth, or throat. Rarely do these reactions progress to systemic anaphylaxis. Many of these sensitivities are associated with cross-reactivities between food and pollen allergens (e.g., melon with ragweed pollen; peach and apple with birch pollen). Also, the food epitopes associated with this syndrome are typically conformational (rather than linear), and thus they are more easily destroyed by heating, protease degradation, and acid denaturation.

Galactose-alpha-1,3-galactose moieties, also known as alpha-gal, are an increasingly recognized cause of anaphylaxis, particularly in the southeastern United States. Alpha-gal allergy is relatively unique in that the allergen is a polysaccharide, not protein, determinant. The enzyme that produces the alpha-gal linkage, alpha-1,3-galactosyltransferase, is functional in all orders of mammals except apes, Old World monkeys, and humans. Thus eating beef, pork, lamb, venison, or other mammalian meat can trigger anaphylaxis in sensitized individuals. The geographic distribution of alpha-gal allergy closely matches the natural range of the lone star tick, *Amblyomma americanum*. Epidemiologic evidence suggests that

production of IgE against alpha-gal is triggered by bites from the tick, possibly as a result of exposure to alpha-gal from animals the tick previously fed upon. Unlike most reactions triggered by foods, symptoms of alpha-gal-mediated anaphylaxis typically occur 3–7 h after ingestion of the offending food. Thus, reactions to alpha-gal are sometimes termed *delayed anaphylaxis to mammalian meat*. The cause of the delay in symptoms is not known but is likely due to delayed emergence of the multivalent antigen in the circulation. Present on glycolipids and glycoproteins, alpha-gal may be incorporated into chylomicrons, which enter the bloodstream via the thoracic duct several hours after eating, triggering symptoms after metabolic processing and resultant exposure of the antigen to mast cells and basophils.

Insects

Insect sting anaphylaxis is primarily caused by the Hymenoptera order that includes the families Apidae (honeybees, bumblebees), Vespidae (hornets, yellow jackets, paper wasps), and Formicidae (fire ants). Cross-reactivity within families is high but low between families. Furthermore, cross-reactivity explains why a person may exhibit an anaphylactic reaction on the first exposure to one insect's sting when previously exposed to a different one. In contrast to stinging insects, allergens from biting insects of the Diptera order (mosquitoes, gnats, midges, true flies) are salivary in origin and do not cross-react with Hymenoptera venom allergens. Anaphylaxis to these salivary proteins appears to be uncommon, but precise epidemiologic data is problematic because people are often unaware of an ongoing mosquito bite, and commercial diagnostic reagents of high quality are not yet commercially available.

Latex

Latex allergens are derived from the rubber tree, *Hevea brasiliensis*. Irritant dermatitis is the most frequent contact reaction and does not involve acquired immunity. Contact hypersensitivity results from cell-mediated immunity to haptenic chemicals added to latex during processing and produces a poison ivy-like local reaction. In contrast, immediate hypersensitivity occurs when IgE is made against the water-soluble, heat-stable, membrane-bound proteins naturally found in this plant-derived product. Cutaneous (elastic materials), mucosal or intravascular (catheters), oral (balloon), or inhaled (powdered latex gloves) routes of exposure have been well documented. IgE-mediated cross-reactivities between latex proteins with allergens in certain fresh foods such as banana, chestnut, avocado, kiwi, peach, bell pepper, and tomato have been reported and may necessitate avoidance of these foods.

Miscellaneous

Although food, drugs, insects, and latex are the most common triggers of anaphylaxis, exercise, seminal fluid, and progesterone are rare causes worth mentioning. Exercise-induced anaphylaxis is a form of physical allergy resulting from activation of mast cells. It can occur after mild to vigorous exercise and is often associated with ingestion of a specific food or medication, particularly wheat or shrimp. In such patients, exercise is not recommended 1 h before or within 4 h after eating. Seminal fluid has induced anaphylaxis by IgE to a specific protein in seminal plasma, spermatozoa, and exogenous allergens transferred through semen. Fertility is intrinsically unaffected and can be achieved with excellent success via in vitro methods. Finally, progesterone-induced anaphylaxis is a cyclic premenstrual reaction to progesterone produced during the luteal phase of a woman's menstrual cycle with a variety of presentations, including erythema multiforme, eczema, urticaria, angioedema, and anaphylaxis.

Epidemiology

Overall Incidence

Because of the lack of a precise definition, underreporting, and misdiagnosis, the annual incidence and prevalence of those at risk for anaphylaxis have been difficult to assess accurately. In the most comprehensive population survey study to date, it was estimated that the prevalence of anaphylaxis in the United States was at least 1.6 % and likely higher. Medications, foods, and insect stings were found to be the most common triggers, corroborating earlier studies. One estimate from an older study in the United States attributes approximately 1,500–2,000 deaths per year from systemic anaphylaxis. Nonfatal cases are much more common, estimated to occur at an incidence of 10–100 cases per 100,000 person-years. Furthermore, between 1 % and 15 % of the US population may be at risk for anaphylaxis from food, drugs, latex, or insect stings.

Drugs

Drugs are the most common cause of anaphylaxis overall, being responsible for 34 % of anaphylactic reactions, as well as the majority of cases of fatal anaphylaxis. Studies have estimated the rate of medication-induced reactions at 1 per 3,000 hospitalized patients. β-Lactam antibiotics and radiocontrast media provoke most such events, but the list of offending agents is lengthy and continues to increase. Furthermore, the risk of drug-induced anaphylaxis increases with age, which is most likely related to the higher likelihood of multiple drug use. During general anesthesia, systemic anaphylactic reactions occur with an estimated frequency of

about 1 in 4,000 to 1 in 25,000, and muscle relaxants, latex, and induction drugs are the three classes of agents most commonly implicated.

Foods

About a third of all anaphylactic reactions treated in US emergency departments are food induced, and these reactions account for about 100 deaths per year. Population data indicate that 31 % of anaphylactic episodes are food related, trailing slightly behind drugs as the most common cause of anaphylaxis. However, because food allergy is more common in children than adults, this figure likely underestimates the prevalence of food-induced anaphylaxis given a bias toward adults in the study populations to date. Food allergy is found in about 6 % of children and 3 % of adults, placing these individuals at risk for food-induced anaphylaxis. Sensitivities to peanut, tree nuts, and seafood are typically lifelong, whereas most children lose sensitivities to cow's milk, egg, wheat, and soy by 5 years of age. About 20 % of children lose peanut sensitivity by school age. However, a small portion will regain the sensitivity later in life, particularly if they continue to avoid it.

Insects

Systemic allergic reactions to insect stings are reported by 0.4–3 % of individuals, comprising 20 % of all anaphylactic reactions. The incidence of Hymenoptera venom allergy in children is approximately 0.4–0.8 % with clinical features that usually range from urticaria to anaphylaxis. There is a 2:1 male-to-female ratio that probably reflects relative exposure. Annually, about 45 deaths are attributed to insect stings in the United States. Approximately half of the fatal reactions occur in individuals with no prior history of allergic reactions to stings. Many more men than women die from insect sting reactions, and greater than 80 % of the deaths from insect stings occur in persons older than 40 years.

A European multicenter study of insect sting reactions demonstrated that the most severe reactions occurred in those subjects with high baseline serum tryptase levels (>5 μg/l), though mast cell clonality was not assessed. An investigation in Italy established that the majority of this risk is held by individuals with underlying clonal mast cell disease, such as systemic mastocytosis. Indeed, among individuals with a systemic reaction to an insect sting, venom IgE hypersensitivity, and an elevated serum baseline tryptase (>11.4 ng/ml), the majority were determined to have clonal mast cell disease—a rate much higher than the general population. Moreover, in a series of patients with severe reactions to insect stings and normal serum tryptase (<11.4 μg/l), 16 of 22 were ultimately found to have systemic mastocytosis; these data still require confirmation using a larger, more generalized population. Conversely, the incidence of Hymenoptera venom allergy among adults with mastocytosis is reported at 6–27 %.

Latex

The incidence of latex allergy dramatically increased when the widespread use of contact precautions was implemented throughout the health-care system. Estimates of the prevalence of latex hypersensitivity range from 1 % to 6 % in the general population and about 10 % among regularly exposed health-care workers. Other populations at risk include those with congenital neural tube defects, congenital urinary tract disorders, and others who have undergone multiple surgical procedures early in life. However, the incidence of latex-induced anaphylaxis now appears to have declined dramatically with the elimination of powdered latex gloves, better recognition of the condition, and the availability of latex-free paraphernalia at most hospitals.

Diagnosis and Differential Diagnosis

Signs and Symptoms

Systemic anaphylaxis may include any combination of common signs and symptoms (Table 42.1). In the acute event, the initial diagnosis is based on clinical observations and a history of exposure to an offending agent. Cutaneous manifestations of anaphylaxis, including urticaria and angioedema, are by far the most common symptoms, occurring in greater than 90 % of cases. The respiratory and cardiovascular systems are involved less frequently than the skin, but they are responsible for producing signs and symptoms that are clinically more recognized as systemic anaphylaxis. Dyspnea, wheezing, laryngeal edema, presyncope, syncope, and hypotension are signs and symptoms associated with severe reactions. Gastrointestinal manifestations, such as

Table 42.1 Clinical signs and symptoms of anaphylaxis

Category	Examples
Skin and mucosal symptoms	Pruritus
	Urticaria
	Flushing
	Angioedema
Respiratory symptoms	Dyspnea
	Wheeze or bronchospasm
	Stridor
	Hypoxemia
	Decreased peak expiratory flow
Gastrointestinal symptoms	Vomiting
	Diarrhea
	Crampy abdominal pain
End-organ dysfunction	Hypotension
	Collapse
	Syncope
	Incontinence

nausea, vomiting, diarrhea, and abdominal pain, also affect about a third of patients. Headache, rhinitis, substernal pain, pruritus, and seizure occur less frequently.

Time Course

Symptom onset varies widely but generally occurs within seconds or minutes of exposure. Anaphylaxis can be protracted, lasting for more than 24 h, or recur after initial resolution. The incidence of biphasic reactions is estimated to be less than 5 %, with food-induced reactions being a negative risk factor and hypotensive events or an unknown trigger being positive risk factors. Manifestations can be identical, worse, or less severe than the initial phase, and fatalities have occurred. The median time of onset is 11 h from the moment of likely exposure but varies widely. The cause of biphasic reactions is unknown. Current guidelines recommend observing anaphylaxis patients for 6–24 h after successful treatment of the initial reaction; observation for a longer period may be prudent for those patients with hypotensive reactions or an unknown trigger.

Clinical Diagnostic Criteria

Up to 57 % of persons presenting to emergency rooms with clinical signs and symptoms of anaphylaxis can be misdiagnosed, due in equal part to the varying symptoms of anaphylaxis and the time needed to perform and report the necessary laboratory tests. A working diagnosis in this setting can be based entirely on clinical criteria, with the goal of administering proper treatment without delay.

Patients in the emergency room can be diagnosed with anaphylaxis in three different scenarios if the following criteria are fulfilled (Table 42.2). In the first instance, history of exposure to antigen is not needed, and the diagnosis is made with evidence of IgE-mediated skin findings plus either respiratory symptoms or end-organ dysfunction. In the second, after exposure to a likely allergen, a patient must rapidly develop signs or symptoms in two or more organ systems, including the skin and respiratory, cardiovascular, and gastrointestinal systems. In the final situation, a patient only needs to develop hypotension if they have recently been exposed to a known allergen for that patient.

Laboratory Diagnosis

Anaphylaxis can be precisely confirmed in the laboratory by demonstrating antigen-specific IgE (sensitization) and an elevated level of mast cell mediators in serum or plasma (mast cell activation) (Table 42.3). Skin testing or in vitro measurement of

Table 42.2 Clinical criteria for the diagnosis of anaphylaxis in an emergency room setting

Clinical scenario[a]	Time course	Requirements
Unknown allergen exposure	Rapid onset (minutes to several hours)	Skin or mucosal symptoms, *plus either*:
		Respiratory symptoms
		End-organ dysfunction
Exposure to *likely* allergen	Rapid onset (minutes to several hours)	*Two or more of the following*:
		Skin or mucosal symptoms
		Respiratory symptoms
		Persistent gastrointestinal symptoms
		End-organ dysfunction
Exposure to *known* allergen	Rapid onset (minutes to several hours)	Hypotension

[a]Anaphylaxis is considered likely when requirements for any one of the three scenarios are met

Table 42.3 Laboratory tests in the differential diagnosis of anaphylaxis

Test	Comment
Serum or plasma tryptase	Mature tryptase or total tryptase in either serum or plasma peak 15–60 min after the onset of anaphylaxis and then decline with a $t_{1/2}$ of ~2 h. Comparing acute and baseline levels improves sensitivity and specificity
Plasma histamine	Histamine in plasma peaks 5–10 min after symptom onset and declines to baseline by 10–30 min. Histamine may be released ex vivo by passing basophils in blood through a small-bore needle under vacuum or when blood clots
24-h urinary histamine or histamine metabolites (methylhistamine, methylimidazole acetic acid)	May be elevated in the urine for up to 24 h after symptom onset, but histamine-containing foods and histamine-producing bacteria may be problematic
Plasma fractionated metanephrines	Elevated in pheochromocytoma, not anaphylaxis
24-h urinary fractionated catecholamines and metanephrines	Elevated in pheochromocytoma, not anaphylaxis
Urinary 5-hydroxyindoleacetic acid	Elevated in carcinoid syndrome, not anaphylaxis
Urinary serotonin	Elevated in carcinoid syndrome, not anaphylaxis
Vasoactive intestinal peptide	Elevated in gastrointestinal tumors secreting vasoactive mediators, not anaphylaxis
Calcitonin	Elevated in gastrointestinal tumors or medullary thyroid carcinomas secreting vasoactive mediators, not anaphylaxis
C1 esterase inhibitor	Decreased function, with normal or decreased level, in hereditary angioedema, not anaphylaxis
C4	Decreased in hereditary angioedema, not anaphylaxis

antigen-specific IgE should be delayed for at least 2 weeks after the precipitating event to prevent false-negative results. An increased level of mature tryptase in serum, which peaks 15–60 min after the onset of anaphylaxis and then declines with a half-life of about 2 h (normal levels being undetectable), indicates that mast cell

activation occurred. Alternatively, a significant increase in total tryptase levels during the acute event compared to a baseline level (which can be obtained either before or more than 24 h after signs and symptoms have resolved) can also be used. Current guidelines recommend that a significant increase in serum total tryptase be defined as a level greater than 2 ng/ml plus 120 % of the baseline tryptase. For example, in a patient with a baseline serum tryptase of 5 ng/ml, a level greater than 8 ng/ml would be considered significantly increased [2 + (baseline tryptase × 1.2) = 2 + (5 × 1.2) = 8]. In systemic anaphylaxis induced experimentally by an insect sting, the increased serum level of mature tryptase correlates closely with the drop in mean arterial pressure, indicating that the magnitude of mast cell activation is a primary determinant of clinical severity. Although an elevated serum mature tryptase level may be useful for distinguishing anaphylaxis from other conditions in the differential, some cases of putative anaphylaxis, particularly after food ingestion, are not associated with an elevated level of mature tryptase. This observation raises questions of whether there are anaphylactic pathways that bypass mast cells, perhaps involving basophil activation.

Plasma histamine levels rise more rapidly than those of mature tryptase, 5–10 min after symptom onset, and remain elevated for a very limited period of time, usually only 15–30 min. Thus it is usually less useful than serum tryptase because most patients are seen after peak histamine levels have declined to baseline. Urinary histamine or methylhistamine levels also may reflect overall levels of released histamine but are affected by ingested histamine-containing foods, histamine-producing mucosal bacteria, and variability in histamine metabolism.

Differential Diagnosis

Anaphylaxis should be distinguished from a variety of disorders with overlapping presentations. Vasovagal syncope is the most common condition that mimics anaphylaxis. The presence of bradycardia and lack of cutaneous symptoms such as urticaria, pruritus, and angioedema during a vasovagal event helps distinguish it from anaphylaxis. However, bradycardia, though uncommon, can occur during anaphylaxis, possibly indicating underlying coronary artery disease or due to a cardioinhibitory reflex. Flushing disorders such as carcinoid syndrome and pheochromocytoma can be confused with anaphylaxis but are not typically associated with urticaria or hypotension. Determining urinary serotonin, 5-hydroxyindole acetic acid, catecholamines, and metanephrines, along with plasma fractionated metanephrines, confirm the diagnosis of these disorders. Nonorganic diseases such as panic attacks and vocal cord dysfunction can be a challenge to distinguish from anaphylaxis, especially by history alone, but nevertheless must be considered.

Scombroidosis presents with flushing, palpitations, headache, and gastrointestinal symptoms and occurs within 5–90 min of ingesting histamine in poorly stored fish. Signs and symptoms can last several hours depending on the amount of histamine ingested. It usually responds to histamine blockers but occasionally requires epinephrine and intravenous (IV) fluids.

Acute attacks of hereditary and acquired angioedema due to C1 esterase inhibitor deficiency are not associated with pruritic urticaria, and they persist longer than attacks of anaphylaxis. Hypotensive shock can occur in the absence of mast cell activation after infusion of substances that activate the contact (factor XII) pathway, leading to excessive bradykinin production. This was recently seen with injections of heparin contaminated with an over-sulfated chondroitin sulfate. Shock due to complement activation by contaminated hemodialysis tubing, without involving mast cell activation, also has been reported. Acute serum sickness, various cell activation syndromes, endotoxin-mediated septic shock, and superantigen-mediated toxic shock syndromes present with fever, which is not characteristic of anaphylaxis by itself. Also, hypoglycemia, seizure, and primary pulmonary or cardiac events present with similar symptoms.

Systemic mastocytosis is an important condition to consider in the differential diagnosis of anaphylaxis. In adults, a somatic activating mutation in the gene for c-kit in mast cell progenitors results in an excessive body burden of mast cells. In children with this disorder, the disease may regress spontaneously. Patients with too many mast cells are at increased risk for anaphylaxis, and anaphylaxis may be a presenting manifestation of systemic mastocytosis. For example, anaphylaxis to an insect sting should raise the possibility of systemic mastocytosis. Diagnostic tests for systemic mastocytosis might include a biopsy of a skin lesion suspected to be urticaria pigmentosa, a bone marrow biopsy, polymerase chain reaction test for an activating mutation of c-kit (most commonly the D816V mutation), and an elevated serum level ($\geq$20 ng/mL) of total tryptase during a non-acute interval. Bone marrow biopsies for diagnosing systemic mastocytosis, stained for mast cells (anti-tryptase or anti-CD117 immunohistochemistry being most sensitive), may reveal mast cell aggregates, spindle-shaped mast cells, or mast cells expressing CD2 or CD25; flow cytometry of the bone marrow aspirate may reveal mast cells expressing surface CD2 and CD25.

Treatment

Acute

Fatal outcomes in anaphylaxis are principally due to either airway constriction or hypotension. Accordingly, the acute treatment of systemic anaphylaxis requires that airway patency, blood pressure, and cardiac status be assessed (Fig. 42.1 and Table 42.4). Oxygen should be administered and an airway established. Epinephrine, the most critical drug to administer, should be immediately injected intramuscularly (IM) into the thigh for any signs of airway compromise. The dose is 0.2–0.5 mg for adults and 0.01 mg/kg, up to 0.3 mg, for children. The dose may be repeated every 10–20 min. Early use is associated with improved outcomes. Patients exhibiting signs and symptoms of hypotension should immediately assume the Trendelenburg position to prevent progression to anaphylactic shock and the so-called empty ventricle syndrome and then they should receive epinephrine. Most hypotensive

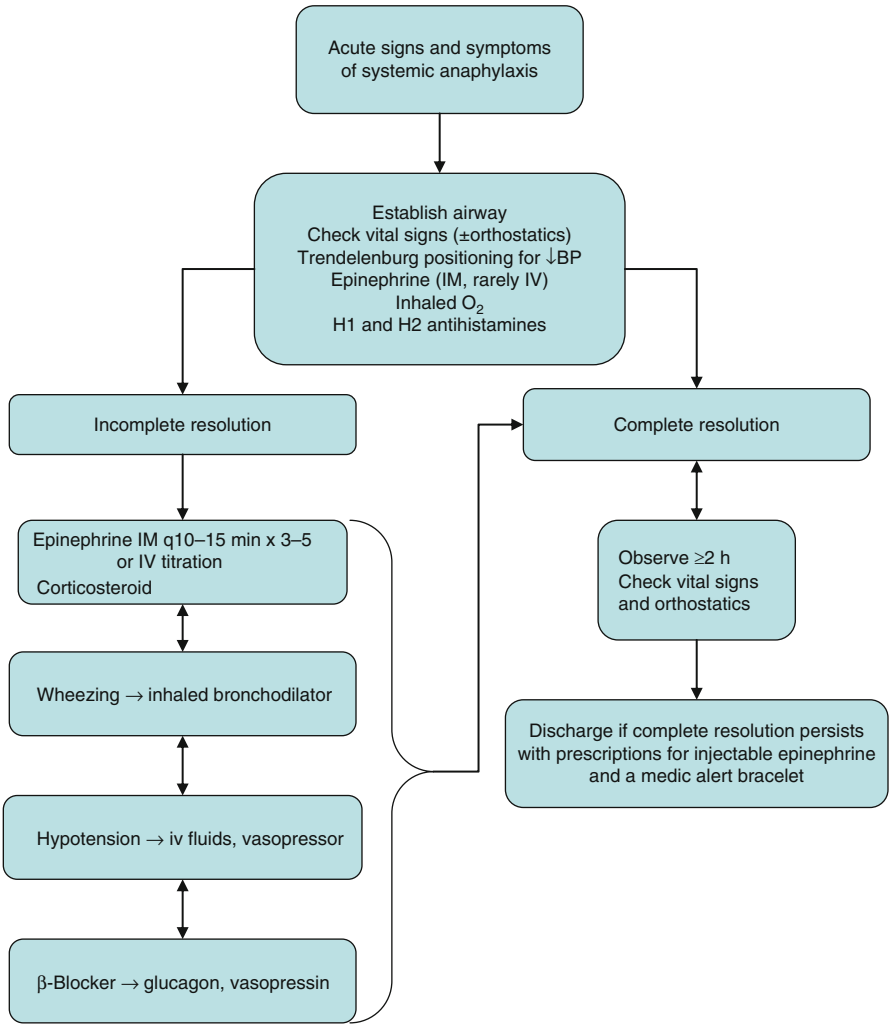

Fig. 42.1 Acute management of systemic anaphylaxis. *BP* blood pressure, *IM* intramuscular, *IV* intravenous, O_2 oxygen

anaphylactic deaths are preceded by syncope occurring in the sitting or upright position. Assuming the Trendelenburg position, even without the administration of epinephrine, is likely to abort any life-threatening shock from occurring.

Epinephrine relaxes bronchial smooth muscle and improves vasomotor tone and vasopermeability, thereby counteracting bronchospasm, hypotension, and tissue edema. However, the benefits of epinephrine need to be weighed against its disadvantages in elderly patients and in those with cerebrovascular disease, coronary artery disease, hypertension, diabetes, hyperthyroidism, cardiomyopathy, and narrow-angle glaucoma, where it can precipitate myocardial infarction,

Table 42.4 Drugs and other agents used to treat anaphylaxis

Drug/agent	Dose and route of administration	Comment
Alpha and beta adrenergic agonists		
Epinephrine	0.3–0.5 mg IM (adult) or 0.01 mg/kg IM (child)	*Initial drug of choice* should be given immediately but may repeat q10–15 min
	0.1–1.0 mg in 10 ml normal saline IV bolus	If no response to IM administration and patient in shock with cardiovascular collapse
	0.1–1.0 mg in 10 ml normal saline IV bolus	Delivered with a calibrate pump and titrated to blood pressure in an emergency department or intensive care setting
	1 mg in 100 ml normal saline at 30–100 ml/h continuous IV infusion	
Antihistamines		
Diphenhydramine	25–50 mg (adult) or 1–2 mg/kg (child) PO, IM, or IV	Do not give in lieu of epinephrine. Route of administration depends on severity of symptoms. Can consider second generation-antihistamine if PO route
Ranitidine	50 mg (adult) or 1 mg/kg (child) IV	Other H2 receptor antihistamines also acceptable. Cimetidine administered too rapidly may be associated with hypotension
Corticosteroids		
Methylprednisolone	1–2 mg/kg IV	Do not give in lieu of epinephrine. No conclusively proven benefit. For milder episodes, may consider prednisone 30–60 mg (or 1 mg/kg) PO
Drugs for resistant bronchospasm		
Aerosolized β-agonist (albuterol)	2–6 puff as MDI or 2.5–5 mg in 3 ml saline nebulized	For bronchospasm not responding to epinephrine. May repeat as necessary
Volume expanders		
Crystalloids (normal saline or Ringer's lactate)	1–2 L IV over 15–60 min (adult) or 30 ml/kg IV over 60 min (child)	Rate of administration titrated against blood pressure response. After initial infusion, further administration requires tertiary care monitoring. In patients receiving β-blockers, larger amounts may be needed
Pressors and inotropes		
Dopamine	1–50 mcg/kg/min (adult) or 5–20 mcg/kg/min (child)	Rate of administration titrated against blood pressure response

Table 42.4 (continued)

Drug/agent	Dose and route of administration	Comment
Norepinephrine	2–4 mcg/min (adult) or 0.1–2 mcg/kg/min (child)	As above
Vasopressin	40 IU IV or 0.01–0.04 IU/min (adult)	As above. May facilitate effects of epinephrine and norepinephrine
Drugs used in patients who are β-blocked		
Glucagon	1–5 mg (adult) or 20–30 mcg/kg (child) IV push, then 5–15 mcg/min IV	Drug of choice in patients with hypotension that fails to respond to epinephrine and volume expansion. Titrate rate against blood pressure
Atropine sulfate	0.5 mg (adult) or 0.02 mg/kg (child)	Useful to reverse paradoxical bradycardia in the setting of hypotension. May repeat q3–5 min to a maximum of 3 mg in adults
Ipratropium	0.5 mg (adult) or 0.25–0.5 mg (child) nebulized	Might be consider as an alternative or adjunctive to inhaled β-agonist for bronchospasm

IM intramuscular, *IU* international units, *IV* intravenous, *MDI* metered-dose inhaler, *PO* by mouth

arrhythmias, stroke, and pulmonary edema. Despite these relative contraindications, there are no absolute contraindications to administering epinephrine for systemic anaphylaxis. The route of administration should be IM into the lateral midthird of the thigh to obtain good systemic distribution. IM administration reaches peak serum concentration in less than 10 min versus around 30 min for subcutaneous injections. IV administration of a 1 mg/100 mL solution, titrated clinically at 30–100 mL/h, should only be considered in a medical facility with appropriate equipment and expertise for administration and monitoring. It should be reserved for refractory anaphylaxis or circulatory collapse because of the risk of serious complications.

Other drugs used to treat anaphylaxis include antihistamines, prednisone, volume expanders, and vasopressors. Parenteral administration of H1 receptor (diphenhydramine, 1–2 mg/kg up to 50 mg) and H2 receptor (ranitidine, 300 mg IV over 5 min) antihistamines may prevent progression of some of the signs and symptoms, particularly urticaria and pruritus, but are not likely to reverse hypotension or tissue edema. High-quality data on corticosteroid use in anaphylaxis are lacking, but studies thus far have failed to demonstrate any benefit in preventing biphasic reactions. If given, methylprednisolone or a comparably potent corticosteroid such as prednisone may be used at a dose of 1–2 mg/kg. An aerosolized β-agonist might attenuate bronchospasm not responding to parenteral epinephrine. Volume expanders should be administered for persistent hypotension and the rate titrated against blood pressure response. If hypotension persists despite Trendelenburg positioning, epinephrine, and volume expanders, a pressor such as dopamine or norepinephrine should be initiated.

Patients taking antihypertensive medications, in particular β-blockers, ACE inhibitors, and diuretics, may be at increased risk for severe systemic anaphylaxis. Those taking a nonselective β-blocker are more likely to experience severe anaphylaxis characterized by paradoxical bradycardia, profound hypotension, and severe bronchospasm because the actions of epinephrine released naturally are blocked. Furthermore, they are often resistant to administered epinephrine. Glucagon administered at the initial dose of 1–5 mg IV for adults and 20–30 mcg/kg IV for children, followed by infusion of 5–15 μg/min titrated against blood pressure, should be considered. Glucagon increases cyclic adenosine monophosphate (cAMP), which increases cardiac output. Vasopressin (40 IU IV or 0.01–0.04 IU/min IV) also should be considered in epinephrine-resistant hypotensive anaphylactic shock. Atropine sulfate (0.3–0.5 mg IV) should be considered if bradycardia is associated with hypotension. Ipratropium might be considered as an alternative to or added to inhaled β-adrenergic agents for wheezing.

Prevention

Patients at greatest risk for anaphylaxis are those who already have experienced an anaphylactic reaction. An auto-injectable epinephrine device (Auvi-Q®, Epi-Pen®, Epi-Pen Jr®, or Twinject®) should be prescribed and available at all times. Patient compliance with these lifesaving devices is suboptimal secondary to lack of knowledge about anaphylaxis and the proper instruction about use of the device. A demonstration using a training device should accompany every prescription. Furthermore, the patient should be instructed to check the expiration date frequently and keep the device at room temperature. Temperatures at either extreme will affect epinephrine stability and cause the solution to become yellow or cloudy. Medical alert jewelry, available on the Internet, also should be recommended. Finally, a referral to an allergist is recommended for further evaluation and treatment options.

In subjects with recurrent anaphylaxis, prophylactic use of H1 and H2 receptor antihistamines appears to be beneficial. A leukotriene antagonist and/or COX inhibitor may provide additional benefit but have not been systematically studied. In several small case series, omalizumab, a monoclonal antibody that binds the Fc portion of IgE antibodies, has shown promise in preventing anaphylaxis in subjects with idiopathic anaphylaxis and systemic mastocytosis. A randomized, placebo-controlled trial of omalizumab for recurrent anaphylaxis is currently underway. Cyclosporine A (3–5 mg/kg) might be considered in difficult cases of recurrent anaphylaxis because of its ability to inhibit mast cell activation in vitro and cutaneous mast cell activation (urticaria) in vivo. Finally, tyrosine kinase inhibitors, such as imatinib, have proven to be effective in certain subsets of patients with systemic mastocytosis, as well as in animal models of food-induced anaphylaxis. Whether corticosteroids, which do not inhibit mast cell activation in vitro or immediate skin test responses to allergens in vivo, provide a major benefit in most patients with recurrent anaphylaxis is debatable.

Specific anaphylactic syndromes have unique considerations. Food-allergic subjects are asked to avoid the offending agent. Prevention of peanut allergy in young children at high risk for developing this condition, namely, infants with eczema, a

low level of peanut IgE sensitization, and a negative oral peanut challenge test, by having them ingest peanut or placebo at least three times per week for 5 years, appeared to occur, because the incidence of peanut allergy dramatically decreased in those ingesting peanut compared to placebo. Education about how to read food labels and avoid exposure in the community is essential. Referral to Food Allergy Research & Education, formerly the Food Allergy Network, is also recommended. A school action plan should be put in place for all children. Definitive treatment such as immunotherapy is not available currently, but trials are now being conducted for certain foods such as peanuts. Anti-IgE therapy to reduce sensitivity is another therapy being evaluated experimentally.

Radiocontrast media reactions can be prevented or attenuated by pretreatment with prednisone, 50 mg, given at 13, 7, and 1 h prior and 50 mg of diphenhydramine and 300 mg ranitidine orally or IV 1 h prior. Administration of 25 mg of ephedrine orally 1 h prior may provide a small additional benefit. In general, patients who are sensitive to an antibiotic need to avoid it. However, desensitization protocols for many patients with IgE-mediated drug allergies are available. Desensitization protocols also exist for non-IgE-dependent aspirin-sensitive patients, and they are particularly effective for those with asthma and nasal polyps. In both cases, desensitization lasts for as long as the drug is continuously/regularly administered; in contrast to immunotherapy, once the drug has cleared, sensitivity is likely to return.

Venom immunotherapy is recommended for anaphylaxis associated with Hymenoptera stings. In children and adults, venom immunotherapy is safe and 95 % or more effective at attenuating clinically significant reactions to future stings. In children, there is also a significantly lower risk of systemic reaction to stings even 10–20 years after treatment is stopped, which seems to be greater than the temporal benefit seen in adults. For patients with severe anaphylactic reactions to insect venom, especially those with elevated baseline serum tryptase, an evaluation for clonal mast cell disease should be considered.

In addition to prophylactic pharmacologic measures, systemic mastocytosis patients should avoid using direct mast cell agonists such as codeine, morphine, and vancomycin. Given the high prevalence of allergy to Hymenoptera venom in those with systemic mastocytosis, all such patients should be tested for stinging insect sensitivity and, if positive, receive immunotherapy. Women who experience seminal fluid-induced anaphylaxis should have their male partner wear a condom; desensitization protocols are also available at some centers. Finally, progesterone-induced anaphylaxis may respond to the luteinizing hormone-releasing hormone analog Lupron or to oophorectomy.

Evidence-Based Medicine, Individualized Medicine, and Future Directions

Because anaphylaxis is a life-threatening condition, ethical limitations impede systematic or provocation studies. Consequently, human data on the safety and efficacy of pharmacological treatments for anaphylaxis are limited. Management guidelines, which emphasize a central role for epinephrine, are based largely on expert opinion

and non-controlled studies. Reactions can spontaneously resolve with endogenous compensatory responses, but failure to use adrenaline has been considered a major factor contributing to lethal outcomes. Ongoing and future research will provide more precise diagnostic tools that also delineate different pathways of anaphylaxis, indicating which cell types and biochemical pathways are involved. The factors that increase risk for an anaphylactic response will be better understood, and individuals with clonal mast cell disease may benefit from therapies that target their mutated protein, depending on the specific mutations present, e.g., c-kit-activating mutations that increase the risk of severe anaphylactic reactions to insect venoms (see Zanotti et al.). Consequently, interventions that reduce anaphylactic risk, including more effective and long-lasting desensitization therapies, such as peanut immunotherapy in infants that are sensitive to but not yet clinically reactive to peanut (see Du et al.) and that more effectively reverse the acute signs and symptoms of this potentially fatal disorder will be developed.

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