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Allergic Disorders

PART XIII

Chapter 182

Allergy and the Immunologic Basis of Atopic Disease

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Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin E (IgE) antibodies to the antigens that trigger their illness. The term *allergy* represents the clinical expression of IgE-mediated allergic diseases that have a familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal (GI) tract, and nose. The significant increase in the prevalence of allergic diseases in the last few decades is attributed to changes in environmental factors such as exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity, and perhaps a decline in certain infectious diseases (hygiene hypothesis).

The incidence of allergic asthma and atopic dermatitis started to grow to epidemic proportions after the 1960s. Since 2000, the prevalence of food allergy, eosinophilic esophagitis, and drug-induced anaphylaxis has also risen to epidemic proportions. Currently more than 1 billion patients worldwide are expected to have at least one kind of allergic disease. The hygiene hypothesis, biodiversity hypothesis and epithelial barrier hypothesis are the three main hypotheses that propose mechanisms for the development of allergic diseases.

HYGIENE HYPOTHESIS

The relatively recent onset of the epidemics of allergic, autoimmune, and metabolic conditions leads to the question of what might underlie their development. A prominent hypothesis is the hygiene hypothesis, which proposes that certain microorganisms or infections protect against inflammatory diseases, and that their loss, due to hygiene measures, results in an increase in allergy, asthma, and autoimmunity. Growing up on a traditional farm has a protective effect from asthma and allergies, which provides a prominent example of the hygiene hypothesis. Children in Amish communities in the United States, where traditional dairy farming is practiced, are highly protected from asthma and allergies. In contrast, Hutterite communities have a significantly higher prevalence of asthma and allergies in children. Interestingly, they practice industrialized farming with extensive cleaning measures. Early development of a **T-helper type 1 (Th1)** response together with **T-regulatory cell (Treg)** response were proposed to play a role in prevention of allergic diseases.

BIODIVERSITY HYPOTHESIS

Allergic diseases are associated with a microbiome with increased colonization of opportunistic pathogens. The biodiversity hypothesis states that the observed increase in allergies is due to a loss of symbiotic relationships with bacteria and dysbiosis caused by changes in the microbiome of the gut, skin, and respiratory system. Healthy microbiota on the surface of the mucosal barrier regulates many aspects of epithelial barrier homeostasis, such as the modulation of barrier permeability and expression of epithelial barrier molecules, angiogenesis, vascular permeability, local microinflammation, and mucosal tolerance. Young children at risk of developing allergies have been shown to suffer from gut microbiome dysbiosis with an overall reduced microbiome diversity. The dysbiotic microbiota has been characterized by an underrepresentation of certain bacterial taxa that may produce immune regulatory and epithelial barrier healing or protective factors, such as short-chain fatty acids, retinoic acid, and vitamin D.

Several shortcomings of the hygiene and biodiversity hypotheses include the fact that water sanitation was established in many western cities in the 1920s, but allergy and asthma epidemics only started in the 1960s. The protective role of parasitic infections that increase biodiversity has been questioned for the same reason. Many parasitic infections started to decrease in 1910 in New York, whereas allergies started to increase after the 1960s. Allergic asthma is still on the rise in some cities in Asia and Africa, which have low standards of hygiene. Another limitation of the hygiene hypothesis and biodiversity hypothesis is that probiotics are not viable alternatives for the prevention or treatment of allergies. Moreover, studies of migrants who move from developing countries to affluent regions demonstrate a rapid increase in asthma and allergic diseases. It appears that domestic living conditions, increased birth by cesarean section, antibiotic usage, dietary practices, urbanization, and indoor air pollution are more prominent factors compared with general public hygiene.

EPITHELIAL BARRIER HYPOTHESIS

The epithelial barrier hypothesis is a broader hypothesis that covers hygiene and biodiversity hypotheses and adds further insights in the pathogenesis and recent development of allergic diseases. The defective epithelial barrier concept also applies to many autoimmune and metabolic diseases showing increased prevalence during the last few decades, such as diabetes, rheumatoid arthritis, multiple sclerosis, liver steatosis, and obesity. There is epidemiologic evidence from humans and disease models in laboratory animals that demonstrate that even trace amounts of certain toxic substances can damage epithelial barriers, initiate inflammation of the epithelium, and increase microbial dysbiosis and bacterial translocation toward the inside and beneath the epithelium. The epithelial barrier consists of four main components: the epithelial microbiota; the epithelial cell; structural proteins, such as filaggrin, loricrin, and involucrin and tight junctions and adherence junctions; and secreted epithelial products, such as mucus, antimicrobial peptides and fatty acids. Humans are exposed daily to a variety of toxins and chemicals, and substantial data demonstrate disruption of the epithelial barrier by allergens, certain bacteria and their toxins, fungi, viruses, laundry and dishwasher detergents, household cleaners, surfactants, enzymes and emulsifiers used in the food industry, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics.

Epithelial cell activation and release of epithelial cell cytokines, such as interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) play a major role in the development and exacerbation of allergic diseases. Local tissue inflammation opens epithelial barriers. Open epithelial barriers in the mucosa allow the entrance of foreign substances, including allergens, into deeper tissues. Both Th1 and **T-helper type 2 (Th2)** inflammation affect the skin and mucosal epithelial barriers. Th2 cells and group 2 innate lymphoid cells (ILCs-2) play major roles utilizing IL-13 as major cytokines in the opening of the tight junction barrier.

Microbial dysbiosis caused by transepithelial translocation of commensal microbes, colonization by opportunistic pathogens, and decreased biodiversity are hallmarks of barrier damaged tissues. Colonization by opportunistic pathogens in the microbiota takes place in tissues with a defective epithelial barrier. A dysregulated subepithelial immune response, local inflammation, and incorrect regeneration and remodeling take place as the continuum and chronicity of the local inflammation. Migration of inflamed cells to other affected tissues and systemic low-level immune activation and microinflammation are additional players in the development and exacerbation of many chronic inflammatory diseases (Fig. 182.1).

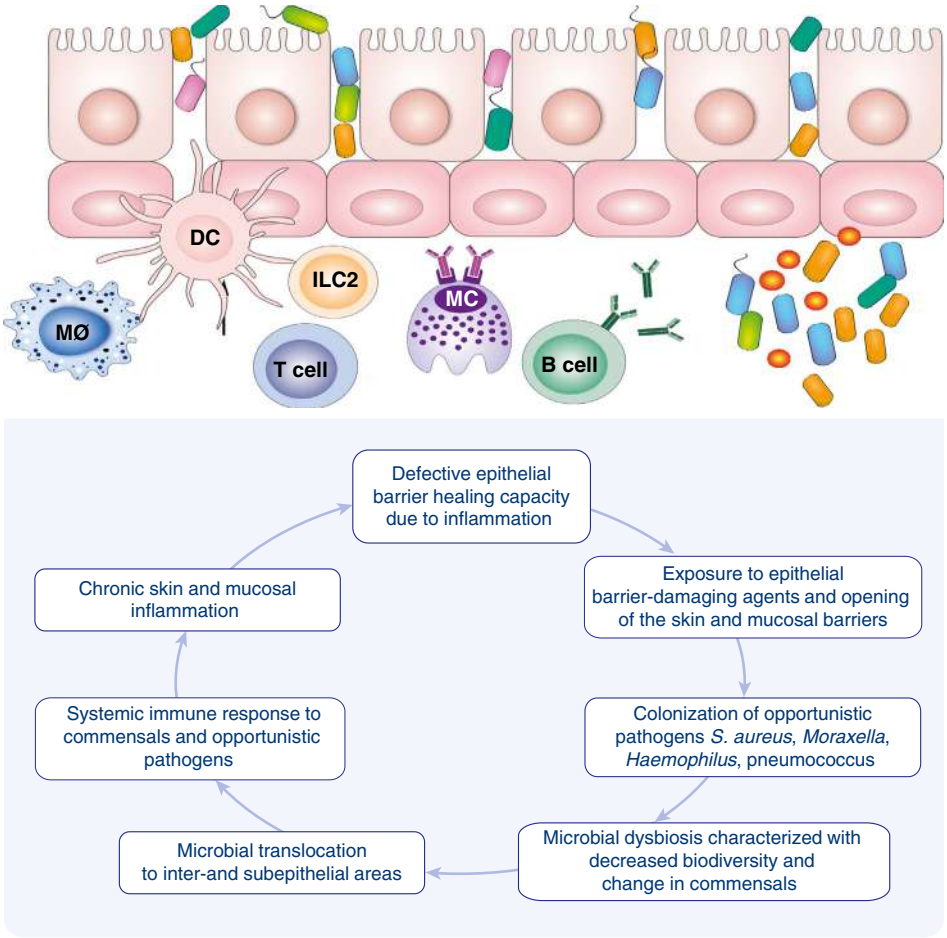

Fig. 182.1 The physiopathology of the epithelial barrier hypothesis. Genetic defects in barrier-related molecules or exposure to epithelial barrier-damaging agents cause an opening of the skin and mucosal tight junction barriers. This is followed by translocation of microbiota to inter- and subepithelial areas and colonization of opportunistic pathogens, such as *Staphylococcus aureus*, *Moraxella*, *Haemophilus* and pneumococcus. An immune response develops toward commensals and opportunistic pathogens in the gut and respiratory system and systemic inflammation takes place. In most cases of allergic diseases, a systemic type 2 inflammation predominates, and is directed against allergens, but also commensals and opportunistic pathogens. Anti–*S. aureus* antibodies show a very high prevalence in asthma, chronic sinusitis, and atopic dermatitis. This is associated with microbial dysbiosis and decreased biodiversity of commensals. Chronic inflammation in the subepithelial area develops as the main pathogenetic feature of these diseases. Defective epithelial barrier healing capacity due to inflammation and epigenetic changes take place, developing a vicious circle of leaky barriers, microbial dysbiosis, and chronic inflammation. DC, Dendritic cell; IL, interleukin; ILC, innate lymphoid cells; MC, mast cell; Mø, macrophage.

KEY ELEMENTS OF ALLERGIC DISEASES

Allergens

Allergens are almost always *proteins,* but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response on subsequent exposure to the same protein. Biochemical properties of the allergen; stimulating factors of the innate immune response around the allergen substances at the time of exposure; stability of the allergen in the tissues, digestive system, skin, or mucosa; and the dose and time of stay in lymphatic organs during the interaction with the immune system are factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins with a molecular weight of 10-70 kDa. Molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils. Most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach **antigen-presenting cells (APCs)** for stimulation of the immune system. Allergens frequently contain **proteases**, which promote skin and mucosal epithelial barrier dysfunction and increase allergen penetration into host tissues. A relatively high dose of exposure and stability of the allergenic protein in body fluids to reach the immune cells are important determinants of an allergen. Low molecular weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of *biologics* in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose.

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of **Th2** cells that secrete cytokines, such as IL-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on skin-prick testing. The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 182.2). IL-5 and IL-9 are important in the differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. T-cell and eosinophil migration to allergic inflammation areas are controlled by IL-4 and IL-13 upregulating their adhesion to endothelial cell walls. IL-9 is responsible for mucus production. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and **TSLP** secreted from epithelial cells on exposure to allergens and respiratory viruses contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergens results in activation and proliferation of **Th1** cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because

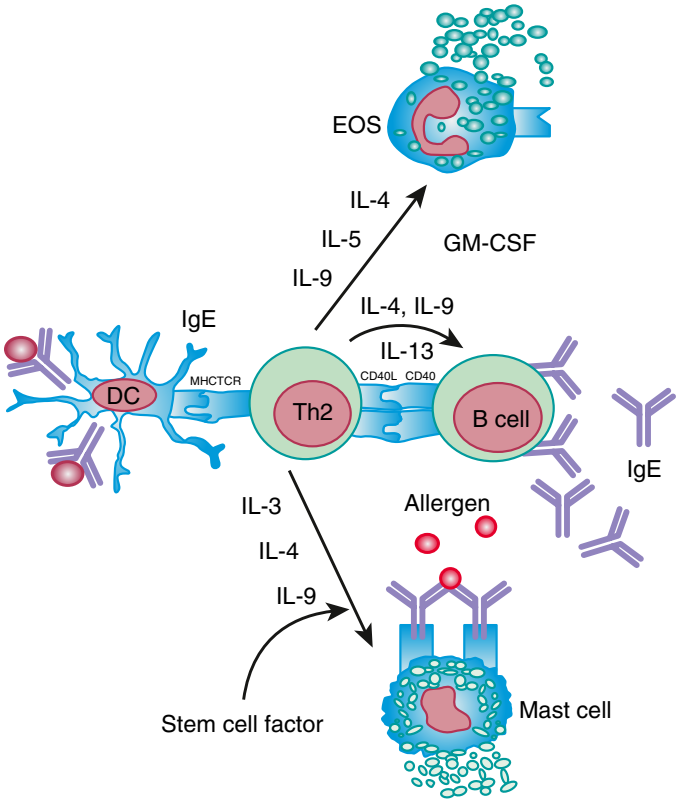

Fig. 182.2 Role of Th2 cytokines in allergic cascade. DC, Dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin.

of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor (TNF)-α, and Fas-ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and **Th17 cells**. This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils, thereby contributing to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Figure 182.3 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17, and Th22 cells.

Tregs are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of Th1, Th2, Th9, Th17, and Th22 phenotypes (Fig. 182.4). Tregs express $CD4^+CD25^+$ surface molecules and immunosuppressive cytokines such as IL-10, IL-35, and transforming growth factor-β (TGF-β_1). The forkhead box/winged-helix transcription factor gene *FOXP3* is expressed specifically by $CD4^+CD25^+$ Tregs and programs their development and function. Adoptive transfer of Tregs inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Tregs. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat

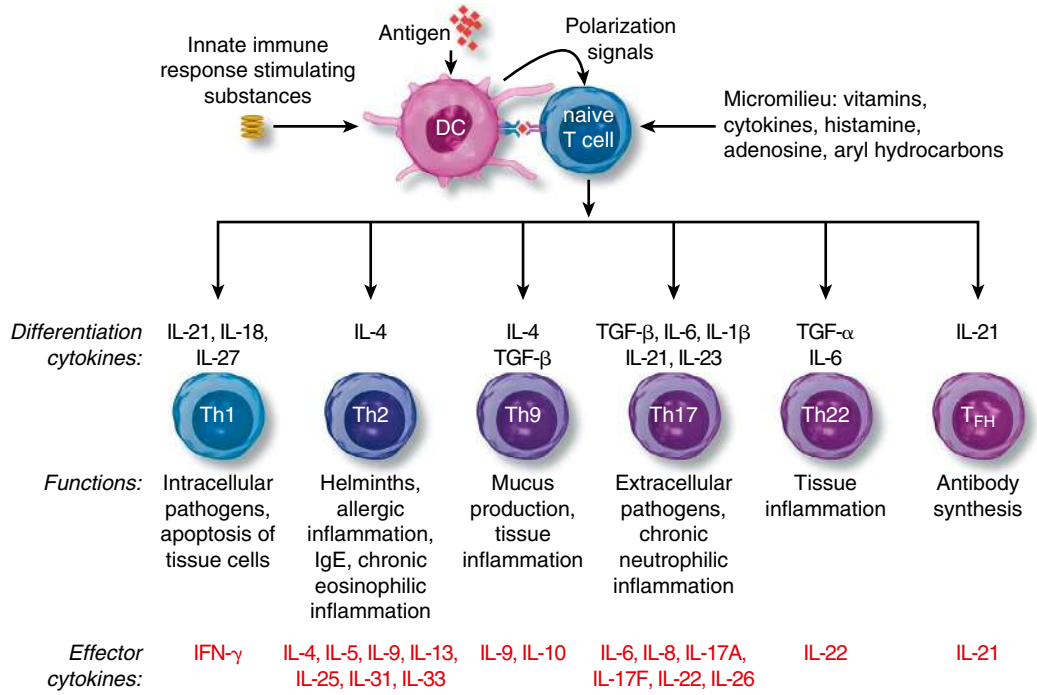

Fig. 182.3 Effector T-cell subsets. Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper (TFH) effector subsets. Their differentiation requires cytokines and other cofactors that are released from DCs and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, Interferon-γ; TGF-β, transforming growth factor-β. *(From Akdis M, Palomares O, van de Veen W, et al. TH17 and TH22 cells: A confusion of antimicrobial response with tissue inflammation versus protection. J Allergy Clin Immunol. 2012;129:1438–1449.)*

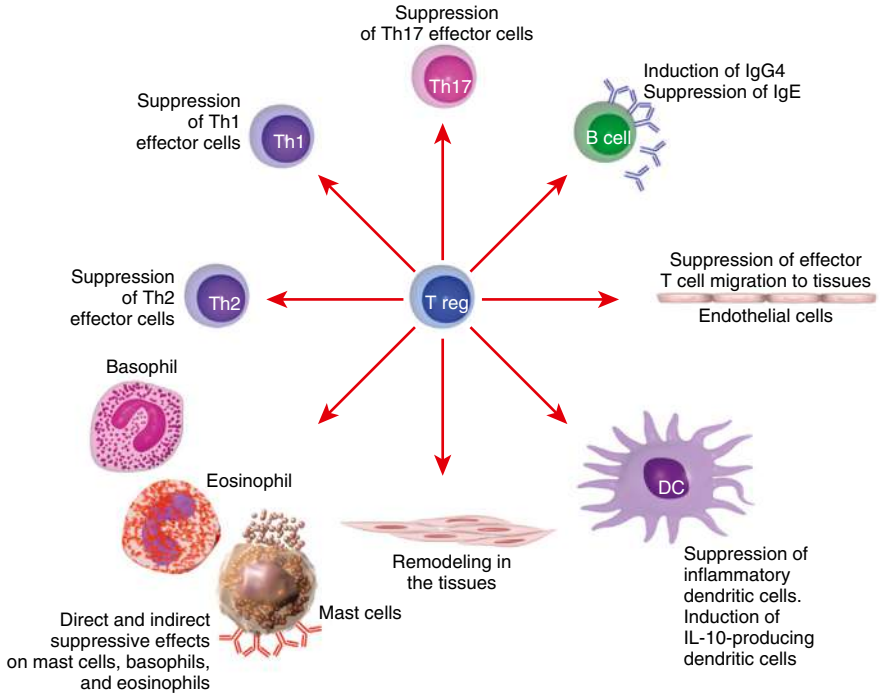

Fig. 182.4 Control of allergen-specific immune responses. FoxP3$^+$, CD4$^+$, CD25$^+$, and Tr1 cells contribute to the control of allergen-specific immune responses in several major ways: suppression of dendritic cells (DCs) that support the generation of effector T cells; suppression of Th1, Th2, and Th17 cells; suppression of allergen-specific IgE, and induction of IgG_4 and/or IgA; suppression of mast cells, basophils, and eosinophils; interaction with resident tissue cells and remodeling; and suppression of effector T-cell migration to tissues. IL, Interleukin. *(From Akdis CA, Akdis M. Mechanisms and treatment of allergic disease in the big picture of regulatory T cells. J Allergy Clin Immunol. 2009;123:735–746.)*

owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Tregs. It is thought that CD4$^+$CD25$^+$ Tregs play an important role in mitigating the allergic immune response, and that the lack of such cells may predispose to the development of allergic diseases. Patients with pathogenic variants in the human *FOXP3* gene lack CD4$^+$CD25$^+$ Tregs and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/IPEX disease) (see Chapter 165.4). In addition to Treg cells, IL-10–secreting and allergen-specific Breg cells increase during allergen-specific immunotherapy and may play a role in allergen tolerance.

Innate Lymphoid Cells

Immune responses in populations of lymphoid cells that lack rearranged T- and B-cell antigen receptors and surface markers for myeloid and lymphoid lineages, such as T, B, and natural killer (NK) cells, show similarities to Th1, Th2, and Th17/Th22 types of immune responses. These latter cells are defined as **ILC1s, ILC2s,** and **ILC3s,** respectively, based on their transcription factors and cytokine production patterns. ILC1s mainly produce IFN-γ; ILC2s produce IL-5, IL-9, and IL-13; and ILC3s produce IL-17 and IL-22 without any need of antigen/allergen exposure. Strong evidence indicates that ILCs play substantial roles in protection against infection and the pathogenesis of inflammatory diseases, such as asthma, allergic diseases, and autoimmune diseases. ILCs control the mucosal environment through close interaction with epithelial cells and other tissue cells, cytokine production, and induction of chemokines that recruit suitable cell populations to initiate and promote distinct types of immune response development and tissue inflammation. ILC2s are likely involved in the induction of asthma, allergic rhinitis, eosinophilic esophagitis, and atopic dermatitis through activation by epithelium-derived cytokines (e.g., IL-33, IL-25, TSLP) and interaction with other immune cells. IL-10–secreting ILCs with an immune regulatory function have been reported. These cells develop from ILC2s and play suppressive roles in allergic inflammation, particularly through IL-10.

Antigen-Presenting Cells

Dendritic cells (DCs), Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells, thereby modulating allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. DCs and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the **sensitization phase** of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses on reexposure to allergen, which characterizes the **elicitation phase** of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and co-stimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as **myeloid** or **plasmacytoid** on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. In contrast, plasmacytoid DCs have low levels of IL-12. Plasmacytoid DCs particularly play a role in antiviral immunity by rapid production of high amounts of IFN-α and help B cells for antibody production. There is considerable interest in the role of TSLP, which is overexpressed in the mucosal surfaces and skin of atopic individuals. TSLP enhances Th2 differentiation by inducing expression of OX40L on immature myeloid DCs in the absence of IL-12 production.

Tissue macrophages are also acting as APCs. They show two main effector subsets in tissues, namely the M1 and M2 macrophages. M1 macrophages are classically activated, typically by IFN-γ or lipopolysaccharide (LPS) like innate immune response stimulating substances, and produce proinflammatory cytokines, phagocytize microbes, and initiate an immune response. M1 macrophages produce nitric oxide (NO) or reactive oxygen intermediates (ROIs) to protect against bacteria and viruses. M2 macrophages are alternatively activated by allergen exposure and certain cytokines such as IL-4, IL-10, or IL-13. M2 macrophages will produce either polyamines to induce proliferation or proline to induce collagen production. These macrophages are associated with wound healing and tissue repair remodeling and activation of Th2 cells and ILC2s.

Presence of allergen-specific IgE on the cell surfaces of APCs is a unique feature of atopy. Importantly, the formation of high-affinity IgE receptor I (**FcεRI**)/IgE/allergen complexes on APC surfaces greatly facilitates allergen uptake and presentation. The clinical importance of this phenomenon is supported by the observation that FcεRI-positive Langerhans cells bearing IgE molecules are a prerequisite for skin-applied, aeroallergen provocation of eczematous lesions in patients with atopic dermatitis. The role of the low-affinity IgE receptor II **(FcεRII, CD23)**

on monocytes/macrophages is less clear, although under certain conditions it apparently can also facilitate antigen capture. Cross linking of FcεRII, as well as FcεRI, on monocytes/macrophages leads to the release of inflammatory mediators. There is a critical role for DCs in induction of oral tolerance; tolerogenic DCs are compartmentalized within the mucosa and present antigen through a mechanism designed to produce a Th1/Treg-suppressive response that ablates allergen-specific T cells.

Immunoglobulin E and Its Receptors

The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade, followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross linking and FcεRI aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 174). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires two major signals. The first signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The second signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in DNA switch recombination. Interactions between several co-stimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ), IL-10 from Tregs, Breg cells, and regulatory DCs and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

Eosinophils

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins (see Fig. 169.1). These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and **leukotrienes (LTs);** in particular, cysteinyl LT C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and ROIs, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated on activation, normal T-cell expressed and secreted), macrophage inflammatory protein-1α (MIP-1α), and eotaxins are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5–dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

Mast Cells

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. On entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand, the stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are instead widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, GI tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least two subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the GI submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell–derived lipid mediators are the **cyclooxygenase** and **lipoxygenase** metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is **prostaglandin D_2**, and the major lipoxygenase products are the sulfidopeptide **LTs:** LTC_4 and its peptidolytic derivatives LTD_4 and LTE_4. Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α, IL-6) and regulate tissue remodeling (TGF, vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in patients receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

MECHANISMS OF ALLERGIC TISSUE INFLAMMATION

IgE-mediated immune responses can be classified chronologically according to three reaction patterns. The **early-phase response** is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of 1-30 minutes after allergen exposure and resolving within 1-3 hours. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and GI tract, respectively, depending on the targeted organ.

A second, **late-phase response** can occur within hours of allergen exposure, reaching a maximum at 6-12 hours and resolving by 24 hours. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils, followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., $\alpha_4\beta_1$-integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells. ILC2s receive signals from the epithelial cells, such as IL-33, TSLP, and IL-25, and are activated and start to release their cytokines IL-5 and IL-13 to initiate a type 2 immune response.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemoattractants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemoattractants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the third reaction pattern, **chronic allergic disease**, tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, **remodeling** involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Generally, it is considered that a type 2 immune response underlines a majority of asthma cases, atopic dermatitis, chronic rhinosinusitis, and allergic rhinitis as a general characteristic of an immune/inflammatory response. Type 2 immune response involves Th2 cells, type 2 B cells, ILC2, IL-4–secreting NK T cells, basophils, eosinophils, and mast cells and their major cytokines. From a complex network of cytokines, IL-4, IL-5, IL-9, and IL-13 are mainly secreted from the immune system cells, and IL-25, IL-31, IL-33, and TSLP from tissue cells, particularly epithelial cells. Many asthma-related antigens, such as protease allergens, fungal extracts, and viral infection, trigger IL-33, TSLP, and IL-25 production from epithelial cells and various immune cells and induce eosinophilic asthma–like airway inflammation through activation of lung ILC2s.

IL-31 plays a role in pruritus in atopic dermatitis. Th2 cytokines do not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGF-β produced by eosinophils and fibroblasts can also enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating due to a general type 2 immune response and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1-cell and Th17-cell autoreactivity.

GENETIC BASIS OF ATOPY

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) and that are usually expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., skin in atopic dermatitis, lung in asthma, GI tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses (Fig. 182.5). Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23-35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, *IL4* is a well-studied potential candidate gene. A nucleotide change at position 589 of the *IL4* promoter region is associated with the formation of a unique binding site for **n**uclear **f**actor for **a**ctivated **T** cells (NF-AT) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, *IL13* coding region variants have been associated with asthma and atopic dermatitis. An association has been found between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen *Der p* I, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma. A recent genome-wide association study showed that genetic polymorphisms in the gene encoding IL-33, which is a major activator of ILC2s, and its receptor IL-1RL1 (ST2) are strongly linked to asthma development.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. **Filaggrin** is a protein that is essential in the formation of the stratum corneum. Null pathogenic variants of the filaggrin gene are strongly associated with early-onset and severe atopic dermatitis. Pathogenic variants in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause **Netherton disease**, a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical to neutralizing the proteolytic activity of *Staphylococcus aureus* and common allergens such as *Der p* I, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding tight junctions. Epithelial tight junctions form a strong barrier on the apical side of mucosal epithelial cells and stratum granulosum of the skin. Epithelial tight junction defects shown in asthma and atopic dermatitis have been linked to two mechanisms, such as polymorphisms in certain claudin molecules or epigenetic regulation of the tight junction molecules. Epithelial cells obtained from asthmatic tissues cannot form a strong barrier in cultures. Chemical inhibition of histone deacetylases strengthens the barrier development capacity of these epithelial cells.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: *GPRA* (G-protein–coupled receptor for asthma susceptibility on chromosome 7p14), *ADAM-33* (a disintegrin and metalloproteinase 33 on chromosome 20p), and

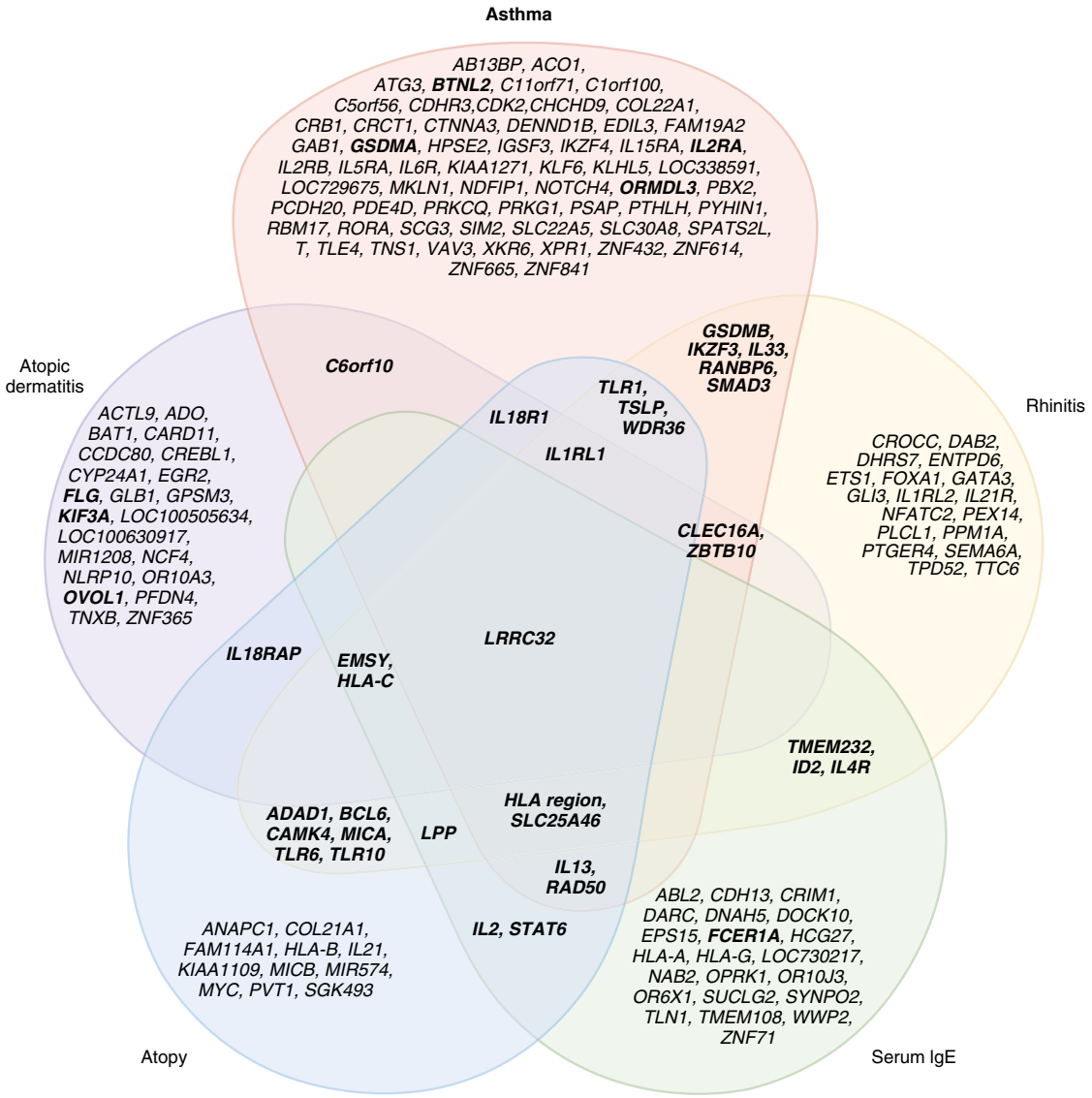

Fig. 182.5 Overlapping sets of genes have been reported in genome-wide association studies (GWASs) for asthma, rhinitis, serum immunoglobulin E (IgE) levels, atopy, and atopic dermatitis, supporting a common genetic element within the mechanisms predisposing individuals toward different allergic disease phenotypes. GWASs have also identified many genes in association with only one allergic disease phenotype; these most likely represent the tissue-specific component of each allergic disease (e.g., *FLG* in the epidermal barrier in atopic dermatitis). More GWASs have been conducted analyzing genetic variants associated with asthma than with other allergic diseases. In the future it is likely that more risk variants for other allergic diseases will be identified. Genes reported in more than one GWAS are shown in bold font. The genes reported for SNPs detected to be significantly associated ($P \leq 1 \times 10^{-5}$) with each allergic disease phenotype were obtained by searching the National Human Genome Research Institute GWAS catalog. *(From Holloway JW. The genetics of allergic disease and asthma. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig. 3.3, p 22.)*

DPP10 (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. *GPRA* encodes a G-protein–coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. *ADAM-33* is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. *DPP10* encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial components. Polymorphisms in CD14 (engages endotoxin), Toll-like receptor 2 (which engages *S. aureus*), and T-cell immunoglobulin domain and mucin domain (which engage hepatitis A virus) correlate with asthma and/or atopic dermatitis susceptibility. Dysregulation of these frontline immune defense systems would permit abnormal response to common environmental allergens.

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Chapter 183

Diagnosis of Allergic Disease

Supinda Bunyavanich, Jacob Kattan, and Scott H. Sicherer

ALLERGY HISTORY

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than one allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy, should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when one parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal **pruritus** and **rhinorrhea**, children with allergic rhinitis often perform the **allergic salute** by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the **nasal crease**, a horizontal wrinkle over the bridge of the nose. Characteristic vigorous **rubbing** of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The **allergic cluck** is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens, such as **pollens** and fungal spores, are prominent causes of allergic disease. The concentrations of these allergens in outdoor air fluctuate seasonally. Correlating symptoms with **seasonal** pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States, with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollens may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to **perennial allergens** usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as *Aspergillus* and *Penicillium,* are found indoors, whereas *Alternaria* is found in both indoor and outdoor environments. Cockroach and rodent allergens are often problematic in urban environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are often first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory and cardiovascular symptoms. Symptoms of immediate or IgE-mediated hypersensitivity food reactions typically develop within minutes to 2 hours after ingestion of the offending food. Symptoms of non–IgE-mediated food allergies are often delayed or chronic (see Chapter 192).

Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough **environmental** survey should be performed, focusing on potential sources of allergen and/or irritant exposure, particularly when respiratory symptoms (upper/lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the use of dust mite covers on pillows and mattresses, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers living in the home, and what and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in other environments where the child spends long periods, such as a relative's home or school setting.

PHYSICAL EXAMINATION

In patients with **asthma**, *spirometry* should be performed. If respiratory distress is observed, *pulse oximetry* should be performed.

The child presenting with a chief complaint of **rhinitis** or **rhinoconjunctivitis** should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing **pruritus**; see Chapter 184). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional change in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may experience growth suppression, an accurate height should be plotted at regular intervals. The

use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (1 cm) that may persist as a reduction in adult height. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus**, defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airway obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child's lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners** (Fig. 183.1). They are found in up to 60% of allergic patients and almost 40% of patients *without* allergic disease. Thus "shiners" may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atopy (see Fig. 183.1). These are prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

In patients with **allergic conjunctivitis**, involvement of the eyes is typically bilateral (see Chapter 188). Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as "stringy" or "ropy." In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus**, or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atopic dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.

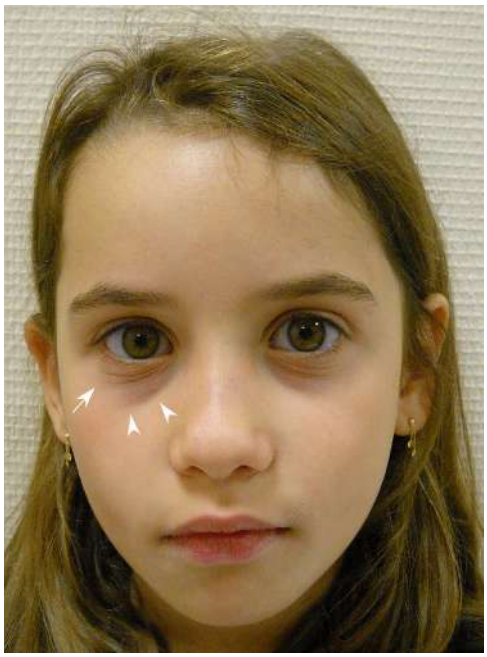

Fig. 183.1 Bilateral Dennie-Morgan folds. Several linear wrinkles beneath the lower eyelashes *(arrow)* associated with bilateral allergic shiners: dark circles beneath the lower eyelid *(arrowheads)*. *(From Blanc S, Bourrier T, Albertini M, et al. Dennie-Morgan fold plus dark circles: suspect atopy at first sight. J Pediatr. 2015;166:1541.)*

The external ear should be examined for eczematous changes in patients with atopic dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyps. Nasal polyps in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple compared with the beefy-red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort **(lip licker's dermatitis)**. Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia ("cobblestoning").

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles (retractions), wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests **foreign body aspiration**. Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with **vocal cord dysfunction.** Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of **urticaria/angioedema** or **atopic dermatitis** (see Chapters 189 and 186). **Xerosis**, or dry skin, is the most common skin abnormality of allergic children. **Keratosis pilaris**, often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases **(hyperlinearity)** in children with moderate to severe atopic dermatitis.

DIAGNOSTIC TESTING

In Vitro Tests

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. **Eosinophilia**, defined as the presence of >500 eosinophils/μL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence

Table 183.1 Differential Diagnosis of Childhood Eosinophilia

PHYSIOLOGIC
Prematurity
Infants receiving hyperalimentation
Hereditary

INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)

PULMONARY
Allergic (rhinitis, asthma)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia

DERMATOLOGIC
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)

HEMATOLOGIC/ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis

IMMUNOLOGIC
T-cell immunodeficiencies
Hyper-IgE (Job) syndromes
Wiskott-Aldrich syndrome
Autoimmune lymphoproliferative syndrome (ALPS)
Sarcoidosis
Graft-versus-host disease
Drug hypersensitivity including drug reaction with eosinophilia and systemic symptoms (DRESS)
Postirradiation
Postsplenectomy

ENDOCRINE
Addison disease
Hypopituitarism

CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis

GASTROINTESTINAL
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α; HTLV, human T-lymphotropic virus 1.

of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy; eosinophil counts >1,500 without an identifiable etiology should suggest one of the two hypereosinophilic syndromes (Table 183.1; see Chapter 169).

Nasal and bronchial secretions may be examined for the presence of eosinophils and neutrophils. The presence of eosinophils in the sputum of patients with atopic asthma is frequently seen. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis.

An elevated **IgE** value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels, whereas patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such that the diagnostic value of a total IgE level is poor. Approximately half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of **allergic bronchopulmonary aspergillosis** is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 283.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 183.2).

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of **allergen-specific IgE (sIgE)** levels in the serum (Table 183.3). The first test for documenting the presence of sIgE was called the radioallergosorbent test (RAST) because it used a radiolabeled anti-IgE antibody. RAST has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These immunoassays typically use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient's serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient's sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE–antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample, kU_A/L). Laboratory reports may specify classes, counts, or units, but quantification of results in kU_A/L is most useful. sIgE immunoassays are available for foods, environmental allergens, insect venoms, natural rubber latex, and a small number of β-lactam drugs. The sensitivity and specificity of immunoassays for particular allergens vary widely from 30–95%. These immunoassays are not diagnostic for allergy and should not be used for allergy screening. Only targeted sIgE levels for specific antigens should be measured when there is a clinical indication to suspect a specific allergy.

Table 183.2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

PARASITIC INFESTATIONS
Ascariasis
Capillariasis
Echinococcosis
Fascioliasis
Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans

INFECTIONS
Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
HIV type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections

IMMUNODEFICIENCY
Autosomal dominant hyper-IgE syndrome (*STAT3* variants)
Autosomal recessive hyper-IgE syndrome (*DOCK8, TYK2* variants)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome

NEOPLASTIC DISEASES
Hodgkin disease
IgE myeloma
Bronchial carcinoma

OTHER DISEASES AND DISORDERS
Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medication related
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Juvenile idiopathic arthritis

Table 183.3 Determination of Allergen-Specific IgE by Skin Testing vs In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermatographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

*Skin testing may be the prick test or intradermal (ID) injection.

Component testing refers to diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut, Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

In Vivo Tests

Allergen skin testing is the primary in vivo procedure for the diagnosis of allergic disease. Mast cells with sIgE antibodies attached to high-affinity receptors on their surface reside in the skin of allergic patients. The introduction of minute amounts of an allergen into the skin of the sensitized patient results in cross linking of IgE antibodies on the mast cell surface, thereby triggering local mast cell activation. Once activated, these mast cells release a variety of preformed and newly generated mediators that act on surrounding tissues. **Histamine** is the mediator most responsible for the immediate **wheal and flare reactions** observed in skin testing. Examination of the site of a positive skin test result reveals a pruritic wheal surrounded by erythema. The time course of these reactions is rapid in onset, reaching a peak within 10-20 minutes and usually resolving over the next 30 minutes.

Skin testing is performed using the **prick/puncture technique.** With this technique, a small drop of allergen is applied to the skin surface, and a tiny amount is introduced into the epidermis by lightly pricking or puncturing the outer layer of skin through the drop of extract with a small needle or other device. When the **skin-prick test (SPT)** result is negative but the history suggestive, selective skin testing (for vaccines, venom, drugs, and aeroallergens) using the **intradermal technique** may be performed. This technique involves using a 26-gauge needle to inject 0.01-0.02 mL of an allergen extract diluted 1,000- to 10-fold into the dermis of the arm. Intradermal skin tests are *not recommended for use with food allergens* because of the risk of triggering anaphylaxis. Irritant rather than allergic reactions can occur with intradermal skin testing if higher concentrations of extracts are used. Although skin-prick testing is less sensitive than intradermal skin testing, positive SPT results tend to correlate better with clinical symptoms.

The number of skin tests performed should be individualized, with the allergens suggested by the history. A positive and negative control SPT, using histamine and saline, respectively, is performed with each set of skin tests. A negative control is necessary to assess for **dermatographism**, in which reactions are caused merely by applying pressure to overly sensitive skin. A positive control is necessary to establish the presence of a cutaneous response to histamine. Medications with antihistaminic properties, in addition to adrenergic agents such as ephedrine and epinephrine, suppress skin test responses and should be avoided for appropriate intervals (approximately five half-lives) before skin testing. Prolonged courses of systemic corticosteroids may suppress cutaneous reactivity by decreasing the number of tissue mast cells as well as their ability to release mediators.

Whether identified via serologic or skin testing, detection of sIgE denotes a sensitized state (i.e., atopy or a tendency toward development of allergic disease) but is not equivalent to a clinically relevant allergic diagnosis. **Many children with positive tests have no clinical symptoms on exposure to the allergen**. Increasingly strong test results (higher serum sIgE results or larger SPT wheal sizes) generally correlate with increasing likelihood of clinical reactivity (but not severity). Neither serologic testing nor skin testing for allergy is predictive of reaction severity or threshold of reactivity, and these tests will be negative when the allergy is not IgE mediated, such as in food protein–induced enterocolitis syndrome. The limitations of these test modalities underscore the need for a detailed medical history that can guide the selection and interpretation of test results. **Large panels of indiscriminately performed screening tests may provide misleading information and are not recommended.**

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. The benefits of the serologic immunoassays are that performance is not limited by the presence of skin disease (i.e., active atopic dermatitis) or medication use (i.e., antihistamines). Advantages of skin testing are that they provide rapid results to the patient/family during the clinic visit, do not require venipuncture, and are less costly.

Under certain circumstances, **provocation testing** is performed to examine the association between allergen exposure and the development of symptoms. The bronchial provocation test most frequently performed clinically is the **methacholine challenge,** which causes potent bronchoconstriction of asthmatic but not of normal airways; it is performed to document the presence and degree of bronchial hyperreactivity in a patient with suspected asthma. After baseline spirometry values are obtained, increasing concentrations of nebulized methacholine are inhaled until a drop occurs in lung function, specifically a 20% decrease in FEV_1 (forced expiratory volume in the first second of expiration), or the patient is able to tolerate the inhalation of a set concentration of methacholine, typically 25 mg/mL.

Oral **food challenges** are performed to determine whether a specific food causes symptoms or whether a suspected food can be added to the diet. Food challenges are performed when the history and results of skin tests and immunoassays for sIgE are insufficient to clarify the diagnosis of an allergy. These challenges may be performed in an open single-blind, double-blind, or double-blind placebo-controlled manner and involve the ingestion of gradually increasing amounts of the suspected food at set intervals until the patient either experiences a reaction or tolerates a normal portion (i.e., one serving size) of the food openly. Although the double-blind placebo-controlled food challenge is currently the gold standard test for diagnosing food allergy, it is typically only performed in research studies due to the time and labor-intensive nature of this method. Because of the potential for significant allergic reactions, oral food challenges should be performed only in an appropriately equipped facility with personnel experienced in the performance of food challenges and the treatment of anaphylaxis, including cardiopulmonary resuscitation.

Upper gastrointestinal **endoscopy** is required to confirm the diagnosis of **eosinophilic esophagitis**. One or more biopsy specimens from the proximal and distal esophagus must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils per high-power field (peak value) is considered a minimum threshold for the diagnosis.

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Chapter 184

Allergic Rhinitis

Tamara T. Perry and Scott H. Sicherer

Allergic rhinitis (AR) is a common chronic disease affecting 20–30% of children. AR is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children derives from its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a threefold increase in risk for asthma at an older age. Over the past 50 years an upsurge in AR has been observed throughout the world, with some symptom surveys reporting incidence rates approaching 40%. Heritability of allergic conditions attests to genetic factors, but the increase stems from changes in the environment, diet, and the microbiome. The symptoms may appear in infancy, with the diagnosis generally established by the time the child reaches age 6 years. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum IgE higher than 100 IU/mL before age 6 years. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children who are exposed to tobacco smoke prenatally, and above all before the infants reach 1 year, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible child is at greatest risk of sensitization. Delivery by cesarean section is associated with AR and atopy in children with a parental history of asthma or allergies. This association may be explained by the lack of exposure to the maternal microbiota through fecal/vaginal flora during delivery.

Children between 2 and 3 years old who have elevated anticockroach and antimouse IgE are at increased risk of wheezing, AR, and atopic dermatitis. The occurrence of three or more episodes of rhinorrhea in the first year of life is associated with AR at age 7 years. Favorably, the exposure to dogs, cats, and endotoxin early in childhood protects against the development of atopy. Prolonged breastfeeding, not necessarily exclusive, is beneficial. There is also a decreased risk of asthma, AR, and atopic sensitization with early introduction to wheat, rye, oats, barley, fish, and eggs. However, reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age.

ETIOLOGY AND CLASSIFICATION

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent.** The two sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent, moderate-severe intermittent, mild-persistent,** and **moderate-severe persistent** (Fig. 184.1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR, symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and there is no incapacity at work or school. Severe symptoms result in sleep disturbance and impairment in daily activities and school performance.

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates they persist throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of symptom occurrence, the regional patterns of pollination and mold sporulation, and the patient's allergen-specific IgE **(sIgE)** is necessary to recognize the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the United States. The allergens from saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners' clothing into such "cat-free" settings as schools and hospitals.

PATHOGENESIS

The exposure of an atopic host to an allergen leads to the production of sIgE, which is strongly associated with eczema throughout childhood and with asthma and rhinitis after age 4 years. The clinical reactions on reexposure to the allergen have been designated as *early-phase* and *late-phase* allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates the early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators, including histamine, prostaglandin 2, and the cysteinyl leukotrienes. The late-phase allergic response appears 4-8 hour following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin (IL)-3, IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes "priming," which is a more brisk response even with a lesser provocation. Over the course of an allergy season, a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease.

CLINICAL MANIFESTATIONS

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the **allergic salute**, an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the **nasal crease**, a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include

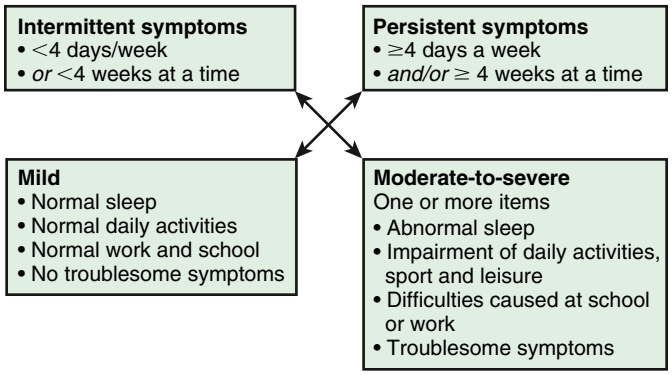

Fig. 184.1 Global Allergic Rhinitis and Its Impact on Asthma (ARIA) classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-severe persistent seasonal rhinitis in June and July and may be suitable for specific allergen immunotherapy. *(From Scadding GK, Durham SR, Mirakian R, et al. BASCI guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy. 2008;38:19–42.)*

intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste, though this has also been noted as a symptom of mild COVID-19 or other viral upper respiratory infections. Some experience headaches, wheezing, and coughing. Preschoolers with chronic wheezing and rhinitis experience more severe wheezing than children without rhinitis. Nasal congestion is often more severe at night, inducing mouth breathing and snoring, interfering with sleep, and rousing irritability.

Signs on physical examination include abnormalities of facial development, dental malocclusion, the **allergic gape** (continuous open-mouth breathing), chapped lips, **allergic shiners** (dark circles under the eyes; see Fig. 183.1), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

DIFFERENTIAL DIAGNOSIS

Evaluation of AR entails a thorough history, including details of the patient's environment and diet and a family history of allergic conditions (e.g., eczema, asthma, AR), physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms such as sneezing, rhinorrhea, nasal itching, and congestion and lab findings of elevated IgE, sIgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. **Nonallergic rhinitides** give rise to sporadic symptoms; their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. **Vasomotor rhinitis** is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis, structural problems (e.g., nasal polyps, septal deviation), **rhinitis medicamentosa** (caused by overuse of topical vasoconstrictors), hormonal rhinitis associated with pregnancy or hypothyroidism, neoplasms, vasculitides, and granulomatous disorders may mimic AR (Table 184.1 and Fig. 184.2). Occupational risks for rhinitis include exposure to allergens (grain dust, insects, latex, enzymes) and irritants (wood dust, paint, solvents, smoke, cold air).

COMPLICATIONS

AR is associated with complications and comorbid conditions. Undertreated AR detracts from the quality of life, aggravates asthma, and enhances its progression. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness, and swelling of the conjunctivae, has been reported in at least 20% of the population and >70% of patients with AR, most frequently in older children and young adults. The two conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 188). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia.

Aspirin-exacerbated respiratory disease (AERD) is characterized by the presence of chronic rhinosinusitis with nasal polyposis, asthma, and aspirin sensitivity. The pathophysiology of AERD is not fully understood and symptoms often respond poorly to therapy such as leukotriene modifiers, intranasal or systemic steroids, and aspirin desensitization. Surgical removal of nasal polyps is also a common intervention; however, the rate of recurrence is high with frequent regrowth of polyps. New biologic therapies are available for patients with chronic rhinosinusitis with nasal polyposis and patients with AERD may benefit from the addition of these new therapies.

Table 184.1 Causes of Rhinitis

ALLERGIC RHINITIS
Seasonal
Perennial
Perennial with seasonal exacerbations
NONALLERGIC RHINITIS
Structural/Mechanical Factors
Deviated septum/septal wall anomalies
Hypertrophic turbinates
Adenoidal hypertrophy
Foreign bodies
Nasal tumors
Benign
Malignant
Choanal atresia
CSF leakage
Infectious
Acute infections
Chronic infections
Congenital syphilis
Inflammatory/Immunologic
Granulomatosis with polyangiitis
Sarcoidosis
Midline granuloma
Systemic lupus erythematosus
Sjögren syndrome
Nasal polyposis
Physiologic
Primary ciliary dyskinesia
Atrophic rhinitis
Hormonally induced
Hypothyroidism
Pregnancy
Oral contraceptives
Menstrual cycle
Exercise
Atrophic
Drug induced
Rhinitis medicamentosa
Oral contraceptives
Antihypertensive therapy
Aspirin
Nonsteroidal antiinflammatory drugs
Cocaine
Reflex induced
Gustatory rhinitis
Chemical or irritant induced
Posture reflexes
Nasal cycle
Environmental factors
Odors
Temperature (cold air)
Weather/barometric pressure
Occupational (irritants)
OTHER
Nonallergic rhinitis with eosinophilia syndrome
Perennial nonallergic rhinitis (vasomotor rhinitis)
Emotional factors

From Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(1 Suppl);108:S2–S8.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction

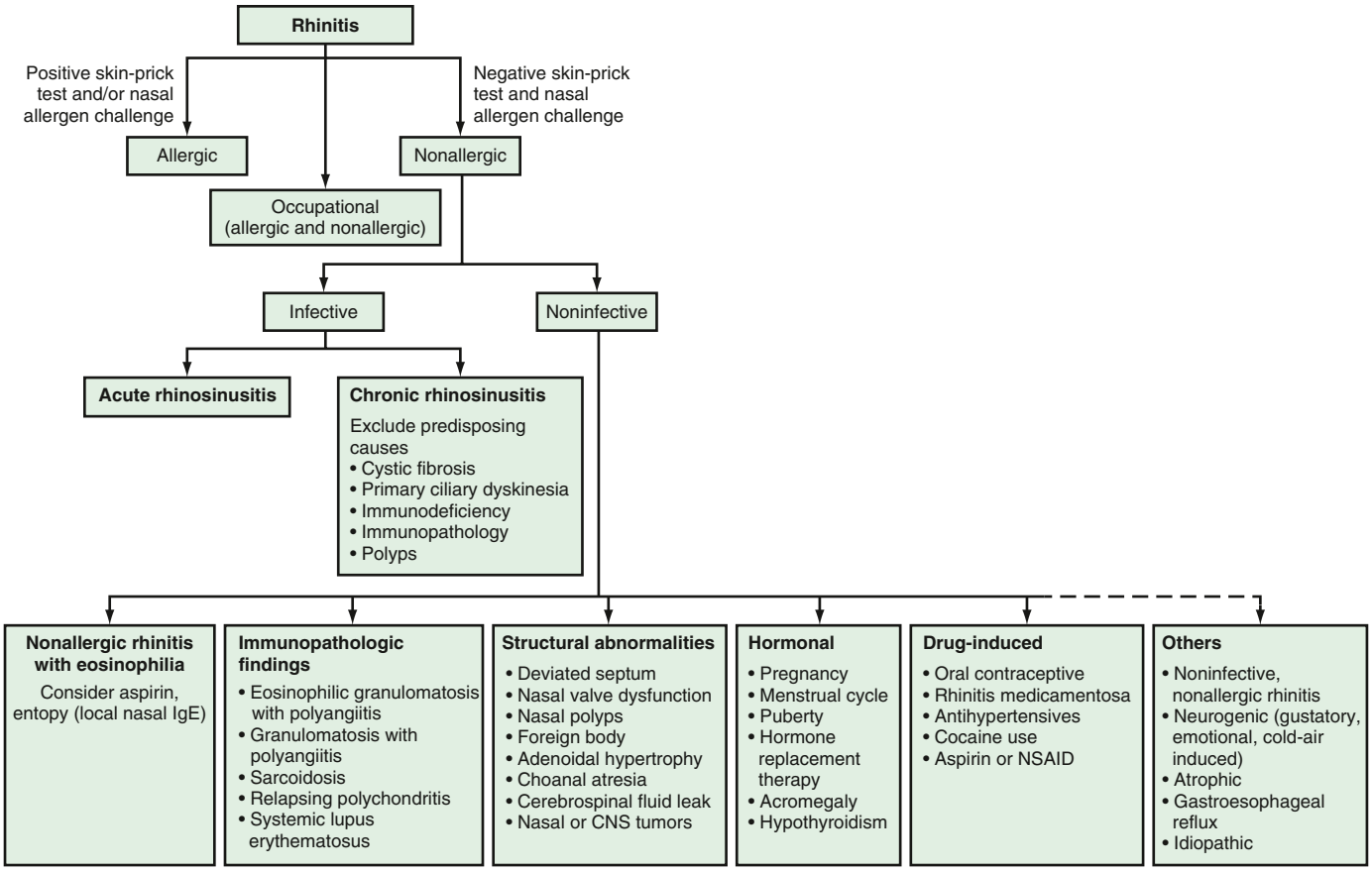

Fig. 184.2 Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. CNS, Central nervous system; NSAID, nonsteroidal antiinflammatory drug. *(From Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet. 2011;378:2112–2120.)*

and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented and may require multidisciplinary intervention.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 years old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 years old. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. AR causes an estimated 824,000 missed school days and 4,230,000 days of decline in quality-of-life activities. Patients with AR report an impairment in the activities of daily living similar to patients with moderate to severe asthma. Some (but not many) patients improve during their teenage years, only to develop symptoms again as young adults. Symptoms often abate in the fifth decade of life.

LABORATORY FINDINGS

Epicutaneous skin tests provide the best method for detection of sIgE, with a positive predictive value (PPV) of 48.7% for epidemiologic diagnosis of AR. Skin tests are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before two seasons of exposure, and children <1 year old seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and nonsedating antihistamines for 5-7 days. Serum immunoassays for sIgE provide a suitable alternative (PPV of 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in the nasal smear supports the diagnosis of AR, and neutrophils suggest infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

TREATMENT

Guideline-directed management has been shown to improve disease control. **Global Allergic Rhinitis and its Impact on Asthma (ARIA)** provides an evidence-based approach to treatment and includes quality-of-life measures useful for the evaluation of symptoms and the assessment of the response to therapy. Safe effective prevention and relief of symptoms are the current goals of treatment. **Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease.** Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergen. Bed linen and blankets should be washed every week in hot water (>54.4°C [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air (HEPA) filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea, and ocular symptoms. Administered as needed, antihistamines provide acceptable treatment for mild-intermittent disease. Antihistamines have been

Table 184.2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES *Desloratadine*			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo to 5 yr: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr: 2.5 mg once daily
			Adults and adolescents ≥12 yr: 5 mg once daily
LEUKOTRIENE ANTAGONIST† *Montelukast*			
Singulair	10 mg	Tablets	6 mo to 5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine
†As advised by the FDA, montelukast should be used to treat allergic rhinitis only in patients who are not treated effectively with or cannot tolerate other alternative therapies.
Dosing recommendations taken in part from Kleinman K, McDaniel L, Molloy M for the Johns Hopkins Hospital. *The Harriet Lane Handbook*. 22nd ed. Philadelphia: Elsevier; 2021.

classified as **first generation** (relatively sedating) or **second generation** (relatively nonsedating). Antihistamines usually are administered by mouth but are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. **Second-generation antihistamines are preferred because they cause less sedation.** Preparations containing **pseudoephedrine**, typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. These are not considered first-line agents and should be used with caution. Pseudoephedrine is available without prescription generally in fixed combination with other agents such as first-generation antihistamines (brompheniramine, chlorpheniramine, triprolidine), second-generation antihistamines (desloratadine, fexofenadine, loratadine), antipyretics (acetaminophen, ibuprofen), antitussives (guaifenesin, dextromethorphan), and an anticholinergic (methscopolamine). Pseudoephedrine is an oral vasoconstrictor distrusted for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 years) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children <4 years old. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Tables 184.2, 184.3, and 184.4 provide examples of prescription, nonprescription, and combined oral agents, respectively, for treatment of AR. Oral leukotriene receptor antagonists are not recommended for initial treatment of AR because of reduced efficacy compared to other agents and serious neuropsychiatric events that have been reported with montelukast.

The anticholinergic **nasal spray** ipratropium bromide is effective for the treatment of *serous* rhinorrhea (Table 184.5). **Intranasal decongestants** (oxymetazoline and phenylephrine) should be used for <5 days and should not to be repeated more than once a month to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, every 4 hours. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 185 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require **intranasal corticosteroids**, the most effective therapy for AR, which may also be beneficial for concomitant allergic conjunctivitis (Table 184.6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Allergen-specific immunotherapy is a well-defined treatment for IgE-mediated allergic disease. It may be administered by subcutaneous or sublingual routes. **Sublingual immunotherapy** (SLIT) has been used successfully in Europe and South America and is now approved by the U.S. Food and Drug Administration. **Allergy immunotherapy** (AIT) is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Immunotherapy for AR prevents the onset of asthma. Moreover, progress in molecular characterization of allergens raises the possibility of defined vaccines for allergen immunotherapy. Omalizumab (anti-IgE antibody) is effective for difficult-to-control asthma and is likely to have a beneficial effect on coexisting AR. Dupilumab (IL-4 antagonist) is approved *in adults* for the treatment of chronic rhinosinusitis with nasal polyposis and has shown improvement in nasal symptoms scores as well as improvements in lung function among patients with AERD.

Typically, treatment of AR with oral antihistamines and nasal corticosteroids provides sufficient relief for most patients with coexisting **allergic conjunctivitis**. If it fails, additional therapies directed primarily at allergic conjunctivitis may be added (see Chapter 188). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but ophthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy, although they carry the risk of adverse effects such as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataracts. Ophthalmic corticosteroids are only suited for the treatment of allergic conjunctivitis that does not respond to the medications previously discussed. Sound practice calls for the assistance of an ophthalmologist.

Table 184.3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton OTC	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (max 6 mg/day) 6-11 yr: 2 mg every 4-6 hr (max 12 mg/day)
Chlor-Trimeton Syrup OTC	2 mg/5 mL	Syrup	>12 yr: 4 mg every 4-6 hr (max 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup OTC	1 mg/mL	Syrup	6-11 mo: 2.5 mg daily
Children's Zyrtec Chewable OTC	5 mg, 10 mg	Chewable tablets	12-23 mo: initial 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec Tablets OTC	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to max of 5 mg/day given either as a single dose or divided into two doses
Zyrtec Liquid Gels OTC	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into two doses
Levocetirizine Xyzal	5 mg 0.5 mg/mL	Tablet Oral solution	6 mo-5 yr: 1.25 mg daily in the evening 6-11 yr: 2.5 mg daily in the evening ≥12 yr: 5 mg daily in the evening
Desloratadine			
Clarinex	0.5 mg/mL	Oral solution	6-11 mo: 1 mg daily 1-5 yr: 1.25 mg daily 6-11 yr: 2.5 mg daily
Clarinex	5 mg	Tablet	≥12 yr 5 mg daily
Fexofenadine HCl OTC	30 mg, 60 mg, 180 mg	Tablet	6-11 yr: 30 mg twice daily 12-adult: 60 mg twice daily; 180 mg daily
Children's Allegra OTC ODT*	30 mg	ODTs	6-11 yr: 30 mg twice daily
Children's Allegra Oral Suspension OTC	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra OTC	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg daily
Loratadine			
Children's Claritin OTC	5 mg/5 mL	Syrup	2-5 yr: 5 mg daily 6-adult: 10 mg daily
Alavert OTC ODT*	10 mg 10 mg 10 mg 5 mg 1 mg/mL	ODTs Tablets Liquid-filled caps Chewable tablets Syrup	2-5 yr: 5 mg daily >6 yr: 10 mg once daily or 5 mg twice daily

*Contains phenylalanine.
ODT, Orally disintegrating tablet; OTC, over the counter.
Dosing recommendations taken in part from Kleinman K, McDaniel L, Molloy M for the Johns Hopkins Hospital. *The Harriet Lane Handbook*. 22nd ed. Philadelphia: Elsevier; 2021.

Table 184.4 Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine HCl Sudafed Sinus & Allergy	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr, not to exceed 6 tablets per day
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended-release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Kleinman K, McDaniel L, Molloy M for the Johns Hopkins Hospital. *The Harriet Lane Handbook*. 22nd ed. Philadelphia: Elsevier; 2021.

Table 184.5 Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established *Adverse effects:* Epistaxis, nasal dryness, nausea
Atrovent nasal spray (0.06%)	Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril tid ≥12 yr and adults: 2 sprays in each nostril tid-qid	
Azelastine	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus *M:* Antagonism of histamine H_1 receptor	May cause drowsiness *Adverse effects:* Headache, somnolence, bitter taste
Astelin	6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	
Cromolyn sodium	*I:* AR *M:* Inhibition of mast cell degranulation	Not effective immediately; requires frequent administration
NasalCrom	>2 yr: 1 spray tid-qid; max 6 times daily	
Oxymetazoline Afrin Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril bid; therapy should not exceed 3 days	Excessive dosage may cause profound CNS depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, or diabetes *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, dizziness
Neo-Synephrine	2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed *Note:* Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed *Note:* Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion *Note:* Therapy should not exceed 3 continuous days	

bid, 2 times daily; CNS, central nervous system; tid, 3 times daily; qid, 4 times daily.

Table 184.6 Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Beconase AQ (42 μg/spray) Qnasl (80 μg/spray) OTC	6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	
Flunisolide OTC	6-14 yr: 1 spray in each nostril tid *or* 2 sprays in each nostril bid; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays in each nostril bid (morning and evening); may increase to 2 sprays tid; maximum dose: 8 sprays/day in each nostril (400 μg/day)	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth

Table 184.6 Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone Nasacort AQ (55 µg/spray) OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as generic preparation) OTC	2-6 yr: 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	
	I: AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flonase (50 µg/spray) OTC	≥4 yr: 1-2 sprays in each nostril qd	
Fluticasone furoate Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril qd (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril qd (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg qd Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril qd (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril qd (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day	
Mometasone	*I:* AR *M:* Antiinflammatory, immune modulator	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk before pollen season Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Nasonex (50 µg/spray)	2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	
Budesonide OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude one nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Rhinocort Aqua (32 µg/spray) OTC	6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (max dose)	
Ciclesonide	*I:* AR *M:* Antiinflammatory, immune modulator	Before initial use, gently shake, then prime the pump by actuating 8 times If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Omnaris Zetonna (50 µg/spray)	2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	
Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista	≥6 yr: 1 spray in each nostril bid	Shake bottle gently before using Blow nose to clear nostrils Keep head tilted downward when spraying Insert applicator tip 1/4 to 1/2 inch into nostril, keeping bottle upright, and close off the other nostril Breathe in through nose While inhaling, press pump to release spray

OTC, Over the counter; AR, allergic rhinitis; qd, once daily; bid, 2 times daily; tid, 3 times daily.

PROGNOSIS

Therapy with nonsedating antihistamines and topical corticosteroids, when taken appropriately, improves health-related quality-of-life measures in patients with AR. The reported rates of remission among children are 10–23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

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Chapter 185

Childhood Asthma

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Asthma is a chronic inflammatory condition of the airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways **(airways hyperresponsiveness [AHR])** to common provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller antiinflammatory medications, and controlling comorbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and especially pharmacotherapy enable all but the uncommon child with difficult asthma to live normally.

ETIOLOGY

Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated. In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues (Fig. 185.1). Lung dysfunction (AHR, reduced airflow) and airway remodeling develop. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

Genetics

To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma. Consistent loci include genetic variants that underlie susceptibility to common exposures such as respiratory viruses and air pollutants.

Environment

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially rhinoviruses, respiratory syncytial virus (RSV), enteroviruses, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. RSV symptomatic

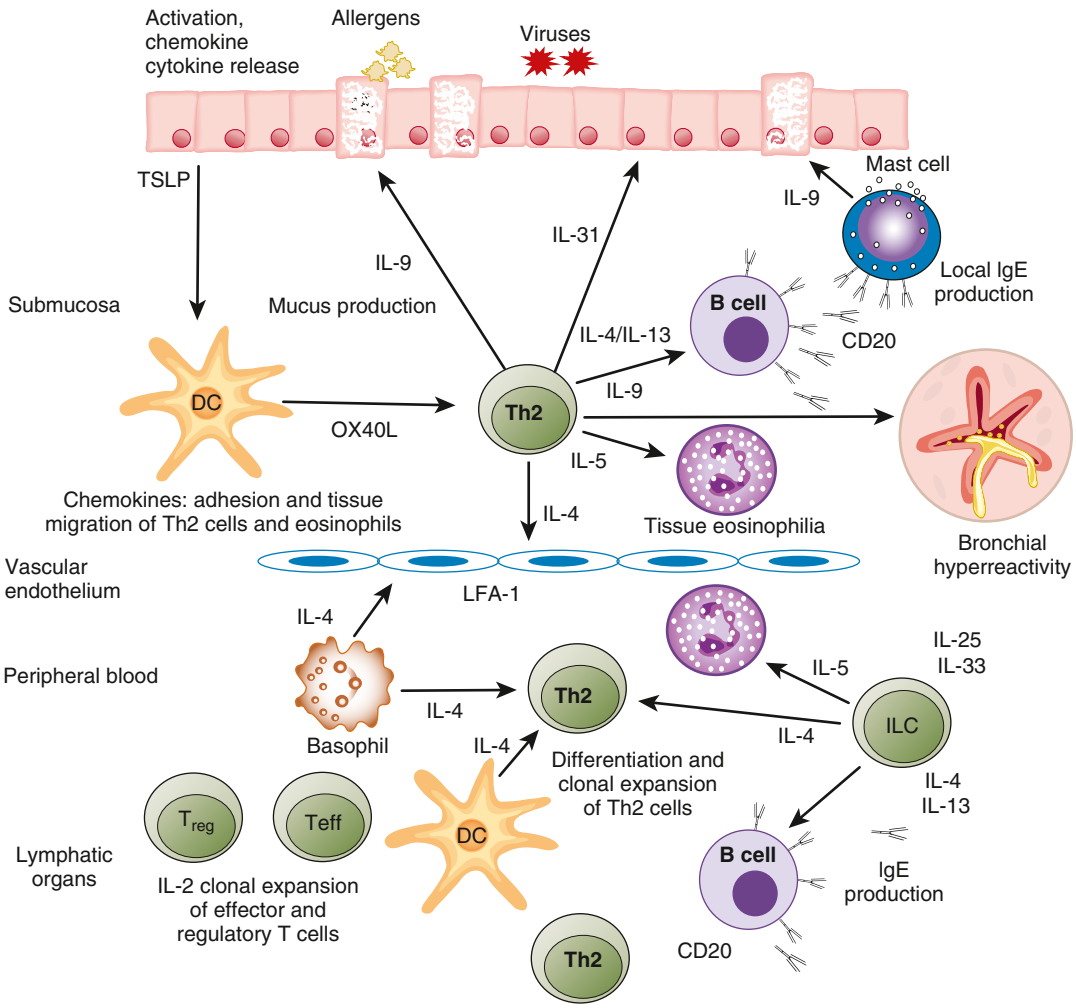


Fig. 185.1 Asthmatic inflammation (effector phase). Epithelial cell activation with production of proinflammatory cytokines and chemokines induces inflammation and contributes to a T-helper cell type 2 (Th2) response with tumor necrosis factor (TNF)-α, interleukin (IL)-13, thymic stromal lymphopoietin (TSLP), IL-25, IL-31, and IL-33. Migration of inflammatory cells to asthmatic tissues is regulated by chemokines. Th2 and eosinophil migration are induced by eotaxin, monocyte-derived chemokine (MDC), and activation-regulated chemokine (TARC). Epithelial apoptosis and shedding is observed, mainly mediated by interferon (IFN)-γ and TNF-α. The adaptive Th2 response includes the production of IL-4, IL-5, IL-9, and IL-13. Innate lymphoid cells, particularly ILC2, also secrete IL-5 and IL-13. Tissue eosinophilia is regulated by IL-5, IL-25, and IL-33. Local and systemic IgE production is observed in bronchial mucosa. Cross-linking of IgE receptor FcεRI on the surface of mast cells and basophils and their degranulation take place on allergen challenge *(From Leung DYM, Szefler SJ, Bonilla FA, et al, editors: Pediatric allergy principles and practice, ed 3, Philadelphia, 2016, Elsevier, p 260).*

bronchiolitis in the first year of life is a significant predisposing factor for asthma at age 5 years. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in early childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures and are causally linked to disease severity, exacerbations, and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air; hyperventilation from physical play or exercise; and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental features underlying the development of host susceptibilities to the various common airway exposures are not as well defined. Living in rural or farming communities may be a protective environmental factor.

EPIDEMIOLOGY

Asthma is a common chronic disease, causing considerable morbidity. In 2020 >7 million children (~11% of U.S. children) had been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the United States. About 13% of males vs 9% of females have had asthma, and ~15% of all children living in poor families (family income less than poverty threshold) have asthma. Childhood asthma is among the most common causes of childhood emergency department (ED) visits, hospitalizations, and missed school days. In the United States in 2019, childhood asthma accounted for >750,000 ED visits, nearly 75,000 hospitalizations, and 178 deaths. However, there are ethnic disparities in asthma outcomes, with nearly three times more deaths as a result of asthma in Black non-Hispanic vs White non-Hispanic children.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Although childhood asthma may have plateaued in the United States after 2008, numerous studies conducted in other countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6–7-year-old children (2.4–37.6%) and 13–14-year-old children (0.8–32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset before 6 years of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 185.1) and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. *Allergen sensitization (allergy) in young children with recurrent cough and/or wheeze* is the strongest identifiable factor for the persistence of childhood asthma.

Types of Childhood Asthma

There are two common types of childhood asthma based on different natural courses: (1) **recurrent wheezing** in *early* childhood, primarily triggered by common respiratory viral infections, that usually resolves during the preschool/lower school years and (2) **chronic asthma** associated with *allergy* that persists into later childhood and often adulthood

Table 185.1 Early Childhood Risk Factors for Persistent Asthma

Parental asthma*
Allergy
• Atopic dermatitis (eczema)*
• Allergic rhinitis
• Food allergy
• Inhalant allergen sensitization*
• Food allergen sensitization
Severe lower respiratory tract infection
• Pneumonia
• Bronchiolitis requiring hospitalization
Wheezing apart from colds
Male sex
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth
Formula feeding rather than breastfeeding

*Major risk factors.

(Table 185.2). School-age children with mild to moderate persistent asthma generally improve as teenagers. About 40% of these children, most of whom have milder disease, will develop intermittent disease. Inhaled corticosteroid (ICS) controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, reduced lung growth and progressive decline in lung function can be features of persistent, problematic disease.

Asthma is also classified by **disease severity** (e.g., intermittent or persistent [mild, moderate, or severe]) or **control** (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as (1) **easy to control** (well controlled with low levels of controller therapy); (2) **difficult to control** (not as well controlled with multiple and/or high levels of controller therapies); (3) **exacerbators** (despite being controlled, continue to have severe exacerbations); and (4) **refractory asthma** (continue to have poorly controlled asthma despite multiple and high levels of controller therapies; see Table 185.2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

PATHOGENESIS

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airway's lumen. T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 185.3) can lead to airways inflammation, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion, which are all processes that contribute to the clinical manifestations of asthma. Although most children with asthma manifest this proallergic "type 2" immunity and inflammation, other pathologic pathways can underlie asthma.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Asthma is characterized by repeated episodes of intermittent dry coughing and expiratory wheezing. Older children and adults report

Table 185.2 Asthma Patterns in Childhood, Based on Natural History and Asthma Management

TRANSIENT NONATOPIC WHEEZING

Common in early preschool years

Recurrent cough/wheeze, primarily triggered by common respiratory viral infections

Usually resolves during the preschool and lower school years, without increased risk for asthma in later life

Reduced airflow at birth, suggestive of relatively narrow airways; AHR near birth; improves by school age

PERSISTENT ATOPY-ASSOCIATED ASTHMA

Begins in early preschool years

Associated with atopy in early preschool years

- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum IgE, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities

- Those with onset before 3 yr of age acquire reduced airflow by school age
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood

ASTHMA WITH DECLINING LUNG FUNCTION

Children with asthma with progressive increase in airflow limitation

Associated with hyperinflation in childhood, male gender

ASTHMA MANAGEMENT TYPES

(From national and international asthma management guidelines)

*Severity Classification**

- Intrinsic disease severity while not taking asthma medications

Intermittent

Persistent

- Mild
- Moderate
- Severe

*Control Classification**

- Clinical assessment while asthma being managed and treated

Well controlled

Not well controlled

Very poorly controlled

Management Patterns

- *Easy-to-control:* well controlled with low levels of daily controller therapy
- *Difficult-to-control:* inadequately controlled with multiple and/or high levels of controller therapies
- *Frequent exacerbators:* have severe exacerbations
- *Refractory:* continue to have poorly controlled asthma despite multiple and high levels of controller therapies

*From National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): *Guideline for the Diagnosis and Management of Asthma,* NIH Pub No 07-4051, Bethesda, MD, 2007, US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report.

AHR, Airways hyperresponsiveness.

Table 185.3 Asthma Triggers

COMMON VIRAL INFECTIONS OF THE RESPIRATORY TRACT

AEROALLERGENS IN SENSITIZED ASTHMATIC PATIENTS

Indoor Allergens

- Animal dander
- Dust mites
- Cockroaches
- Molds

Seasonal Aeroallergens

- Pollens (trees, grasses, weeds)
- Seasonal molds

AIR POLLUTANTS

- Environmental tobacco smoke
- Ozone
- Nitrogen dioxide
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Mycotoxins
- Endotoxin
- Dust

STRONG OR NOXIOUS ODORS OR FUMES

- Perfumes, hairsprays
- Cleaning agents

OCCUPATIONAL EXPOSURES

- Farm and barn exposures
- Formaldehydes, cedar, paint fumes
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

DRUGS

- Aspirin and other nonsteroidal antiinflammatory drugs
- β-Blocking agents

OTHER

- Cold dry air
- Exercise
- Crying, laughter, hyperventilation
- Comorbid conditions

associated shortness of breath and chest congestion and tightness; younger children may report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators and/or corticosteroids) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 185.3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, RSV, enterovirus, coronavirus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae, Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry, cold air and irritant exposures. An environmental history is essential for optimal asthma management.

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma typically present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal.

Deeper breaths with forced exhalation can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 minutes) or convincing improvement in symptoms and signs of asthma with administration of an **inhaled short-acting β-agonist** (**SABA**; e.g., albuterol) is supportive of the diagnosis of asthma.

Asthma exacerbations can be classified by their severity based on symptoms, signs, and functional impairment (Table 185.4). Coughing and shortness of breath are common. Expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lung field, are consistent with regional hypoventilation caused by airways obstruction. **Rhonchi** and **crackles** (or **rales**) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard **(silent chest)**.

DIFFERENTIAL DIAGNOSIS

Many childhood respiratory conditions can present with symptoms and signs like those of asthma (Table 185.5). Along with asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

In early life, consideration of congenital and anatomic conditions is essential. Chronic coughing and wheezing can indicate recurrent aspiration, **tracheobronchomalacia** (congenital anatomic abnormality of airways), vascular ring/sling, foreign body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, **vocal cord dysfunction (VCD)** can manifest as intermittent daytime wheezing, most often in the setting of exercise (Table 185.6). The vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals truncated and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Hypercarbia and severe hypoxia are uncommon in uncomplicated VCD. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. Before the diagnosis, patients with VCD are often treated unsuccessfully

Table 185.4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant: softer, shorter cry, difficulty feeding)	While at rest (infant: stops feeding)	Extreme dyspnea Anxiety
	Can lie down	Prefers sitting	Sits upright	Upright, leaning forward
Talks in…	Sentences	Phrases	Words	Unable to talk
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate†	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)‡	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40–69% or response lasts <2 hr	<40%	<25%§
Pa_{O_2} (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
P_{CO_2}	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
Sa_{O_2} (breathing air) at sea level	>95% (test not usually necessary)	90–95% (test not usually necessary)	<90%	Hypoxia despite oxygen therapy
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

*Notes:
- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other; thus they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

†Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.
‡Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.
§Peak expiratory flow testing may not be needed in very severe attacks.
Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). *Guideline for the Diagnosis and Management of Asthma*, NIH Pub No 07-4051, Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program: 2007. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report.

Table 185.5 Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS

Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body

LARGE/CENTRAL AIRWAYS CONDITIONS

Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Endobronchial or mediastinal tumor
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Repaired tracheoesophageal fistula
Toxic inhalations

PERIPHERAL AIRWAYS CONDITIONS

Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis
- Cystic fibrosis
- Immunodeficiency
- Allergic bronchopulmonary mycoses (e.g., aspergillosis)
- Chronic aspiration

Primary ciliary dyskinesia
Bronchiolitis obliterans
Interstitial lung diseases
Hypersensitivity pneumonitis (acute or chronic)
Loeffler syndrome
Eosinophilic granulomatosis with angiitis
Eosinophilic pneumonia
Tropical pulmonary eosinophilia
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Pulmonary vascular congestions (congenital or acquired heart disease)
Vasculitis
Sarcoidosis
Visceral larva migrans
Medications associated with chronic cough
- Acetylcholinesterase inhibitors
- β-Adrenergic antagonists
- Angiotensin-converting enzyme inhibitors
- Daptomycin

*More common asthma masqueraders.

Table 185.6 Features Distinguishing Paradoxical Vocal Cord Motion Disorder from Asthma

FEATURE	PVCM	ASTHMA
Incidence	Less common	More common
Age and sex	Young, female	Any
Triggers	Usually exercise or emotional stress	Many triggers
History of allergy	Usually absent	May be present
Family history	Usually absent	May be present
Sensation of tightness	Throat	Chest
Inspiratory stridor	More common, heard loudly over larynx	Rare
Sputum production	Rare	Common
Nocturnal awakening with symptoms	Rare	Common
Response to bronchodilators and steroids	No response	Good response
Hypoxemia	Rare	Common
Eosinophilia	Rare	Common in allergic asthma
Chest radiograph	Usually normal	May show hyperinflation and peribronchial thickening
Residual volume and total lung capacity	Normal	May be increased
Flow volume loop	Flattening of inspiratory loop	Obstructive pattern
Bronchial provocation test	May be positive	Usually positive
Laryngoscopy	Inspiratory adduction of the anterior two thirds of vocal folds with posterior chink	Usually normal

PVCM, Paradoxical vocal cord motion.
Modified from Ibrahim WH, Gheriani HA, Almohamed AA, Raza T. Paradoxical vocal cord motion disorder: Past present and future. *Post Grad Med J*. 2007;83:164–172. Table 2, p 168.

with multiple different classes of asthma medications. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be causes of chronic coughing and/or wheezing. Rare mimics of asthma in childhood are noted in Table 185.5.

Chronic pulmonary diseases often produce clubbing (e.g., in cystic fibrosis), but clubbing is a very unusual finding in childhood asthma.

LABORATORY FINDINGS

Laboratory tests such as blood eosinophil counts and allergen-specific IgE testing may be useful for ascertaining allergy, but are not diagnostic for asthma itself. Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

Pulmonary Function Testing

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction, or when physical signs of asthma do not occur until airflow obstruction is severe.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. **Spirometry** is a helpful objective measure of airflow limitation (Fig. 185.2). It is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >4-5 years old (with some younger exceptions).

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 185.2). Because asthmatic patients typically have hyperinflated lungs, forced expiratory volume in 1 second (FEV_1) can be simply adjusted for full expiratory lung volume (the forced vital capacity [FVC]) with an FEV_1/FVC ratio, which is generally an FEV_1/FVC ratio below the lower limit of normal (Table 185.7). Normative values for these measures of lung function have been determined for children by height, gender, and age. Abnormally low FEV_1 as a percentage of predicted norms is one of six criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the **Global Initiative for Asthma (GINA)**.

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow limitation. In addition, approximately 50% of children with mild to moderate persistent asthma will have normal spirometric values when well. **Bronchodilator**

Table 185.7 Lung Function Abnormalities in Asthma

Spirometry (in clinic)*†:

Airflow limitation

- Low FEV_1 (relative to percentage of predicted norms), although many children with asthma have normal FEV_1
- FEV_1/FVC ratio below the lower limit of normal for age

Bronchodilator response (to inhaled β-agonist) assesses *reversibility* of airflow limitation

Reversibility is determined by an increase in either FEV_1 >9–12% or predicted FEV_1 >10% after inhalation of a short-acting β-agonist (SABA)‡

Exercise challenge

- Worsening in FEV_1 ≥15%‡

Daily peak expiratory flow (PEF)* or FEV_1 monitoring: day-to-day and/or am-to-pm variation ≥20%‡

*PEF variability is insensitive, while being highly specific for asthma.
†Of note, >50% of children with mild to moderate asthma will have a normal FEV_1 and will not have a significant bronchodilator response.
‡Main criteria consistent with asthma.
FEV_1, Forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroid; ppb, parts per billion.

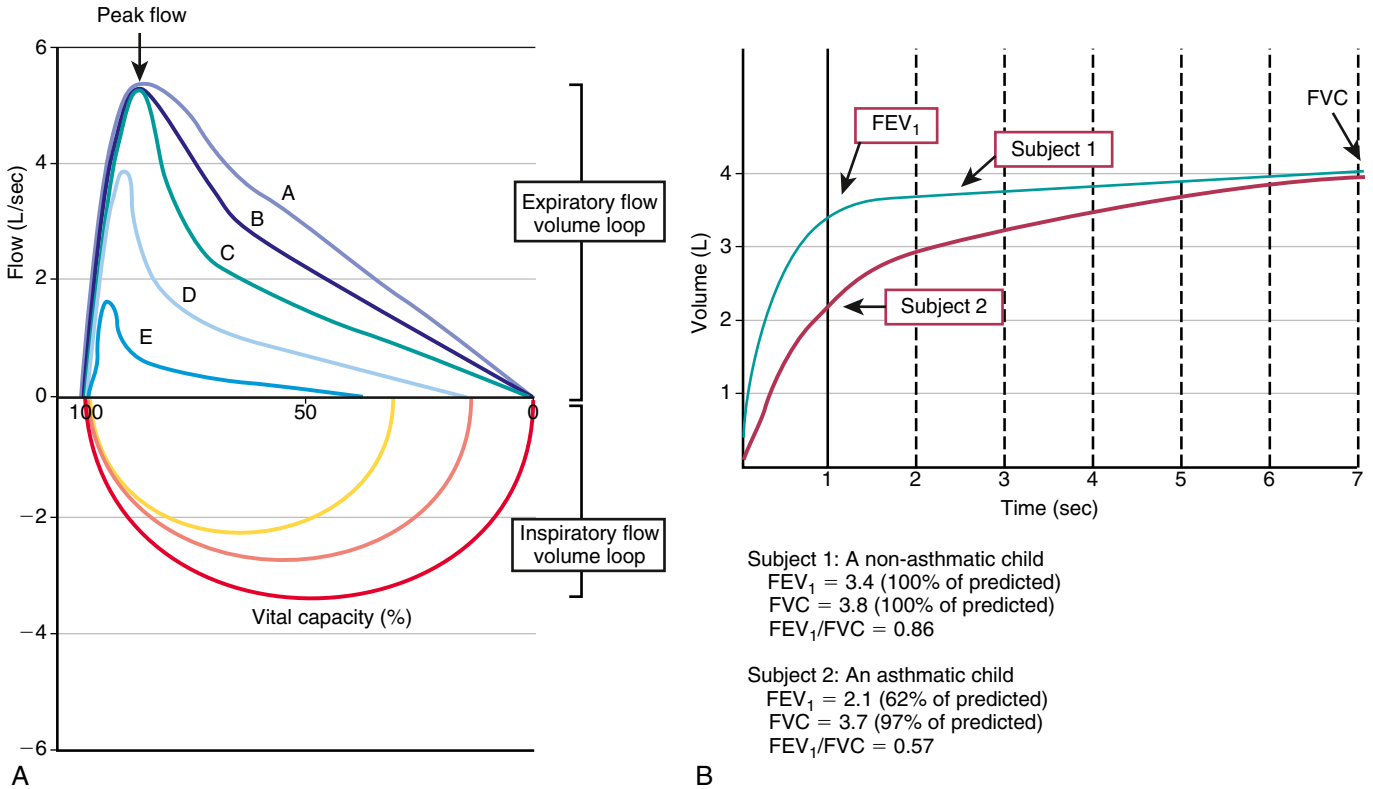


Fig. 185.2 Spirometry. **A**, Spirometric flow-volume loops. *Loop A* is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. *Loops B through E* are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." **B**, Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV_1 and FVC lung volumes are obtained. The FEV_1 is the volume of air exhaled in the first second of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV_1 and FEV_1:FVC ratio are smaller than subject 1's ratio, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

Table 185.8 Interpretations of FeNO Test Results for Asthma Diagnosis in Nonsmoking Individuals Not Taking Corticosteroids

FeNO LEVEL		
<25 PPB (<20 IN CHILDREN AGE 5-12 YR)	**25-50 PPB (20-35 IN CHILDREN AGE 5-12 YR)**	**>50 PPB (>35 IN CHILDREN AGE 5-12 YR)**
• Recent or current corticosteroid use • Alternative diagnoses • Phenotype less likely to benefit from ICS • Noneosinophilic asthma • COPD • Bronchiectasis • CF • Vocal cord dysfunction • Rhinosinusitis • Smoking • Obesity	• Evaluate in clinical context • Consider other diagnoses • Consider other factors influencing result • Eosinophilic asthma less likely	• Eosinophilic airways inflammation likely • Phenotype more likely to respond to ICS • Allergic asthma • Eosinophilic bronchitis

CF, Cystic fibrosis; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; ppb, parts per billion.
From NAEPPCC Expert Panel Working Group: 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol.* 2020;146(6):1217–1269. Table II.

response to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV_1 ≥12% is consistent with asthma. However, many children will not demonstrate an improvement with bronchodilator when well. **Bronchoprovocation challenges** can be helpful in diagnosing asthma. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. **Exercise challenges** (aerobic exertion or "running" for 6-8 minutes) can help to identify children with exercise-induced bronchospasm (EIB). Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV_1 slightly (5–10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV_1 typically decreases during or after exercise by >15% (see Table 185.7). The onset of EIB usually begins within 5 minutes, reaching a peak at 15 minutes after vigorous exercise, and often spontaneously resolves within 30-60 minutes. Studies of exercise challenges in school-age children typically identify an additional 5–10% with EIB and previously unrecognized asthma. There are two caveats regarding exercise challenges: (1) treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field and (2) exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for both bronchoprovocation and exercise challenges and preparedness for severe asthma exacerbations are required.

Peak expiratory flow (PEF) monitoring devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in some circumstances. Like spirometry in clinics, poor perceivers of asthma may benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction; they are less sensitive and reliable than spirometry to detect airflow obstruction, such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore PEF monitoring should be started by measuring morning and evening PEFs (best of three attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a "personal best," and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Table 185.7). If PEF monitoring is employed, morning measurements are preferable when peak flows are typically lower.

Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is a noninvasive measure of allergic/eosinophilic airways inflammation measured in exhaled breath (Table 185.8). FeNO can be used in children as young as 5 years to help distinguish asthma from other airways diseases that are mediated by nonallergic/noneosinophilic inflammation, such as GER, VCD, and cystic fibrosis. FeNO can substantiate the diagnosis of asthma in untreated patients, complement the assessment of asthma control, predict response to ICS and biologic therapy, assess adherence with ICS therapy, predict loss of control with ICS tapering, and predict future asthma exacerbations. However, an elevated FeNO level alone is not diagnostic of asthma and can be seen in children with allergic rhinitis without asthma.

Additional Tests to Consider

Other tests, such as allergy testing to assess sensitization to inhalant allergens (skin testing or allergen specific IgE levels) and peripheral blood total eosinophil counts, are markers of allergic "type 2" immunity and inflammation and can help with the management and prognosis of asthma. In a comprehensive U.S. study of 5–12-year-old asthmatic children, the Childhood Asthma Management Program (CAMP), 88% of patients had inhalant allergen sensitization according to results of allergy skin-prick testing.

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 185.3). Chest radiographs can help identify abnormalities that are hallmarks of asthma mimics (retained foreign body, vascular rings, aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. **Bronchiectasis**, which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implicates an asthma mimic such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

TREATMENT

National and international guidelines have been published to help promote evidence-based asthma management. These include the NIH-sponsored National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 4 (EPR4), *Guidelines for the Diagnosis and Management of Asthma*,* and The *Global Strategy for Asthma Management and Prevention (GINA), 2022*.† NAEPP and GINA guidelines are generally consistent in their management recommendations for children with asthma, with some key differences that are noted in this chapter.

The key components to optimal asthma management are specified (Fig. 185.4). Management of asthma should have the following

* https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates
† https://ginasthma.org/gina-reports/

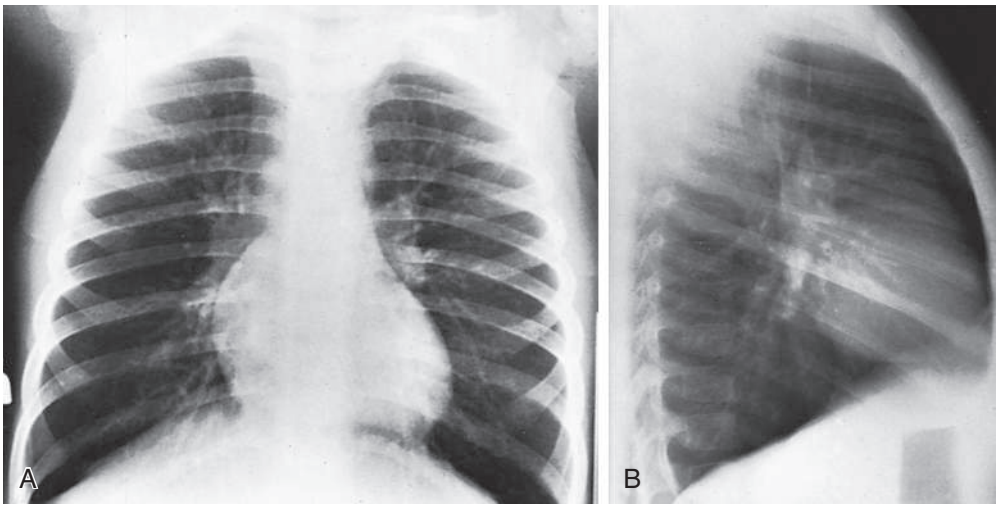


Fig. 185.3 Frontal (A) and lateral (B) radiographs of a 4-year-old with asthma show pulmonary hyperinflation, flattening of the diaphragms, and minimal peribronchial thickening. No asthmatic complication is apparent.

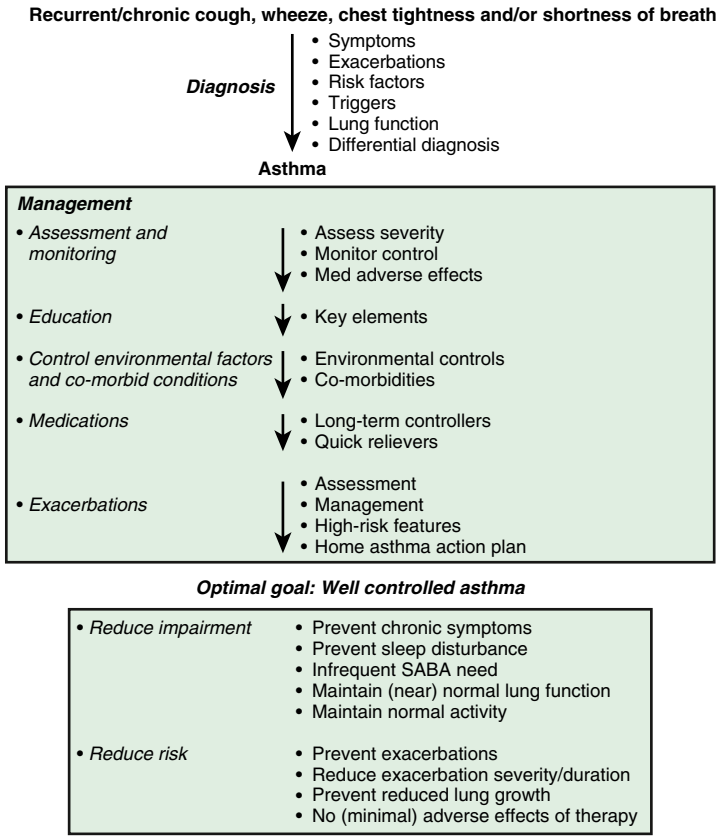


Fig. 185.4 The key elements to optimal asthma management. SABA, Short-acting β-agonist.

components: (1) assessment and monitoring of disease activity, (2) education to enhance patient and family knowledge and skills for self-management, (3) identification and management of precipitating factors and comorbid conditions that worsen asthma, and (4) appropriate selection of medications to address the patient's needs. The long-term goals of asthma management are to attain and maintain asthma control, to reduce risk of severe exacerbations, and to minimize impairment of daily activities.

Component 1: Regular Assessment and Monitoring

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. **Asthma severity** is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Therefore assessing asthma severity directs the initial level of therapy. The two general categories are **intermittent** asthma and **persistent** asthma, the latter being further subdivided into **mild, moderate,** and **severe.** In contrast, **asthma control** is dynamic and refers to the day-to-day variability of an asthmatic patient. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized into three levels: well controlled, not well controlled, and very poorly controlled. **Responsiveness to therapy** is the ease or difficulty with which asthma control is attained by treatment.

Classification of asthma severity and control is based on the domains of **impairment** and **risk**. These domains do not necessarily correlate with each other and may respond differently to treatment. Childhood asthma is often characterized by minimal day-to-day impairment, with the potential for frequent, severe exacerbations most often triggered by viral infections. The NIH and GINA guidelines have distinct criteria for three childhood age-groups, 0-4 years (GINA 0-5 years), 5-11 years (GINA 6-11 years), and ≥12 years, for the evaluation of both severity (Table 185.9) and control (Table 185.10). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, **impairment** consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the three age-groups), SABA use for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children ≥5 years. **Risk** refers to the likelihood of developing severe asthma exacerbations. Of note, even in the absence of frequent symptoms, persistent asthma can be diagnosed and long-term controller therapy initiated. For children ≥5 years, two exacerbations requiring oral corticosteroids (OCSs) in 1 year, and for infants and preschool-age children who have risk factors for asthma (see earlier) and four or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or two or more exacerbations in 6 months requiring systemic corticosteroids, qualifies them as having persistent asthma.

Asthma management can be optimized through regular clinic visits every 2-6 weeks until good asthma control is achieved. For children on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the three age-groups (see Table 185.10). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA use for quick relief, ability to engage in normal or desired activities, and for older children, airflow measurements. Validated asthma control questionnaires such as the **Asthma Control Test** (ACT, for adults and children ≥12 years), the **Childhood ACT** (C-ACT, for children 4-11 years), and the **Test for Respiratory and Asthma Control in Kids** (TRACK, for children <4 years) can also be used to assess level of control. An ACT score of ≥20 indicates a child with **well-controlled** asthma, a value of 16-19 indicates **not well-controlled** asthma, and ≤15 indicates **very poorly controlled** asthma. For the C-ACT, a score ≥20 indicates *well controlled*, 13-19 indicates *not well controlled*, and ≤12 indicates *very poorly controlled*. For the TRACK, a score of less than 80 points suggests that a child's breathing problems might not be controlled.

Assessment of risk, in addition to considering severity and frequency of exacerbations requiring systemic corticosteroids, includes tracking the lung growth of older children to identify those with reduced and/or progressive loss of lung function, and monitoring adverse effects of

Table 185.9 Assessing Asthma Severity*

	CLASSIFICATION OF ASTHMA SEVERITY			
		PERSISTENT		
	INTERMITTENT	MILD	MODERATE	SEVERE
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2-agonist use for symptoms (not for EIB prevention)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60–80% predicted	<60% predicted
FEV_1/FVC ratio†:				
Age 5-11 yr	>85%	>80%	75–80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic CS *or* ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
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.				

*Notes:
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. 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. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma, may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

†Normal FEV_1/FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV_1, Forced expiratory volume in 1 sec; FVC, forced vital capacity; CS, corticosteroid; EIB, exercise-induced bronchospasm.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94–S138.

Table 185.10 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	WELL CONTROLLED	**NOT WELL CONTROLLED**	**VERY POORLY CONTROLLED**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2-agonist use for symptoms (not for EIB pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60–80% predicted or personal best	<60% predicted or personal best
FEV_1/FVC:	>80%	75–80%	<75%
Age ≥12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60–80% predicted or personal best	<60% predicted or personal best
Validated questionnaires†:			
Age ≥12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome; the level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care		
RECOMMENDED ACTION FOR TREATMENT			
	Maintain current step Regular follow-up every 1-6 mo to maintain control Consider step down if well controlled for at least 3 mo	Step up‡ (1 step) and reevaluate in 2-6 wk If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy For side effects, consider alternative options	Consider short course of oral corticosteroids Step up§ (1-2 steps) and reevaluate in 2 wk If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy For side effects, consider alternative options

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. 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 not well-controlled asthma, even in the absence of impairment levels consistent with not well-controlled asthma.

†Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0.
- ACQ, Asthma Control Questionnaire; MID = 0.5.
- ACT, Asthma Control Test; MID not determined.

‡ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

§Before step-up therapy: (1) review adherence to medications, inhaler technique, and environmental control and (2) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV_1, Forced expiratory volume in 1 sec; FVC, forced vital capacity; EIB, exercise-induced bronchospasm; N/A, not available.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR 3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94–S138.

medications. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well controlled, not well controlled, or very poorly controlled. Children with *well-controlled asthma* have daytime symptoms ≤2 days/week and need a rescue bronchodilator ≤2 days/week, an FEV_1 of >80% of predicted (and FEV_1/FVC ratio >80% for children 5-11 years), no interference with normal activity, and <2 exacerbations in the past year and an ACT score of ≥20. The impairment criteria vary slightly depending on age-group. Children whose status does not meet all the criteria of well-controlled asthma are determined to have either *not well-controlled* or *very poorly controlled* asthma, which is determined by the single criterion with the poorest rating.

Two to four asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, is inadequately controlled, and/or lung function is abnormally low.

Component 2: Patient Education

Asthma education that focuses on home management and medication adherence is critical for optimal clinical care of children with asthma (Table 185.11). Asthma education should consider sociocultural and ethnic factors and provide an open forum for concerns about asthma and its treatment. Families should be active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 184.4). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

All children with asthma should benefit from a written Asthma Action Plan (Fig. 185.5). This plan has two main components: (1) a daily "routine" management plan describing regular asthma medication use and other measures to keep asthma under good control and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Regular follow-up visits are recommended to help to maintain optimal asthma control. Follow-up visits provide the opportunity to reassess asthma medication perceptions and delivery techniques. The Asthma Action Plan can be revised as needed.

Table 185.11 Key Elements of Productive Clinic Visits for Asthma

Standardize assessment of asthma control (e.g., Asthma Control Test, exacerbations in past 12 mo)
Specify goals of asthma management
Explain basic facts about asthma
• Contrast normal vs asthmatic airways
• Link airways inflammation, "twitchiness," and bronchoconstriction
• Long-term-control and quick-relief medications
• Address concerns about potential adverse effects of asthma pharmacotherapy
Teach, demonstrate, and have patient show proper technique
• Inhaled medication use (spacer use with metered-dose inhaler)
Investigate and manage factors that contribute to asthma severity
• Environmental exposures
• Comorbid conditions
Create written two-part Asthma Action Plan (see Fig. 185.5)
• Daily management
• Action plan for asthma exacerbations
Regular follow-up visits
• Twice yearly (more often if asthma not well controlled)
• Monitor lung function at least annually

Adherence

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane and exacerbations may be infrequent. A natural tendency is to reduce or discontinue daily controller therapies once asthma symptoms improve. As such, adherence to a daily controller regimen is frequently suboptimal; ICSs are underused 60% of the time. In one study, children with asthma who required an OCS course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

Component 3: Control of Factors Contributing to Poor Asthma Control

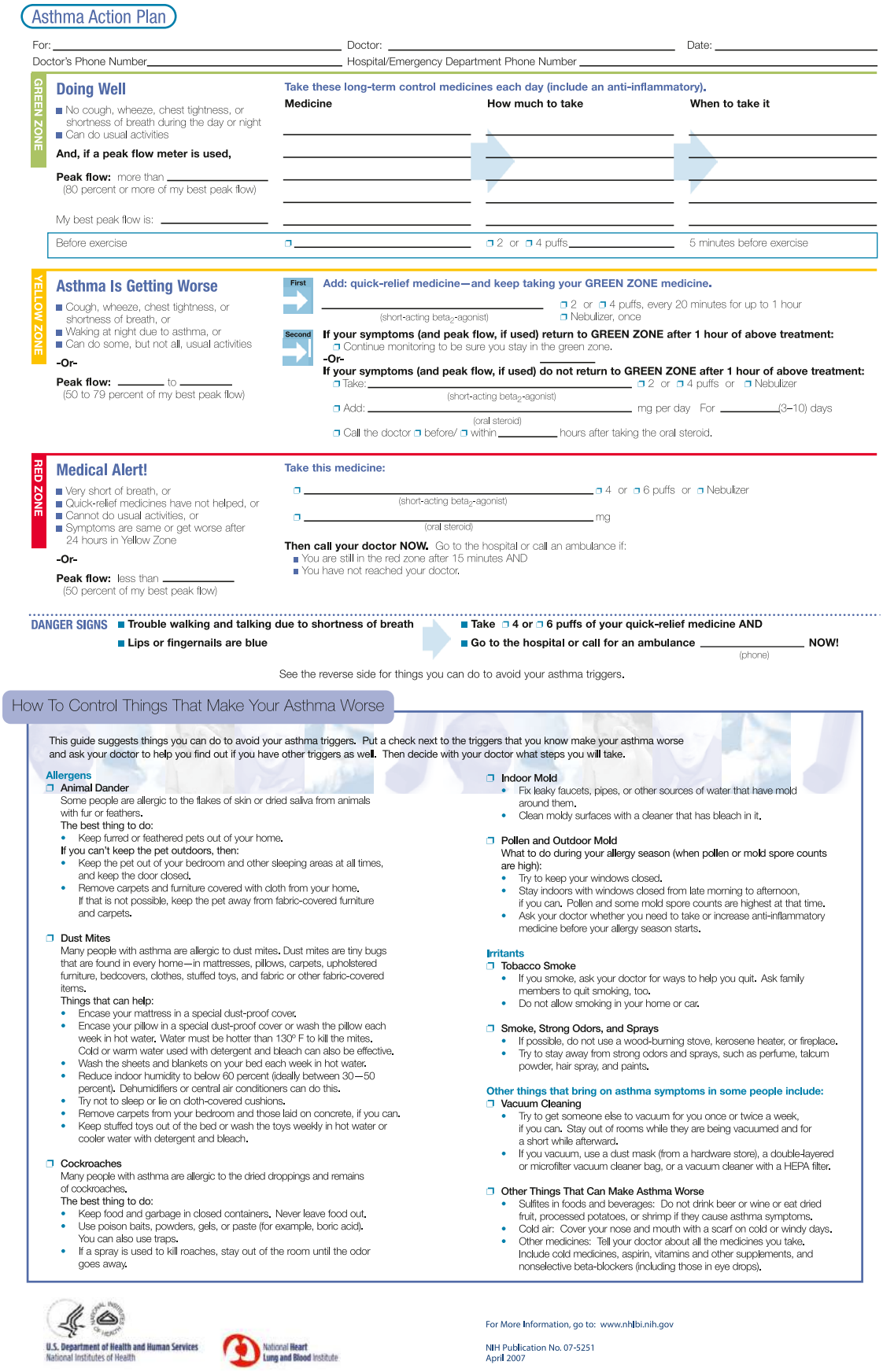
Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 185.12).

Eliminating and Reducing Problematic Environmental Exposures

Steps should be taken to investigate and minimize exposures in asthmatic patients. These exposures include allergens as well as irritants (e.g., smoke, pollutants, and other chemicals such as perfumes), in the patient's home or school. However, patients often cannot identify potential triggers. **Allergy testing** should be considered for all patients with persistent asthma to identify allergens that may contribute to airway inflammation, asthma symptoms, and exacerbations. For asthmatic patients who are allergic to allergens in their homes and/or schools or daycare centers, reducing or eliminating these indoor allergen exposures can reduce asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home, school, and daycare allergen exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats, cockroaches), and occult indoor allergens such as dust mites and molds.

Allergen mitigation strategies can be used in patients with allergy of all ages and asthma severities, but these strategies should be tailored to the individual. Multicomponent interventions are recommended to control indoor allergens, because single component interventions are often not effective. Examples of single component interventions for dust mite allergy include (1) encasing bedding and pillows in allergen-impermeable covers, (2) washing bedding weekly in hot water (>130°F), (3) removing wall-to-wall carpeting and upholstered furniture, or (4) reducing and maintaining indoor humidity <50%. In contrast, a multicomponent strategy for dust mite allergy might include all of these measures. Integrated pest management strategies are also recommended for patients exposed to cockroaches, mice, or rats in the home who have sensitization to these allergens. Integrated pest management can also be used with other interventions to reduce exposures to pest-related allergens. Families should be educated that it can take ≥6 months for the levels of these indoor allergens to drop significantly and for asthma control to improve after intervention. Allergen mitigation strategies are not recommended for patients with no allergy to indoor allergens.

Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants (e.g., nitrogen dioxide from inadequately vented gas stoves and furnaces) can also aggravate asthma. These airway irritants should be eliminated from or reduced in the homes, schools/daycare centers, and automobiles/school transportation used by children with asthma. Care providers can be strong influencers of smoking cessation by parents, caregivers, and adolescent patients (see also Chapters 157.2 and 759.1). Secondhand marijuana smoke contains many of the same chemicals and



Asthma Action Plan

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number _____ Hospital/Emergency Department Phone Number _____

GREEN ZONE

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____ (80 percent or more of my best peak flow)

My best peak flow is: _____

Take these long-term control medicines each day (include an anti-inflammatory).

Medicine	How much to take	When to take it
Before exercise	❒ _____	❒ 2 or ❒ 4 puffs _____	5 minutes before exercise

YELLOW ZONE

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____ (50 to 79 percent of my best peak flow)

First

Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

_____ (short-acting beta$_2$-agonist) ❒ 2 or ❒ 4 puffs, every 20 minutes for up to 1 hour ❒ Nebulizer, once

Second

If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:

❒ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:

❒ Take: _____ (short-acting beta$_2$-agonist) ❒ 2 or ❒ 4 puffs or ❒ Nebulizer

❒ Add: _____ (oral steroid) mg per day For _____ (3–10) days

❒ Call the doctor ❒ before/ ❒ within _____ hours after taking the oral steroid.

RED ZONE

Medical Alert!

- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____ (50 percent of my best peak flow)

Take this medicine:

❒ _____ (short-acting beta$_2$-agonist) ❒ 4 or ❒ 6 puffs or ❒ Nebulizer

❒ _____ (oral steroid) mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:

- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS

- **Trouble walking and talking due to shortness of breath**
- **Lips or fingernails are blue**

- **Take ❒ 4 or ❒ 6 puffs of your quick-relief medicine AND**
- **Go to the hospital or call for an ambulance _____ (phone) NOW!**

See the reverse side for things you can do to avoid your asthma triggers.

How To Control Things That Make Your Asthma Worse

This guide suggests things you can do to avoid your asthma triggers. Put a check next to the triggers that you know make your asthma worse and ask your doctor to help you find out if you have other triggers as well. Then decide with your doctor what steps you will take.

Allergens

❒ **Animal Dander**

Some people are allergic to the flakes of skin or dried saliva from animals with fur or feathers.

The best thing to do:

- Keep furred or feathered pets out of your home.

If you can't keep the pet outdoors, then:

- Keep the pet out of your bedroom and other sleeping areas at all times, and keep the door closed.
- Remove carpets and furniture covered with cloth from your home. If that is not possible, keep the pet away from fabric-covered furniture and carpets.

❒ **Dust Mites**

Many people with asthma are allergic to dust mites. Dust mites are tiny bugs that are found in every home—in mattresses, pillows, carpets, upholstered furniture, bedcovers, clothes, stuffed toys, and fabric or other fabric-covered items.

Things that can help:

- Encase your mattress in a special dust-proof cover.
- Encase your pillow in a special dust-proof cover or wash the pillow each week in hot water. Water must be hotter than 130° F to kill the mites. Cold or warm water used with detergent and bleach can also be effective.
- Wash the sheets and blankets on your bed each week in hot water.
- Reduce indoor humidity to below 60 percent (ideally between 30—50 percent). Dehumidifiers or central air conditioners can do this.
- Try not to sleep or lie on cloth-covered cushions.
- Remove carpets from your bedroom and those laid on concrete, if you can.
- Keep stuffed toys out of the bed or wash the toys weekly in hot water or cooler water with detergent and bleach.

❒ **Cockroaches**

Many people with asthma are allergic to the dried droppings and remains of cockroaches.

The best thing to do:

- Keep food and garbage in closed containers. Never leave food out.
- Use poison baits, powders, gels, or paste (for example, boric acid). You can also use traps.
- If a spray is used to kill roaches, stay out of the room until the odor goes away.

❒ **Indoor Mold**

- Fix leaky faucets, pipes, or other sources of water that have mold around them.
- Clean moldy surfaces with a cleaner that has bleach in it.

❒ **Pollen and Outdoor Mold**

What to do during your allergy season (when pollen or mold spore counts are high):

- Try to keep your windows closed.
- Stay indoors with windows closed from late morning to afternoon, if you can. Pollen and some mold spore counts are highest at that time.
- Ask your doctor whether you need to take or increase anti-inflammatory medicine before your allergy season starts.

Irritants

❒ **Tobacco Smoke**

- If you smoke, ask your doctor for ways to help you quit. Ask family members to quit smoking, too.
- Do not allow smoking in your home or car.

❒ **Smoke, Strong Odors, and Sprays**

- If possible, do not use a wood-burning stove, kerosene heater, or fireplace.
- Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, and paints.

Other things that bring on asthma symptoms in some people include:

❒ **Vacuum Cleaning**

- Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- If you vacuum, use a dust mask (from a hardware store), a double-layered or microfilter vacuum cleaner bag, or a vacuum cleaner with a HEPA filter.

❒ **Other Things That Can Make Asthma Worse**

- Sulfites in foods and beverages: Do not drink beer or wine or eat dried fruit, processed potatoes, or shrimp if they cause asthma symptoms.
- Cold air: Cover your nose and mouth with a scarf on cold or windy days.
- Other medicines: Tell your doctor about all the medicines you take. Include cold medicines, aspirin, vitamins and other supplements, and nonselective beta-blockers (including those in eye drops).

U.S. Department of Health and Human Services
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For More Information, go to: www.nhlbi.nih.gov

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Fig. 185.5 Asthma action plan for home use. This plan has two main components: (1) a daily management plan to keep asthma in good control and (2) an action plan to recognize and manage worsening asthma. *(From U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Pub No 07-5251, April 2007.* https://www.nhlbi.nih.gov/health/asthma/treatment-action-plan.*)*

Table 185.12 Control of Factors Contributing to Asthma Severity

ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES
Environmental tobacco smoke elimination or reduction in home and automobiles
Allergen exposure elimination or reduction in sensitized asthmatic patients
• Pets (cats, dogs, rodents, birds)
• Pests (mice, rats)
• Dust mites
• Cockroaches
• Molds
Other airway irritants
• Wood- or coal-burning smoke
• Strong chemical odors and perfumes (e.g., household cleaners)
• Dusts
TREAT COMORBID CONDITIONS
Rhinitis
Sinusitis
Gastroesophageal reflux

particulates as tobacco smoke, and should also be avoided (see Chapter 759.2). Exposure to electronic cigarette aerosol may also aggravate asthma.

Annual influenza vaccination (both inactivated and live attenuated) is safe in children with asthma and continues to be recommended for all children with asthma to reduce the risk of severe complications, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

Identifying and Treating Comorbid Conditions

Rhinitis, sinusitis, GER, and obesity often accompany asthma and may make the asthma difficult to treat. These conditions can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions, along with asthma, are the most common causes of chronic cough. Poor conditioning from obesity may also be confused with asthma-related dyspnea. Effective management of these comorbid conditions may improve asthma symptoms, such that less asthma medication is needed to achieve good asthma control.

Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2020) provides treatment recommendations that vary by level of asthma severity and age-groups (Table 185.13). There are six treatment steps. Patients at **Treatment Step 1** have intermittent asthma. Children with mild persistent asthma are at **Treatment Step 2**. Children with moderate persistent asthma can be at **Treatment Step 3 or 4**. Children with severe persistent asthma are at **Treatment Steps 5 and 6**. The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing or minimizing symptoms, infrequently needing quick-reliever medications, maintaining "normal" lung function and normal activity levels) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medication adverse effects). The recommendations for initial therapy are based on assessment of asthma severity, whereas level of control determines any modifications of treatment in children who are already using controller therapy. **A major objective of this approach is to identify and treat all "persistent" and inadequately controlled asthma with anti-inflammatory controller medication.** *Treatment Step 1 (intermittent asthma)* management is simply the use of a SABA as needed for symptoms and for pretreatment in those with EIB. For children <5 years with recurrent episodic wheeze in the setting of viral illness, a short course of daily high-dose ICS may also be considered.

The preferred treatment for all patients with persistent asthma includes an ICS-containing therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating.

At *Treatment Step 2 (mild persistent asthma)*, low-dose daily ICS therapy is the treatment of choice for all children. Common alternative medications include a leukotriene receptor antagonist (LTRA) such as montelukast.

At *Treatment Step 3 (moderate persistent asthma)*, for school-age children, the preferred treatment has recently been modified to the daily and as-needed use of a low-dose ICS/formoterol (a rapid onset, long-acting β_2-agonist [LABA]) combination inhaler, used twice daily as both maintenance therapy and as-needed reliever therapy (in place of a separate SABA inhaler).

Single maintenance and reliever therapy (SMART) is a fundamental change from the conventional distinct daily controllers vs quick reliever medications. Although SMART has been determined to be effective in reducing asthma exacerbations relative to use of SABA as a reliever (i.e., favorable benefit-harm ratio), some current challenges to implementation for providers and patients include ICS/formoterol availability/affordability, FDA approval for use as a reliever therapy, and asthma management and action plan reeducation for home and school, including the appropriate use of SABA in asthma care (e.g., exercise pretreatment). A SABA/ICS combination inhaler (albuterol/budesonide 90 mcg/80 mcg per actuation) is FDA approved for as-needed use as a quick reliever in adults ages 18 years and older (not in children).

Common alternate choices for the treatment of school-age children at Treatment Step 3 include (1) medium-dose ICS or (2) low-dose ICS used in combination with an inhaled LABA. In a study of children with uncontrolled asthma receiving low-dose ICS, the addition of LABA was more likely to provide improvement than either adding an LTRA or increasing ICS dosage. However, some children had a good response to medium-dose ICS or the addition of an LTRA, justifying them as step-up controller therapy options. Thus if a child is not well controlled with a given step 3 treatment, trials of the alternate treatment approaches should be considered before stepping up to step 4. In patients 12 years and older with uncontrolled persistent asthma for whom a LABA is not used, current guidelines recommend addition of a LABA or a long-acting muscarinic antagonist (LAMA) to the ICS as a step-up approach. Adding a LAMA is not more efficacious than adding a LABA, so LAMAs should not be selected over a LABA unless necessary. LAMAs also have a less favorable benefit-harm profile and should not be used in patients with a risk of urinary retention or glaucoma. LAMAs can also be added to ICS/LABA combination therapy if the patient remains symptomatic.

For young children (≤4 years) at Treatment Step 3, NAEPP guidelines recommend daily medium dose ICS, whereas GINA recommends three co-equal preferred options: (1) daily low-dose ICS/LABA, (2) daily low-dose ICS + LTRA, or (3) daily medium-dose ICS.

At *Treatment Step 4 (moderate persistent asthma)*, the preferred therapy for school-age children is daily and as-needed use of a medium-dose ICS/formoterol combination inhaler, used twice daily for maintenance and as needed for reliever therapy. Alternatives include daily medium-dose ICS with either a LABA, LTRA, or other controller (such as a LAMA in patients 12 years and older). For preschool-age children at Treatment Step 4, daily medium-dose ICS/LABA is recommended.

For children age ≥5 years with allergic asthma requiring Treatment Steps 2-4 care, *subcutaneous allergen immunotherapy (SCIT)* can be considered. Current guidelines recommend SCIT as an adjunct treatment to standard pharmacotherapy in patients whose asthma can be adequately controlled and managed at the initiation, buildup, and maintenance phases of SCIT. Some requirements for effective and safe SCIT include (1) allergen sensitization evaluation using either immediate hypersensitivity skin testing or in vitro antigen-specific IgE antibody testing, and by a trained healthcare professional skilled in proper testing and result interpretation; (2) before each SCIT injection, evaluation to ensure that asthma is well controlled because poorly controlled asthma is a major risk factor for life-threatening and fatal

Table 185.13 Stepwise Approach for Managing Asthma in Children*

Age	Treatment	Intermittent Asthma	Persistent Asthma				
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
0–4 years	**Preferred**	PRN SABA And At the start of RTI: Add short course daily ICS	Daily low-dose ICS and PRN SABA	Daily low-dose ICS-LABA and PRN SABA Or Daily low-dose ICS + montelukast or daily medium-dose ICS and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroids and PRN SABA
	Alternative		Daily montelukast or Cromolyn and PRN SABA		Daily medium-dose ICS + montelukast and PRN SABA	Daily high-dose ICS + montelukast and PRN SABA	Daily high-dose ICS-LABA + montelukast + oral systemic corticosteroids and PRN SABA
				For children age 4 years only, see Step 3 and Step 4 for ages 5–11 years			
5–11 years	**Preferred**	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol	Daily and PRN combination medium-dose ICS-formoterol	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroids and PRN SABA
	Alternative		Daily LTRA, or Cromolyn, or Nedocromil, or Theophylline, and PRN SABA	Daily medium-dose ICS and PRN SABA Or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA, or daily low-dose ICS + theophylline, and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA Or Daily medium-dose ICS + LTRA, or daily medium-dose ICS + theophylline, and PRN SABA	Daily high-dose ICS + LTRA or daily high-dose ICS + Theophylline, and PRN SABA	Daily high-dose ICS + LTRA + oral systemic corticosteroid or daily high-dose ICS + Theophylline + oral systemic corticosteroid, and PRN SABA
			Steps 2–4: Conditionally recommend use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy			Consider omalizumab	
12+ years	**Preferred**	PRN SABA	Daily low-dose ICS and PRN SABA Or PRN concomitant ICS and SABA	Daily and PRN combination low-dose ICS-formoterol	Daily and PRN combination medium-dose ICS-formoterol	Daily medium-high dose ICS-LABA + LAMA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroids and PRN SABA
	Alternative		Daily LTRA and PRN SABA Or Cromolyn, or Nedocromil, or Theophylline, and PRN SABA	Daily medium-dose ICS and PRN SABA Or Daily low-dose ICS-LABA, or Daily low-dose ICS + LAMA, or daily low-dose ICS + LTRA, or daily low-dose ICS + theophylline, and PRN SABA	Daily medium-dose ICS or daily medium-dose ICS + LAMA, and PRN SABA Or Daily medium-dose ICS + LTRA, or daily medium-dose ICS + theophylline, and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA, and PRN SABA	
			Steps 2–4: Conditionally recommend use of subcutaneous allergen immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy			Consider adding asthma biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13R, anti-TSLP)	

Assess control

- First check adherence, inhaler technique, environmental factors, and comorbid conditions.
- **Step up** if needed, reassess in 4–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 3 or higher is required for those 0–4 years of age (and consider consultation at Step 2) or if Step 4 is required for those 5+ years of age (and consider consultation at Step 3).

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Continued

Table 185.13 Stepwise Approach for Managing Asthma in Children*—cont'd

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited.
- Clinicians who administer allergen immunotherapy or biologic therapy should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels. The 2016 GINA guidelines do not recommend the use of theophylline as a controller medication and in IV forms to treat status asthmaticus due to its severe adverse effects profile.

†Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.

ICS, Inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; prn, as needed; SABA, inhaled short-acting β_2-agonist.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma --summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94-S138, 2007 and 2020 Focused Updates to Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group.

allergic reactions from SCIT; and (3) being well prepared to respond to systemic allergic/anaphylactic reactions to SCIT injections. Patients with allergic asthma may also benefit from improvements in comorbid allergic rhinitis and conjunctivitis, which could additionally improve quality of life. SCIT efficacy with regard to asthma medication use and exacerbations is not clear. SCIT is not recommended in patients with severe asthma given the potential for systemic reactions of potentially great severity. Sublingual immunotherapy is not currently recommended based on available data.

At *Treatment Steps 5 and 6 (severe persistent asthma)*, all children should receive daily high-dose ICS plus LABA as the preferred approach; alternative secondary controllers to LABA include LTRA or LAMA. Long-term administration of OCSs as controller therapy may be effective but is rarely required and should be avoided whenever possible due to potential for significant corticosteroid side effects. In addition, biologics should be considered in children with specific asthma phenotypes: (1) omalizumab can be used in children ≥6 years old with severe allergic asthma; (2) mepolizumab (≥6 years), dupilumab (≥6 years), and benralizumab (≥12 years) can be used in children with severe eosinophilic asthma; and (3) tezepelumab (≥12 years) can be used in children with severe asthma. A rescue course of systemic corticosteroids may be necessary at any step for very poorly controlled asthma.

Adjusting Asthma Pharmacotherapy

By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. ***Asthma controller therapy can be stepped down after good asthma control has been achieved and maintained for at least 3 months.*** Stopping ICS controller therapy should be given careful consideration in children with a history of exacerbations. For example, in children with a history of fall seasonal asthma exacerbations and whose asthma becomes well controlled in the summer, ICS may be reduced but not completely discontinued. Regular follow-up is still emphasized because the variability of asthma's course is well recognized. When asthma is not well controlled, adherence, inhaler technique, and comorbidities should be considered first before increasing controller treatment. If increased treatment is required, the recommendation is to step up by one level and closely monitor for clinical improvement. For a child with very poorly controlled asthma, the recommendations are to consider a short course of prednisone and/or to increase therapy by two step levels, with reevaluation in 2 weeks.

Referral to Asthma Specialist

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining good asthma control. For children ≤4 years, referral is recommended if the patient requires at least Treatment Step 3 care, and should be considered if the patient requires Treatment Step 2 care. For children ≥5 years, consultation with a specialist is recommended if the patient requires Treatment Step 4 care or higher, and should be considered if Treatment Step 3 is required. Referral is also recommended if allergen immunotherapy (AIT) or biologic therapy is being considered.

Long-Term Controller Medications

All levels of persistent asthma should be treated with an ICS-containing therapy to reduce airway inflammation, improve long-term control, and reduce exacerbation risk (see Table 185.13). Other long-term controller medications include LABAs, leukotriene modifiers, LAMAs, SCIT, cromolyn, sustained-release theophylline, and tiotropium in adolescents. Omalizumab and mepolizumab are approved by the FDA for use as an add-on therapy in children ≥6 years who have severe allergic asthma or eosinophilic asthma, respectively, that remains difficult to control. For adolescents 12 years and older, benralizumab is approved by the FDA for severe asthma with an eosinophilic phenotype. Dupilumab is approved by the FDA for moderate to severe asthma with an eosinophilic phenotype for children 6 years and older. Tezepelumab is approved by the FDA for severe asthma in adolescents 12 years and older (see Tables 185.13 and 185.14).

Inhaled Corticosteroids

ICS therapy serves as the cornerstone of therapy in persistent asthma, as it improves lung function; reduces asthma symptoms, AHR, and use of "rescue" medications; improves quality of life; and most importantly reduces exacerbations, the need for systemic corticosteroids, urgent care visits, and hospitalizations. Epidemiologic studies have also shown that ICS therapy in adults substantially lowers the risk of death attributable to asthma if used regularly. Because ICS therapy frequently achieves all the goals of asthma management, it is viewed as first-line treatment for persistent asthma. The selection of the initial ICS dose is based on the determination of disease severity.

Seven ICSs are approved by the FDA for use in children. The NIH and GINA guidelines provide equivalence classifications (Table 185.15), although direct comparisons of efficacy and safety outcomes are lacking. ICSs are available in metered-dose inhalers (MDIs) using hydrofluoroalkane (HFA) as their propellant, in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, and to a lesser extent budesonide are considered "second-generation" ICSs, in that they have greater antiinflammatory potency and less systemic bioavailability.

Even though ICSs are very effective in most patients, there has been some reluctance to treat children with ICSs due to parental and occasionally physician concerns regarding their potential for adverse effects with chronic use. The most serious adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency of administration (Table 185.16). High doses (≥1,000 μg/day in children) and frequent administration (4 times per day) are more likely to have both local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require frequent systemic corticosteroid courses for asthma exacerbations, further increasing their risk of corticosteroid adverse effects.

The most common ICS adverse effects are local: oral **candidiasis** (thrush) and **dysphonia** (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression, and dysphonia

Table 185.14 Usual Dosages for Long-Term Control Medications

MEDICATION	AGE 0-4 YR	5-11 YR	≥12 YR
INHALED CORTICOSTEROID MONOTHERAPIES (SEE TABLE 185.13)			
Inhaled Corticosteroid/Long-Acting β-Agonist (ICS/LABA) Combination Therapies:			
Fluticasone/salmeterol (Advair):	N/A		
DPI: 100, 250, or 500 µg/50 µg		1 inhalation bid; dose depends on level of severity or control (the 100/50 dosage is indicated in children ≥4 yr)	1 inhalation bid; dose depends on level of severity or control
HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg			2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol (Symbicort): HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	N/A		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol (Dulera): HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Leukotriene Receptor Antagonists:			
Montelukast (Singulair): 4 or 5 mg chewable tablet; 4 mg granule packets; 10 mg tablet **Black box warning** (see text)	4 mg qhs (1-5 yr)	5 mg qhs (6-14 yr)	10 mg qhs (indicated in children ≥15 yr)
Zafirlukast (Accolate): 10 mg or 20 mg tablet	N/A	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
Biologic Therapies:			
Omalizumab (anti-IgE; Xolair): SC injection, 150 mg	N/A	75-375 mg SC q 2-4 wk (6-11 yr), depending on body weight and pretreatment serum IgE level	75-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level
Mepolizumab (anti–IL-5; Nucala): SC injection, 100 mg	N/A	40 mg SC q 4 wk (6-11 yr)	100 mg SC q 4 wk
Benralizumab (anti–IL-5 Rα; Fasenra) SC injection, 30 mg	N/A	N/A	30 mg SC q 4 wk × 3 doses, then 30 mg SC q 8 wk
Dupilumab (anti–IL-4 Rα; Dupixent) SC injection, 200 mg, 300 mg	N/A	15 to <30 kg:100 mg q 2 wk or 300 mg q 4 wk ≥30 kg: 200 mg q2 wk	400 mg or 600 mg SC starting dose, then 200 or 300 mg SC q 2 wk
Tezepelumab (anti-TSLP; Tezspire) SC injection, 210 mg	N/A	N/A	210 mg SC q 4 wk

bid, Two times daily; DPI, dry powder inhaler; HFA, hydrofluoroalkane; IL, interleukin; q, every; qhs, every night; SC, subcutaneous(ly).

is the result of vocal cord myopathy. These effects are dose dependent and are most common in individuals receiving high-dose ICS or OCS therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI with the ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use had been an unanswered concern. A long-term, prospective NIH-sponsored study (CAMP) followed the growth and bone mineral density (BMD) of >1,000 children (age 6-12 years at entry) with mild to moderate asthma until they reached adulthood and found slight growth suppression and osteopenia in some children who received long-term ICS therapy. A small (1.1 cm), limited (1 year) growth suppressive effect was noted in children receiving budesonide, 200 µg twice daily, after 5 years of therapy. Height was then followed until all children had reached adulthood (mean age 25 years). Those who received ICS therapy remained approximately 1 cm shorter than those who received placebo. Thus children treated with long-term low-dose ICS therapy may be about 1 cm shorter than expected as an adult, which is of little clinical significance. BMD was no different in those receiving budesonide vs placebo during the duration of the study, whereas a follow-up study after a mean of 7 years found a slight dose-dependent effect of ICS therapy on bone mineral accretion only among males. A much greater effect on BMD was observed with increasing numbers of OCS bursts for acute asthma, as well as an increase in risk for osteopenia, which was again limited to males. These findings were with use of low-dose budesonide; higher ICS doses, especially of agents with increased potency, are likely to have a greater potential for adverse effects. Thus osteoporosis screening and prevention measures are recommended for patients receiving higher ICS doses, because these patients are also likely to require systemic courses for exacerbations (see Table 185.16).

Systemic Corticosteroids

The development of second-generation ICSs, especially when used in combination with a LABA in a single device, along with the addition of biologics, have allowed almost all children with asthma to achieve and maintain good control without need for maintenance OCS therapy. Thus short courses of OCSs are used primarily to treat asthma exacerbations and, very rarely, as maintenance therapy in children with very severe disease. In these patients, every attempt should be made to exclude comorbid conditions and to keep the OCS dose at ≤20 mg every other day. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 615). To determine the need for continued OCS therapy, tapering of the OCS dose over several weeks should be attempted, with close monitoring of the patient's symptoms and lung function.

Prednisone, prednisolone, methylprednisolone, and dexamethasone are rapidly and completely absorbed, with peak plasma

Table 185.15 Estimated Comparative Inhaled Corticosteroid Doses

GLUCOCORTICOID	LOW DAILY DOSE	MEDIUM DAILY DOSE	HIGH DAILY DOSE
Beclomethasone (Qvar) MDI: 40 or 80 μg (Approved for children ≥5 yr)	80-160 μg	160-320 μg	>320 μg
Budesonide (Pulmicort Flexhaler) DPI: 90, 180 μg (Approved for children ≥6 yr)	200 μg	200-400 μg	>400 μg
Budesonide suspension for nebulization (Generic and Pulmicort Respules) 0.25 mg, 0.5 mg, 1 mg (Approved for children 1-8 yr)	0.5 mg	1.0 mg	2.0 mg
Ciclesonide (Alvesco) MDI: 80, 160 μg (Approved for children ≥12 yr)	80 μg	80-160 μg	160 μg
Flunisolide (Aerospan) MDI: 80 μg/puff (Approved for children ≥6 yr)	80 μg	80-160 μg	160 μg
Fluticasone propionate (Flovent, Flovent Diskus) MDI: 44, 110, 220 μg DPI: 50, 100, 250 μg (44 and 50 μg approved for children ≥4 yr)	88-176 μg 100-200 μg	176-440 μg 200-500 μg	>440 μg >500 μg
Fluticasone furoate (Arnuity Ellipta) DPI: 100, 200 μg (Approved for children ≥12 yr)	100 μg	100-200 μg	200 μg
Mometasone Furoate (Asmanex, Asmanex Twisthaler) MDI: 100, 200 μg DPI: 110, 220 μg (Approved for children ≥4 yr)	110 μg 100 μg	110 μg 100 μg	110 μg 100 μg

DPI, Dry powder inhaler; MDI, metered-dose inhaler.
Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94–S138.

concentrations occurring within 1-2 hours. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. For asthma exacerbations in children, oral dexamethasone is also commonly used given its long half-life of 36-54 hours and association with less vomiting when compared with oral prednisone. These corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketoconazole, oral contraceptives) can significantly delay corticosteroid metabolism. Some macrolide antibiotics, such as erythromycin and clarithromycin, delay the clearance of only methylprednisolone.

Long-term OCS therapy can cause numerous adverse effects over time (see Chapter 617). Some occur immediately (metabolic effects), whereas others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of OCSs, especially with concurrent high-dose ICSs and often intranasal corticosteroids, should receive corticosteroid adverse effects screening (see Table 185.16) and osteoporosis preventive measures (see Chapter 749).

Long-Acting Inhaled β-Agonists

Although considered daily controller medications, LABAs (salmeterol, formoterol) are not intended for use as monotherapy for persistent asthma because they can increase the risk for serious asthma exacerbations (ICU admission, endotracheal intubation) and asthma-related deaths when used without an ICS. The likely mechanism involves the ability of LABAs to "mask" worsening asthma inflammation and asthma severity, leading to a delay in seeking urgent care and increased risk of a life-threatening exacerbation. Although both salmeterol and formoterol have a prolonged duration of effect (≥12 hours), salmeterol has a prolonged onset of effect (60 minutes), whereas formoterol's onset of effect is rapid (5-10 minutes) after administration. Given their long duration of action, LABAs are well suited for patients with nocturnal asthma and for individuals who require frequent use of SABA inhalations during the day to prevent EIB, but only in combination with ICSs. The FDA recommends that once a patient is well controlled on combination ICS/LABA therapy, the LABA component should be discontinued while continuing treatment with the ICS, although many patients experience disease worsening on LABA discontinuation.

Combination ICS/LABA Therapy

Combination ICS/LABA therapy is recommended for patients who are suboptimally controlled with ICS therapy alone and those with moderate or severe persistent asthma. In most patients who are inadequately controlled with ICS alone, combination ICS/LABA therapy is superior to add-on therapy with either an LTRA or LAMA or doubling the ICS dose. Benefits include improvement in baseline lung function, less need for rescue SABA therapy, improved quality of life, and fewer asthma exacerbations. A large study found that in children inadequately controlled with low-dose ICS therapy, combination low-dose fluticasone/salmeterol (100 μg/21 μg) twice daily was almost twice as likely to be effective as other step-up regimens, including fluticasone (250 μg) twice daily or low-dose fluticasone (100 μg twice daily) plus montelukast once daily, with the greatest improvement in reducing exacerbations requiring prednisone and study withdrawals due to poorly controlled asthma. In addition, combination fluticasone/salmeterol was as likely to be effective as medium-dose fluticasone and

Table 185.16 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 185.13)	Monitor blood pressure and weight with each physician visit Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay Encourage regular physical exercise Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed. Avoid smoking and alcohol Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 185.13) At least four courses of OCS per year	As above, *plus*: Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma Baseline bone densitometry (DEXA scan) Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥7 OCS burst treatments per year Very-high-dose ICS (e.g., fluticasone propionate ≥800 μg/day)	As above, *plus*: DEXA scan: if DEXA *z* score ≤1.0, recommend close monitoring (every 12 mo) Consider referral to a bone or endocrine specialist Bone age assessment Complete blood count Serum calcium, phosphorus, and alkaline phosphatase determinations Urine calcium and creatinine measurements Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin Urine telopeptides for those receiving long-term systemic or frequent OCS treatment Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, alcohol intake).

DEXA, Dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; OCS, oral corticosteroid; TSH, thyroid-stimulating hormone.

was superior to combination fluticasone/montelukast therapy in Black children, arguing against the notion that Black children are more prone to serious asthma exacerbations than White children when treated with combination ICS/LABA therapy.

Despite their efficacy and widespread use, the long-term safety of LABAs, even when used in combination with ICS in a single inhaler, has been questioned. To address this concern of rare, severe asthma-related events with LABA/ICS use, large randomized controlled trials (RCTs) compared the safety of combination ICS/LABA vs ICS monotherapy. Two studies of >23,000 adults and adolescents ≥12 years old with various levels of asthma severity were randomized to receive ICS (low or medium dose) monotherapy vs equivalent ICS/LABA (fluticasone vs fluticasone/salmeterol; budesonide vs budesonide/formoterol) over 26 weeks to determine whether small but significant differences might occur in asthma hospitalization, intubation, or death attributable to ICS/LABA. No intubations or asthma deaths occurred during the study, and no differences in asthma hospitalizations between treatment groups were observed. The similar pediatric study enrolled >6,000 children age 4-11 years with various levels of asthma severity to receive either fluticasone (low or medium dose) or equivalent fluticasone/salmeterol dose over 26 weeks, with similar findings of no significant differences in severe asthma-related events between treatment groups. *These results strongly suggest that the use of combination ICS/LABA products in children and adults with moderate to severe persistent asthma is both effective and safe.*

Leukotriene-Modifying Agents

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. LTRAs may be an alternative treatment for mild persistent asthma and as an add-on medication with ICS for moderate persistent asthma. Two LTRAs with FDA-approved use in children are montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and modestly improve lung function. **Montelukast** is approved for use in children ≥1 year of age and is administered once daily, whereas **zafirlukast** is approved in children ≥5 years and is given twice daily. LTRAs are less effective than ICSs in patients with mild persistent asthma (e.g., ICSs improve baseline lung function 5–15%, whereas LTRAs improve lung function 2.5–7.5%). *The FDA has identified serious behavior and mood-related changes in some patients treated with montelukast and suggests that the benefits of montelukast may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with other medicines.* When initially prescribing montelukast, a precaution is to inform the child and family that, if mood changes are noted after starting montelukast, they should discontinue its use and contact their physician.

Long-Acting Inhaled Anticholinergics

Tiotropium is a LAMA (24-hour duration of action) that is approved by the FDA for use in children with asthma ≥6 years old. In studies in children and adolescents with moderate persistent asthma, tiotropium improved lung function as an add-on therapy to ICS. Adding a LAMA is not more efficacious than adding a LABA, so LAMAs should not be selected over a LABA unless necessary. LAMAs can also be added to ICS/LABA combination therapy if the patient remains symptomatic.

Allergen Immunotherapy

AIT involves administering gradually increasing doses of allergens to a person with allergic disease to reduce or eliminate the patient's allergic response to those allergens, including allergic rhinoconjunctivitis and asthma. Conventional AIT is given subcutaneously (**SCIT**) under the direction of an experienced allergist. The goal of SCIT is to increase the dose of allergen extract administered to reach a therapeutic maintenance dose of each major allergen, in a manner that minimizes the likelihood of systemic allergic reactions. Allergen extracts are formulated for each patient based on documented allergen sensitizations

and problematic exposures. Maintenance doses are generally given monthly, to complete a 3–5-year course. A meta-analysis of 20 trials examining the effects of SCIT on allergic asthma revealed significant improvement with fewer symptoms, improved lung function, less need for medication, and AHR reduction.

Although AIT is regarded as safe, the potential for **anaphylaxis** always exists when patients receive extracts containing allergens to which they are sensitized. Local transient allergic reactions at the injection site are common. Systemic allergic reactions can also occur with SCIT, with fatal anaphylaxis occurring in approximately 1 per 2 million injections. Because of the risks of systemic allergic reactions to SCIT, standard precautions include administering SCIT in medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 190). Patients should be observed in the office for 30 minutes after each injection because most systemic reactions to SCIT begin within this time frame. *SCIT should never be given at home or by untrained personnel.* Because of the complexities and risks of administration, SCIT should only be administered by an experienced allergist. SCIT is not recommended for patients with severe and uncontrolled asthma.

AIT should be discontinued in patients who have not shown improvement after 1 year of receiving maintenance doses of an appropriate allergen extract(s), or who have a serious systemic allergic or adverse reaction.

Biologic Therapies

Biologic therapies are genetically engineered proteins derived from human genes and designed to inhibit specific immune mediators of disease. Several are approved by the FDA as add-on controller therapies (i.e., in addition to conventional controller therapies) for severe asthma in adults and children.

Omalizumab (Anti-IgE Antibody). Omalizumab is a humanized monoclonal antibody (mAb) that binds IgE and prevents its binding to the high-affinity IgE receptor on mast cells and basophils, thereby blocking IgE-mediated allergic responses and inflammation. It is approved by the FDA for patients >6 years old with severe allergic asthma who continue to have inadequate disease control despite treatment with high-dose ICS and/or OCS. Omalizumab is given every 2-4 weeks subcutaneously, with the dosage based on body weight and serum IgE levels. Omalizumab can improve asthma control while allowing ICS and/or OCS dose reduction. Omalizumab has been studied in inner-city children with exacerbation-prone asthma. When added to guideline-based controller management, omalizumab reduced exacerbations (50%), particularly those that peak in the spring and fall seasons. A follow-up prospective preseasonal treatment study confirmed the effect on fall seasonal exacerbations and demonstrated how omalizumab restores antiviral (interferon [IFN]-α) immune responses to rhinovirus (the most common infectious trigger of exacerbations) that are impaired by IgE-mediated mechanisms. Omalizumab is generally well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) have been reported following approximately 0.1% of injections. As a result, omalizumab has an FDA black box warning of potentially serious and life-threatening anaphylactic adverse reactions, and an epinephrine autoinjector should be available to all patients receiving omalizumab.

Mepolizumab and Reslizumab (Anti–IL-5 Antibodies). **Mepolizumab**, an anti–IL-5 mAb that blocks IL-5-mediated eosinophilopoiesis, reduces severe asthma exacerbations and lowers sputum and blood eosinophils while allowing for a significant reduction in OCS dose in adults and adolescents with severe exacerbation-prone eosinophilic asthma. It is administered subcutaneously every 4 weeks and is approved by the FDA for severe eosinophilic asthmatic children ≥6 years old. **Reslizumab**, another anti–IL-5 mAb therapeutic, is administered intravenously and is approved by the FDA for severe asthmatics ≥18 years old (i.e., not currently approved for use in children).

Benralizumab (Anti–IL-5Ra Antibody). Benralizumab is also an mAb that binds to the IL-5 receptor α subunit, resulting in apoptosis of eosinophils and basophils. Benralizumab is approved for patients ≥12 years old with severe eosinophilic asthma with a suggested absolute blood eosinophil count of at least 300 cells/μL. Benralizumab is administered subcutaneously every 4 weeks for three doses followed by every 8-week dosing.

Dupilumab (Anti–IL-4 Receptor α Antibody). Dupilumab, an anti–IL-4 receptor α human mAb that inhibits both IL-4 and IL-13 production (both cytokines share the same IL-4 receptor α chain) and atopic immune responses, reduces exacerbations and symptoms and improves lung function in moderate to severe asthmatic patients with an eosinophilic phenotype. Dupilumab is administered subcutaneously every 2 weeks and is approved by the FDA for patients ≥6 years old with moderate to severe eosinophilic asthma. It is suggested that patients have an absolute eosinophil count of at least 150 cells/μL or an exhaled nitric oxide level of at least 25 parts per billion (ppb). In meta-analysis, dupilumab was associated with significant reductions of the annualized rate of severe asthma exacerbations and OCS use and a statistical improvement in lung function.

Tezepelumab (Anti-Thymic Stromal Lymphopoietin [TSLP] Antibody). Tezepelumab, an anti-TSLP human mAb, binds and blocks TSLP's inflammatory actions, reduces asthma exacerbations and symptoms, and improves lung function. Tezepelumab is administered subcutaneously every 4 weeks and is approved by the FDA for patients ≥12 years old with severe asthma.

Quick-Reliever Medications

Quick-reliever or "rescue" medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 185.17).

Short-Acting Inhaled β-Agonists

Given their rapid onset of action, effectiveness, and 4–6-hour duration of action, SABAs (albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute asthma symptoms ("rescue" medication) and for preventing EIB. β-Adrenergic agonists cause bronchodilation by inducing airway smooth muscle relaxation, reducing vascular permeability and airways edema, and improving mucociliary clearance. Levalbuterol, the R-isomer of albuterol, is associated with less tachycardia and tremor, which can be bothersome to some asthmatic patients. Overuse of β-agonists is associated with an increased risk of death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on the frequent use of SABAs as a "quick fix" for their asthma, rather than using controller medications in a preventive manner. It is helpful to monitor the frequency of SABA use, in that use of one or more MDIs per month or three or more MDIs per year (200 inhalations per MDI) indicates inadequate asthma control and necessitates improving other aspects of asthma therapy and management. Of note, a SABA/ICS combination inhaler (albuterol/budesonide 90 mcg/80 mcg per actuation) has recently been FDA approved for as-needed use as a quick reliever in adults ages 18 years and older (not in children).

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (e.g., ipratropium bromide) are less potent than the β-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the ED with acute asthma. Ipratropium has few central nervous system adverse effects and is available in both MDI and nebulizer formulations. Although widely used in all children with asthma exacerbations, it is approved by the FDA for use in children >12 years old. A combination ipratropium/albuterol product is also available in both nebulized and mist formulations.

Table 185.17 Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION	
Focused history	Onset of current exacerbation Frequency and severity of daytime and nighttime symptoms and activity limitation Frequency of rescue bronchodilator use Current medications and allergies Potential triggers History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes
Clinical assessment	Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status Pulse oximetry Lung function (defer in patients with moderate to severe distress or history of labile disease)
Risk factors for asthma morbidity and death	See Table 185.18

TREATMENT

DRUG AND TRADE NAME	MECHANISMS OF ACTION AND DOSING	CAUTIONS AND ADVERSE EFFECTS
Oxygen (mask or nasal cannula)	Treats hypoxia	Monitor pulse oximetry to maintain O_2 saturation >92% Cardiorespiratory monitoring
Inhaled short-acting β-agonists	Bronchodilator	During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume.
Albuterol MDI (90 µg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids	Antiinflammatory	If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis For daily dosing, 8 AM administration minimizes adrenal suppression Children may benefit from dosage tapering if course exceeds 7 days Adverse effects monitoring: frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 615); see Table 185.14 for adverse effects screening recommendations
Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution	Short course oral "burst" for exacerbation: 1-2 mg/kg/day divided qd or bid for 3-7 days (maximum 40 mg/day)	
Depo-Medrol (IM); Solu-Medrol (IV)	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day qd or bid	
Dexamethasone: 0.5, 0.75, 1, 1.5, 2, 4, 6 mg tablets; 0.5 mg/5 mL, 1 mg/mL Intensol solution	Short course oral "burst" for exacerbation: 0.6 mg/kg, maximum 16 mg; can be repeated next day	
Anticholinergics	Mucolytic/bronchodilator	Should not be used as first-line therapy; added to β_2-agonist therapy
Ipratropium Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 µg/inhalation)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine	Bronchodilator	For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)

Continued

Table 185.17 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	
Terbutaline		Terbutaline is β-agonist–selective relative to epinephrine Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 μg/kg loading dose, followed by 0.1-0.4 μg/kg/min Titrate in 0.1-0.2 μg/kg/min increments every 30 min, depending on clinical response.	
Other medications		
Magnesium sulfate	25-75 mg/kg over 20 min Max 2 gm	Flushing, headache, hypotension (rare)
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 185.10	

IM, Intramuscular; IV, intravenous; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; $\dot{V}/\dot{Q}$, ventilation/perfusion; bid, 2 times daily; tid, 3 times daily; qid, 4 times daily; qd, every day.

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in an MDI, as a DPI formulation, or in a suspension form delivered via a nebulizer. **Spacer devices, recommended for the administration of all MDI medications, are simple and inexpensive tools that (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of drug and propellant-mediated oropharyngeal adverse effects (dysphonia and thrush)**. Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5-second) inhalation, then a 5–10-second breath hold. No waiting time is required between puffs of medication. Preschool-age children cannot perform this inhalation technique. As a result, MDI medications in this age-group are delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 seconds or 5-10 breaths; a tight seal must be maintained; and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

DPI devices (e.g., Diskus, Flexhaler, Autohaler, Twisthaler, Aerolizer, Ellipta) are popular because of their simplicity of use, although adequate inspiratory flow is needed. DPIs are breath-actuated devices (the drug comes out only as it is breathed in), and spacers are not needed. Mouth rinsing is recommended after ICS use to remove ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrush.

Nebulizers are the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants greatly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include the need for a power source, inconvenience in that treatments take a significantly longer time, are more expensive, and have the potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 AM), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airways obstruction is not resolved with SABA use, ventilation/perfusion mismatching can cause hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis (common) and air leaks in the chest (pneumomediastinum, pneumothorax; rare).

A severe exacerbation of asthma that does not improve with standard therapy is termed **status asthmaticus**. Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (Fig. 185.6; see Tables 185.4 and 185.17). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient's asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they have severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 185.18).

Follow this plan for After Hours patients only. Nurse may decide not to follow this home management plan if:
- Parent does not seem comfortable with or capable of following plan
- Nurse is not comfortable with this plan, based on situation and judgment
- Nurse's time does not allow for callbacks

In all cases, tell parent to call 9-1-1 if signs of respiratory distress occur during the episode
NOTE: If action plan has already been attempted without success, go to "RED ZONE — poor response" or "YELLOW ZONE — incomplete response" as symptoms indicate.

Assess symptoms/peak flow

YELLOW ZONE
Mild-to-moderate exacerbation
PEF 50–80% predicted or personal best
or
Signs and symptoms
- Coughing, shortness of breath or chest tightness (correlate imperfectly with severity of exacerbation), or
- Unable to sleep at night due to asthma, or
- Decreased ability to perform usual activities
- With or without wheezing

RED ZONE
Severe exacerbation
PEF < 50% predicted or personal best or
Signs and symptoms
- Very hard time breathing; constant coughing
- Trouble walking or talking due to asthma (unable to complete sentences; only using 2- to 3-word phrases)
- Nails blue
- Suprasternal or supraclavicular retractions
- Albuterol not relieving symptoms within 10–15 minutes
- With or without wheezing

Instructions to patient
Inhaled short-acting β_2-agonist:
- 2–4 puffs of inhaler or nebulizer treatment every 20 minutes up to 3 times in 1 hour
- Assess asthma symptoms and/or peak flow 15–20 minutes after each treatment
- Nurse to call family after 1 hour
- If patient worsens during treatment, have parent call back immediately or call 9-1-1

GREEN ZONE — Good response
Mild exacerbation
PEF > 80% predicted or personal best
or
Signs and symptoms
- No wheezing, shortness of breath, cough or chest tightness, and
- Response to β_2-agonist sustained for 4 hours

Instructions to patient
- May continue 2–4 puffs (or nebulizer) β_2-agonist every 3–4 hours for 24–28 hours prn
- For patients on inhaled steroids, double dose for 7–10 days
- Contact PCP within 48 hours for instructions

YELLOW ZONE — Incomplete response
Moderate exacerbation PEF
50–80% predicted or personal best
or
Signs and symptoms
- Persistent wheezing, shortness of breath, cough or chest tightness

Instructions to patient
- Take 2–4 puffs (or nebulizer) β_2-agonist every 2–4 hours for 24–48 hours prn
- Add oral steroid* (see contraindications below)
- Contact PCP urgently (within 24 hours) for instructions

RED ZONE — Poor response
Severe exacerbation
PEF < 50% predicted or personal best
or
Signs and symptoms
- Marked wheezing, shortness of breath, cough, or chest tightness
- Distress is severe and nonresponsive
- Response to β_2-agonist last < 2 hours

Instructions to patient
- Proceed to ED, or call ambulance or 9-1-1 and repeat treatment while waiting

Instructions to patient
IMMEDIATELY:
- Take 4-6 puffs (or nebulizer) β_2-agonist
- Start oral steroids* if available (see contraindications below)
- Instruct parent to call back in 5 minutes after treatment finished
- If still in **RED ZONE** proceed to ED, or call ambulance or 9-1-1 and repeat treatment while waiting
- If in **YELLOW ZONE**, move to **YELLOW ZONE** protocol (top left box)

Documentation faxed or given to PCP within 24 hours; phone or verbal contact sooner as indicated.

* Ask patient about preexisting conditions that may be contraindications to oral steroids (including type 1 diabetes, active chicken pox, chicken pox exposure or varicella vaccine within 21 days, MMR within 14 days). If so, nurse to contact PCP before initiating steroids. Oral steroid dosages: Child: 2 mg/kg/day, maximum 60 mg/day, for 5 days.

Date: _____
Signature _____

Fig. 185.6 Algorithm for treatment of acute asthma symptoms. ED, Emergency department; PCP, primary care physician; PEF, peak expiratory flow. *(Courtesy BJC Healthcare/Washington University School of Medicine, Community Asthma Program, January 2000.)*

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that develop over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure because of fatigue can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (Pco_2) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

Home Management of Asthma Exacerbations

Families of all children with asthma should have a **written Asthma Action Plan** (see Fig. 185.5) to guide their recognition and management of exacerbations, along with the necessary education, medications, and tools to manage them. Early recognition of asthma exacerbations to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. The NIH guidelines recommend immediate treatment with "rescue" medication (inhaled SABA, 2-4 puffs, up to 3 times every 20 minutes in 1 hour). A good response is characterized by resolution of symptoms within 1 hour and no further symptoms over the next 4 hours. The child's physician should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hours. If the child has an incomplete response to initial treatment with rescue medication, a short course of OCS therapy (for example, prednisone, 1-2 mg/kg/day [not to exceed 40 mg/day] for 4 days) should be instituted, in addition to inhaled β-agonist therapy. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (e.g., previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if abrupt in onset, an epinephrine autoinjector and perhaps portable oxygen at home can be considered. Use of either of these extreme measures for home management of asthma exacerbations would be an indication to call 911 for emergency support services.

Table 185.18 Risk Factors for Asthma Morbidity and Mortality

BIOLOGIC
Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
Sudden asphyxia episodes (respiratory failure, arrest)
Two or more hospitalizations for asthma in past year
Three or more emergency department visits for asthma in past year
Increasing and large diurnal variation in peak flows
Use of >2 canisters of short-acting β-agonists per month
Poor response to systemic corticosteroid therapy
Male sex
Low birthweight
Non-White
Sensitivity to *Alternaria*
ENVIRONMENTAL
Allergen exposure
Environmental tobacco smoke exposure
Air pollution exposure
Urban environment
ECONOMIC AND PSYCHOSOCIAL
Poverty
Crowding
Mother <20 yr old
Mother with less than high school education
Inadequate medical care
Inaccessible
Unaffordable
No regular medical care (only emergency)
Lack of written Asthma Action Plan
No care sought for chronic asthma symptoms
Delay in care of asthma exacerbations
Inadequate hospital care for asthma exacerbation
Psychopathology in the parent or child
Poor perception of asthma symptoms or severity
Alcohol or substance abuse

Emergency Department Management of Asthma Exacerbations

In the ED, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors associated with asthma morbidity and mortality (see Table 185.18). Indicators of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV_1 value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 minutes for 1 hour, and, if necessary, oral, injectable or IV systemic corticosteroids (see Tables 185.4 and 185.17, and Fig. 185.6). Inhaled ipratropium may be added to the β-agonist treatment, especially if no significant response is seen with the first inhaled β-agonist treatment. In the ED, single oral, IV, or intramuscular (IM) dose dexamethasone (0.6 mg/kg, maximum 16 mg) is an effective alternative to prednisone and with a lower incidence of emesis. A second dose of dexamethasone can be given the next day whether discharged or admitted to the hospital. An IM injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 minutes after SABA administration to compensate for possible ventilation/perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the first hour suggests that the exacerbation will not remit quickly. The patient may be discharged home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, and oxygen saturation >92% while the patient is breathing room air for 4 hours. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hours plus a short course of an OCS. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of OCS in the ED setting reduces the risk of exacerbation recurrence over the subsequent month.

Hospital Management of Asthma Exacerbations

For patients with severe exacerbations that do not adequately improve within 1-2 hours of intensive treatment, observation and/or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 185.18). Admission to an ICU is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 185.17). Supplemental oxygen is administered because many children hospitalized with acute asthma have or will eventually have hypoxemia, especially at night and with increasing

SABA administration. SABAs can be delivered frequently (every 20 minutes to 1 hour) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs, and thus continuous nebulization can obviate the need for IV β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia; lactic acidosis is an uncommon complication. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation/perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium is often added to albuterol every 6 hours if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium may be beneficial in patients who have mucus hypersecretion or who are receiving β blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as IV corticosteroids. Accordingly, OCS therapy can often be used, although children with sustained respiratory distress and those unable to tolerate oral preparations or liquids are obvious candidates for IV corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluation, such as complete blood count, arterial blood gases, serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased antidiuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are not recommended during asthma exacerbations because they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (e.g., air leaks) related to asthma exacerbations increase with intubation and assisted ventilation, so every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including parenteral β-agonists, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 minutes), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of magnesium sulfate requires monitoring of serum levels and cardiovascular status. Noninvasive positive pressure ventilation (e.g., continuous positive airway pressure [CPAP] or biphasic positive airway pressure [BiPAP]) might improve severe asthma exacerbations through a variety of mechanisms. Their use in the care of children with severe persistent asthma exacerbations has increased in efforts to avert mechanical ventilation, even though evidence supporting the intervention has been considered weak, and current NAEPP and GINA guidelines do not recommend the intervention. Parenteral (SC, IM, or IV) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because inhaled medication may not reach the lower airway in such patients.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. **Mechanical ventilation** in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum; see Chapter 461). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to moderate hypercapnia (Pco_2 50-70 mm Hg) to minimize barotrauma. As measures to relieve mucus plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by corticosteroid-induced myopathy, which can lead to severe muscle weakness requiring prolonged rehabilitation.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 weeks of a child's discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

Special Management Circumstances

Management of Infants and Young Children

Recurrent wheezing episodes in preschool-age children are common, occurring in as much as one-third of this population. Of these, most improve and even become asymptomatic during the prepubescent school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems. The NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 185.9, 185.10, 185.13, and 185.14). **For young children with recurrent episodic wheeze in the setting of viral illness, a short course of daily high-dose ICS may also be considered.** For young children with a history of moderate to severe exacerbations, nebulized budesonide is approved by the FDA, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are two delivery systems for inhaled medications for this age-group: the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred because of limited published information and lack of FDA approval for children <4 years of age.

Asthma Management During Surgery

Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, which may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment to improve asthma stability before surgery, if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV_1 or PEF values <80% of the patient's personal best. In addition, patients who have received >2 weeks of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide "stress" replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period.

PROGNOSIS

Recurrent coughing and wheezing occur in 35% of preschool-age children. Of these, approximately one third continue to have persistent asthma into later childhood, and approximately two thirds improve on their own through their teen years. Concomitant atopic disorders (such as allergen sensitization or atopic dermatitis) are associated with greater likelihood of disease persistence. Asthma severity by ages 7-10 years is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years).

PREVENTION

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional antiinflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling through early microbiome and innate immune development. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, these findings may foster new strategies for asthma prevention.

Several nonpharmacologic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 months), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Care providers can be strong influencers of smoking cessation by parents, caregivers, and adolescent patients (see Chapters 157.2 and 759.1). Immunizations are not considered to increase the likelihood of development of asthma; therefore all standard childhood immunizations are recommended for children with asthma, including varicella, SARS-CoV-2, and annual influenza vaccines.

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Chapter 186

Atopic Dermatitis (Atopic Eczema)

Donald Y.M. Leung and Scott H. Sicherer

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to the development of food allergy, allergic rhinitis, and asthma later in childhood, a process called *the atopic march*.

ETIOLOGY

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and primarily type 2 adaptive immune responses to environmental allergens and microbes that lead to chronic skin inflammation.

PATHOLOGY

Acute AD skin lesions are characterized by **spongiosis**, or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells (APCs) in the epidermis, such as Langerhans cells, exhibit surface-bound IgE molecules with cell processes that reach into the upper epidermis to sense allergens and pathogens. These APCs play an important role in cutaneous responses to type 2 immune responses (see Chapter 182). There is marked perivascular T-cell and inflammatory monocyte-macrophage infiltration in acute AD lesions. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

PATHOGENESIS

AD is associated with multiple phenotypes and endotypes that have overlapping clinical presentations. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70–80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20–30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of T-helper type 2 (Th2) cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another type 2 cytokine, IL-5, plays an important role in eosinophil development and IL-31 is a key itch cytokine (Fig. 186.1). Nonatopic eczema is associated with lower IL-4 and IL-13 but increased IL-17 and IL-23 production than in atopic eczema. Age has also been found to affect the immune profile in AD.

Compared with the skin of healthy individuals, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4, IL-13, and IL-31. Chronic AD skin lesions, by contrast, have fewer cells that express IL-4 and IL-13, but they have more cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Despite increased type 1 and type 17 immune responses in chronic AD, IL-4 and IL-13 as well as other type 2 cytokines (e.g., thymic stromal lymphopoietin [TSLP], IL-31, IL-33) predominate and reflect increased numbers of type 2 innate lymphoid cells and Th2 cells. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia. The importance of IL-4 and IL-13 in driving severe persistent AD has been validated by multiple clinical trials now demonstrating that biologics blocking IL-4 and IL-13 action lead to clinical improvement in moderate to severe AD.

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. *Severely dry skin is a hallmark of AD.* This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin**, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function, including moisturization of the skin. Genetic pathogenic variants in the filaggrin gene *(FLG)* family have been identified in patients with ichthyosis vulgaris (dry skin, palmar hyperlinearity) and in up to 50% of patients with severe AD. *FLG* pathogenic variant is strongly associated with the development of food allergy and eczema herpeticum. Nonetheless, up to 60% of carriers of an *FLG* pathogenic variant do not develop atopic diseases. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, and IL-25, and tumor necrosis factor, can also reduce filaggrin

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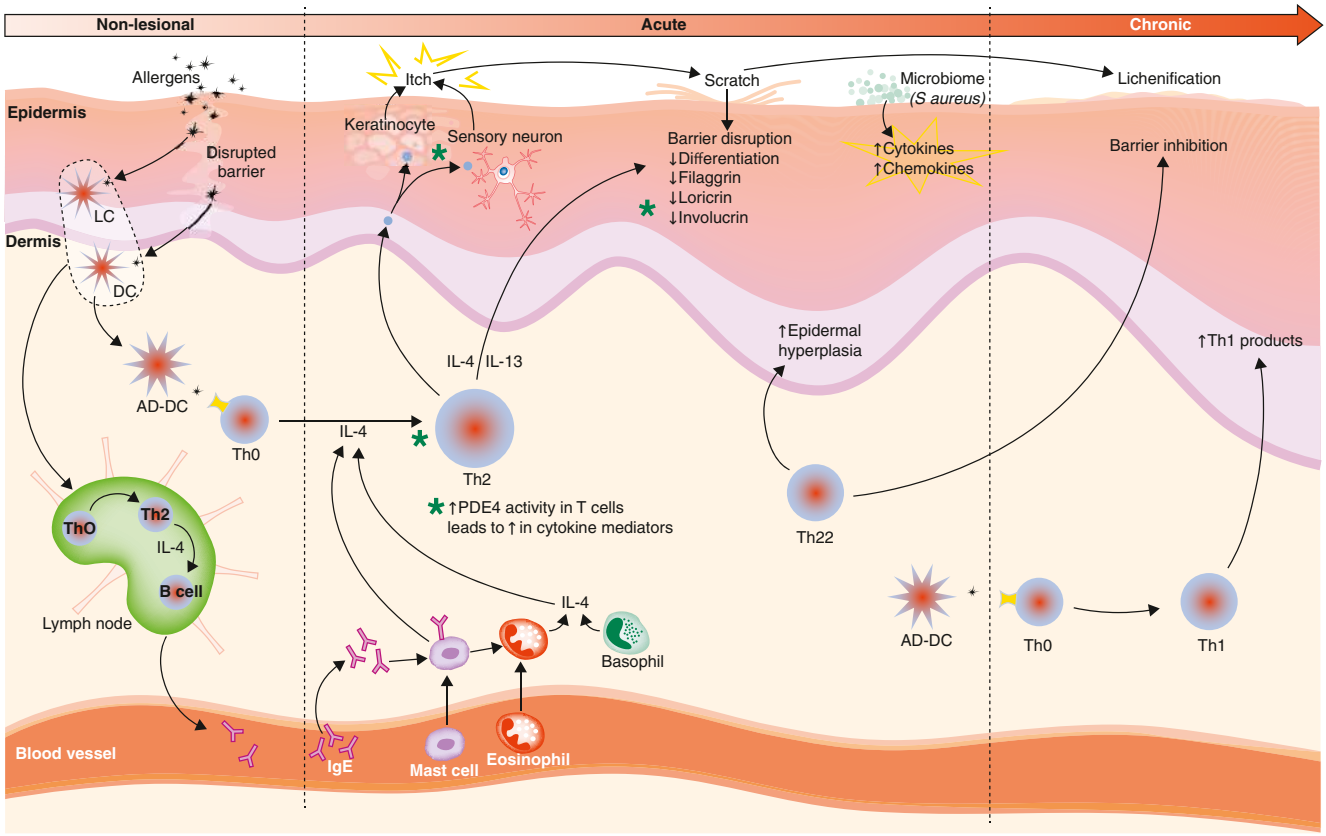

Fig. 186.1 Pathogenic pathways and immunologic targets in atopic dermatitis (AD). Skin barrier defects in nonlesional atopic dermatitis leads to penetration by allergens, which encounter antigen-presenting Langerhans cells (LCs) in the epidermis and dendritic cells (DCs) in the dermis, resulting in immune activation and inflammatory cell recruitment. Elevated T-helper type 2 (Th2) cell counts in the acute state leads to increased secretion of cytokines, especially interleukin (IL)-4 and IL-13, which disrupt the skin barrier by decreasing expression of barrier proteins (i.e., filaggrin, loricrin, and involucrin). In addition, Th2 cytokines recruit eosinophils and basophils to lesional sites, and increase B-cell IgE production. Eosinophils, basophils, and activated IgE-bound mast cells release proinflammatory mediators, further potentiating pathogenesis. Th2 cytokines also impair antimicrobial peptide responses to pathogens which, in combination with barrier disruption, increases the risk of colonization and barrier penetration by allergens and pathogens (i.e., *Staphylococcus aureus*). Chronic atopic dermatitis results in a skewed Th1 response, leading to further inflammation and immune activation. Processes mediated by Janus kinase (JAK) receptors are marked with a green asterisk. PDE4, phosphodiesterase-4. *(From Vahharia PP, Silverberg JI. New and emerging therapies for paediatric atopic dermatitis. Lancet Child Adolesc. 2019;3:343–352.)*

and other epidermal proteins and lipids. AD patients are at increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, disturbances in the microbiome, skin epithelial dysfunction, and overexpression of polarized immune pathways, which dampen host antimicrobial responses. Patients with the combination of AD and food allergy have significantly lower levels of filaggrin and increased type 2 immune activation than patients with AD only.

CLINICAL MANIFESTATIONS

AD typically begins in infancy. Approximately 50% of patients experience symptoms in the first year of life, and an additional 30% are diagnosed between 1 and 5 years of age. Intense **pruritus**, especially at night, and **cutaneous reactivity** are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow's milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (*Staphylococcus aureus*, herpes simplex, coxsackievirus, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can trigger pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 186.2 and 186.3). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by **lichenification** (Fig. 186.4), or thickening of the skin with accentuated surface markings, and **fibrotic papules**. In chronic AD, all three types of skin reactions may coexist in the same individual. Most patients with AD have dry, lackluster skin regardless of their stage of illness. Skin reaction pattern and distribution vary with the patient's age and disease activity. AD is generally more acute in infancy and involves the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared. Older children and children with chronic AD have lichenification and localization of the rash to the flexural folds of the extremities. AD can go into remission as the patient grows older; however, many children with AD have persistent eczema as an adult (see Fig. 186.2*C*).

LABORATORY FINDINGS

There are no specific laboratory tests to diagnose AD. Many patients have peripheral blood eosinophilia, increased serum IgE levels, and T cells expressing type 2 cytokines. Serum IgE measurement or skin-prick testing can identify the allergens (foods, inhalant/microbial allergens) to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

AD is diagnosed on the basis of three major features: pruritus, an eczematous dermatitis that fits into a typical pattern of skin inflammation, and a chronic or chronically relapsing course (Table 186.1). Associated features, such as a family history of asthma, hay fever, food

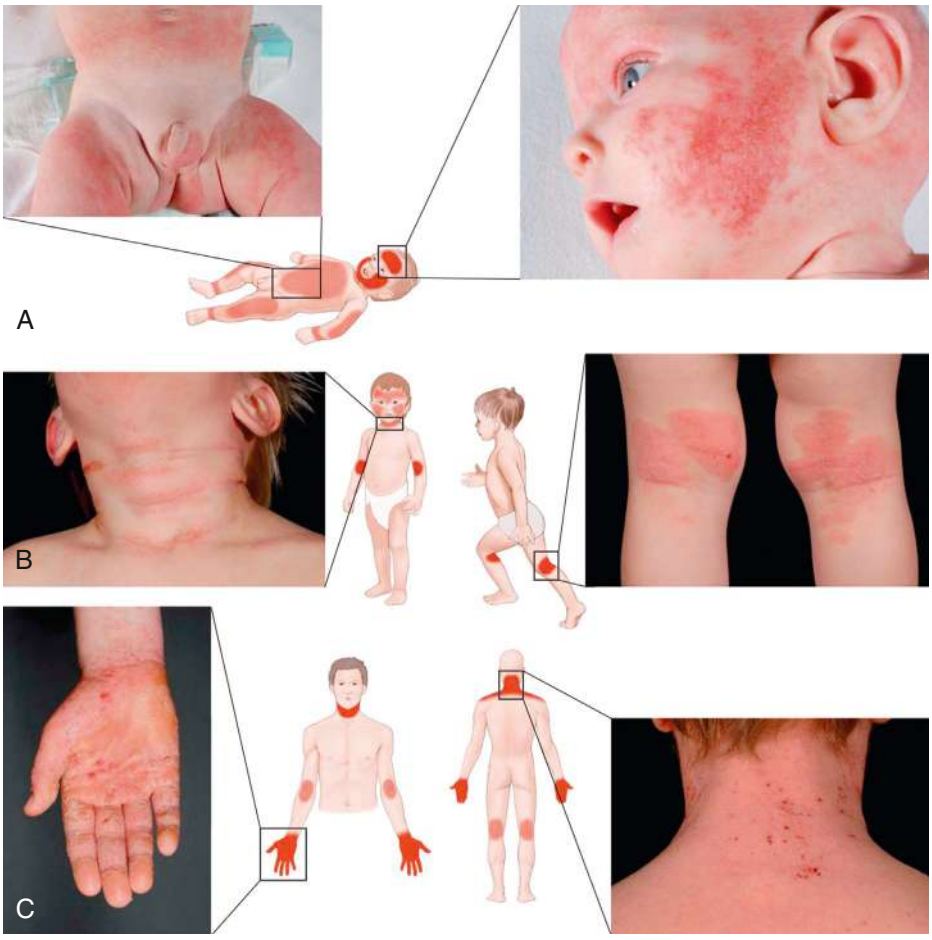

Fig. 186.2 Typical clinical appearance and locations of atopic dermatitis at different ages. A, In infants, atopic dermatitis is generally acute, with lesions mainly on the face and the extensor surfaces of the limbs. The trunk might be affected, but the napkin area is typically spared. B, From age 1-2 years onward, polymorphous manifestations with different types of skin lesions are seen, particularly in flexural folds. C, Adolescents and adults often present lichenified and excoriated plaques at flexures, wrists, ankles, and eyelids; in the head and neck type, the upper trunk, shoulders, and scalp are involved. Adults might have only chronic hand eczema or present with prurigo-like lesions. (*From Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387:1111.*)

allergy, elevated IgE, and immediate skin test reactivity, reinforce the diagnosis of AD.

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Tables 186.2 and 186.3). Severe combined immunodeficiency (see Chapter 165.1) should be considered for infants presenting in the first year of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis should be excluded in any infant with AD and failure to thrive (see Chapter 556). Wiskott-Aldrich syndrome, an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD (see Chapter 165.4). One of the hyper-IgE syndromes is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant *STAT3* pathogenic variants. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a dedicator of cytokinesis 8 gene *(DOCK8)* pathogenic variants. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic **contact dermatitis**. A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis receiving topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyosis, and seborrheic dermatitis.

TREATMENT

The treatment of AD requires a systematic, multifaceted approach that incorporates skin moisturization, topical antiinflammatory therapy, identification and elimination of flare factors (Table 186.4), and, if necessary, systemic therapy (Fig. 186.5). Assessment of the severity also helps direct therapy (Table 186.5; see Fig. 186.5).

Cutaneous Hydration

Because patients with AD have impaired skin barrier function from reduced filaggrin and skin lipid levels, they present with diffuse, abnormally dry skin, or **xerosis**. **Moisturizers are first-line therapy**. Lukewarm soaking baths or showers for 15-20 minutes followed by the

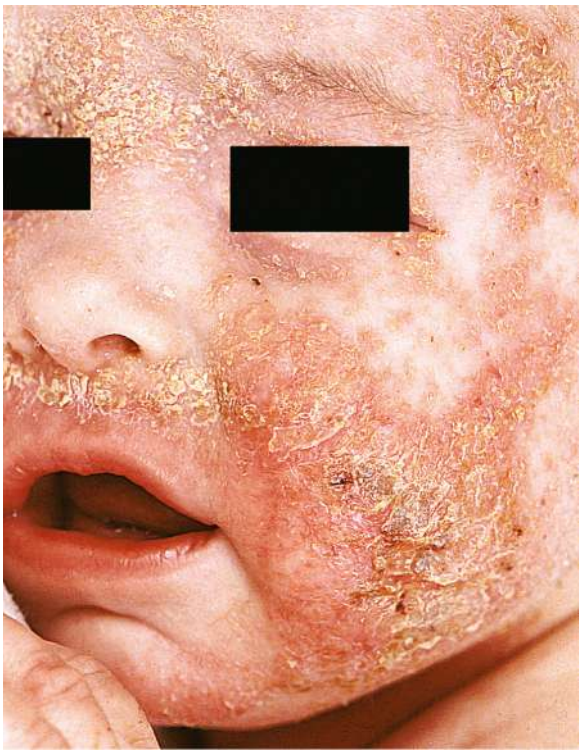

Fig. 186.3 Crusted lesions of atopic dermatitis on the face. (*From Eichenfield LF, Friedan IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001. p 242.*)

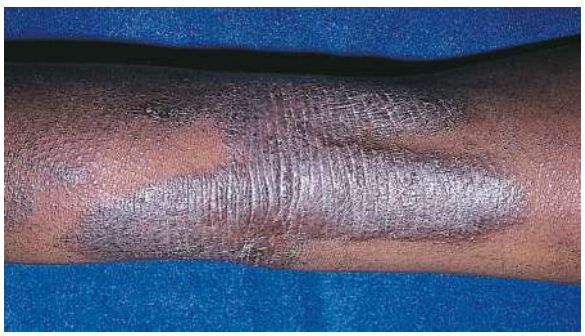

Fig. 186.4 Lichenification of the popliteal fossa from chronic rubbing of the skin in atopic dermatitis. (*From Weston WL, Lane AT, Morelli JG. Color Textbook of Pediatric Dermatology. 2nd ed. St Louis: Mosby; 1996. p 33.*)

application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient's preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these patients, less occlusive agents should be used. Several prescription (classified as a medical device) "therapeutic moisturizers" or "barrier creams" are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are minimal data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

Table 186.1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES
Pruritus
Facial and extensor eczema in infants and children
Flexural eczema in adolescents
Chronic or relapsing dermatitis
Personal or family history of atopic disease
ASSOCIATED FEATURES
Xerosis
Cutaneous infections (*Staphylococcus aureus*, group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
Nonspecific dermatitis of the hands or feet
Ichthyosis, palmar hyperlinearity, keratosis pilaris
Nipple eczema
White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum IgE levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors
Lichenification
Perioral, periauricular sites
Prurigo

Topical Corticosteroids

Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD. Patients should be carefully instructed on their use of topical glucocorticoids to avoid potential adverse effects. There are seven classes of topical glucocorticoids, ranked according to their potency, as determined by vasoconstrictor assays (Table 186.6). Because of their potential adverse effects, the ultra-high-potency glucocorticoids should not be used on the face or intertriginous areas and should be used only for very short periods on the trunk and extremities. Mid-potency glucocorticoids can be used for longer periods to treat chronic AD involving the trunk and extremities. Long-term control can be maintained with twice-weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to relapse, once control of AD is achieved after a daily regimen of topical corticosteroids. Compared with creams, ointments have a greater potential to occlude the epidermis, resulting in enhanced systemic absorption.

Adverse effects of topical glucocorticoids can be divided into local adverse effects and systemic adverse effects, the latter resulting from suppression of the hypothalamic-pituitary-adrenal axis. *Local* adverse effects include the development of striae and skin atrophy. *Systemic* adverse effects are related to the potency of the topical corticosteroid, site of application, occlusiveness of the preparation, percentage of the body surface area covered, and length of use. The potential for adrenal suppression from potent topical corticosteroids is greatest in infants and young children with severe AD requiring intensive therapy.

Topical Calcineurin Inhibitors

The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 years whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable

Table 186.2 Differential Diagnosis of Atopic Dermatitis

	MAIN AGE GROUP AFFECTED	FREQUENCY*	CHARACTERISTICS AND CLINICAL FEATURES
OTHER TYPES OF DERMATITIS			
Seborrheic dermatitis	Infants	Common	Salmon-red greasy scaly lesions, often on the scalp (cradle cap) and napkin area; generally presents in the first 6 wk of life; typically clears within weeks
Seborrheic dermatitis	Adults	Common	Erythematous patches with yellow, white, or grayish scales in seborrheic areas, particularly the scalp, central face, and anterior chest
Nummular dermatitis	Children and adults	Common	Coin-shaped scaly patches, mostly on legs and buttocks; usually no itch
Irritant contact dermatitis	Children and adults	Common	Acute to chronic eczematous lesions, mostly confined to the site of exposure; history of locally applied irritants is a risk factor; might coexist with AD
Allergic contact dermatitis	Children and adults	Common	Eczematous rash with maximum expression at sites of direct exposure but might spread; history of locally applied irritants is a risk factor; might coexist with AD
Lichen simplex chronicus	Adults	Uncommon	One or more localized, circumscribed, lichenified plaques that result from repetitive scratching or rubbing because of intense itch
Asteatotic eczema	Adults	Common	Scaly, fissured patches of dermatitis overlying dry skin, most often on lower legs
INFECTIOUS SKIN DISEASES			
Dermatophyte infection	Children and adults	Common	One or more demarcated scaly plaques with central clearing and slightly raised reddened edge; variable itch
Impetigo	Children	Common	Demarcated erythematous patches with blisters or honey-yellow crusting
Scabies	Children	Common†	Itchy superficial burrows and pustules on palms and soles, between fingers, and on genitalia; might produce secondary eczematous changes
HIV	Children and adults	Uncommon	Seborrhea-like rash
CONGENITAL IMMUNODEFICIENCIES (SEE TABLE 186.3)			
KERATINIZATION DISORDERS			
Ichthyosis vulgaris	Infants and adults	Uncommon	Dry skin with fine scaling, particularly on the lower abdomen and extensor areas; perifollicular skin roughening; palmar hyperlinearity; full form (i.e., 2 *FLG* pathogenic variants) is uncommon; often coexists with AD
NUTRITIONAL DEFICIENCY–METABOLIC DISORDERS			
Zinc deficiency (acrodermatitis enteropathica)	Children	Uncommon	Erythematous scaly patches and plaques, most often around the mouth and anus; rare congenital form accompanied by diarrhea and alopecia
Biotin deficiency (nutritional or biotinidase deficiency)	Infants	Uncommon	Scaly periorofacial dermatitis, alopecia, conjunctivitis, lethargy, hypotonia
Pellagra (niacin deficiency)	All ages	Uncommon	Scaly crusted epidermis, desquamation, sun-exposed areas, diarrhea
Kwashiorkor	Infants and children	Geographic dependent	Flaky scaly dermatitis, swollen limbs with cracked peeling patches
Phenylketonuria	Infants	Uncommon	Eczematous rash, hypopigmentation, blonde hair, developmental delay
NEOPLASTIC DISEASE			
Cutaneous T-cell lymphoma	Adults	Uncommon	Erythematous pink-brown macules and plaques with a fine scale; poorly responsive to topical corticosteroids; variable itch (in early stages)
Langerhans cell histiocytosis	Infants	Uncommon	Scaly and purpuric dermatosis, hepatosplenomegaly, cytopenias

*Common = approximately 1 in 10 to 1 in 100; uncommon = 1 in 100 to 1 in 1,000; rare = 1 in 1,000 to 1 in 10,000; very rare = <1 in 10,000.
†Especially in developing countries.
AD, Atopic dermatitis; FLG, filaggrin gene.

because of potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, patients with steroid phobia, and those with face and neck dermatitis, in whom ineffective, low-potency topical corticosteroids are typically used because of fears of steroid-induced skin atrophy.

Phosphodiesterase Inhibitor

Crisaborole (Eucrisa) is an approved nonsteroidal topical antiinflammatory phosphodiesterase-4 (PDE-4) inhibitor indicated for the treatment of mild to moderate AD of children 3 months or older. It may be used as an alternative to topical corticosteroids or calcineurin inhibitors.

Table 186.3 Features of Primary Immunodeficiencies Associated with Eczematous Dermatitis

DISEASE	GENE	INHERITANCE	CLINICAL FEATURES	LAB ABNORMALITIES
AD-HIES	*STAT3*	AD, less commonly sporadic	Cold abscesses Recurrent sinopulmonary infections Mucocutaneous candidiasis Coarse facies Minimal trauma fractures Scoliosis Joint hyperextensibility Retained primary teeth Coronary artery tortuosity or dilation Lymphoma	High IgE (>2,000 IU/μL) Eosinophilia
DOCK8 deficiency	*DOCK8*	AR	Severe mucocutaneous viral infections Mucocutaneous candidiasis Atopic features (asthma, allergies) Squamous cell carcinoma Lymphoma	High IgE Eosinophilia With or without decreased IgM
PGM3 deficiency	*PGM3*	AR	Neurologic abnormalities Leukocytoclastic vasculitis Atopic features (asthma, allergies) Sinopulmonary infections Mucocutaneous viral infections	High IgE Eosinophilia
WAS	*WASP*	XLR	Hepatosplenomegaly Lymphadenopathy Atopic diathesis Autoimmune conditions (especially hemolytic anemia) Lymphoreticular malignancies	Thrombocytopenia (<80,000/μL) Low mean platelet volume Eosinophilia is common Lymphopenia Low IgM, variable IgG
SCID	Variable, depends on type	XLR and AR most common	Recurrent, severe infections Failure to thrive Persistent diarrhea Recalcitrant oral candidiasis Omenn syndrome: lymphadenopathy, hepatosplenomegaly, erythroderma	Lymphopenia common Variable patterns of reduced lymphocyte subsets (T, B, natural killer cells) Omenn syndrome: high lymphocytes, eosinophilia, high IgE
IPEX	*FOXP3*	XLR	Severe diarrhea (autoimmune enteropathy) Various autoimmune endocrinopathies (especially diabetes mellitus, thyroiditis) Food allergies	High IgE Eosinophilia Various autoantibodies
Netherton syndrome	*SPINK5*	AR	Hair shaft abnormalities Erythroderma Ichthyosis linearis circumflexa Food allergies Recurrent gastroenteritis Neonatal hypernatremic dehydration Upper and lower respiratory infections	High IgE Eosinophilia

AD, Autosomal dominant; AD-HIES, autosomal-dominant hyper-IgE syndrome; AR, autosomal recessive; *DOCK8*, dedicator of cytokinesis 8 gene; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PGM3, phosphoglucomutase 3; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; XLR, X-linked recessive.
From Kliegman RM, Bordini BJ, eds. Undiagnosed and rare diseases in children. *Pediatr Clin N Amer*. 2017;64(1):41–42.

Tar Preparations

Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, their antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Therefore topical tar preparations are not a preferred approach for management of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines

Systemic antihistamines act primarily by blocking the histamine H_1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H_1- and H_2-receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria. For children, melatonin may be effective in promoting sleep because production is deficient in AD.

Systemic Corticosteroids

Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, as during an asthma exacerbation, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids, and frequent bathing, followed by application of emollients or proactive topical corticosteroids, to prevent rebound flaring of AD.

Table 186.4 Counseling and Aggravating Factors for Patients with Atopic Dermatitis

Maintain cool temperature in bedroom, and avoid too many bed covers.
Increase emollient use with cold weather.
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect.
Clothing: Avoid skin contact with irritating fibers (wool, large-fiber textiles).
Do not use tight and too-warm clothing to avoid excessive sweating.
New, nonirritating clothing designed for AD children is being evaluated.
Tobacco: Avoid exposure.
Vaccines: Normal schedule in noninvolved skin, including egg-allergic patients (see text).
Sun exposure: No specific restriction.
Usually helpful because of improvement of epidermal barrier.
Encourage summer holidays in altitude or at beach resorts.
Physical exercise, sports: No restriction.
If sweating induces flares of AD, progressive adaptation to exercise.
Shower and emollients after swimming pool.
Food allergens:
Maintain breastfeeding exclusively to 4-6 mo if possible.
Consider evaluation for early introduction of allergens (see Chapter 192).
Otherwise normal diet, unless an allergy workup has proved the need to exclude a specific food.
Indoor aeroallergens: House dust mites.
Use adequate ventilation of housing; keep the rooms well aerated even in winter.
Avoid wall-to-wall carpeting.
Remove dust with a wet sponge.
Vacuum floors and upholstery with an adequately filtered cleaner once a week.
Avoid soft toys in bed (cradle), except washable ones.
Wash bedsheets at a temperature higher than 55°C (131°F) every 10 days.
Use bed and pillow encasings made of Gore-Tex or similar material.
Furred pets: Advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal.
Pollen: Close windows during peak pollen season on warm and dry weather days and restrict, if possible, time outdoors.
Windows may be open at night and early in the morning or during rainy weather.
Avoid exposure to risk situations (lawn mowing).
Use pollen filters in motor vehicles.
Clothes and pets can vectorize aeroallergens, including pollen.

Adapted from Darsow U, Wollenberg A, Simon D, et al. ETFAD/EADV Eczema Task Force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2010;24:321.

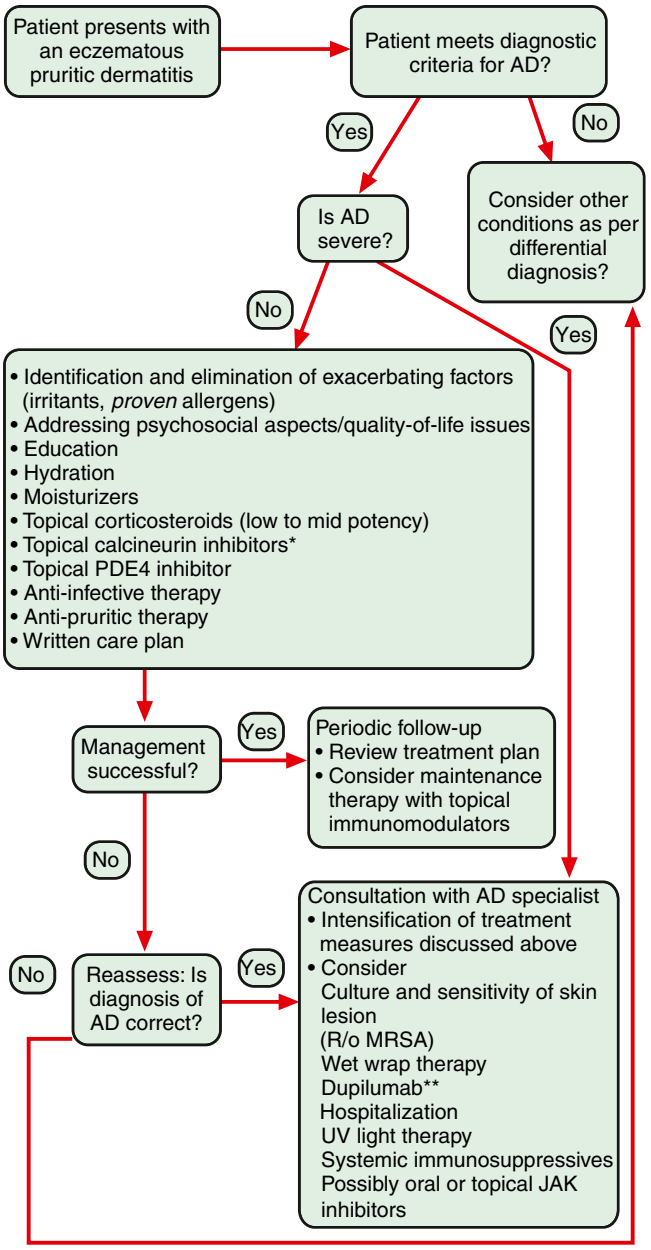

Fig. 186.5 Approach to the patient with atopic dermatitis (AD). *Per boxed warning: second-line, intermittent therapy for patients ≥2 years of age. **Approved for patients ≥12 years of age with moderate to severe AD. JAK, Janus kinase; MRSA; methicillin-resistant *Staphylococcus aureus*; PDE, phosphodiesterase; UV, ultraviolet. (*Modified from Boguniewicz M, Fonacier L, Leung DYM. Atopic dermatitis and allergic contact dermatitis. In Hershey GKK, Sheikh A, O'Hehir RE, Holgate ST, eds. Allergy Essentials. 2nd ed. Philadelphia: Elsevier; 2022. Fig 11.5.*)

Dupilumab

A monoclonal antibody that binds to the IL-4 receptor α subunit, dupilumab (Dupixent) inhibits the signaling of IL-4 and IL-13, cytokines associated with AD. In children with moderate to severe AD not controlled by standard topical therapy, dupilumab reduces pruritus and improves skin clearing. Dupilumab is approved for children 6 years or older. Lebrikizumab, an IgG4 monoclonal antibody that targets IL-13, has shown efficacy in adolescents and adults with moderate to severe atopic dermatitis.

Phototherapy

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription and has been shown to be effective in the control of severe AD. Cyclosporine forms a complex with an intracellular protein, cyclophilin, and this complex in turn inhibits calcineurin, a phosphatase required for activation of nuclear factor of activated T cells (NFAT), a transcription factor necessary for cytokine

Table 186.5 Categorization of Physical Severity of Atopic Eczema

Clear: Normal skin, with no evidence of atopic eczema
Mild: Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate: Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe: Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA, Guideline Development Group. Management of atopic eczema in children aged up to 12 years: summary of NICE guidance. *BMJ.* 2007;335:1263–1264.

gene transcription. Cyclosporine (5 mg/kg/day) for short-term and long-term (1 year) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

Janus Kinase Inhibitors

Oral and topical Janus kinase (JAK) inhibitors have demonstrated rapid improvement in adults and older children with severe AD. These inhibitors also have potential side effects including infections (tuberculosis), malignancy (cutaneous lymphoma), and headaches. Topical therapy is effective and has fewer side effects. Clinical trials are in progress to address the efficacy and safely of JAK inhibitors.

Antimetabolites

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex retinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore mycophenolate mofetil should be discontinued if the disease does not respond within 4-8 weeks.

Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis.

Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyltransferase levels may identify individuals at risk.

Before any of these drugs are used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

Unproven Therapies

Other therapies may be considered in patients with refractory AD.

Interferon-γ

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are common side effects during the treatment course.

Omalizumab

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials supporting omalizumab as a preferred therapy for moderate to severe AD. Most reports show inconsistent responses to anti-IgE.

Table 186.6 Selected Topical Corticosteroid Preparations*

GROUP 1
Clobetasol propionate (Temovate) 0.05% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel
Fluocinonide (Vanos) 0.1% cream
GROUP 2
Mometasone furoate (Elocon) 0.1% ointment
Halcinonide (Halog) 0.1% cream
Fluocinonide (Lidex) 0.05% ointment/cream
Desoximetasone (Topicort) 0.25% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% cream
GROUP 3
Fluticasone propionate (Cutivate) 0.005% ointment
Halcinonide (Halog) 0.1% ointment
Betamethasone valerate (Valisone) 0.1% ointment
GROUP 4
Mometasone furoate (Elocon) 0.1% cream
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
Fluocinolone acetonide (Synalar) 0.025% ointment
GROUP 5
Fluocinolone acetonide (Synalar) 0.025% cream
Hydrocortisone valerate (Westcort) 0.2% ointment
GROUP 6
Desonide (DesOwen) 05% ointment/cream/lotion
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
GROUP 7
Hydrocortisone (Hytone) 2.5%, 1%, 0.5% ointment/cream/lotion

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).
Adapted from Stoughton RB. Vasoconstrictor assay-specific applications. In: Malbach HI, Surber C, eds. *Topical Corticosteroids*. Basel, Switzerland: Karger; 1992. p 42–53.

Allergen Immunotherapy

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest that specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical corticosteroid use.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the first 2 years of life. The treatment response has been found to be more pronounced in patients with positive skin-prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

Chinese Herbal Medications

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The patients had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

Vitamin D

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation, and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease, especially in patients with low baseline vitamin D, as during winter, when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

AVOIDING TRIGGERS

It is essential to identify and eliminate triggering factors for AD, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 186.4).

Irritants

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. *Patients with AD should use soaps with minimal defatting properties and a neutral pH.* New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a second rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be as normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high sun protection factor (SPF) sunscreens should be used to avoid sunburn.

Foods

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 192). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet may lead to clinical improvement but also carries a risk of the patient developing immediate type allergic reactions to the food allergen removed.

Potential allergens can be identified by a careful history and performing selective skin-prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple positive skin test results, the majority of patients react to fewer than three foods under controlled challenge conditions.

Aeroallergens

In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections

Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *S. aureus*. Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus*. Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic clindamycin or trimethoprim/sulfamethoxazole needed for methicillin-resistant *S. aureus* (MRSA). Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus*. This finding supports the importance of combining effective antiinflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus*. Dilute bleach baths (½ cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial, the group who received the bleach baths plus intranasal mupirocin (5 days/month) had significantly decreased severity of AD at 1 and 3 months compared with placebo. Patients rinse off after the soaking. Bleach baths may not only reduce *S. aureus* abundance on the skin but also have antiinflammatory effects.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection (Fig. 186.6). The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical

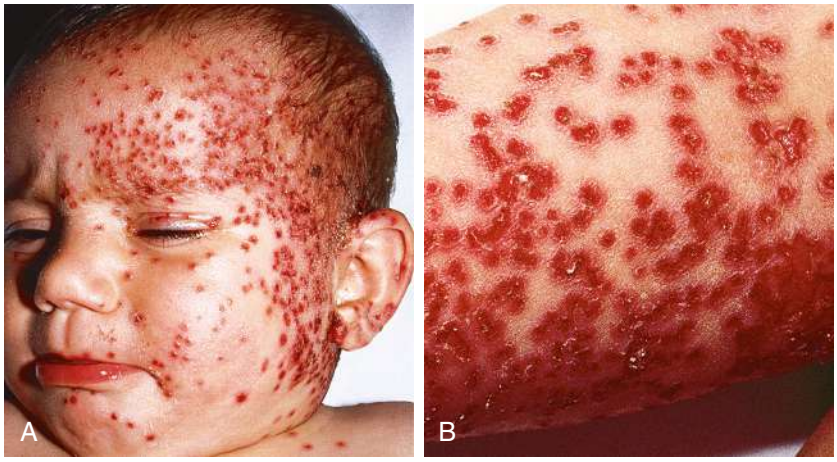

Fig. 186.6 Eczema herpeticum infection in a patient with atopic dermatitis. Numerous punched-out vesicles and erosions involving the face (**A**) and extremities (**B**). (*From Papulosquamous eruptions. In Cohen BA, ed. Pediatric Dermatology. Philadelphia: Saunders; 2013. pp 68–103.*)

corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to **eczema vaccinatum**, which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination.

Cutaneous warts, coxsackievirus, and molluscum contagiosum are additional viral infections affecting children with AD.

Dermatophyte infections can also contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic controls. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in these patients after treatment with antifungal agents.

COMPLICATIONS

Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma.

Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. **Atopic keratoconjunctivitis** is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. **Keratoconus** is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

PROGNOSIS

AD generally tends to be more severe and persistent in young children, particularly if they have homozygous null pathogenic variants in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 years in 40–60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as *hand dermatitis,* especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, *FLG* null pathogenic variants, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

PREVENTION

Breastfeeding may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breastfeeding mother may need to eliminate the implicated food allergen from her diet. For infants with severe eczema, introduction of infant-safe forms of peanut as early as 4-6 months, after other solids are tolerated, is recommended after consultation with the child's pediatrician and/or allergist for allergy testing. This approach may prevent peanut allergy (see Chapter 192). Identification and elimination of triggering factors are the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the first few months of life may enhance the cutaneous barrier and reduce the risk of eczema.

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Chapter 187

Insect Allergy

Julie Wang and Scott H. Sicherer

Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. **Allergic reactions** caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and asthma.

ETIOLOGY

Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are usually attributed to IgE antibody–mediated responses, which are caused primarily by stings from venomous insects of the order **Hymenoptera** and more rarely from ticks, spiders, scorpions, and *Triatoma* (kissing bug). Members of the order Hymenoptera include *apids* (honeybee, bumblebee), *vespids* (yellow jacket, wasp, hornet), and *formicids* (fire and harvester ants) (Fig. 187.1). Among winged stinging insects, yellow jackets are the most notorious for stinging because they are aggressive and ground dwelling, and they linger near activities involving food. Hornets nest in trees, whereas wasps build honeycomb nests in dark areas such as under porches; both are aggressive if disturbed. Honeybees are less aggressive and nest in tree hollows; unlike the stings of other flying Hymenoptera, honeybee stings almost always leave a barbed stinger with venom sac.

In the United States, fire ants are found in the Southeast, living in large mounds of soil. When disturbed, the ants attack in large numbers, anchor themselves to the skin by their mandibles, and sting multiple times in a circular pattern. Sterile pseudopustules form at the sting sites. Systemic reactions to stinging insects occur in 0.4–0.8% of children and 3% of adults and account for approximately 40 deaths each year in the United States.

Although reactions to insect bites are common, IgE-mediated reactions are infrequently reported and anaphylaxis is rare. The *Triatoma* (kissing bug) bite causes an erythematous plaque that is painless. Mosquito bites generally result in local reactions that are pruritic. Large,

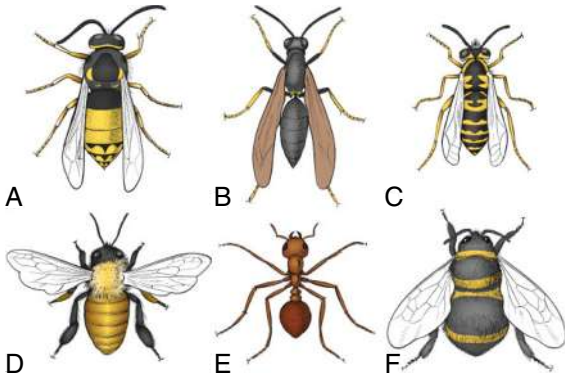

Fig. 187.1 Representative venomous Hymenoptera. **A,** Hornet *(Vespula maculata).* **B,** Wasp *(Chlorion ichneumerea).* **C,** Yellowjacket *(Vespula maculiforma).* **D,** Honeybee *(Apis mellifera).* **E,** Fire ant *(Solenopsis invicta).* **F,** Bumblebee *(Bombus species). (From Erickson TB, Marquez A. Arthropod envenomation and parasitism. In: Auerbach PS, Cushing TA, Harris NS, eds. Auerbach's Wilderness Medicine. 7th ed. Philadelphia: Elsevier; 2017: Fig 41-1, p 937.)*

local reactions to mosquito bites can occur in some young children; this is known as **skeeter syndrome** and is often misdiagnosed as cellulitis. The *tabanid* species (horsefly, deerfly), typically found in rural and suburban areas, are large flies that induce painful bites.

IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. **Perennial allergy** is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has eight rather than six legs.

PATHOGENESIS

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross reactivity among vespid venoms, but these venom allergies are distinct from honeybee venom allergies.

Localized skin responses to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva; they rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

CLINICAL MANIFESTATIONS

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple **local reactions** involve limited swelling and pain and generally last <24 hours. **Large local reactions** develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. **Generalized cutaneous reactions** typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. **Systemic reactions** are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. A subset of patients with hypotension and persistently elevated (once recovered) tryptase levels may have mast cell activation syndrome (see Chapter 190). Stings from numerous insects at once may result in **toxic reactions** of fever, malaise, emesis, and nausea because of the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as **delayed/late reactions** to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. **Papular urticaria** affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large, local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, or asthma.

DIAGNOSIS

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by skin-prick testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when **venom immunotherapy** (**VIT**) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of five Hymenoptera (honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp), as well as the jack jumper ant in Australia and whole body extract of fire ant, are available for skin testing. Although skin tests are considered to be the most sensitive modality for detection of venom-specific IgE, additional evaluation with an in vitro serum assay for venom-specific IgE is recommended if skin test results are negative in the presence of a convincing history of a severe systemic reaction. In vitro tests have a 20% incidence of both false-positive and false-negative results, so it is not appropriate to exclude venom hypersensitivity based on this test alone. If initial skin-prick and in vitro test results are negative in the context of a convincing history of a severe reaction, repeat testing is recommended before concluding that allergy is unlikely. Skin tests are usually accurate within 1 week of a sting reaction, but occasionally a refractory period is observed that warrants retesting after 4-6 weeks if the initial results are negative.

An elevated **basal tryptase** level is associated with more severe reactions to venom stings. Therefore basal tryptase should be measured if there is a history of severe reaction to a sting, hypotensive reaction, lack of urticaria in a systemic sting reaction, or negative venom IgE in a patient who has a history of systemic reaction to a sting. As many as 40% of skin test–positive patients may not experience anaphylaxis on sting challenge, so testing without an appropriate clinical history is potentially misleading.

The diagnosis of inhalant insect allergy may be evident from a history of typical symptoms. A chronic respiratory symptom during long-term exposure, as may occur with cockroach allergy, is less amenable to identification by history alone. Skin-prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy. Allergy tests may be particularly warranted for potential cockroach allergy in patients with persistent asthma and known cockroach exposure.

TREATMENT

For local cutaneous reactions caused by insect stings and bites, treatment with cold compresses, topical medications to relieve itching, and occasionally a systemic antihistamine and oral analgesic are appropriate. Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom. Sting sites rarely become infected, possibly because of the antibacterial actions of venom constituents. Vesicles left by fire ant stings that are scratched open should be cleansed to prevent secondary infection.

Anaphylactic reactions after a Hymenoptera sting are treated the same as anaphylaxis from any cause; *epinephrine is the drug of choice.* Adjunctive treatment includes antihistamines, corticosteroids, intravenous fluids, oxygen, and transport to the emergency department (see Chapter 190). Referral to an allergist-immunologist should be considered for patients who have experienced a generalized cutaneous or systemic reaction to an insect sting, who need education about avoidance and emergency treatment, who may be candidates for VIT, or who have a condition that may complicate management of anaphylaxis (e.g., use of β blockers).

Venom Immunotherapy

Hymenoptera VIT is highly effective (95–97%) in decreasing the risk for **severe anaphylaxis**. The selection of patients for VIT depends on several factors (Table 187.1). Individuals with local reactions,

Table 187.1 Risk of Systemic Reaction in Untreated Patients with History of Sting Anaphylaxis and/or Positive Venom Skin Test Results

ORIGINAL STING REACTION		RISK OF SYSTEMIC REACTION	
SEVERITY	**AGE**	**ANY SYSTEMIC (%)**	**ANAPHYLAXIS (%)**
No reaction	Adult	5-15	<3
Large local	All	4-10	<
Cutaneous systemic	All	10	<3
Anaphylaxis	Child	40	30
	Adult	60	40

From Golden DBK: Insect allergy. In Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy Principles and Practice*, ed 9, vol 2, Philadelphia: Elsevier, 2020, Table 76.2, p. 1253.

regardless of age, are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large, local reaction is approximately 7%; testing or VIT is usually not recommended, and prescription of self-injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. **Those who experience severe systemic reactions, such as airway involvement or hypotension, and who have specific IgE to venom allergens, should receive immunotherapy.** Immunotherapy against winged Hymenoptera is generally not required when stings have caused only generalized urticaria or angioedema, because the risk for a systemic reaction after a subsequent sting is approximately 10% and the chance of a more severe reaction is <3%. VIT may be considered if there are potential high-risk cofactors such as comorbid cardiovascular disease or use of specific cardiovascular medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, β blockers), elevated basal tryptase level, or high likelihood of future stings. VIT is usually not indicated if there is no evidence of IgE to venom.

The incidence of adverse effects in the course of *treatment* is not trivial in adults; 50% experience large, local reactions, and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT; thus some experts recommend basal tryptase level for risk assessment purposes.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, treatment duration of 3-5 years is recommended because >80% of adults who have received 5 years of therapy tolerate challenge stings without systemic reactions for 5-10 years after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 years of children with moderate to severe insect sting reactions who received VIT for a mean of 3-5 years and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Extended or lifelong treatment may be considered for those who have had life-threatening anaphylaxis with insect stings or severe reaction during VIT, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Lifelong VIT should also be considered for patients with mast cell disorders because they have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat patients who have only cutaneous systemic reactions with VIT. Only whole body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

Inhalant Allergy

The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 184), conjunctivitis (see Chapter 188), and asthma (see Chapter 185).

PREVENTION

Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should have known or suspected nests near the home removed by trained professionals, should wear gloves when gardening, should wear long pants and shoes with socks when walking in the grass or through fields, and should avoid or be cautious about eating or drinking outdoors. Typical insect repellents do not guard against Hymenoptera.

Individuals who are at high risk for future severe reactions to Hymenoptera stings should have immediate access to self-injectable epinephrine. High-risk individuals include those who have a history of severe reactions or have elevated basal tryptase level. Adults responsible for allergic children and older patients who can self-treat must be carefully taught the indications and technique of administration for this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear medical identification jewelry indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly for those living in apartments, where eradication of cockroaches may be problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

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Chapter 188

Ocular Allergies

Leonard Bielory, Brett P. Bielory, and Scott H. Sicherer

The ocular surface of the eye, the conjunctiva, is the most immunologically active tissue of the external eye. The conjunctiva is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. Ocular allergies can occur as isolated target organ disease or more often in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

CLINICAL MANIFESTATIONS

Allergic eye diseases represent a spectrum of conditions that require allergic sensitization and range from acute (seasonal) progressing to the perennial and then to the more chronic forms and potentially sight-threatening forms, vernal and atopic keratoconjunctivitis (Table 188.1).

Allergic Conjunctivitis

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to *chemosis,* or conjunctival swelling, and a watery discharge (Fig. 188.1).

Allergic conjunctivitis occurs in a seasonal or, less frequently, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 184) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons vary significantly in different parts of the United States. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/week or for <4 weeks) and persistent (symptoms present >4 days/week and for >4 weeks) has been proposed.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in two forms, limbal or palpebral. It may threaten eyesight if there is corneal involvement. Vernal keratoconjunctivitis is only associated with positive cutaneous allergic reactivities in 50% of cases, although it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects males twice as often as females

Table 188.1 Allergic Diseases of the Eye

DISEASE	CLINICAL PARAMETERS	SIGNS/SYMPTOMS	DIFFERENTIAL DIAGNOSIS
Seasonal allergic conjunctivitis (SAC)	• Sensitized individuals • Both females and males • Bilateral involvement • Seasonal allergens • Self-limiting	• Ocular itching • Tearing (watery discharge) • Chemosis, redness • Often associated with rhinitis • Not sight threatening	• Infective conjunctivitis • Preservative toxicity • Medicamentosa • Dry eye • PAC/AKC/VKC
Perennial allergic conjunctivitis (PAC)	• Sensitized individuals • Both females and males • Bilateral involvement • Year-round allergens • Self-limiting	• Ocular itching • Tearing (watery discharge) • Chemosis, redness • Often associated with rhinitis • Not sight threatening	• Infective conjunctivitis • Preservative toxicity • Medicamentosa • Dry eye • SAC/AKC/VKC
Atopic keratoconjunctivitis (AKC)	• Sensitized individuals • Peak incidence 20-50 years of age • Both females and males • Bilateral involvement • Seasonal/perennial allergens • Atopic dermatitis • Chronic symptoms	• Severe ocular itching • Red flaking periocular skin • Mucoid discharge, photophobia • Corneal erosions • Scarring of conjunctiva • Cataract (anterior subcapsular) • Sight threatening	• Contact dermatitis • Infective conjunctivitis • Blepharitis • Pemphigoid • VKC/SAC/PAC/GPC
Vernal keratoconjunctivitis (VKC)	• Some sensitized individuals • Peak incidence 3-20 years of age • Males predominate 3:1 • Bilateral involvement • Warm, dry climate • Seasonal/perennial allergens • Chronic symptoms	• Severe ocular itching • Severe photophobia • Thick, ropy discharge • Cobblestone papillae • Corneal ulceration and scarring • Sight threatening	• Infective conjunctivitis • Blepharitis • AKC/SAC/PAC/GPC
Giant papillary conjunctivitis (GPC)	• Sensitization not necessary • Both females and males • Bilateral involvement • Prosthetic exposure • Occurs anytime • Chronic symptoms	• Mild ocular itching • Mild mucoid discharge • Giant papillae • Contact lens intolerance • Foreign body sensation • Protein buildup on contact lens • Not sight threatening	• Infective conjunctivitis • Preservative toxicity • SAC/PAC/AKC/VKC

From Barney NP. Allergic and immunologic diseases of the eye. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy: Principles and Practice.* 9th ed. Philadelphia: Elsevier, 2020: Table 38.1, p. 607)

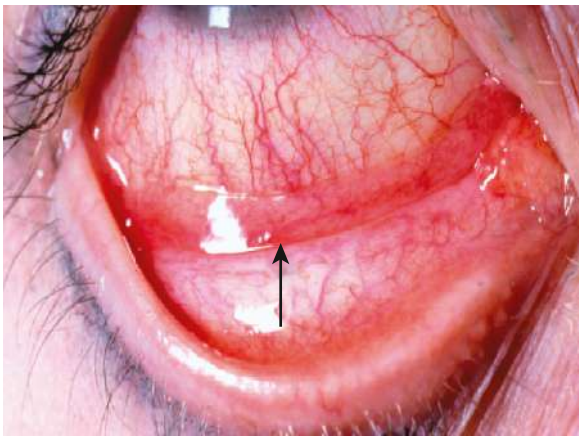

Fig. 188.1 Allergic conjunctivitis. *Arrow* indicates area of chemosis in the conjunctivitis. *(From Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy: Principles & Practice. 8th ed. St Louis: Elsevier, 2014: p. 619.)*

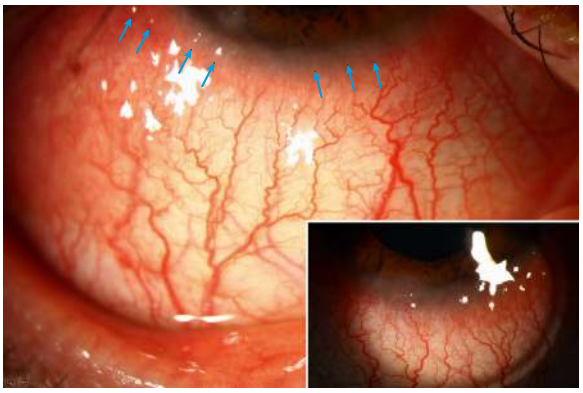

Fig. 188.3 Horner-Trantas dots. Classic appearance of small white-yellow chalky concretions with collections of degenerated epithelial cells and eosinophils around the corneal limbus *(arrows). (From Cheng J, Jiang L, Morrow NC, et al. Recognition of atopic keratoconjunctivitis during treatment with dupilumab for atopic dermatitis. J Am Acad Dermatol. 2021;85(1):265–267. Fig 1.)*

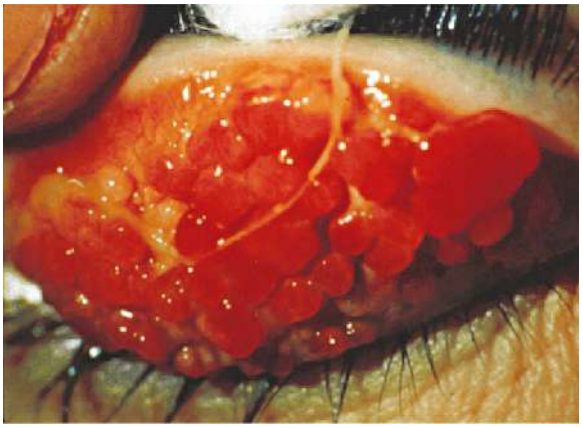

Fig. 188.2 Vernal keratoconjunctivitis. Cobblestone papillae and ropey discharge are seen on the underside (tarsal conjunctiva) of the upper eyelid. *(From Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy: Principles & Practice. 8th ed. St Louis: Elsevier, 2014: p. 627.)*

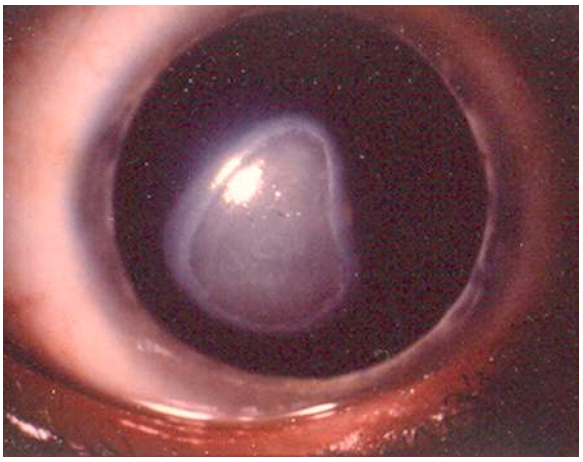

Fig. 188.4 Corneal shield ulcer classic depiction of sterile plaques containing fibrin and mucous that accumulate into macro-erosions forming a shield ulcer. *(From LaMattina K, Thompson L. Pediatric conjunctivitis. Dis Mon. 2014;60(6):231–238. Fig 6.)*

and is more common in the Mediterranean basin and in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer, but can occur throughout the year. Symptoms include intense ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia due to corneal involvement, foreign body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as *cobblestoning* (Fig. 188.2). Other signs include a stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points at the corneal limbus *(Trantas dots)* (Fig. 188.3) and conjunctiva *(Horner points)*, corneal "shield" ulcers (Fig. 188.4), and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a chronic inflammatory ocular disorder most often involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have atopic dermatitis, and a significant number have asthma. Atopic keratoconjunctivitis rarely presents before late adolescence. Symptoms include severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge that are much more severe than in allergic conjunctivitis and persist throughout the year. The bulbar conjunctiva is injected and chemotic; cataracts may occur. Trantas dots at the corneal limbus or giant papillae typically found in inferior palpebral conjunctiva may also be present. Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling. Secondary staphylococcal blepharitis is common because of eyelid induration and maceration. Chronic eye rubbing associated with vernal and atopic keratoconjunctivitis can lead to **keratoconus**, a noninflammatory cone-shaped corneal ectasia. This may lead to corneal thinning and perforation.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis is not associated with IgE sensitization, but has been linked to chronic exposure to foreign bodies, such

as contact lenses (both hard and soft), ocular prostheses, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is frequently associated with increased exposure to topical medications, contact lens solutions, and preservatives.

DIAGNOSIS

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral, but can be bilateral with symptoms initially developing in one eye (see Chapter 666). Symptoms include stinging or burning rather than itching and often a foreign body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharoconjunctivitis, dry eye, uveitis, and trauma.

Dry Eye

Dry eye conditions are being increasingly recognized as a concomitant and comorbid condition in children directly correlated with increased use of computers and gaming and mobile devices that are associated with decreased blinking time and increased evaporative tear film dysfunction.

TREATMENT

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. Secondary treatment regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 188.2). Drugs with dual antihistamine and mast cell–blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictor is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a nasoocular reflex.

Table 188.2 Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	COMMENTS, CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride, 0.05% Optivar	Antihistamine *Children ≥3 yr:* 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Emedastine difumarate, 0.05% Emadine	Antihistamine *Children ≥3 yr:* 1 gtt qid	Soft contact lenses should not be worn if the eye is red Wait at least 10 min after administration before inserting soft contact lenses
Levocabastine hydrochloride, 0.05% Livostin	Antihistamine *Children ≥12 yr:* 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms Not for use with contact lenses
Naphazoline hydrochloride, 0.3% 0.025% Naphcon-A, Opcon-A	*Children >6 yr:* 1-2 gtt qid	Avoid prolonged use (>3-4 days) to avoid rebound symptoms Not for use with contact lenses
Cromolyn sodium, 4% Crolom, Opticrom	Mast cell stabilizer *Children >4 yr:* 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis Not for use with contact lenses
Lodoxamide tromethamine, 0.1% Alomide	Mast cell stabilizer *Children ≥2 yr:* 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis Not for use in patients wearing soft contact lenses during treatment
Nedocromil sodium, 2% Alocril	Mast cell stabilizer *Children ≥3 yr:* 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis
Pemirolast potassium, 0.1% Alamast	Mast cell stabilizer *Children >3 yr:* 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Epinastine hydrochloride, 0.05% Elestat	Antihistamine/mast cell stabilizer *Children ≥3 yr:* 1 gtt bid	Contact lenses should be removed before use Wait at least 15 min after administration before inserting soft contact lenses Not for the treatment of contact lens irritation

Table 188.2 Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	COMMENTS, CAUTIONS AND ADVERSE EVENTS
Ketotifen fumarate, 0.025% Zaditor	Antihistamine/mast cell stabilizer *Children ≥3 yr:* 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Olopatadine hydrochloride, 0.1%, 0.2%, 0.7% Patanol, Pataday, Pazeo	Antihistamine/mast cell stabilizer *Children ≥3 yr:* 1 gtt bid (8 hr apart) *Children ≥2 yr:* 1 gtt qd	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses Wait at least 10 min after administration before inserting soft contact lenses
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer *Children >2 yr:* 1 gtt bid q8-12h	Contact lenses should be removed before application; may be inserted after 10 min Not for the treatment of contact lens irritation
Bepotastine besilate, 1.5% Bepreve	Antihistamine/mast cell stabilizer *Children >2 yr:* 1 gtt bid q8-12h	Contact lenses should be removed before application; may be inserted after 10 min Not for the treatment of contact lens irritation
Cetirizine, 0.24% Zerviate	Antihistamine *Children >2 yr:* 1 gtt bid	Contains lubricant hydrocellulose, preservative free unit doses
Ketorolac tromethamine, 0.5% Acular	NSAID *Children ≥3 yr:* 1 gtt qid	Avoid with aspirin or NSAID sensitivity Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight threatening *Do not use while wearing contact lenses*
Fluorometholone, 0.1%, 0.25% suspension and 0.1% ointment FML, FML Forte, Flarex	Fluorinated corticosteroid *Children ≥2 yr:* 1 gtt into conjunctival sac of affected eye(s) bid-qid During initial 24-48 hr, dosage may be increased to 1 gtt q4h Ointment (~1.3 cm in length) into conjunctival sac of affected eye(s) 1-3 times daily May be applied q4h during initial 24-48 hr of therapy.	If improvement does not occur after 2 days, patient should be reevaluated Patient should remove soft contact lenses before administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 min after administration Close monitoring for development of glaucoma and cataracts
Cyclosporine ophthalmic solution, 01.% Verkazia	Immunomodulation *Children >3 yr:*1 gtt qid	Unpreserved single dose units Approved for treatment of vernal keratoconjunctivitis
loteprednol, 0.5% Lotemax, Alrex	Steroid, antiinflammatory *Children >2 yr:*1-2 gtt qid	Lowest steroid associated with cataract formation or increase in intraocular pressure Comes in suspension and gel formulations

NSAID, Nonsteroidal antiinflammatory drug; bid, 2 times daily; gtt, drops; qid, 4 times daily; q4-6h, every 4-6 hr; qd, every day.

Tertiary treatment of ocular allergy includes topical (or rarely oral) corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine, are used as steroid-sparing agents. Allergen immunotherapy is very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist. *Symptoms that should prompt referral to an ophthalmologist include unilateral red eye with pain, photophobia, change in vision, refractory dry eyes, or corneal abnormality.*

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Chapter 189

Urticaria (Hives) and Angioedema

David A. Khan, Aleena Banerji, and Scott H. Sicherer

Urticaria affects 20% of individuals at some point in their life. Episodes of hives that last for <6 weeks are considered *acute,* whereas those that occur on most days of the week for >6 weeks are designated *chronic.* The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

ETIOLOGY AND PATHOGENESIS

Urticaria is defined as the presence of wheals (hives), angioedema, or both. **Acute urticaria** is often caused by an allergic IgE–mediated reaction (Table 189.1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging-insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells, caused by viral infections, nonsteroidal anti-inflammatory drugs (NSAIDs), and opiates. The diagnosis of **chronic urticaria** is established when lesions occur on most days of the week for >6 weeks (Tables 189.2 and 189.3). In about half the cases, chronic urticaria is accompanied by angioedema. In 20% of chronic urticaria patients, angioedema occurs without wheals. Acute angioedema without wheals is often a result of allergy, but recurrent isolated angioedema raises the possibility of other diagnoses.

A typical **hive** is an erythematous, pruritic, raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with systemic lupus erythematosus (SLE), or other vasculitides in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hours, do not blanch, blister, heal with scarring, or that are associated with bleeding into the skin (purpura) suggest urticarial vasculitis, which is a rare condition in children. Atypical aspects of the gross appearance of the hives or associated systemic symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process (Table 189.4).

Table 189.1 Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, direct mast cell degranulation
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	**Bacterial** (streptococcal pharyngitis, *Mycoplasma*, sinusitis); **Viral** (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); **Parasitic** (*Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella*); **Fungal** (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or intravenous immune globulin administration

From Lasley MV, Kennedy MS, Altman LC. Urticaria and angioedema. In: Altman LC, Becker JW, Williams PV, eds. *Allergy in Primary Care.* Philadelphia: Saunders; 2000: p. 232.

INDUCIBLE URTICARIA

Inducible urticaria and angioedema (previously referred to as physical urticaria) share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (Table 189.5; see also Table 189.2). In contrast to chronic spontaneous urticaria (CSU), the wheals of inducible urticaria are more short-lived, often lasting <1 hour.

Cold-Dependent Disorders

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total body exposure, as seen with swimming in cold water, can cause anaphylaxis, resulting in hypotension, loss of consciousness, and even death if not promptly treated. The diagnosis is most easily confirmed by challenge testing by holding an ice cube in place on the patient's skin for 5 minutes. In patients with cold urticaria, a urticarial lesion develops about 10 minutes after removal of the ice cube and on rewarming of the chilled skin. Most cases of acquired cold urticaria are idiopathic. Cold urticaria is rarely associated with the presence of **cryoproteins** such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis (paroxysmal cold hemoglobinuria). Multiple subtypes of atypical cold urticaria with a negative ice cube test have also been reported. Cold

Table 189.2 Etiology of Chronic Urticaria

Spontaneous/autoimmune	Approximately 30% of chronic urticaria cases are inducible urticaria, and 60–70% are spontaneous; of the spontaneous cases approximately 20–60% have autoantibodies (see text)
Inducible	Dermographism Cholinergic urticaria Cold urticaria (see Table 189.6) Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid disease (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Urticarial vasculitis
Autoinflammatory/periodic fever syndromes	See Tables 189.3 and 189.6.
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema Acquired angioedema Angiotensin-converting enzyme inhibitors

Modified from Lasley MV, Kennedy MS, Altman LC. Urticaria and angioedema. In: Altman LC, Becker JW, Williams PV, eds. *Allergy in Primary Care.* Philadelphia: Saunders; 2000: p. 234.

Table 189.3 Febrile Autoinflammatory Diseases Causing Urticaria in Children

DISEASE	GENE (PROTEIN)	INHERITANCE	ATTACK LENGTH	TIMING OF ONSET	CUTANEOUS FEATURES	EXTRACUTANEOUS CLINICAL FEATURES
FCAS	*NLRP3* (cryopyrin)	AD	Brief; minutes to 3 days	Neonatal or infantile	Cold-induced pseudourticaria	Arthralgia Conjunctivitis Headache
Muckle-Wells syndrome	*NLRP3* (cryopyrin)	AD	1-3 days	Neonatal, infantile, childhood (can be later)	Widespread pseudourticaria	Arthralgia/arthritis Sensorineural hearing loss Conjunctivitis/episcleritis Headache Amyloidosis
Neonatal-onset multisystem inflammatory disease (aka chronic infantile neurologic cutaneous articular syndrome)	*NLRP3* (cryopyrin)	AD	Continuous flares	Neonatal or infantile	Widespread pseudo-urticaria	Deforming osteoarthropathy, epiphyseal overgrowth Sensorineural hearing loss Dysmorphic facies Chronic aseptic meningitis, headaches, papilledema, seizures Conjunctivitis/uveitis, optic atrophy Growth retardation Developmental delay Amyloidosis
HIDS	*MVK* (mevalonate kinase)	AR	3-7 days	Infancy (<2yr)	Intermittent morbilliform or urticarial rash Aphthous mucosal ulcers Erythema nodosum	Arthralgia/arthritis Cervical lymphadenopathy Severe abdominal pain Diarrhea/vomiting Headache Elevated IgD and IgA antibody levels Elevated urine mevalonic acid during attacks
Tumor necrosis factor receptor–associated periodic syndrome	*TNFRSF1A* (TNFR1)	AD	>7 days	Childhood	Intermittent migratory erythematous macules and edematous plaques overlying areas of myalgia, often on limbs Periorbital edema	Migratory myalgia Conjunctivitis Serositis Amyloidosis
Systemic-onset juvenile idiopathic arthritis (SoJIA)	Polygenic	Varies	Daily (quotidian)	Peak onset at 1-6yr	Nonfixed erythematous rash; may be urticarial With or without dermographism With or without periorbital edema	Polyarthritis Myalgia Hepatosplenomegaly Lymphadenopathy Serositis
PLAID	*PLCG2*	AD	N/A	Infancy	Urticaria induced by evaporative cooling Ulcers in cold-exposed areas	Allergies Autoimmune disease Recurrent sinopulmonary infections Elevated IgE antibody levels Decreased IgA and IgM antibody levels Often elevated antinuclear antibody titers

AD, Autosomal dominant; AR, autosomal recessive; HIDS, hyperimmunoglobulinemia D syndrome; FCAS, familial cold-induced autoinflammatory syndrome; N/A, not available; PLAID, PLCG2-associated antibody deficiency and immune dysregulation.

From Youseff MJ, Chiu YE. Eczema and urticaria as manifestations of undiagnosed and rare diseases. *Pediatr Clin North Am.* 2017;64:39–56. Table 2, pp. 49–50.

urticaria must be distinguished from the **familial cold autoinflammatory syndrome** (see later, Diagnosis) (Table 189.6; see also Table 189.3 and Chapter 204). Because 20% of pediatric patients with cold urticaria may experience anaphylaxis, counseling on risks of anaphylaxis and prescribing epinephrine autoinjectors should be considered.

Cholinergic Urticaria

Cholinergic urticaria is characterized by the onset of small, punctate pruritic wheals surrounded by a prominent erythematous flare and associated with exercise, hot showers, emotional stress, and sweating. Once the patient cools down, the rash usually subsides in 30-60 minutes. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

Table 189.4 Distinguishing Features Between Urticaria and Systemic Urticarial Syndromes

COMMON URTICARIA	URTICARIAL SYNDROMES (≥1 OF FOLLOWING)
Only typical wheals:	Atypical "wheals":
Erythematous edematous lesions	Infiltrated plaques
Transient (<24-36 hr)	Persistent (>24-36 hr)
Asymmetric distribution	Symmetric distribution
Resolution without signs	Resolution with signs (hypo/hyperpigmentation, bruising, or scarring)
No associated different elementary lesions (papules, vesicles, purpura, crustae)	Associated different elementary lesions (papules, vesicles, purpura, scaling, crustae)
Pruritic (rarely stinging/burning)	Not pruritic; rather painful or burning
Possibly associated with angioedema	Usually no associated angioedema
No associated systemic symptoms	Often associated with systemic symptoms (fever, malaise, arthralgia, abdominal pain, weight loss, acral circulatory abnormalities, neurologic signs

From Peroni A, Colato C, Zanoni G, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria. *J Am Acad Dermatol*. 2009;62(4):559.

Symptomatic Dermographism

Symptomatic dermographism (also called *dermatographism* or *urticaria factitia*) may occur as an isolated disorder or may accompany chronic urticaria or other inducible urticarias. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear wheal caused by secondary dilation of the vessel and extravasation of plasma. Symptomatic dermographism is distinct from the more common "simple dermographism," affecting 4% of the population, whereas whealing but no itch occurs with stroking the skin.

Delayed Pressure Urticaria

Delayed pressure urticaria differs from other inducible urticaria in that symptoms typically occur 4-6 hours after pressure has been applied. Some patients may complain of swelling, with or without pruritus, secondary to pressure, without hives. Other lesions are predominantly wheals and may or may not be associated with significant swelling. When wheals are present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in CSU. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with CSU or can occur separately. The diagnosis is confirmed by challenge testing, most commonly via the "sand bag test." This test can be performed by using 15 lb of weights attached to a strap applied to the shoulder, thigh, or forearm for 15 minutes and observing the site over the next 24 hours for evidence of hives or edema.

Solar Urticaria

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 seconds, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hours after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into six types, depending on the wavelength of light that induces skin lesions and the ability or inability to transfer the disorder passively with serum IgE.

Aquagenic Urticaria

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. Rarely, chlorine or other trace contaminants may be responsible for the reaction.

CHRONIC SPONTANEOUS URTICARIA

CSU is the most common form of chronic urticaria and is associated with normal routine laboratory values and no evidence of systemic disease. CSU differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and shape but generally rounded.

Biopsy of a typical lesion reveals nonnecrotizing, perivascular, mononuclear cellular infiltration. Varying histopathologic processes can occur in the skin and manifest as urticaria. Patients with urticarial **vasculitis** can have urticaria and/or angioedema. Biopsy of these lesions in patients who may present with urticaria, arthralgias, myalgias, an elevated erythrocyte sedimentation rate (ESR), and in some cases **hypocomplementemia** as manifestations of urticarial vasculitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. Although urticarial vasculitis lesions are typically less blanchable, the lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

The immunopathogenesis of CSU is not entirely clear; however, mast cell activation is thought to have a key role. A key activating receptor in mast cells is the high-affinity IgE receptor (FcεRI). Two theories suggest that autoimmune factors may lead to FcεRI activation. In **type 1 autoimmunity (aka autoallergy)**, patients have IgE autoantibodies to self-antigens such as thyroperoxidase or interleukin (IL)-24, which can cross link the IgE autoantibodies leading to mast cell activation and urticaria. In **type II autoimmunity**, patients have autoantibodies (IgG, IgM, IGA) directed against FcεRI or IgE itself, which can similarly lead to mast cell activation. Direct measurement of these autoantibodies is limited to research studies with no clear clinical utility at present. However, the autoallergy theory is an attractive explanation for the effectiveness of anti-IgE therapies like omalizumab.

Diagnosis

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the clinician be aware of the various forms of urticaria (wheals and angioedema).

Hives are transient, pruritic, erythematous, raised wheals that may become tense and painful. The lesions may coalesce and form polymorphous, serpiginous, or annular lesions (Figs. 189.1 and 189.2). Individual lesions usually last minutes to several hours and rarely more than 24 hours. The lesions often disappear, only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, and in the case of hereditary angioedema (HAE), the wall of the gastrointestinal (GI) tract (see Chapter 189.1).

Viral infections, drugs, and foods are the most common identifiable causes of acute urticaria in children. Allergy skin testing for foods can be helpful in identifying a cause of acute urticaria, but only when supported by historical evidence. The role of an offending food can then be proved by elimination and food challenge, when needed. In the absence of information implicating an ingestant cause, skin testing for foods and implementation of elimination diets are generally not useful for either acute or chronic urticaria. Patients with delayed urticaria 3-6 hours after a meal consisting of mammalian meat should be evaluated for IgE to galactose-α-1,3-galactose **("alpha-gal")**, a carbohydrate allergen. Alpha-gal has been identified as a trigger in this circumstance,

Table 189.5 Comparison of the Physical Urticarias

URTICARIA	RELATIVE FREQUENCY	PRECIPITANT	TIME OF ONSET	DURATION	LOCAL SYMPTOMS	SYSTEMIC SYMPTOMS	TESTS	MECHANISM	TREATMENT
Symptomatic dermographism	Most frequent	Stroking skin	Minutes	2-3 hr	Irregular pruritic attacks	None	Stroke skin	Passive transfer, IgE, histamine, possible role of adenosine triphosphate, substance P, possible direct pharmacologic mechanism	Continual antihistamines
Delayed dermographism	Rare	Stroking skin	30 min to 8 hr	<48 hr	Burning, deep swelling	None	Stroke skin, observe early and late	Unknown	Avoidance of precipitants
Pressure urticaria	Frequent	Pressure	3-12 hr	8-24 hr	Diffuse, tender swelling	Flulike symptoms	Apply weight	Unknown	Avoidance of precipitants; if severe, omalizumab
Solar urticaria	Frequent	Various wavelengths of light	2-5 min	15 min to 3 hr	Pruritic wheals	Wheezing, dizziness, syncope	Phototest	Passive transfer, reverse passive transfer, IgE, possible histamine	Avoidance of precipitants; antihistamines, sunscreens, antimalarials
Familial cold urticaria	Rare	Change in skin temperature	30 min to 3 hr	<48 hr	Burning wheals	Tremor; headache; arthralgia; fever	Expose skin to cold air	Unknown	Avoidance of precipitants
Essential acquired cold urticaria	Frequent	Cold contact	2-5 min	1-2 hr	Pruritic wheals	Wheezing, syncope, drowning	Apply ice-filled copper beaker to arm, immerse	Passive transfer, reverse passive transfer, IgE (IgM), histamine; vasculitis can be induced	Cyproheptadine hydrochloride, other antihistamines; desensitization; avoidance of precipitants
Heat urticaria	Rare	Heat contact	2-5 min (rarely delayed)	1 hr	Pruritic wheals	None	Apply hot water–filled cylinder to arm	Possibly histamine; possibly complement	Antihistamines, desensitization; avoidance of precipitants
Cholinergic urticaria	Very frequent	General overheating of body	2-20 min	30 min to 1 hr	Papular, pruritic wheals	Syncope; diarrhea; vomiting, salivation; headaches	Bathe in hot water; exercise until perspiring, inject methacholine chloride	Passive transfer; possible immunoglobulin; product of sweat gland stimulation; histamine, reduced protease	Application of cold water or ice to skin; antihistamines; omalizumab
Aquagenic urticaria	Rare	Water contact	Several minutes	30-45 min	Papular, pruritic wheals	None reported	Apply water compresses to skin	Unknown	Avoidance of precipitants; antihistamine; application of inert oil
Vibratory angioedema	Very rare	Vibrating against skin	2-5 min	1 hr	Angioedema	None reported	Apply vibration to forearm	Unknown	Avoidance of precipitants

Ig, Immunoglobulin.
From Lee AD, Jorizzo JL. Urticaria. In: Callen JP, Jorizzo JL, Bolognia JL, et al., eds. *Dermatological Signs of Internal Disease*. 4th ed. Philadelphia: Elsevier; 2009: p. 59, Table 6.4.

Table 189.6 Hereditary Diseases with Cold-Induced Urticaria

		EPISODIC SYMPTOMS	SUSTAINED/PROGRESSIVE SYMPTOMS
CAPS	FCAS	Urticarial rash, arthralgia, myalgia, chills, fever, swelling of extremities	Renal amyloidosis
	MWS	Urticarial rash, arthralgia, chills, fever	Sensorineural deafness, renal amyloidosis
	CINCA	Fever	Rash, arthritis, chronic meningitis, visual defect, deafness, growth retardation, renal amyloidosis
NAPS12 (FCAS2)		Fever, arthralgia, myalgia, urticaria, abdominal pain, aphthous ulcers, lymphadenopathy	Sensorineural deafness
PLAID (FCAS3)		Urticaria induced by evaporative cooling, sinopulmonary infections	Serum low IgM and IgA levels; high IgE levels; decreased B and NK cells; granulomata; antinuclear antibodies

CAPS, Cryopyrin-associated periodic syndromes; FCAS, familial cold-induced autoinflammatory syndrome; MWS, Muckle-Wells syndrome; CINCA, chronic infantile neurologic cutaneous articular syndrome; NAPS, NLRP-12–associated periodic syndrome; PLAID, PLCG2-associated antibody deficiency and immune dysregulation; NK, natural killer; Ig, immunoglobulin.
From Kanazawa N. Hereditary disorders presenting with urticaria. *Immunol Allergy Clin N Amer.* 2014;34:169–179. Table 4, p. 176.

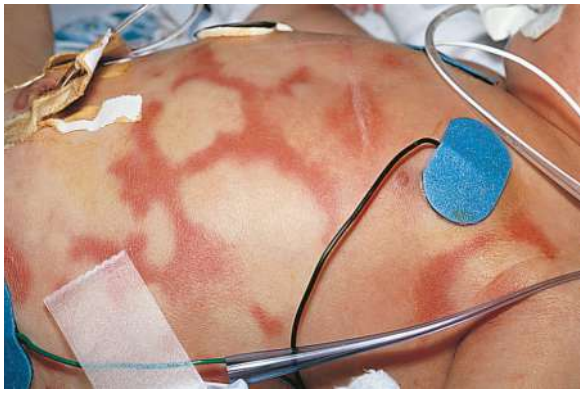

Fig. 189.1 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion. *(From Eichenfield LF, Friedan IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001: p. 300.)*

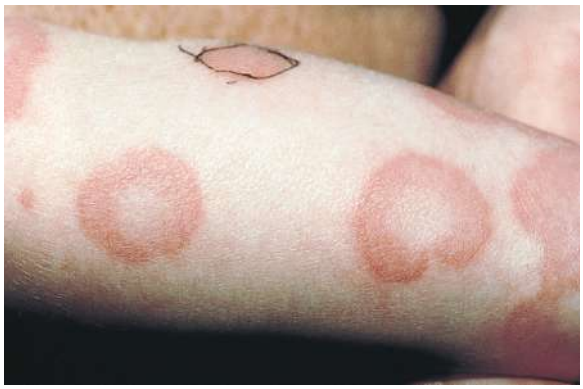

Fig. 189.2 Annular urticaria of unknown etiology. *(From Eichenfield LF, Friedan IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001: p. 301.)*

with sensitization linked to tick bites in specific geographic regions, such as the mid-Atlantic area of the United States. Skin testing for aeroallergens is not indicated unless there is a concern about contact urticaria (animal dander or grass pollen).

Autoimmune diseases are very rare causes of chronic urticaria or angioedema. Clinically available tests marketed for chronic urticaria such as basophil activation tests (used as surrogates for detecting type 2 autoantibodies) are generally not recommended. The **differential diagnosis** of chronic urticaria includes atopic or contact dermatitis, cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blistering disorders (e.g., bullous pemphigoid; see Table 189.2). Routine laboratory testing in chronic urticaria in the absence of other history has not been found to be cost-effective as it rarely changes management. Urticaria guidelines recommend either no testing or limited laboratory testing such as a complete blood cell count with differential and ESR or CRP. Further studies are warranted if the patient has fever, arthralgias, or elevated ESR (Table 189.7; see also Table 189.4). **HAE** is potentially life-threatening, usually associated with deficient C1 inhibitor (C1-INH) activity, and the most important familial form of angioedema (see Chapter 189.1), but it is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A rare syndrome of episodic (approximately 3- to 4-week intervals) angioedema less often with urticaria, weight gain, and occasionally fever with associated **hypereosinophilia** has been described in both adults and children.

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the *same location* for >24 hours, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as SLE may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivenular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

Mastocytosis is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. Maculopapular cutaneous mastocytosis (aka **urticaria pigmentosa)** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching **(Darier sign)**. This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Inducible urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Tables 189.2 and 189.5). Papular "urticaria" often occurs in small children, generally on the extremities, but the lesions are more persistent than true urticaria. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, or hypotension after exercise (see Chapter 190). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence

Table 189.7 Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Chronic spontaneous urticaria	No testing required for diagnosis
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50}, C1q, C4, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Cold urticaria	Ice cube test usually positive but may be negative in familial autoinflammatory disorders
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermographism	Stroking with narrow object (e.g., tongue blade)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C1-INH testing by protein and function
Familial cold autoinflammatory syndrome	Genetic testing for *NALP3* pathogenic variants

Table 189.8 Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg	Twice daily
	>12 yr: 60 mg	
	Adult: 180 mg	Once daily
Loratadine	2-5 yr: 5 mg	Once daily
	>6 yr: 10 mg	
Desloratadine	6-11 mo: 1 mg	Once daily
	12 mo-5 yr: 1.25 mg	
	6-11 yr: 2.5 mg	
	>12 yr: 5 mg	
Cetirizine	6-23 mo: 2.5 mg	Once daily
	2-6 yr: 2.5-5 mg	
	>6 yr: 5-10 mg	
	>12 yr: 10 mg	Once daily
Levocetirizine	6 mo-5 yr: 1.25 mg	Once daily
	6-11 yr: 2.5 mg	Once daily
	>12 yr: 5 mg	Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day	Divided q6-12h
	Children: 20-40 mg/kg/day	
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day	Divided q12h
	1-16 yr: 1-2 mg/kg/day	
LEUKOTRIENE PATHWAY MODIFIERS		
Montelukast	12 mo-5 yr: 4 mg	Once daily
	6-14 yr: 5 mg	
	>14 yr: 10 mg	
Zafirlukast	5-11 yr: 10 mg	Twice daily
IMMUNOMODULATORY DRUGS		
Omalizumab (anti IgE)	>11 yr: 300 mg	Every 28 days
Cyclosporine	1-4 mg/kg/day	Divided q12h*

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

of anaphylactic shock. The combination of ingestion of various food allergens and postprandial exercise has been associated with urticaria/angioedema and anaphylaxis. In patients with this combination disorder, the offending food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and familial cold autoinflammatory syndrome are rare, autosomal dominantly inherited conditions associated with recurrent urticaria-like lesions. **Muckle-Wells syndrome** is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR (see Tables 189.3 and 189.6), hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. **Familial cold autoinflammatory syndrome** is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea.

Treatment

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and frequently used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced sedation (Table 189.8). Epinephrine 1:1,000, 0.01 mg/kg (maximum 0.5 mg) intramuscularly, usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids may be given for more severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

The best treatment of inducible urticaria is avoidance of the stimulus; however, for some conditions like cholinergic urticaria, this can be very difficult. Antihistamines with appropriate updosing, should be tried in all inducible urticarias but may not be effective in many patients.

Management of chronic urticaria through dietary manipulation is not recommended by U.S. guidelines. The mainstay of therapy for chronic urticaria is the use of nonsedating or low-sedating H_1 antihistamines. In those patients not showing response to standard doses, increasing the dose up to fourfold the recommended dose is recommended; however, studies on the safety and efficacy of this approach in children are lacking. The addition of H_2 antihistamines and/or leukotriene receptor antagonists (e.g., montelukast) is controversial. These medications are generally benign but evidence supporting their efficacy is weak. For chronic urticaria patients that are not well controlled, brief courses of oral corticosteroids may be considered, but long-term corticosteroid use is not recommended. The monoclonal antibody omalizumab (anti-IgE) is approved by the US Food and Drug Administration (FDA) for the treatment of chronic urticaria in children 12 years and older. Other agents that have been used for chronic urticaria but are not approved by the FDA include cyclosporine, tacrolimus, mycophenolate, dapsone, hydroxychloroquine, sulfasalazine, and azathioprine. Ultraviolet light therapy may also be beneficial in refractory cases. Bruton tyrosine kinase (BTK) inhibitors have demonstrated efficacy in treating chronic spontaneous urticaria and have a rapid onset of action with few side effects.

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189.1 Hereditary Angioedema

Aleena Banerji, David A. Khan, and Scott H. Sicherer

ETIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, AND DIAGNOSTIC APPROACH

HAE (types 1 and 2) is an inherited autosomal dominant genetic disease caused by low functional levels of the plasma protein **C1-INH**. Patients typically report unpredictable episodic attacks of angioedema or deep localized swelling, most often on a hand or foot, that begin during childhood or adolescence. Cutaneous nonpitting and nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about several hours and then resolves over 2-5 days when left untreated. However, the duration of attacks can be quite variable. In some patients, attacks are preceded by the development of a rash, **erythema marginatum**, that is erythematous, not raised, and not pruritic. A second major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery, including appendectomy. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks. Patients may have a *prodrome,* a tightness or tingling in the area that will swell, usually lasting several hours, followed by the development of angioedema.

Laryngeal edema, the most worrisome complication of HAE, can cause complete respiratory obstruction with a high risk of mortality when untreated. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Laryngeal edema can be triggered by local trauma but can also occur spontaneously without any identifiable trigger. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over hours. Soft tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. As symptoms are bradykinin mediated, patients with HAE typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients, trauma, infections or emotional stress clearly precipitates attacks. Drugs such as estrogen or angiotensin-converting enzyme (ACE) inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse. In some females, menstruation can be associated with an increase in attacks. The frequency of attacks varies greatly among affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1:1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with elevated serum C1-INH levels. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene variation, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks. Figure 189.3 shows the diagnostic approach.

Although named for its action on the first component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin-activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classical complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the proteins following in the complement cascade. Levels of C3 are normal. C1-INH also inhibits serine proteases associated with activation of the lectin activation pathway. The major factor responsible for the edema formation is bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high molecular weight kininogen by the plasma enzyme kallikrein.

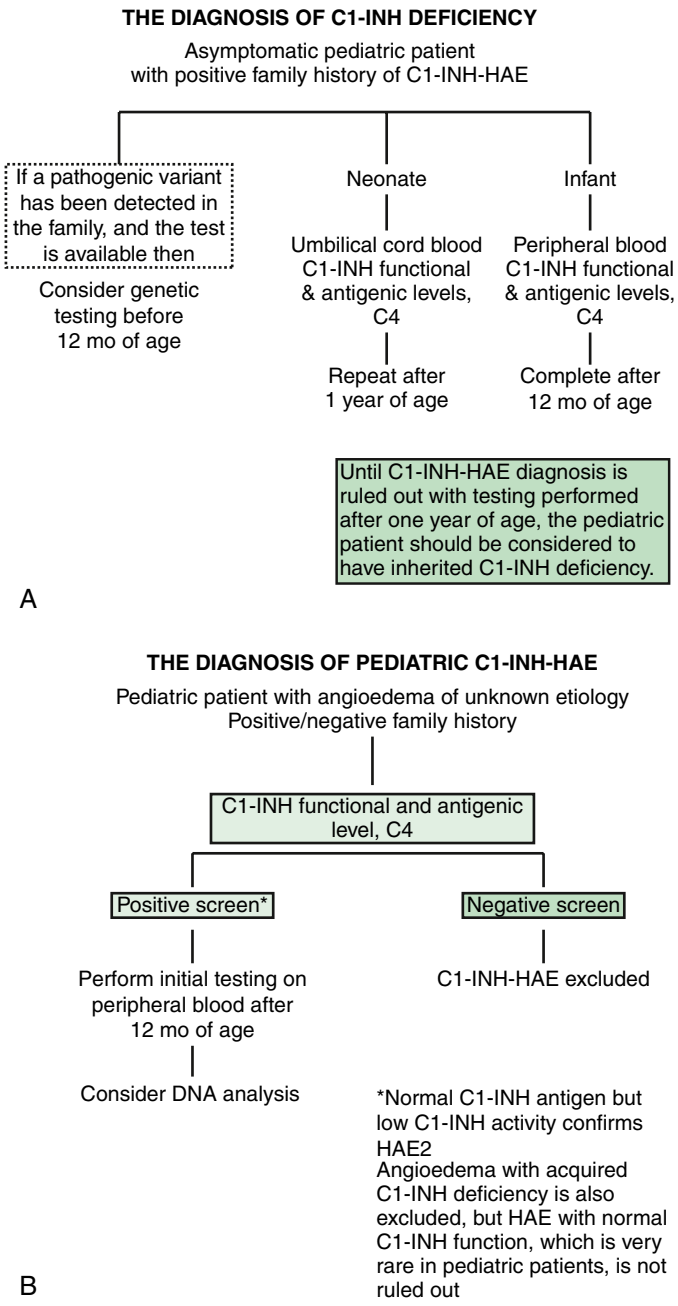

Fig. 189.3 A, Diagnosis of C1-INH deficiency in families with known C1-INH hereditary angioedema (HAE). B, Diagnosis of C1-INH HAE in pediatric patients with angioedema of unknown etiology. *(From Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Eur J Allergy Clin Immunol. 2017;72:300–313. Fig. 1, p. 304.)*

Two major genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The *C1-INH* gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the variant gene can have a clinical spectrum ranging from asymptomatic to severely affected. **Type 1** HAE is the most common form, accounting for approximately 80–85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele, or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH approximately 20–40% of normal. **Type 2** HAE accounts for approximately 15–20% of cases. Pathogenic variants of one of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein but low values in assays of C1-INH function.

A clinical syndrome resembling HAE termed **HAE with normal C1-INH** has been described that more commonly affects females, with a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. A small number of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause of this syndrome is still unknown. Additional pathogenic variants including ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-*O*-sulfotransferase 6) have been identified. Acquired C1-INH is associated with low levels of C4, C1-INH, and C1q (Table 189.9).

TREATMENT

Treatment of HAE is aimed at use of on-demand treatment when an attack starts along with long-term prophylaxis to prevent attacks. Short-term prophylaxis is used prior to a known trigger such as a surgical or dental procedure. The medical management of HAE has improved significantly in recent years with the availability of several new safe and effective therapies approved by the FDA in the United States. To provide optimal care and restore a normal quality of life, treatment of patients with HAE needs to be individualized based on patient-specific factors including patient preference and access to emergency care.

Options for **long-term prophylaxis** in patients with HAE include an intravenous formulation of plasma-derived C1-INH concentrate (Cinryze) given twice a week. Cinryze was FDA approved in 2008 for adolescents and adults. The half-life of this plasma protein is relatively short, about 40 hours, and the approved regimen is 1,000 units twice a week. In 2017, a **subcutaneous C1-INH** concentrate formulation given twice a week was approved for long-term prophylaxis in adolescents and adults. **Lanadelumab**, a monoclonal antibody that inhibits plasma kallikrein, given subcutaneously once every 2-4 weeks, along with **berotralstat,** an oral once a day pill, which inhibits plasma kallikrein, are the newest treatment options available for long-term prophylaxis in patients with HAE (see Table 189.10). Garadacimab, a fully human recombinant monoclonal antibody targeting activated factor XII, has shown efficacy as a prophylactic agent.

Androgens, like the gonadotropin inhibitor danazol, were previously used more frequently for long-term prophylaxis to prevent attacks. Weak androgens have many side effects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are

Table 189.9 Complement Evaluation of Patients with Recurrent Angioedema

	C4	C1-INH LEVEL	C1-INH FUNCTION	C1q
Idiopathic angioedema	Normal	Normal	Normal	Normal
Type 1 HAE	Low	Low	Low	Normal
Type 2 HAE	Low	Normal	Low	Normal
HAE-nlC1-INH	Normal	Normal	Normal	Normal
Acquired C1-INH deficiency	Low	Low	Low	Low
Urticarial vasculitis	Low or normal	Normal	Normal	Low or normal

C1-INH, C1 inhibitor; HAE-nlC1-INH, hereditary angioedema with normal C1-INH; nl, normal.
From Joshi SR, Khan DA. Urticaria and angioedema. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice*. 4th ed. Philadelphia: Elsevier; 2021: Table 39.3, p. 338.

Table 189.10 Long-Term Prophylactic Treatment Options for Patients with Hereditary Angioedema in the United States

DRUG	DATE OF FDA APPROVAL IN US	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	OTHER CONSIDERATIONS
Intravenous plasma-derived C1-INH	2008	Replacing missing protein	Intravenous	Dependent on plasma supply Extensive clinical experience
Subcutaneous plasma-derived C1-INH	2017	Replacing missing protein	Subcutaneous	Dependent on plasma supply Improved steady-state C1-INH levels
Lanadelumab	2018	Plasma kallikrein inhibitor	Subcutaneous	Unknown safety in pregnancy Infrequent dosing every 2-4 wk
Berotralstat	2020	Plasma kallikrein inhibitor	Oral	Unknown safety in pregnancy Once a day pill
Attenuated androgens	1976	Increases circulating levels of C1-INH protein	Oral	Significant adverse effects Contraindicated in pregnancy, lactation and children
Antifibrinolytics	1986	Reduces complement activation and C1-INH protein consumption	Oral	Significant adverse effects Inferior efficacy compared with other agents

Table 189.11 On-Demand Treatment Options for Patients with Hereditary Angioedema in the United States

DRUG	DATE OF FDA APPROVAL IN US	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	OTHER CONSIDERATIONS
Intravenous plasma-derived C1-INH	2009	Replacing missing protein	Intravenous	Dependent on plasma supply Extensive clinical experience
Recombinant C1-INH	2014	Replacing missing protein	Intravenous	No human virus risk Scalable supply
Ecallantide	2009	Plasma kallikrein inhibitor	Subcutaneous	No infectious risk 3–4% risk of anaphylaxis Requires administration by a healthcare provider
Icatibant	2011	B2 bradykinin receptor antagonist	Subcutaneous	No infectious risk Stable at room temperature Local injection reactions

not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid **(EACA)** is also effective in preventing attacks and has been used in children, but its use is attenuated by the development of severe fatigue and muscle weakness over time. A cyclized analog of EACA, **tranexamic acid**, has been used extensively in Europe; because of side effects and increased availability of other novel treatment options, it has been used less extensively in the United States. Tranexamic acid is believed to be more effective than EACA and has lower toxicity, but there have been few direct studies. Its mechanism of action is not clearly defined, and not all patients respond to this agent.

There are four **on-demand treatment** options FDA approved in the United States for patients with HAE. The first, approved in 2009, is a purified C1-inhibitor product **(Berinert)** that is administered as 20 U/kg intravenously. It was approved for the *treatment* of attacks. In 2009 the FDA approved a kallikrein inhibitor, **ecallantide**, given subcutaneously, for *acute treatment* in patients age 16 years and older. This 60–amino acid peptide causes anaphylaxis rarely and is approved only for administration by medical personnel. In 2010 a bradykinin type 2 receptor antagonist, **icatibant**, was approved for *acute treatment* in patients age 18 years and older. An intravenous **recombinant C1-INH** product has been FDA approved in 2014 for *treatment* of acute attacks (and in Europe) in adolescents and adults (see Table 189.11). All treatments are most effective when given early in an attack and begin to have a noticeable effect about 1-4 hours after treatment.

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Chapter 190

Anaphylaxis

Hugh A. Sampson, Julie Wang, and Scott H. Sicherer

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, may be underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent, biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (GI; nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 190.1 and Fig. 190.1).

Table 190.1 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

And at least one of the following:

   A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   B. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

OR

2. Two or more of the following that occur rapidly after exposure to a **likely allergen** (or other trigger) for that patient (minutes to several hours)
   A. Involvement of the skin/mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   B. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   C. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   D. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

OR

3. Reduced blood pressure after exposure to a **known allergen** or other trigger for that patient (minutes to hours).
   A. Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   B. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

From Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117(2):391-7.

ETIOLOGY

The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. **Food allergy** is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 190.2). **Peanut allergy** is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products.

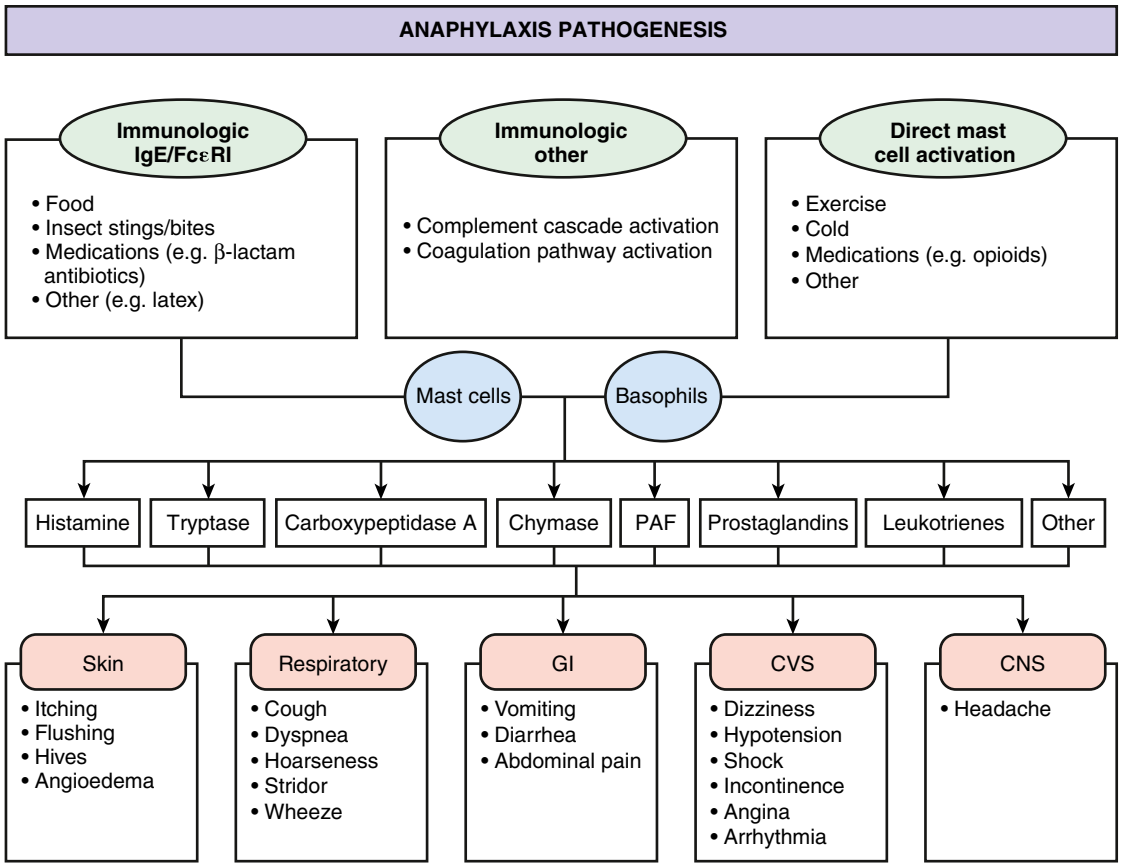

Fig. 190.1 Summary of the pathogenesis of anaphylaxis. See text for details about mechanisms, triggers, key cells, and mediators. Two or more target organ systems are typically involved in anaphylaxis. CNS, Central nervous system; CVS, cardiovascular system; GI, gastrointestinal; PAF, platelet-activating factor. *(From Leung DYM, Szefler SJ, Bonilla FA Akdis CA, Sampson HA, eds. Pediatric Allergy Principles and Practice. 3rd ed. Philadelphia: Elsevier; 2016: p. 525.)*

Table 190.2 Anaphylaxis Triggers in the Community*

ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)*	OTHER IMMUNE MECHANISMS (IgE INDEPENDENT)
Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])	IgG mediated (infliximab, high molecular weight dextrans)
Food additives (e.g., spices, colorants, vegetable gums, contaminants)	Immune aggregates (IVIG)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, fire ants)	Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Medications (e.g., β-lactam antibiotics, ibuprofen)	Complement activation
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])	Physical factors (e.g., exercise,† cold, heat, sunlight/ultraviolet radiation)
Natural rubber latex	Ethanol
Vaccines	Idiopathic*
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)	

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.
†Exercise with or without a co-trigger, such as a food or medication, cold air, or cold water.
IVIG, Intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.
Adapted from Leung DYM, Sampson HA, Geha RS, et al. *Pediatric Allergy Principles and Practice*. Philadelphia: Elsevier; 2010. p. 652.

Patients with **latex allergy** may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hours after eating red meat (see Chapter 189). Anaphylaxis may be **idiopathic** and in some of these patients related to mast cell activation syndrome (Fig. 190.2; see Chapter 700.1) or familial hypertryptasemia. **Exercise-induced anaphylaxis** has been associated with the combination of certain foods *and* exercise. Ingestion of the food without exercise does not produce allergic symptoms or anaphylaxis.

EPIDEMIOLOGY

The overall annual incidence of anaphylaxis in the United States is estimated at 42 cases per 100,000 person-years, totaling >150,000 cases per year. Food allergens are the most common trigger in children, with an incidence rate of approximately 20 per 100,000 person-years. An Australian parental survey found that 0.59% of children 3-17 years of age had experienced at least one anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 190.3). In addition, patients with systemic

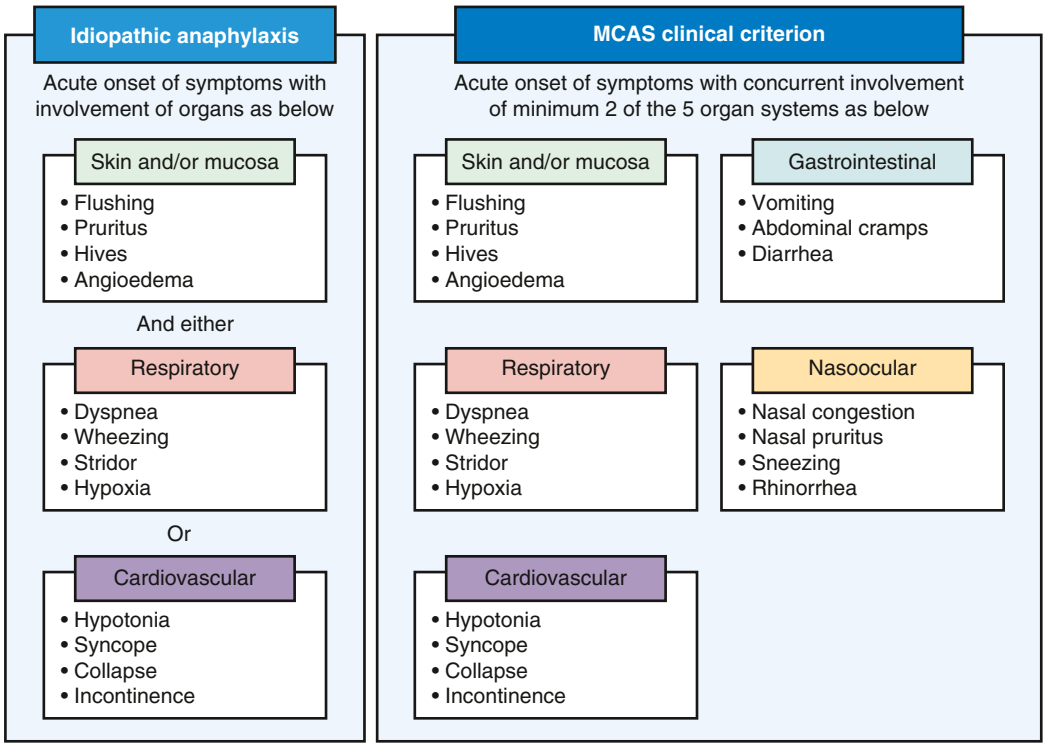

Fig. 190.2 The criteria of idiopathic anaphylaxis versus mast cell activation syndrome. Note that when there is no likely cause of the reactions, if the onset of illness is acute, a diagnosis of idiopathic anaphylaxis can only be made when either reduced blood pressure (or its symptoms such as syncope) and/or respiratory compromise are present accompanied by the involvement of the skin mucosal tissue symptoms. (*From Gulen T, Akin C. Idiopathic anaphylaxis: A perplexing diagnostic challenge for allergists. Curr Allergy Asthma Rep. 2021;21[2]:11. Fig. 1.*)

mastocytosis or monoclonal mast cell–activating syndrome are at increased risk for anaphylaxis, as are patients with an elevated baseline serum tryptase level.

PATHOGENESIS

Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific IgE molecules (see Fig. 190.1). Patients initially must be exposed to the responsible allergen to generate allergen-specific IgE antibodies. In many cases the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or exposure to inflamed skin (e.g., eczematous lesions). When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (opiates, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high molecular weight dextran, chimeric or humanized monoclonal antibodies) (see Table 190.2).

Idiopathic anaphylaxis (IA) is a diagnosis of exclusion when no inciting agent is identified, and other disorders have been excluded (see Chapter 700.1). Symptoms are similar to IgE-mediated causes of anaphylaxis; episodes often recur (see Fig. 190.2). IA may be secondary to mast cell activation syndrome with bone marrow expansion of mast cells exhibiting a D816V *KIT* pathologic variant or aberrant mast cell clonality on flow cytometry expressing CD117, CD2, or CD25 markers. Associated features of IA-associated mast cell activation syndrome include insect (venom) sting anaphylaxis with hypotension and persistent (once recovered) elevations of tryptase at times associated with autosomal dominant familial hypertryptasemia.

CLINICAL MANIFESTATIONS

The onset of symptoms may vary depending on the cause of the reaction. Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hours) compared with those from injected allergens (insect sting, medications) and tend to have more GI symptoms. Initial symptoms may include any of the following constellation of symptoms: pruritus about the mouth and face; flushing, urticaria and angioedema, and oral or cutaneous pruritus; a sensation of warmth, weakness, and apprehension (sense of doom); tightness in the throat, dry staccato cough and hoarseness, periocular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 10% of cases, and the *acute* onset of severe bronchospasm in a previously well person with asthma should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 189.1). Symptoms in infants may not be easy to identify. Infants may manifest nonspecific symptoms such as sudden crying, fussiness, flushing, dysphonia, drooling, vomiting, and becoming quiet or drowsy.

Table 190.3 Patient Risk Factors for Anaphylaxis

AGE-RELATED FACTORS
Infants: anaphylaxis can be difficult to recognize, especially if the first episode; patients cannot describe symptoms
Adolescents and young adults: increased risk-taking behaviors, such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently
Pregnancy: risk of iatrogenic anaphylaxis, as from β-lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
Older people: increased risk of death because of concomitant disease and drugs
CONCOMITANT DISEASES
Asthma and other chronic respiratory diseases
Cardiovascular diseases
Systemic mastocytosis or monoclonal mast cell–activating syndrome
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse
DRUGS
NSAIDs
β-Adrenergic blockers†
Mast cell destabilizers
ACE inhibitors†
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms.
Caffeine
FACTORS THAT MAY INCREASE RISK FOR ANAPHYLAXIS OR MAKE IT MORE DIFFICULT TO TREAT
Age
Asthma
Eczema
Drugs
Alcohol
Other cofactors such as exercise, infection, menses

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings.
†Those taking β-blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.
ACE, Angiotensin-converting enzyme; NSAID, nonsteroidal antiinflammatory drugs.
Adapted from Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341–384. Table I-9.

Table 190.4 Differential Diagnosis of Anaphylaxis

Anaphylaxis to exogenously administered agents
Physical factors
Exercise
Cold, heat, sunlight
Idiopathic
VASODEPRESSOR (VASOVAGAL) RESPONSES
Flushing syndromes
Carcinoid, pheochromocytoma, medullary carcinoma of the thyroid
Menopause
Side effects of chlorpropamide, alcohol, calcium channel blockers
Autonomic epilepsy
FOOD-ASSOCIATED SYNDROMES
Scombroidosis
Sulfites
Monosodium glutamate (MSG)
OTHER FORMS OF SHOCK
Cardiogenic
Septic
Vascular
EXCESS ENDOGENOUS PRODUCTION OF HISTAMINE SYNDROMES
Mast cell activation syndrome
Systemic mastocytosis
Cutaneous mastocytosis
Mast cell leukemia
Acute promyelocytic leukemia
NONORGANIC DISEASE
Panic attacks
Munchausen stridor
Vocal cord dysfunction
Undifferentiated somatoform anaphylaxis
MISCELLANEOUS
Acute urticaria with or without angioedema
Hereditary angioedema
Idiopathic angioedema
Neurologic (seizure, stroke)
Red man syndrome (vancomycin)
Capillary leak syndrome

From Dreskin SC, Stitt JM. Anaphylaxis. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. *Middleton's Allergy: Principles and Practice*. 9th ed. Philadelphia: Elsevier; 2020: Box 75.6, p. 1237.

LABORATORY FINDINGS

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. **Plasma tryptase** is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions. Plasma tryptase may also be elevated with chronic renal disease, eosinophilic GI disorders, parasitic infections, Gaucher disease, and mast cell activation syndrome or as a familial trait.

DIAGNOSIS

A National Institutes of Health (NIH)–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (see Table 190.1). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic), vasopressor reactions, including flushing syndromes (e.g., carcinoid syndrome), ingestion of monosodium glutamate, scombroidosis, and hereditary angioedema (Table 190.4). In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and vancomycin-induced flushing should be considered.

TREATMENT

Anaphylaxis is a medical emergency requiring aggressive management with intramuscular (IM, first line) or intravenous (IV) epinephrine. Oral (PO), IM, or IV H_1 and H_2 antihistamine antagonists, oxygen, IV fluids, inhaled β-agonists, and corticosteroids are adjunctive medications that may be used (Table 190.5 and Fig. 190.3). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. **Epinephrine** is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the IM route to the lateral thigh (1:1000 dilution, 0.01 mg/kg; maximum 0.5 mg). Children weighing 25 kg or more should receive 0.3 mg IM, with many recommending 0.5 mg IM for older adolescents. The IM dose can be repeated at intervals of 5-15 minutes if symptoms persist or worsen. If there is no response to multiple doses of epinephrine, IV epinephrine using the 1:10,000 dilution

Table 190.5 Management of a Patient with Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.3 mg IM in lateral thigh (0.5 mg autoinjectors are not available in the United States) Epinephrine autoinjector: 0.1 mg for 7.5-13 kg 0.15 mg for <25 kg 0.3 mg for 25 kg or more A second dose may be given in 5 min if symptoms worsen or do not improve	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 mL 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, paradoxical excitement
Transport to an emergency facility			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.1 mg for 7.5-13 kg 0.15 mg for <25 kg 0.3 mg for 25 kg or more 0.01 mL/kg/dose of 1:1,000 (vial) solution, up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/dose of 1:10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor
Supplemental oxygen and airway management			
Volume Expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in first hour	Rate titrated against BP response If tolerated, place patient supine with legs raised
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against BP response If tolerated, place patient supine with legs raised
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 mL 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg, up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg, up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alternative: Cimetidine	Antihistamine (competitive of H_2 receptor)	4 mg/kg, up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV): 1-2 mg/kg, up to 125 mg IV Depo-Medrol (IM): 1 mg/kg, up to 80 mg IM	Hypertension, edema, nervousness, agitation
Prednisone	Antiinflammatory	1 mg/kg up, to 75 mg PO	Hypertension, edema, nervousness, agitation
Nebulized albuterol	β-Agonist	0.83 mg/mL (3 mL) via mask with O_2	Palpitations, nervousness, CNS stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
Preventive Treatment Prescription for epinephrine autoinjector and antihistamine Provide written plan outlining patient emergency management (may download form from http://www.aap.org or http://www.foodallergy.org; English and Spanish versions available) Follow-up evaluation to determine/confirm etiology Immunotherapy for insect sting allergy *Patient Education* Instruction on avoidance of causative agent Information on recognizing early signs of anaphylaxis Stress early treatment of allergic symptoms to avoid systemic anaphylaxis Encourage wearing medical identification jewelry			

BP, Blood pressure; CNS, central nervous system; IM, Intramuscularly; IV, intravenously; PO, orally; qd, every day.

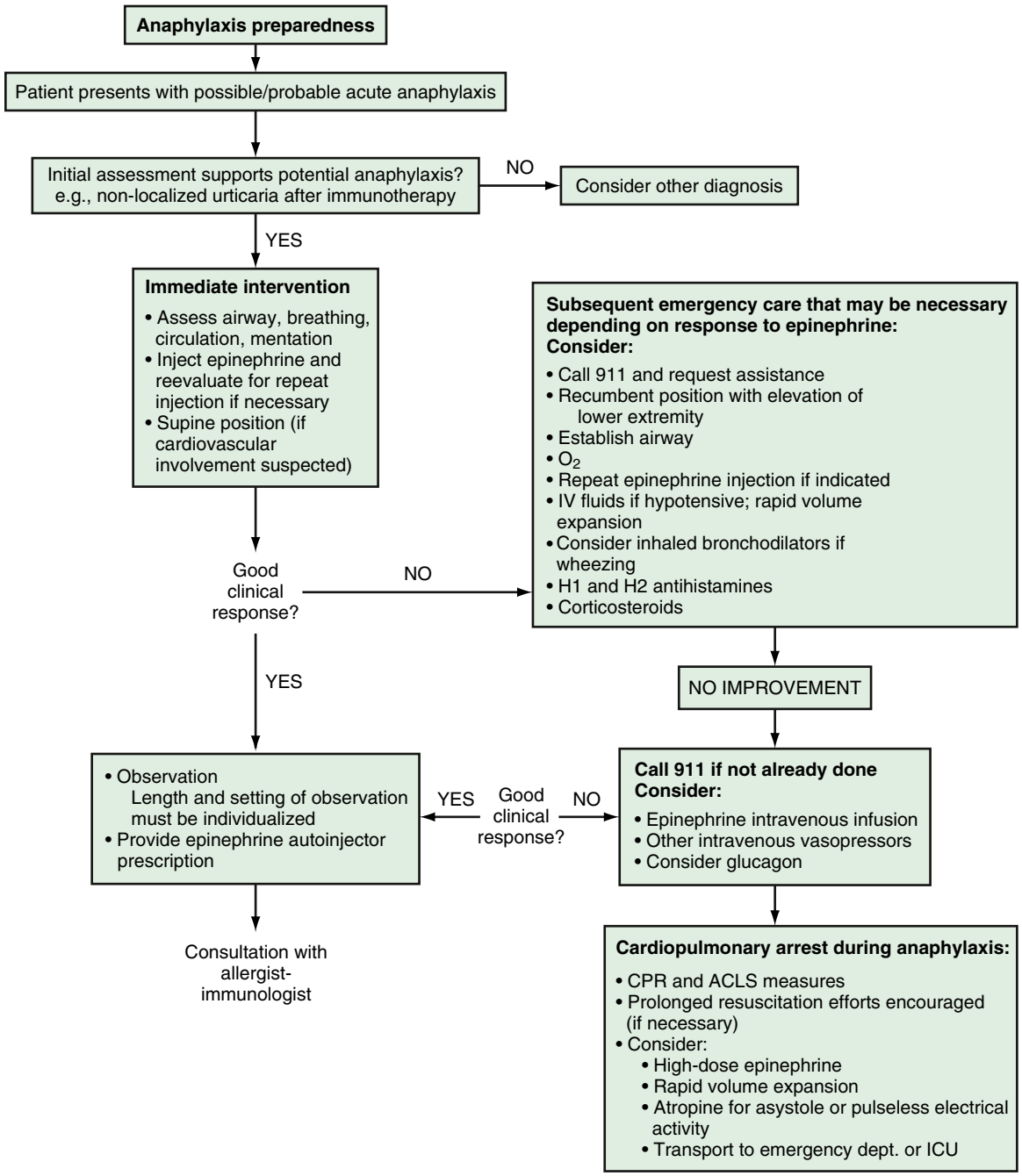

Fig. 190.3 Algorithm for treatment of anaphylactic event in outpatient setting. ACLS, Advance cardiac life support; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IV, intravenous. (*From Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126:477–480 e471-442.*)

may be needed. If IV access is not readily available, epinephrine can be administered via the endotracheal or intraosseous routes.

For refractory hypotension, other vasopressors may be needed. Anaphylaxis refractory to repeated doses of epinephrine in a patient receiving β-adrenergic blockers has anecdotally been treated with glucagon. The patient should be placed in a supine position when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis.

Patients may experience **biphasic anaphylaxis**, which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but more severe initial presentation and the need for more than one dose of epinephrine to treat initial symptoms are risk factors for biphasic anaphylaxis. Treatment with antihistamines or corticosteroids do not provide clear benefit for prevention of biphasic reactions. Extended observation after resolution of initial anaphylaxis symptoms should be considered for patients with risk factors for biphasic anaphylaxis. At discharge,

Table 190.6 Considerations with Epinephrine Injection for Anaphylaxis

WHY HEALTHCARE PROFESSIONALS FAIL TO INJECT EPINEPHRINE PROMPTLY

- Lack of recognition of anaphylaxis symptoms; failure to diagnose anaphylaxis
- Episode appears mild, or there is a history of previous mild episode(s)*
- Inappropriate concern about transient mild pharmacologic effects of epinephrine (e.g., tremor)
- Lack of awareness that serious adverse effects are almost always attributable to epinephrine overdose or IV administration, especially IV bolus, rapid IV infusion, or IV infusion of a 1:1,000 epinephrine solution instead of an appropriately diluted solution (1:10,000 concentration)

WHY PATIENTS AND CAREGIVERS FAIL TO INJECT EPINEPHRINE PROMPTLY

- Lack of recognition of anaphylaxis symptoms; failure to diagnose anaphylaxis
- Episode appears mild, or there is a history of previous mild episode(s)*
- H_1 antihistamine or asthma puffer is used initially instead, relieving early warning signs such as itch or cough, respectively
- Prescription for epinephrine autoinjectors (EAIs) is not provided by physician
- Prescription for EAIs is provided but not filled at pharmacy (e.g., not affordable)
- Patients do not carry EAIs consistently (due to size and bulk, or "don't think they'll need it")
- Patients and caregivers are afraid to use EAIs (concern about making an error when giving the injection or about a bad outcome)
- Patients and caregivers are concerned about injury from EAIs
- Competence in using EAIs is associated with regular allergy clinic visits; it decreases as time elapses from first EAI instruction; regular retraining is needed
- Difficulty in understanding how to use EAIs (15% of mothers with no EAI experience could not fire an EAI immediately after a one-on-one demonstration)
- Errors in EAI use can occur despite education, possibly related to the design of some EAIs

WHY PATIENTS OCCASIONALLY FAIL TO RESPOND TO EPINEPHRINE INJECTION

- Delayed recognition of anaphylaxis symptoms; delayed diagnosis
- Error in diagnosis: problem being treated (e.g., foreign body inhalation) is not anaphylaxis
- Rapid progression of anaphylaxis†

Epinephrine†:

- Injected too late; dose too low on mg/kg basis; dose too low because epinephrine solution has degraded (e.g., past the expiration date, stored in a hot place)
- Injection route or site not optimal; dose took too long to be absorbed
- Patient suddenly sits up or walks or runs, leading to the empty ventricle syndrome
- Concurrent use of certain medications (e.g., β-adrenergic blockers)

*Subsequent anaphylaxis episodes can be more severe, less severe, or similar in severity.
†Median times to respiratory or cardiac arrest are 5 min in iatrogenic anaphylaxis, 15 min in stinging-insect venom anaphylaxis, and 30 min in food anaphylaxis; however, regardless of the trigger, respiratory or cardiac arrest can occur within 1 min in anaphylaxis.
Adapted from Leung DYM, Szefler SJ, Bonilla FA Akdis CA, Sampson HA, eds. *Pediatric Allergy Principles and Practice*. Philadelphia: Elsevier; 2016: p. 531.

referrals should be made to appropriate specialists for further evaluation and follow-up.

PREVENTION

For patients experiencing anaphylactic reactions, the triggering agent should be avoided, and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma and a peanut, tree nut, fish, or shellfish allergy or a previous systemic reaction should be given an epinephrine autoinjector. The expert panel also indicates that epinephrine autoinjectors should be considered for any patient with IgE-mediated food allergy. In addition, liquid cetirizine (or alternatively, diphenhydramine) and a written emergency plan should also be provided in case of accidental ingestion or allergic reaction. A form can be downloaded from the American Academy of Pediatrics (www.aap.org) or Food Allergy Research & Education (www.foodallergy.org).

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-4 hours of ingesting the triggering food; children with exercise-induced anaphylaxis should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth, facial pruritus), and stop exercising and seek help immediately if symptoms develop. Foods associated with exercise-induced anaphylaxis include wheat, vegeas, nuts, fruits, and shellfish.

Children experiencing a systemic anaphylactic reaction, including respiratory symptoms, to an insect sting should be evaluated and treated with immunotherapy, which is >90% protective. Reactions to medications can be reduced and minimized by using oral medications instead of injected forms and avoiding cross-reacting medications. Low-osmolarity radiocontrast dyes and pretreatment can be used in patients with suspected reactions to previous radiocontrast dye. Nonlatex gloves and materials should be used in children undergoing multiple operations.

Any child at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications (Table 190.6), and a written emergency plan in case of accidental exposure. They should be encouraged to wear medical identification jewelry.

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Chapter 191

Serum Sickness

Anna H. Nowak-Wegrzyn and Scott H. Sicherer

Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 191.1).

ETIOLOGY

Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse, sheep, or rabbit are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (antithymocyte globulin [ATG]). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. However, rabbit-generated ATGs, which target human T cells, continue to be widely used as immunosuppressive agents during treatment of kidney allograft recipients; serum sickness is associated with a late graft loss in kidney transplant recipients. A **serum sickness–like reaction** may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor, trimethoprim-sulfamethoxazole, anticonvulsants, prolonged high-dose intravenous penicillin G), infections (streptococcal infections, hepatitis B), or rabies vaccine. In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

Table 191.1 Proteins and Medications That Cause Serum Sickness*

PROTEINS FROM OTHER SPECIES
Antibotulinum globulin
Antithymocyte globulin
Antitetanus toxoid
Antivenin (Crotalidae) polyvalent (horse serum based)
Crotalidae polyvalent immune Fab (ovine serum based)
Antirabies globulin
Infliximab
Rituximab
Etanercept
Omalizumab
Adalimumab
Natalizumab
Anti-HIV antibodies ([PE]HRG214)
Hymenoptera stings
Streptokinase
H1N1 influenza vaccine
Rabies vaccine
DRUGS
Antibiotics
Cefaclor
Penicillins
Trimethoprim sulfamethoxazole
Minocycline
Meropenem
Neurologic
Bupropion
Carbamazepine
Phenytoin
Sulfonamides
Barbiturates

*Based on review of the most current literature. Other medications that are not listed might also cause serum sickness.

Adapted from Aceves SS. Serum sickness. In: Burg FD, Ingelfinger JR, Polin RA, Gershon AA, eds. *Current Pediatric Therapy*. 18th ed. Philadelphia: Elsevier; 2006: p. 1138.

PATHOGENESIS

Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen-antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen-antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, because of the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to IgE or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

CLINICAL MANIFESTATIONS

The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 weeks afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous. Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions (Fig. 191.1). In a prospective study of serum sickness induced by administration of equine ATG, an initial rash was noted in most patients. It began as a thin, serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients the band of erythema was replaced by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 weeks of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 months. Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. **Serum sickness–like reactions** from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 weeks after drug exposure. The urticarial skin eruption becomes increasingly

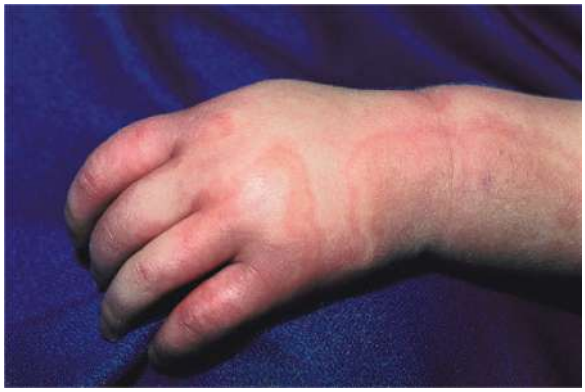

Fig. 191.1 Serum sickness–like reaction (SSLR). Note the swollen hand and large urticarial wheals in this girl with SSLR and arthralgias. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology. 5th ed. Philadelphia: Elsevier; 2016: p. 476.)*

erythematous as the reaction progresses and can evolve into dusky centers with round plaques. Serum sickness and serum sickness–like reactions are more likely to occur with higher doses and intermittent exposures of culprit antigens.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serum sickness and serum sickness–like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic-onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis, autoinflammatory syndromes, acute annular urticaria (urticaria multiforme), Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and erythema multiforme (see Chapters 193 and 686.2).

DIAGNOSIS

In most patients the diagnosis of serum sickness is made clinically based on the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit. Patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

- Complete blood count and differential: Thrombocytopenia is often present.
- Erythrocyte sedimentation rate (ESR) and C-reactive protein: ESR is usually elevated.
- Urinalysis: Mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
- Serum chemistries: Including blood urea nitrogen, creatinine, and liver function tests.
- Complement studies, including CH_{50}, C3, and C4: Serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
- Testing for specific infectious diseases: If indicated by the history or physical examination.
- Appropriate viral or bacterial cultures: If an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

TREATMENT

There are no evidence-based guidelines or controlled trials on which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory drugs and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day; maximum 60 mg/day) for 1-2 weeks is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 weeks. Symptoms lasting longer suggest another diagnosis.

PREVENTION

The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk/benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

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Chapter 192

Food Allergy and Adverse Reactions to Foods

Anna H. Nowak-Wegrzyn, Hugh A. Sampson, Amanda L. Cox, and Scott H. Sicherer

Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into **food intolerances** and **food allergies.** Food intolerances are nonimmunologic physiologic responses and can include metabolic, toxic, pharmacologic, or other mechanisms. **Food allergies** are adverse *immunologic* responses and can be IgE mediated, non–IgE mediated, or mixed (Tables 192.1 and 192.2). Food allergies appear to have increased over the past 3 decades, primarily in westernized/industrialized countries. Worldwide, estimates of food allergy prevalence range from 1–11% with regional variations. The vast majority of food allergies are due to peanut, tree nuts, seeds, milk, egg, soy, wheat, fish, and

Table 192.1 Adverse Food Reactions

FOOD INTOLERANCE (NON–IMMUNE SYSTEM MEDIATED, NONTOXIC, NONINFECTIOUS)
Host Factors
Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia, alcohol dehydrogenase deficiency
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)
Food Factors (Toxic or Infectious or Pharmacologic)
Infectious organisms—*Escherichia coli*, *Staphylococcus aureus*, *Clostridium perfringens*, *Shigella*, botulism, *Salmonella*, *Yersinia*, *Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics
FOOD ALLERGY
IgE Mediated
Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise-induced anaphylaxis
Mixed IgE Mediated and Non–IgE Mediated
Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma
Non–IgE Mediated
Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, Immunoglobulin E.

shellfish, with regional variations in prevalence. It has been estimated that 8–11% of children have food allergy, with 2.4% having multiple food allergies. Up to 6% of children experience food allergic reactions in the first 3 years of life, including approximately 2.5% with cow's milk allergy, 2% with egg allergy, and 2–3% with peanut allergy. Most children "outgrow" milk and egg allergies, with approximately 50% doing so by school-age. In contrast, 80–90% of children with peanut, tree nut, or seafood allergy retain their allergy for life (Table 192.3).

Table 192.2 Differential Diagnosis of Adverse Food Reactions

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)
Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
Enzyme deficiencies (primary or secondary)
Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
Galactosemia
Malignancy with obstruction
Other: pancreatic insufficiency (cystic fibrosis), peptic disease
CONTAMINANTS AND ADDITIVES
Flavorings and preservatives—rarely cause symptoms
Sodium metabisulfite, monosodium glutamate, nitrites
Dyes and colorings—very rarely cause symptoms (urticaria, eczema)
Tartrazine
Toxins
Bacterial, fungal (aflatoxin), fish related (scombroid, ciguatera)
Infectious organisms
Bacteria (*Salmonella, Escherichia coli, Shigella*)
Virus (rotavirus, enterovirus)
Parasites (*Giardia,* Akis simplex [in fish])
Accidental contaminants
Heavy metals, pesticides
Pharmacologic agents
Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)
PSYCHOLOGIC REACTIONS
Food phobias

GENETIC AND ENVIRONMENTAL RISK FACTORS

Allergic sensitization and food allergy development is influenced by genetics, environment, and genome-environment interactions (possible epigenetic effects). Family and twin studies show that family history confers a 2- to 10-fold increased risk, depending on the study setting, population, specific food, and diagnostic test. Candidate gene studies suggest that genetic variants in the HLA-DQ locus (HLA-DQB1*02 and DQB1*06:03P), filaggrin, interleukin (IL)-10, *STAT6*, and *FOXP3* genes are associated with food allergy, although the results are inconsistent across different populations. In a genome-wide association study, differential methylation at the HLA-DR and -DQ regions was associated with food allergy. Epigenetic studies implicate DNA methylation effects on IL-4, -5 and -10, and interferon (IFN)-γ genes and in the mitogen-activated protein kinase (MAPK) pathway.

Many environmental factors have been observed to influence the development of food allergy. Skin exposure to foods in the setting of infantile eczema, characterized by impaired skin barrier and inflammation, can lead to sensitization and allergy. Decreased microbial exposure ("hygiene hypothesis"), decreased microbiome diversity, and the specific makeup of microbial communities in the gastrointestinal (GI) tract, airway, and skin, influence allergic conditions, including food allergy (see Chapter 182). Additional environmental factors that may be associated with increased risk of food allergy include reduced diversity of the diet, delayed introduction of allergenic foods, vitamin D deficiency, and other factors.

PATHOGENESIS

Food intolerances are the result of a variety of nonimmunologic mechanisms, whereas food allergy is predominantly caused by IgE-mediated and cell-mediated immune mechanisms. In food allergy, normal physiologic oral tolerance of food, which is induced largely by regulatory T cells (Tregs) and the microbiome of the gut mucosa, breaks down. Susceptible individuals exposed to certain allergens generate food-specific IgE antibodies that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells, resulting in allergic sensitization. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells, basophils, and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. During acute IgE-mediated reactions, mast cell and basophil

Table 192.3 Natural History of Food Allergy

FOOD	USUAL AGE AT ONSET OF ALLERGY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	5 yr (76% of cases resolve)*
Peanut	1-2 yr	Persistent (20% of cases resolve)
Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Persistent†
Shellfish (crustacean)	Adulthood (in 60% of patients with this allergy)	Persistent
Wheat*	6-24 mo	5 yr (80% of cases resolve)
Soybean*	6-24 mo	2 yr (67% of cases resolve)
Kiwi	Any age	Unknown
Apple, carrot, and peach‡	Late childhood and adulthood	Unknown

*Studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A/L.
†Fish allergy that is acquired in childhood can resolve.
‡Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is typically caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.
Adapted from Lack G. Food allergy. *N Engl J Med.* 2008;359:1252–1260.

degranulation elicits symptoms that can affect the skin (urticaria, angioedema, flushing, pruritus), GI tract (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), respiratory tract (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and cardiovascular system (dysrhythmias, hypotension, loss of consciousness). In non-IgE food allergies, lymphocytes, primarily food allergen–specific T cells, secrete excessive amounts of various cytokines that lead to a "delayed," more chronic inflammatory process affecting the skin (pruritus, erythematous rash), GI tract (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), and respiratory tract (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders, such as atopic dermatitis, asthma, eosinophilic esophagitis (EoE), and eosinophilic gastroenteritis.

Children who develop IgE-mediated food allergies may be sensitized by food allergens penetrating the inflamed skin barrier, e.g., eczema, or GI barrier (referred to as **class 1 food allergens**), or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract (referred to as **class 2 food allergens**). Any food may serve as a class 1 food allergen, but *egg, milk, peanuts, tree nuts, seeds, fish, soy,* and *wheat* account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Class 2 food allergens are typically vegetable, fruit, or nut proteins that are partially homologous to pollen proteins. With the development of seasonal allergic rhinitis from birch/oak, grass, ragweed, or mugwort weed pollens, subsequent ingestion of certain nuts, uncooked fruits, or vegetables provokes the **pollen-food allergy syndrome (also called oral allergy syndrome)**. *Intermittent ingestion* of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas *prolonged exposure* may lead to poor control of chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1 allergens.

The **galactose-α-1,3-galactose (alpha-gal) syndrome** is an IgE-mediated allergy to a carbohydrate allergen, and manifests as delayed allergic reactions 2-6 hours after ingestion of mammalian meats (pork, beef, lamb, venison) and rarely gelatin or milk. Sensitization occurs after multiple tick bites, in particular by the lone star tick *(Amblyomma americanum)*. This unique form of food allergy is seen more often in teenagers and adults.

CLINICAL MANIFESTATIONS

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 192.4) and immune mechanism (see Table 192.1).

Gastrointestinal Manifestations

GI food allergies are often the first form of allergy to affect infants and young children and typically manifest as irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as skin-prick tests and in vitro tests for food-specific IgE antibodies of little diagnostic value. The non–IgE-mediated GI food-allergic disorders food protein–induced enterocolitis syndrome (FPIES), food protein–induced allergic proctocolitis (FPIAP), and eosinophilic GI disorders are discussed in Chapter 192.1.

Pollen-food allergy syndrome (oral allergy syndrome) is an IgE-mediated hypersensitivity to certain uncooked or unprocessed plant-based foods that occurs in many older children who have pollen-induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus; tingling and angioedema of the lips, tongue, palate, and throat; and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short-lived and are caused by local mast cell activation following contact with fresh raw fruit and vegetable proteins that cross react with birch tree pollen (including but not limited to apple, carrot, potato, celery, hazelnuts, peanuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi),

Table 192.4 Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough Dyspnea Wheezing
Gastrointestinal (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
Gastrointestinal (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Other	Uterine contractions Sense of "impending doom"	

From Boyce JA, Assa'ad A, Burks AW, et al. Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010;126(6):S1–S58. Table IV, p. S19.

mugwort weed pollen (celery, fennel, mustard, peach), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

Acute GI allergy generally manifests as acute abdominal pain, vomiting, or diarrhea that accompanies IgE-mediated allergic symptoms in other target organs.

Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronic relapsing course, and association with asthma and allergic rhinitis (see Chapter 186). Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have IgE-mediated food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a pathogenic role in the disorder. Atopic dermatitis is a risk factor for the development of food allergy rather than a result of food allergy.

Acute urticaria and angioedema are among the most common symptoms of food allergic reactions (see Chapter 189). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly implicated in children include egg, milk, peanuts, and tree nuts, although reactions to various seeds (sesame, sunflower, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are very rarely caused by food allergies. **Contact urticaria** may occur in the perioral region of infants and young children, especially in those with eczema, when otherwise tolerated food causes small, self-resolving hives on direct skin contact while eating. In the absence of any other symptoms, food exclusion is not generally needed and the rash could be avoided by wiping the face during feeding or using a barrier ointment (such as petroleum jelly) in the perioral area before feeding.

Perioral dermatitis is a contact dermatitis often caused by substances in toothpaste, gums, lipstick, or medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoic acid in the food. It may also occur in nursing infants. In both situations the effect is benign. Flushing may also be caused by **auriculotemporal nerve (Frey) syndrome** (familial, forceps delivery), which resolves spontaneously.

Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe nasal congestion in infants to be caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periocular pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only 10% of asthmatic patients have food-induced respiratory symptoms.

Anaphylaxis

Anaphylaxis (see Chapter 190) is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the most common cause of anaphylaxis seen in U.S. hospital emergency departments. Fatal food-induced anaphylaxis is rare, with death affecting 0.03-0.3 per million per year. In addition to the rapid onset of cutaneous, respiratory, and GI symptoms, patients with anaphylaxis may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-dependent exercise-induced anaphylaxis** is a special form of acute IgE-mediated food allergy in which moderate intensity exercise performed within a few hours of ingestion of a particular food, most commonly wheat or shellfish, results in anaphylaxis but when ingested without exercise, there is no allergic reaction.

DIAGNOSIS

A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse food reaction (see Table 192.2), whether it is an intolerance or food allergic reaction, and, if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response (Fig. 192.1). An understanding of the basic pathophysiology and clinical presentations of different adverse food reactions is essential and if allergy is suspected, referral to an allergist-immunologist is recommended. The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, because most reactions occur within minutes to 2 hours of ingestion, (3) the types of symptoms elicited by the ingestion, which may suggest the pathophysiology of the adverse reaction, (4) whether ingesting the suspected food produced similar symptoms on other occasions because reproducibility is expected, (5) whether other inciting factors, such as exercise, are necessary, and (6) time interval since last reaction to the food because evaluation for potential resolution of the allergy may be warranted.

Skin-prick tests and in vitro laboratory tests are useful for demonstrating *IgE sensitization,* defined as presence of food-specific IgE antibodies. **Sensitization alone is not diagnostic of a food allergy.** In general, increasingly higher serum food-specific IgE levels or increasingly large skin-test wheal size (especially >8 mm diameter) indicate a higher chance of clinical allergy. A negative serum food-specific IgE test or skin test result virtually excludes an IgE-mediated form of food allergy. In limited studies, serum food-specific IgE levels ≥15 kU_A/L for milk (≥5 kU_A/L for children ≤1 year), ≥7 kU_A/L for egg (≥2 kU_A/L for children <2 years), and ≥14 kU_A/L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected allergy. Evaluation of IgE-binding to specific digestion-resistant allergens that trigger reactions or labile proteins unlikely to cause significant reactions in a food, termed molecular or **component-resolved diagnostic (CRD) testing**, can provide additional clinically relevant information. Identification of sensitization to digestion-resistant proteins (components) in the foods correlates with a greater chance of systemic allergic reactions. Examples of tests for digestion-resistant proteins include Ara h 1, 2, 3, and 6 for peanut; Jug r 1 and Jug r 3 for walnut; Ana o 3 for cashew; Ber e 1 for Brazil nut; and Cor a 9 and Cor a 14 for hazelnut. Ara h 8 in peanut is a labile, birch pollen–related protein generally not associated with significant allergic reactions, and isolated sensitization to this component is typically associated with no or only mild oral reactions.

Importantly, most children with positive serum food-specific IgE or skin test responses do not react when the food is ingested. It is therefore crucial to avoid indiscriminate testing (i.e., sending panels of food tests). In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, and/or a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Table 192.5). When the earlier diagnostic modalities are not definitive,

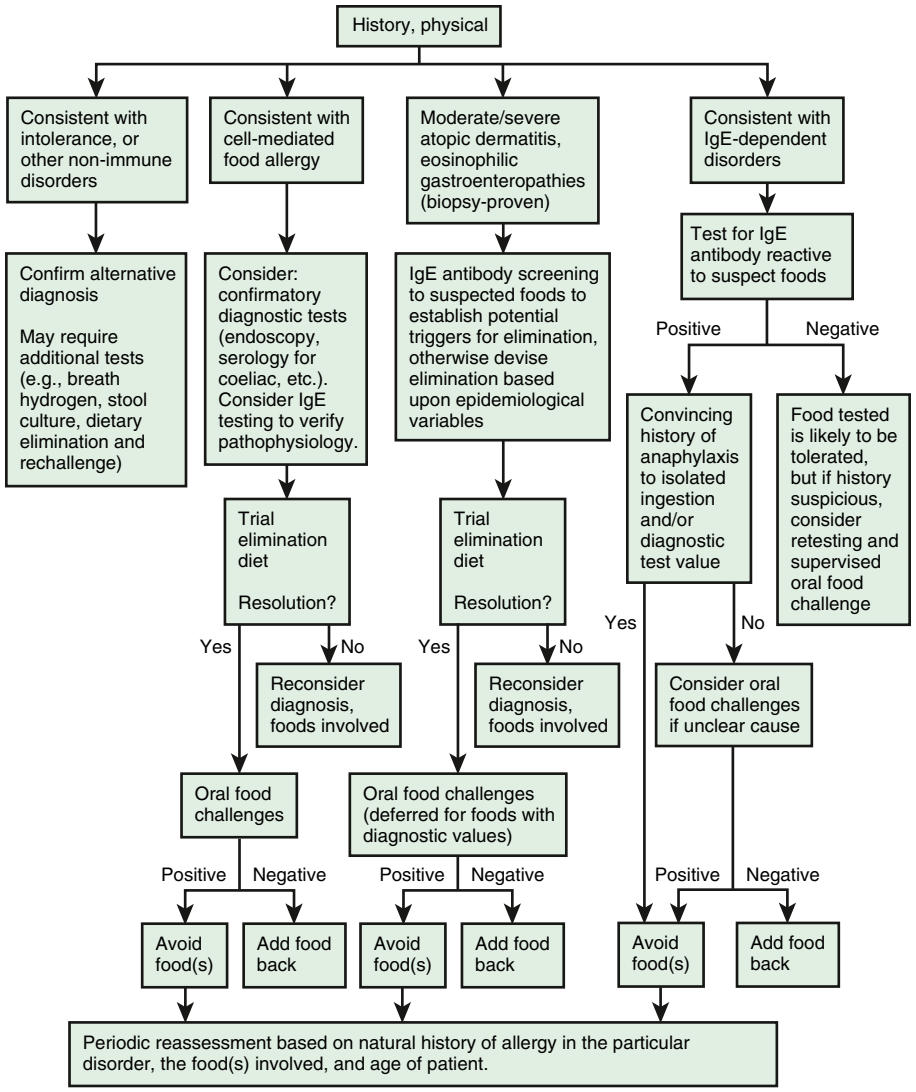

Fig. 192.1 Algorithm for diagnosis of food allergy. *(From Sicherer SH. Food allergy. Lancet. 2002;360:701–710.)*

Table 192.5 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)	FEATURE(S)
Legumes	5–50	If allergic to peanut, 5-20% likelihood of allergy to other legumes (lupine, green bean, green pea, soy) If allergic to chickpea (garbanzo bean), >50% likelihood of allergy to lentil and/or pea.
Tree nuts (e.g., almond, cashew, hazelnut, walnut, Brazil)	15–33	Reactions are often severe
Fish	50	Reactions can be severe
Shellfish (crustaceans)	75 (other crustaceans) 50 (mollusks)	Reactions can be severe
Grains	20	Wheat shows cross-reactivity with barley and rye
Mammalian milks	90	Cow's milk is highly cross reactive to goat's or sheep's milk (92%) but not with mare's milk (4%)
Rosaceae (pitted fruits)	55	Risk of reactions to >3 related foods is very low (<10%); symptoms are usually mild (pollen food allergy syndrome)

Modified from Sicherer SH. Food allergy. *Lancet.* 2002;360:701–710.

which is a common scenario, oral food challenges (OFCs), observed incremental feedings of a food performed under physician supervision, are useful in ruling out or confirming the presence or resolution of a food allergy. *Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges.*

There are no laboratory studies to help identify foods that are already in the diet but may be responsible for non–IgE and cell-mediated food reactions. Consequently, elimination diets followed by OFCs are the only way to establish the diagnosis. This approach may be recommended for atopic dermatitis, eosinophilic GI diseases, and some forms of contact dermatitis. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 weeks for some cell-mediated disorders, such as EoE (see Chapter 192.1). Some children with cell-mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

TREATMENT

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the most established and validated management strategies for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organizations Food Allergy Research and Education (FARE; www.foodallergy.org) and the Asthma & Allergy Foundation of America (Kids with Food Allergies Division; www.kidswithfoodallergies.org/recipes-diet.aspx) provide excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Egg allergy is not a contraindication for vaccination with measles, mumps, rubella, or influenza vaccines, but remains a concern for the yellow fever vaccine where referral to an allergist is recommended.

Children at risk of food-induced anaphylaxis should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 190). Because many food allergies resolve, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are evaluating the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies. Immunotherapy is not typically curative but aims to provide temporary "desensitization," or an increase in the threshold of a food that can be consumed without triggering an allergic reaction. Success depends on continuous treatment exposure. An FDA-approved peanut oral immunotherapy (OIT) agent is commercially available for use in children. Combining OIT with anti-IgE treatment (omalizumab) or other biologic agents is under study and may improve safety or efficacy compared to OIT alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg–allergic children. Regular ingestion of baked products with milk and egg may accelerate resolution of milk and egg allergy.

PREVENTION

It was once thought that avoidance of allergenic foods and delayed introduction to the diet would prevent allergy, but the opposite is probably true; delayed introduction of these foods may increase the risk of allergy, especially in children with atopic dermatitis. A trial of early introduction of dietary peanut randomized 640 infants age 4-11 months with severe eczema, egg allergy, or both to consume or avoid peanut until the age 60 months. The early introduction of peanut dramatically decreased the development of peanut allergy among children at high risk for this allergy. A theory behind this approach is that early oral introduction of peanut induces oral tolerance that precedes the potential sensitization to peanut that can occur with environmental exposure to peanut via the inflamed, disrupted skin barrier seen in infants with eczema. Infants with severe eczema or egg allergy in the first 4-6 months of life might benefit from evaluation by an allergist or physician trained in management of allergic diseases to diagnose any food allergy and assist in promptly implementing appropriate early peanut introduction. For this high-risk group, the clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response or serum peanut-specific IgE >0.35 kU_A/L to determine whether they are clinically reactive before initiating at-home introduction of infant-safe forms of peanut. Additional details for the early introduction of peanut are available from the National Institute of Allergy and Infectious Diseases (NIAID).* Analyses of several early introduction studies have shown that early egg introduction may be associated with reduced egg allergy, while review of data for other allergenic foods is not conclusive. There is however no evidence that delaying the introduction of typically allergenic foods prevents food allergy or other allergic diseases.

There is no compelling evidence to support the practice of restricting the maternal diet during pregnancy or while breastfeeding, or for delaying introduction of various allergenic foods to infants from atopic families. Exclusive breastfeeding for the first 4-6 months of life is strongly encouraged but has not been shown to reduce the development of food allergies. Potentially allergenic foods (eggs, milk, wheat, soy, peanut/tree nut products, fish) should be introduced and maintained in the diet in infant-appropriate forms after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Recent meta-analyses have not supported the use of hydrolyzed infant formulas in cases where breastfeeding cannot be continued for 4-6 months or after weaning to prevent eczema or food allergies in high-risk families. Modulation of the microbiome with probiotics has been an area of interest, where it may affect oral tolerance induction; however, specific interventions have not been proven effective. Probiotic supplements in the third trimester and to the newborn infant may reduce the incidence and severity of eczema, but have not demonstrated effects on food allergy prevention. Other potential influences on the infant/child microbiome are currently being studied, including mode of delivery (vaginal vs C-section), diet diversity, vitamin D supplementation, and household pet exposure. With the recognition that infantile eczema increases the risk of allergic sensitization and food allergy, attention has also focused on early skin care and aggressive treatment of infantile eczema as potential preventive measures. Because some **skin preparations** contain peanut or nut oils, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided. Table 192.6 summarizes approaches to food allergy prevention.

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Table 192.6 Approaches to Prevention of Food Allergy

RECOMMENDED
Infant-safe forms of peanut, egg introduced around age 6 mo, not before 4 mo
Other allergens may be introduced around this time as well
Allergy testing before introduction not usually needed (see text)
Infants with severe eczema or egg allergy may benefit from evaluation for early peanut introduction at 4-6 mo
Diverse infant diet
UNPROVEN/NOT RECOMMENDED
Hydrolyzed formulas
Maternal allergen avoidance during pregnancy or lactation
Purposeful delay in introducing allergens to infants

* https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy..

192.1 Non-IgE Gastrointestinal Food Allergy Disorders

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CLINICAL MANIFESTATIONS

GI food allergies are often the first form of allergy to affect infants and young children, and typically manifest as chronic irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement (non-IgE) predominate, making standard allergy tests such as skin-prick tests and in vitro tests for food-specific IgE antibodies of little diagnostic value (Table 192.7).

FPIES is a non-IgE, cell-mediated food allergy that can have dramatic GI symptoms and in its severe form is considered an allergic emergency. FPIES can present as acute or chronic phenotypes (Fig. 192.2).

EPIDEMIOLOGY

Prevalence: The prevalence of FPIES ranges between 0.34% and 0.7% of infants in Israel and Spain; in a population-based survey, physician-diagnosed FPIES was reported in 0.51% (95% confidence interval [CI]; 0.420.62) of U.S. children.

Food triggers: Globally, cow's milk is the most common trigger of FPIES, although in countries with higher rates of breastfeeding rather than formula feeding, complementary foods introduced into infants' diets early are also reported. Commonly reported triggers include soy, oat, rice, vegetables (avocado, sweet potato), fruits (banana), egg, fish, chicken, turkey, peanut, tree nuts, and fish. Most infants (50–75%) react to one food; however, about 10–15% report more than three food triggers.

Pathophysiology: FPIES is characterized by a strong inflammatory response with significant elevation of CRP, neutrophils, and platelets. There is evidence of innate immune compartment activation (monocytes, neutrophils) along with the pan-activation of T lymphocytes and significant elevation in levels of various cytokines and chemokines in the peripheral blood, including IL-17A, IL-22, IL-17C, and tumor necrosis factor (TNF)-α, and a preferential activation of nonconventional T-cell populations, including γδT cells.

Clinical manifestations: FPIES typically manifests in the first year of life in an **acute** form as projectile, repetitive vomiting within 1-4 hours of food ingestion, frequently accompanied by lethargy, pallor (or dusky appearance), and low muscle tone; in a smaller subset, vomiting is followed by watery diarrhea in 5-10 hours (see Fig. 192.2). Prolonged ingestion of the causal allergen may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive, referred to as **chronic FPIES.** Acute FPIES is considered to be an allergic emergency because hypotension occurs in approximately 5–10% of patients after allergen ingestion, which initially may be attributed to sepsis.

Diagnosis: Acute FPIES is diagnosed based on the recognition of a constellation of symptoms, (Table 192.8; see Fig. 192.2) and allergy tests detecting food-specific IgE are typically negative. OFCs are rarely required for the confirmation of the initial diagnosis, but are utilized for evaluating resolution of FPIES. Chronic FPIES is diagnosed based on the chronic GI symptoms that resolve within days to weeks following elimination of the allergen and recur acutely within 1-2 hours following a subsequent feeding.

Differential diagnosis: The differential diagnosis includes GI infections (viral, bacterial), sepsis, necrotizing enterocolitis, metabolic disorders that induce emesis and lethargy (hyperammonemias, organic acidemias, congenital adrenal hyperplasia), very early onset inflammatory bowel disease and other immune enteropathies (IPEX), gastroesophageal reflux (GER) disease, ileus, anatomical small bowel obstruction, celiac disease, anaphylaxis, cyclic vomiting syndrome, poisoning, pyloric stenosis, seizures, and primary immunodeficiencies.

Emergency management: Severe FPIES reactions are considered allergic emergencies due to the risk of hypotension (in extreme cases, hypovolemic shock), dehydration, and metabolic derangements including acidemia and methemoglobinemia (Fig. 192.3). Acute management entails vigorous intravenous hydration. Additional therapies include intravenous or intramuscular ondansetron as an antiemetic, and a single dose of steroid (e.g., methylprednisolone) may be administered due to a strong inflammatory response. Mild to moderate reactions can be managed with oral rehydration and oral ondansetron. Epinephrine autoinjectors and oral antihistamines are not prescribed for home management; however, vasopressors may be used for treatment of shock in the medical setting.

Dietary management: Breastfeeding mothers rarely need to restrict the foods that trigger symptoms in an infant following direct feeding, unless the infant exhibits symptoms of acute or chronic FPIES during breast milk feeding or has impaired growth. Hypoallergenic infant formulas (extensively hydrolyzed or amino acid) are recommended in non-breastfed infants to avoid cow's milk and soy. Timely introduction of solids is important for nutrition and for the development of oromotor skills. Following acute FPIES reactions to a solid food, foods from an unrelated food group can be chosen for introduction. Tolerance to one food from a food group usually indicates a favorable likelihood of tolerance to the related foods. Table 192.9 discusses practical guidelines for dietary management of FPIES.

Monitoring for resolution: The natural history of infantile FPIES is favorable, with the majority becoming tolerant by 3-5 years of age; persistent FPIES is rare. FPIES to fish and shellfish may start in older children and in adults; the natural history of adult FPIES is unknown. Reintroduction of foods that have caused FPIES is usually done during a physician-supervised OFC. Timing of reintroduction varies based on the nutritional and social importance of the foods; usually attempts are done 6-24 months following the most recent FPIES reaction to the offending food. FPIES induced by cow's milk may (~10%) evolve into IgE-mediated food allergy.

Comorbidities: FPIES is associated with an increased risk of IgE-mediated food allergy to other foods, atopic dermatitis, allergic rhinitis, asthma, and EoE.

FPIAP presents in the first few months of life as blood-streaked stools in otherwise healthy infants that are breastfed and/or formula-fed (see Table 192.7). Blood loss is typically mild, but can occasionally result in anemia. The most commonly implicated dietary triggers are cow's milk and soy proteins, followed by egg; their elimination, either by maternal dietary restriction if breastfeeding or by use of hypoallergenic formulas, leads to symptom and gross blood resolution within 48-72 hours in most infants. FPIAP is diagnosed clinically based on the presence of blood in the stool; sigmoidoscopy with biopsy, confirming an eosinophilic inflammatory response, is no longer done in routine practice for diagnosis of FPIAP. Blood in the infant's stool can be attributed to multiple causes other than food allergy (see Table 192.7). Therefore diagnosis based on clinical observation carries the risk of overdiagnosis (especially when FPIAP is diagnosed based on detection of microscopic blood in stool) and unnecessary dietary restrictions resulting in delayed introduction of foods and an associated increased risk of developing IgE sensitization. Therefore, considering benign, nonspecific nature of the symptoms and favorable natural history, in cases of mild to moderate FPIAP, many authorities recommend a trial of the culprit food 2-3 months following symptom resolution to determine whether the infant has "outgrown" the sensitivity.

Table 192.7 Food Protein–Induced Gastrointestinal Syndromes

	FPIES	FPIAP	FPE	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day to 1 year, later for fish and shellfish	1 day to 6 months	Dependent on age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
FOOD PROTEINS IMPLICATED				
Most common	Cow's milk, egg, oat, rice	Cow's milk, soy	Cow's milk, soy	Cow's milk, wheat, egg white, soy, peanut, seafood
Less common	Soy, chicken, turkey, fish, pea, peanut, avocado, sweet potato	Egg	Wheat, egg	Meats, corn, rice, fruits, vegetables, legumes
Multiple food hypersensitivities	>50% both cow's milk and soy if younger than 6 mo; 40–50% react to more than one grain, 30% react to more than one fish	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breastfeeding	Formula	Formula
ATOPIC BACKGROUND				
Family history of atopy	40–70%	25%	Unknown	~50% (often history of EoE)
Personal history of atopy	30%	22%	22%	~50%
SYMPTOMS				
Emesis	Projectile, repetitive, severe	No	Intermittent	Intermittent
Diarrhea	Severe in chronic FPIES	No	Moderate	Moderate
Bloody stools	Occasionally severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Differential diagnosis	Infection: viral, bacterial Necrotizing enterocolitis, GI obstruction (ileus, pyloric stenosis, Meckel diverticulum); gastroesophageal reflux disease; very early onset inflammatory bowel disease, seizure disorder, metabolic disorder, cardiac disease, anaphylaxis	Rectal fissure, bleeding disorder, vit K deficiency, GI infection e.g., *Shigella*, inflammatory bowel disease	Celiac disease, primary immunodeficiency, inflammatory bowel disease	Gastroesophageal reflux disease, recurrent vomiting due to other causes, parasitic and fungal infections, congenital rings, Crohn disease, periarteritis, allergic vasculitis, connective tissue diseases, bullous pemphigoid, pemphigoid vegetans, graft-versus-host disease, achalasia, drug hypersensitivity, celiac disease, vasculitis, carcinoma, hypereosinophilic syndrome
LABORATORY FINDINGS				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
ALLERGY EVALUATION				
Food skin-prick test	Majority negative†	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Majority negative†	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
BIOPSY FINDINGS				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation, and basal zone hyperplasia
Food challenge	Emesis in 1-4 hr; diarrhea in 5-8 hr (in a subset)	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge under supervision in 0.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate; resume/continue breastfeeding on maternal antigen-restricted diet; reintroduce at home after 9-12 mo of age	Protein elimination, symptoms clear in 1-3 wk; rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent (>90%) response to elemental diet; symptoms clear in 2-3 wk, excellent acute response to oral steroids but with high rate of relapse following discontinuation; in EoE 30–50% response to proton pump inhibitors, 70% to swallowed corticosteroids; rechallenge by introducing food at home and biopsy in 1-2 yr

Continued

Table 192.7 Food Protein–Induced Gastrointestinal Syndromes—cont'd

	FPIES	FPIAP	FPE	EOSINOPHILIC GASTROENTEROPATHIES*
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 mo	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Supervised food challenge	At home, gradually advancing from 1 oz to full feedings over 2 wk	Home, gradually advancing	Home, gradually advancing

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, and gastroenterocolitis.
†If positive, may be a risk factor for persistent disease, referred to as "atypical" FPIES.
FPIES, Food protein–induced enterocolitis syndrome; FPIAP, food protein–induced allergic proctocolitis; FPE, food protein–induced enteropathy; GI, gastrointestinal; EoE, eosinophilic esophagitis.

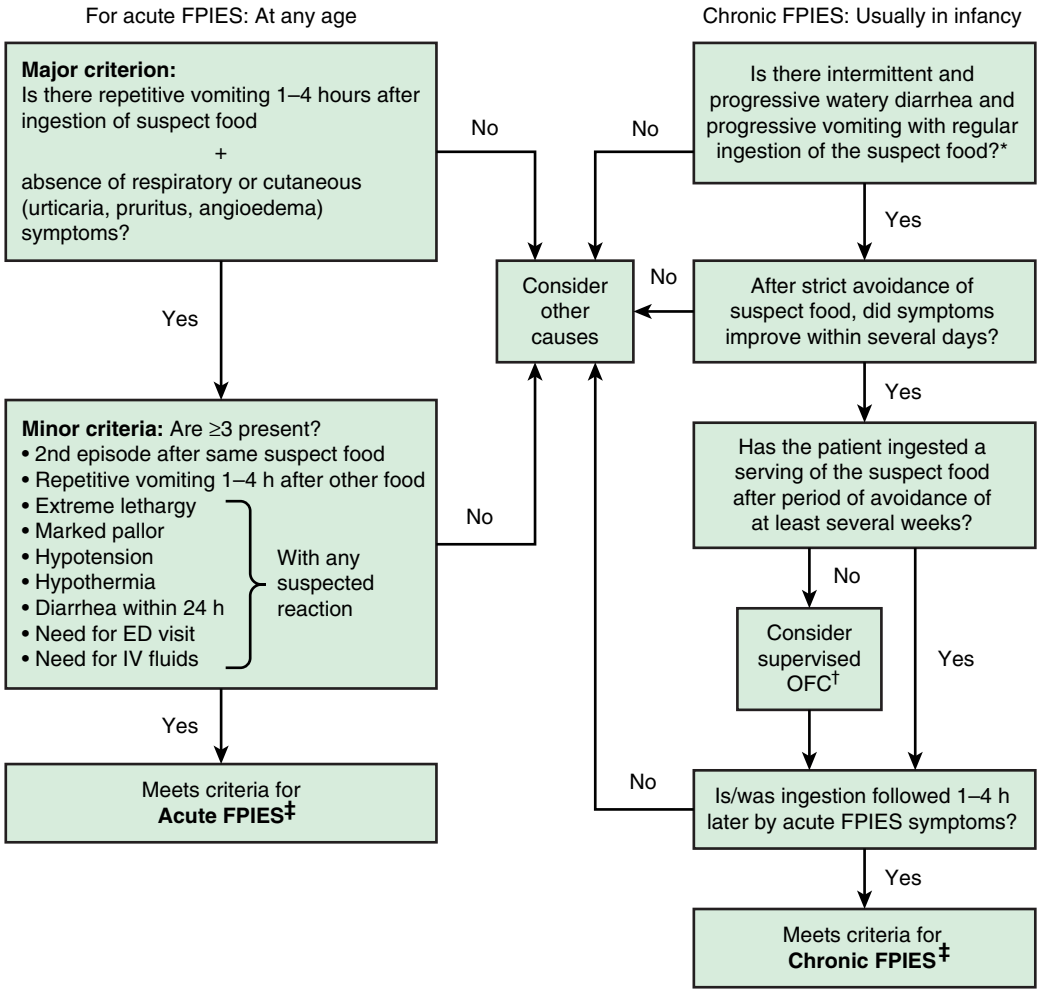

Fig. 192.2 Diagnostic algorithm for food protein–induced enterocolitis syndrome (FPIES). ED, Emergency department; IV, intravenous; OFC, oral food challenge. *Chronic FPIES is described almost exclusively with cow's milk or soy in young infants. †Without a confirmatory OFC or other ingestion with emesis onset in 1-4 hours, diagnosis of chronic FPIES is presumptive. ‡Based on Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2017;139:1111–1126. *(From Sicherer SH, Nowak-Węgrzyn A. Enterocolitis, proctocolitis, and enteropathies. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021: Fig. 33.2.)*

Table 192.8 FPIES Diagnostic Criteria

ACUTE FPIES*	
MAJOR CRITERIA (BOTH MUST BE MET), PLUS	MINOR CRITERIA (≥3 OCCURRING WITH EPISODE)
• Vomiting 1-4 hr after suspect food ingestion • Absence of immediate, IgE-mediated allergic symptoms (hives, itching, swelling, wheezing, cough)	• ≥2 episodes with same food • One episode with a different food • Lethargy • Pallor • Need for ER visit • Need for IV fluid support • Diarrhea within 24 hr (usually 5-10 hr) • Hypotension • Hypothermia
CHRONIC FPIES†	
SYMPTOMS AND SEVERITY	CRITERIA
Milder (lower doses with intermittent ingestion): • Intermittent vomiting and/or diarrhea • Growth faltering • No dehydration or metabolic acidosis **Severe** (higher doses with chronic ingestion): • Intermittent but progressive vomiting and watery diarrhea (occasionally with blood) • Poor weight gain or failure to thrive • Possible dehydration and metabolic acidosis, anemia, hypoproteinemia, neutrophilia, thrombocytosis	• Resolution of symptoms within days to weeks after elimination of offending food(s) • Acute recurrence of symptoms (vomiting in 1-4 hr, diarrhea in <24 hr, usually 5-10 hr) when the food is reintroduced, following a period of elimination • Confirmatory OFC required for conclusive diagnosis; if OFC not performed diagnosis remains presumptive

*Major criterion must be met (both) plus at least three minor criteria.
†General criteria because of paucity of available data.
FPIES, Food protein–induced enterocolitis syndrome; ER, emergency room; IV, intravenous; OFC, oral food challenge.
Adapted from Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111–1126.e4.

Food protein–induced enteropathy (FPE) often manifests in the first several months of life as diarrhea, often with steatorrhea and poor weight gain (see Table 192.7). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally. **Cow's milk sensitivity** is the most common cause of FPE in young infants, but it has also been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease**, the most severe form of FPE, occurs in about 1 per 100 of the U.S. population, although it may be "silent" in many patients (see Chapter 384). The classic form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

EoE may present from infancy through adolescence, more frequently in boys (see Chapter 370). EoE is a cell-mediated disorder, which is often associated with IgE-mediated food allergies in infants and young children, and manifests as chronic GER, intermittent emesis, food refusal, abdominal pain, dysphagia, food impaction, irritability, sleep disturbance, and failure to respond to conventional GER medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are seen on esophageal biopsies. Treatment is possible with elimination of dietary allergens but management with medications is typically included (see Chapter 370). **Eosinophilic gastritis and gastroenteritis** are additional **eosinophilic GI disorders** that are far less common and can occur at any age. **Eosinophilic gastritis** often presents with nausea and abdominal pain or bloating, while **eosinophilic enteritis** may also present with nausea, abdominal pain or bloating with additional diarrhea, anemia, or protein loss. **Eosinophilic colitis** may present with loose stool or blood in stool associated with abdominal cramping/pain. More than 50% of patients with these disorders are atopic; however, food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked **protein-losing enteropathy**.

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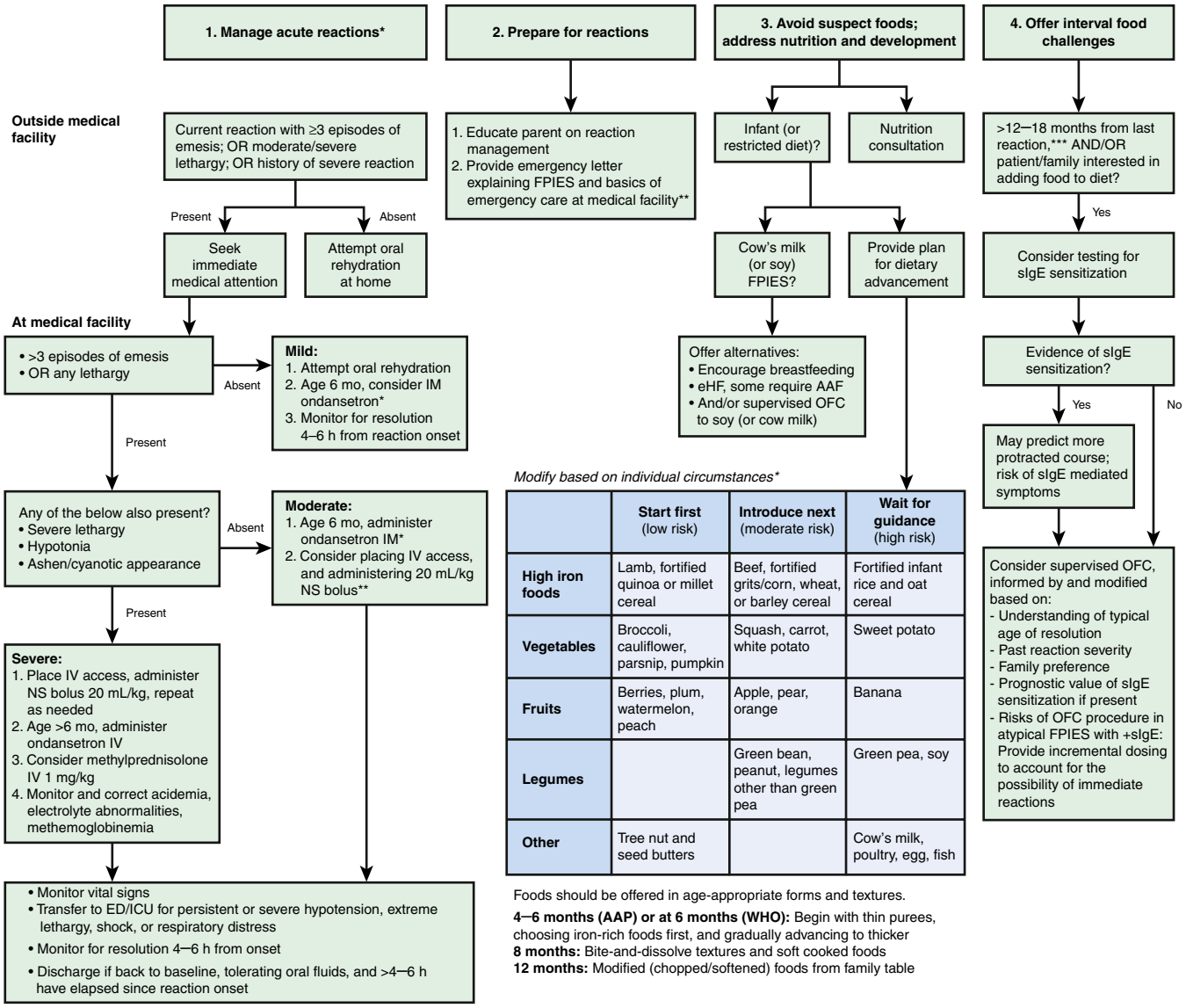

*0.15 mg/kg/dose; maximum, 16 mg
AAF, amino acid–based formula
ED, emergency department
FPIES, food protein–induced enterocolitis syndrome
ICU, intensive care unit
IM, intramuscular
IV, intravenous
mo, months
NS, normal saline
OFC, oral food challenge
sIgE, specific immunoglobulin E
WHO, World Health Organization

** Template may be downloaded at https://www.fpies.org/wp-content/uploads/2018/08/IFPIES-ER-Letter-2018.pdf
*** Interval can be modified at the discretion of the treating physician.

Fig. 192.3 Treatment algorithm for food protein–induced enterocolitis syndrome (FPIES). *Modified from Nowak-Wegrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139:1111–1126. **Template may be downloaded at https://www.fpies.org/wp-content/uploads/2018/08/IFPIES-ER-Letter-2018.pdf. ***Interval can be modified at the discretion of the treating physician. *(From Sicherer SH, Nowak-Węgrzyn A. Enterocolitis, proctocolitis, and enteropathies. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021: Fig. 33.3.)*

Table 192.9 Empiric Guidelines for Selecting Weaning Foods in Infants with FPIES

AGES AND STAGES[a,b]	LOWER RISK FOODS*	MODERATE RISK FOODS*	HIGHER RISK FOODS†
4-6 MO (AS PER AAP, CON) If developmentally appropriate and safe and nutritious foods are available • Begin with smooth, thin, purees and progress to thicker purees • Choose foods that are high in iron • Add vegetables and fruits	**VEGETABLES**		
	Broccoli, cauliflower, parsnip, turnip, pumpkin, kale	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
	FRUITS		
	Blueberries, strawberries, plum, watermelon, peach	Apple, pear, orange	Avocado, banana
6 MO (AS PER WHO) Complementary feeding should begin no later than 6 mo of age • In the breastfed infant, high-iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 mo of age • Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated	**HIGH-IRON FOODS**		
	Lamb, beef, pork, fortified quinoa cereal, millet, amaranth	Fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Fortified, infant rice and oat cereals.
8 MO OF AGE OR WHEN DEVELOPMENTALLY APPROPRIATE • Offer soft-cooked and bite-and-dissolve textures from around 8 mo of age or as tolerated by infant	**OTHER**		
	Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish, shellfish
12 MO OF AGE OR WHEN DEVELOPMENTALLY APPROPRIATE • Offer modified tolerated foods from the family table, chopped meats, soft cooked vegetables, grains, and fruits			

*Risk assessment is based on the clinical experience and the published reports of FPIES triggers.
†This is not an exhaustive list and feeding should not be limited to this list of lower and moderate risk foods. Many other foods are appropriate for infant feeding. One may consider delaying the introduction of higher risk foods until there is a nutritional need for the food, the infant already has a diverse diet, or other lower and moderate risk foods are tolerated.
[a]Exclusive breastfeeding until 4-6 mo of age and continuing breastfeeding through the first year of life or longer as long as mutually desired by both mother and child.
[b]If an infant tolerates a variety of early foods, subsequent introduction may be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered as a favorable prognostic indicator for tolerance of other foods from the same group (legumes).
AAP, CON, American Academy of Pediatrics, Committee on Nutrition; WHO, World Health Organization.
Adapted from Nowak-Wegrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive Summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2017;139(4):1111–1126.e4

Chapter 193

Adverse and Allergic Reactions to Drugs

Roland Solensky and Scott H. Sicherer

Adverse drug reactions (ADRs) can be divided into predictable (type A) and unpredictable (type B) reactions. **Predictable drug reactions**, including drug toxicity, drug interactions, and adverse effects, are dose dependent, are related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. **Unpredictable drug reactions** are generally dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically or otherwise predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. **Allergic reactions** are immune-mediated and require prior sensitization. They manifest as signs and symptoms characteristic of an underlying allergic mechanism (Table 193.1). Anaphylaxis is due to production of drug-specific IgE antibodies, and delayed cutaneous reactions are due to drug-specific T cells. **Pseudoallergic reactions** resemble allergic reactions but are caused by non–IgE-mediated release of mediators from mast cells and basophils, such as vancomycin-induced flushing. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-α-1,3-galactose. This antigen is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group. Sensitization to galactose-α-1,3-galactose may occur from tick bites caused by cross-reactive tick salivary antigens.

EPIDEMIOLOGY

The incidence of ADRs in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal ADRs. Databases such as the U.S. Food and Drug Administration (FDA) MedWatch program (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) likely suffer from underreporting. Cutaneous reactions are the most common form of ADRs, with ampicillin, amoxicillin, penicillin, and trimethoprim/sulfamethoxazole (TMP/SMX) being the most frequently implicated drugs (Tables 193.2 and 193.3). Although the majority of ADRs do not appear to be allergic in nature, 6–10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of re-exposure.

Table 193.1 Classification of Drug Allergies

TYPE	TYPE OF IMMUNE RESPONSE	PATHOPHYSIOLOGY	CLINICAL SYMPTOMS	TYPICAL CHRONOLOGY OF THE REACTION
1	IgE	Mast cell and basophil degranulation	Anaphylactic shock Angioedema Urticaria Bronchospasm	Within 1-6 hr after the last intake of the drug
2	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5-15 days after the start of the eliciting drug
3	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness Urticaria Vasculitis	7-8 days for serum sickness/urticaria 7-21 days after the start of the eliciting drug for vasculitis
4a	Th1 (IFN-γ)	Monocytic inflammation	Eczema	1-21 days after the start of the eliciting drug
4b	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthem, DRESS	1 to several days after the start of the eliciting drug for MPE 2-6 wk after the start of the eliciting drug for DRESS
4c	Cytotoxic T cells (perforin, granzyme B, FASL)	Keratinocyte death mediated by CD4 or CD8	Maculopapular exanthem, SJS/TEN, pustular exanthem	1-2 days after the start of the eliciting drug for fixed drug eruption 4-28 days after the start of the eliciting drug for SJS/TEN
4d	T cells (IL-8/CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1-2 days after the start of the eliciting drug *(but could be longer)*

CXCL8, C-X-C motif chemokine ligand 8; DRESS, drug reaction with eosinophilia and systemic symptoms; FASL, FAS ligand; FcR, Fc receptor; IFN-γ , interferon gamma; IgE, immunoglobulin E; IL, interleukin; MPE, malignant pleural effusion; SJS , Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Th1, Th2, T-helper cell type 1 and type 2.
From Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69(4):420–437.

Table 193.2 Heterogeneity of Drug-Induced Allergic Reactions

ORGAN-SPECIFIC REACTIONS	CLINICAL FEATURES	EXAMPLES OF CAUSATIVE AGENTS
CUTANEOUS		
Exanthems	Diffuse fine macules and papules evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Usually IgE mediated	β-Lactam antibiotics Platinum agents
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, sulfonamides, NSAIDs, carbamazepine
Pustules	Acneiform Acute generalized exanthematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium channel blockers, ACEIs
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillins, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
MULTIORGAN REACTIONS		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, platins
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

ACEI, Angiotensin-converting enzyme inhibitor; DRESS, drug reaction with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Adapted from Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125:S126–S137. Table 1, p. S127.

Table 193.3 Delayed Hypersensitivity Drug Rashes by Category

MACULOPAPULAR EXANTHEMS: ANY DRUG CAN PRODUCE A RASH SEVERAL DAYS INTO THE COURSE
Allopurinol
Antibiotics: penicillins, ampicillin, sulfonamides
Antiepileptics: phenytoin, phenobarbital
Antihypertensives: thiazide diuretics, calcium channel blockers
Radiocontrast material
Gold salts
Hypoglycemic drugs
Meprobamate
Phenothiazines
Quinine
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)
Anticonvulsants: phenytoin, phenobarbital, valproate, lamotrigine, carbamazepine
Antibiotics: sulfonamides, minocycline, dapsone, ampicillin, ethambutol, isoniazid, linezolid, metronidazole, rifampin, streptomycin, vancomycin
Allopurinol
NSAIDs: celecoxib, ibuprofen, diclofenac
Phenothiazines
STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS
Sulfonamides, phenytoin, barbiturates, carbamazepine, allopurinol, amikacin, phenothiazines, acetazolamide, gold, nitrofurantoin, pentazocine, tetracycline, quinidine
ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS
Antibiotics: penicillins, macrolides, cephalosporins, clindamycin, imipenem, fluoroquinolones, isoniazid, vancomycin, minocycline, doxycycline, linezolid, gentamicin, sulfonamides
Antimalarials: chloroquine, hydroxychloroquine
Antifungals: terbinafine, nystatin, amphotericin B, fluconazole, itraconazole
Anticonvulsants: carbamazepine
Calcium-channel blockers
Furosemide, thiazides
Systemic corticosteroids
Protease inhibitors
COLLAGEN VASCULAR OR LUPUS-LIKE REACTIONS
Procainamide, hydralazine, phenytoin, penicillamine, trimethadione, methyldopa, carbamazepine, griseofulvin, nalidixic acid, oral contraceptives, propranolol
ERYTHEMA NODOSUM
Oral contraceptives, penicillins, sulfonamides, diuretics, gold, clonidine, propranolol, opiates
FIXED DRUG REACTIONS
Phenolphthalein, barbiturates, gold, sulfonamides, penicillins, tetracycline, quinolones, carbamazepine, NSAIDs

Note: See Chapter 686 and Table 686.5.
NSAID, Nonsteroidal antiinflammatory drug.
Adapted from Duvic M. Urticaria, drug hypersensitivity rashes, nodules and tumors, and atrophic diseases. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier; 2016: Table 440.3.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Immunologically mediated ADRs have been classified according to the Gell and Coombs classification: immediate hypersensitivity reactions **(type I)**, cytotoxic antibody reactions **(type II)**, immune complex reactions **(type III)**, and delayed-type hypersensitivity reactions **(type IV)** (see Table 193.1). **Immediate hypersensitivity reactions** occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasm, or anaphylaxis. **Cytotoxic antibody reactions** involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte-macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. **Immune complex reactions** are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 weeks into the course of the offending drug and persist for days to weeks after the drug is discontinued. **Delayed-type hypersensitivity reactions** are mediated by cellular immune mechanisms. They are subdivided into four categories involving activation and recruitment of monocytes (type IVa), eosinophils (type IVb), $CD4^+$ or $CD8^+$ T cells (type IVc), and neutrophils (type IVd). Examples include drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and Stevens-Johnson syndrome (SJS) (see Chapter 686.2). Not all allergic drug reactions can be easily classified using the Gell and Coombs system.

Non–IgE-mediated immediate-type reactions mimic Gell and Coombs type I reactions, with indistinguishable symptoms and signs. The most common drugs associated with these reactions are vancomycin, fluoroquinolones, and opiates, which cause nonspecific mast cell degranulation via interaction with the surface receptor MrgprX2. Because these reactions do not require prior sensitization (unlike IgE-mediated reactions), they may occur with first exposure.

The pharmacologic interaction with immune receptors concept **(p-i concept)** is another type of drug hypersensitivity classification. In this scheme, a drug binds noncovalently to a T-cell receptor, which leads to an immune response through interaction with a major histocompatibility complex (MHC) receptor. In this scenario, no sensitization (i.e., previous exposure) is required because there is direct stimulation of memory and effector T cells analogous to the concept of superantigens. Although the various mechanistic schemes of drug-induced allergic reactions are useful, not all drug allergic reactions can be categorized using these various classification systems.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and toxic epidermal necrolysis (TEN; see Chapters 686.2, 695.2 and 695.3). Although their pathophysiology remains incompletely understood, HLA associations including HLA-B*1502 with carbamazepine-induced TEN have been recognized, and the pathogenic roles of drug-specific cytotoxic T cells and granulysin have been reported. SJS is defined as the epidermal detachment of <10%, TEN is >30% detachment, and overlap syndrome is 10–30% detachment. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than one mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. The risks of infection and mortality remain high, but improved outcomes have been demonstrated by immediate withdrawal of the implicated drug, early transfer to a burn unit, and aggressive supportive care. Additional management is reviewed in Chapter 695.3.

Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS (i.e., drug-induced hypersensitivity syndrome) is a potentially life-threatening reaction that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 193.2 and 193.3; see Chapter 686.2). It is likely less common in children compared with adults. DRESS is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of one or more organs, usually hepatic or renal. Onset is delayed, usually 2-8 weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten-protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. Penicillins are highly reactive with proteins and can directly haptenate protein carriers, without prior metabolism, possibly accounting for the higher frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are *slow acetylators* appear to be at increased risk. In addition, cutaneous reactions in patients with AIDS treated with TMP/SMX, rifampin, and other drugs may be caused by glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions due to cefaclor may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for ADRs include prior exposure, previous reactions, age (20-49 years), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), and genetic predisposition. Atopy does not appear to predispose patients to allergic reactions to low molecular weight compounds, but asthmatics who experience allergic reactions are likely at increased risk of more serious reactions, analogous to food-allergic patients. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiocontrast media (RCM). Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions.

DIAGNOSIS

Skin testing is the most rapid and sensitive method of demonstrating the presence of IgE antibodies to a specific allergen. It can be performed with high molecular weight compounds, such as foreign antisera, hormones, enzymes, and toxoids. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated ADRs are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal and flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

In vitro tests (radioallergosorbent test or enzyme-linked immunoassay) for IgE-mediated penicillin allergy have lower sensitivity and comparable specificity compared with skin testing. The positive and negative predictive values (NPVs) of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses using nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum **tryptase** is elevated with systemic mast cell degranulation and can be seen with drug-associated reactions such as anaphylaxis; however, not all patients with well-defined anaphylaxis show increased serum tryptase levels. **Patch testing** is the most reliable technique for diagnosis of contact dermatitis caused by topically applied drugs. **Graded drug challenge** is an incremental (usually two-step) administration of a drug under medical supervision and is used in patients who are deemed unlikely to be allergic to the drug. Unlike desensitization, there is no attempt to modify the underlying immune response. Patients who pass a graded challenge are proven to not be allergic to the drug.

TREATMENT

Drug desensitization alters the immune response to a medication and allows allergic patients to receive it safely. However, the induced tolerance is temporary and if treatment is interrupted, hypersensitivity returns, and patients are again at risk of reacting to the drug. Drug desensitization has classically been used for IgE-mediated allergy, such as penicillin, but the procedure has been successfully applied to immediate non–IgE-mediated reactions, such as taxanes. Rapid desensitization is indicated in patients who are either proven or are strongly suspected to have an immediate-type drug allergy and for whom an alternate drug is not available or appropriate. The procedure warrants close monitoring and preparedness to treat possible anaphylaxis. Depending on the clinical stability of the patient and the severity of the previous reaction (or symptoms during a previous desensitization), it may be performed in outpatient or inpatient settings. Premedications are used for non–IgE-mediated hypersensitivity (such as taxanes and biologic agents), but not for IgE-mediated allergy (such as antibiotics). Desensitization can be performed via parenteral or oral routes. The starting dose is typically 1/10,000 of the full dose, and the dose is doubled every 15 minutes until the full dose is reached. Desensitization has a very high success rate and breakthrough allergic reactions occur about 20–30% of the time, but they are usually mild and do not necessitate aborting the procedure.

Penicillin Allergy

Penicillin allergy is self-reported by approximately 10% of patients, but following evaluation, about 95% of these individuals are shown to not be allergic and able to tolerate penicillins. This incongruity is due to the reaction being the result of the underlying infection (or interaction between the infectious agent and the antibiotic), mislabeling a predictable reaction as allergic, and the waning of penicillin-specific IgE. Being labeled as penicillin allergic is not benign, because patients are more likely to be treated with less effective, more toxic, or more expensive antibiotics such as fluoroquinolones, vancomycin, later generation cephalosporins, and clindamycin. This prescribing practice compromises optimal medical care and increases costs. Penicillin "allergy" has been associated with increased antimicrobial resistance (such as vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus*), increased *Clostridium difficile* colitis, increased surgical site infections, prolonged length of hospital stays, increased intensive care admissions, increased hospital readmissions, and increased mortality. Removal of the penicillin allergy label leads to improved antibiotic selection with decreased use of broad-spectrum antibiotics and decreased healthcare utilization (fewer outpatient visits, fewer emergency department [ED] visits, and fewer hospital days). Therefore a proactive effort should be made to de-label penicillin allergy whenever possible. Ideally, this is done electively such as when patients are well and not in immediate need of antibiotic treatment. De-labeling of penicillin allergy is endorsed by the CDC, allergy/immunology, and infectious disease societies.

The penicillin β-lactam ring opens to form various reactive intermediates, which then interact with self-proteins to stimulate immune reactions. Penicillin skin test reagents are based on the immunochemistry, and they are broadly grouped into major and minor allergenic determinants. (Table 193.4) The positive predictive value of penicillin skin testing is ~80% for immediate type reactions. Alternatively, 95% or more of penicillin skin test–negative patients tolerate these antibiotics. The major determinant (penicilloyl-polylysine [PPL]) should always be used for skin testing, but there is controversy regarding the relative importance of various minor determinants (penicillin G, penicilloate, penilloate and ampicillin/amoxicillin) and what effect this has on the NPV. Although PPL is commercially available in the United States as Pre-Pen, the minor determinants are not. Penicillin G and IV ampicillin can be diluted and used off-label for skin testing, but penicilloate and penilloate require synthesis; therefore they are more difficult to obtain.

Patients who are positive on penicillin skin testing should avoid penicillins but consider being reevaluated at a later time, because penicillin allergy wanes and resolves in most (but not all) individuals. If administration of penicillin is deemed necessary, desensitization can be performed. Skin test–negative patients should ideally undergo an amoxicillin challenge, to unequivocally prove lack of allergy. This alleviates the fear and reluctance on the part of the patient, patient's family, or future prescribing clinicians to treat with penicillins. Additionally, effort should be made to remove the penicillin allergy label in all electronic medical systems (hospitals, clinics, private offices, pharmacies, etc.).

The traditional approach to de-label penicillin allergy has been to first perform penicillin skin testing in all patients with suggestive penicillin allergy histories and then challenge with amoxicillin (if skin testing is negative). However, in recent years several publications have challenged this standard, particularly in the pediatric population, by instead directly challenging "low-risk" patients with amoxicillin (without preceding skin testing). Patients deemed appropriate for direct amoxicillin challenge are those with maculopapular and urticaria eruptions, without other respiratory, cardiovascular, oropharyngeal symptoms, angioedema, and vesicular or exfoliative eruptions. Using this strategy, the rate of observed reactions ranged from 5% to 10% and were no more severe than the historical reactions. For comparison, up to 7% of children (without a previous history of allergy) treated with aminopenicillins develop cutaneous eruptions. The cause of these rashes is presumed to be the underlying infection (typically viral) or an interaction between the infectious agent and the antibiotic. The best characterized example is patients with Epstein-Barr infection, almost 100% of whom develop a nonpruritic morbilliform rash when treated with ampicillin. Pediatric patients who undergo direct amoxicillin challenge should be observed in a clinical setting for at least 1 hour, with preparedness to treat potential allergic reactions including anaphylaxis.

Resensitization is the redevelopment of penicillin allergy after initial resolution. Resensitization after oral treatment with penicillins is rare in both pediatric and adult patients, including after repeated courses, and comparable to the rate of sensitization. Therefore repeat penicillin skin testing is not indicated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin. Data on resensitization after parenteral treatment with penicillins is more limited, but routine repeat penicillin skin testing is likely not necessary in patients with a history of penicillin allergy who have tolerated one or more courses of parenteral penicillin. Consideration may be given to retesting individuals with recent or particularly severe previous reactions.

Table 193.4 Penicillin Skin Test Reagents

REAGENT*	CONCENTRATION USED FOR SKIN TESTING
Penicilloyl-polylysine (PPL)	6×10^{-5} M
Penicillin G	10,000 units/mL
Penicilloate	0.01 M
Penilloate	0.01 M
Ampicillin/amoxicillin	3-25 mg/mL

*PPL is the major allergenic determinant; all the other reagents are minor determinants.

β-Lactam Cross Reactivity

Penicillins, cephalosporins, carbapenems, and aztreonam share a common β-lactam ring and hence the potential for allergic cross reactivity. Additionally, some penicillins and cephalosporins share identical R group side chains, and these are another source of potential allergic cross reactivity (Table 193.5). Combining published reports of patients proven to be allergic via positive penicillin skin testing and then challenged with cephalosporins, only about 2% experienced allergic reactions. This is similar to the incident rate of new drug reactions to structurally dissimilar medications in patients with prior drug allergies (because patients with a history of drug allergy are more likely to react to structurally unrelated drugs). If cephalosporin skin testing (using nonirritating concentrations) is performed in penicillin skin test–positive subjects before challenging with cephalosporins, the reaction rate decreased to 0%.

In general, the preferred approach to patients with a history of penicillin allergy is to electively de-label the allergy because this greatly simplifies all future β-lactam administration recommendations by allowing treatment with any β-lactam antibiotics. Given that less than 5% of patients with an unverified penicillin allergy are truly allergic and 2% of those who are allergic cross react with cephalosporins, the chance

Table 193.5 Groups of β-Lactam Antibiotics That Share Identical Side Chains*

IDENTICAL R1-GROUP SIDE CHAINS					
Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			
IDENTICAL R2-GROUP SIDE CHAINS					
Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

*Each column represents a group with identical side chains.
From Solensky R, Khan DA. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:273e1–273e78. Tables 16, 17, p. 273e49.

of a cephalosporin reaction is extremely low at approximately 0.1% (5% × 2% = 0.1%). *Therefore most experts and guidelines recommend that for patients with a history of nonanaphylactic penicillin allergy, cephalosporins may be administered without prior testing or additional precautions.* In patients with a history of penicillin anaphylaxis (or those positive on penicillin skin testing), cephalosporin graded challenge is preferred because the chance of reaction is still very low.

There are rare patients who have selective IgE-mediated allergy to aminopenicillins but tolerate penicillin VK and penicillin G. The allergic determinant is an R-group side chain, rather than the core β-lactam portion of the molecule. In these patients, the positive challenge rate to cephalosporins sharing identical side group chains (such as ampicillin/cephalexin or amoxicillin/cefadroxil; see Table 193.5) is higher, or about 16%. Therefore, in such patients, administration of cephalosporins with identical side group chains should be avoided, given via two-step graded challenge or desensitization, whereas treatment with other cephalosporins does not require a more cautious approach.

The data on allergic cross reactivity between penicillins and carbapenems mirror the discussion on penicillin/cephalosporin cross reactivity. Patients with unconfirmed penicillin allergy treated with carbapenems showed a higher reaction rate compared to patients without a history of penicillin allergy. In studies of penicillin skin test–positive patients challenged with carbapenems, none of 680 reacted; four carbapenem skin test–positive patients were not challenged. Therefore it is recommended that patients with a history of penicillin allergy may receive carbapenems in usual fashion or via two-step graded challenge.

Aztreonam is the only monobactam and the only β-lactam antibiotic that contains a monocyclic ring structure, in contrast to the bicyclic core of other β-lactams. In vitro, skin testing and challenge studies have demonstrated no evidence of allergic cross reactivity between penicillins and aztreonam, including no positive aztreonam challenges in penicillin skin test–positive patients. Therefore patients with a history of penicillin allergy may receive aztreonam in the usual fashion. The only β-lactam that shows cross reactivity with aztreonam is ceftazidime, because these two antibiotics share an identical R-group side chain. Hence, patients allergic to aztreonam or ceftazidime should avoid the other antibiotic.

Sulfonamides

The most common type of reaction to sulfonamide antibiotics is a maculopapular eruption that occurs about a week into treatment. The incidence of immediate reactions, such as urticaria/angioedema or anaphylaxis, is rare and less frequent than with β-lactam antibiotics. On the other hand, sulfonamides are the most common antibiotic to cause severe cutaneous delayed reactions (SCARs), such as SJS, TEN, and DRESS. Hypersensitivity reactions to sulfonamides occur with greater frequency in HIV-infected individuals. For patients with history of typical delayed maculopapular rashes, both graded one- or two-step challenge and desensitization protocols have been shown to be effective in HIV-positive and non–HIV-positive patients. Because the success rate of graded challenge and desensitization appears comparable, it is not clear that the various desensitization protocols truly modify the immune response. These regimens are not intended for individuals with a history of SJS or TEN. There is no evidence of allergic cross reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides (such as celecoxib, thiazides, furosemide, acetazolamide, sumatriptan, and others).

Macrolides

Macrolides cause allergic reactions less frequently than penicillins, cephalosporins, or sulfonamides. The most common reactions are delayed onset maculopapular eruptions and urticaria, and they occur in about 1% of patients. IgE-mediated reactions are uncommon, limited to case series, and anaphylactic reactions are extremely rare. When pediatric patients with convincing histories of allergic reactions undergo formal evaluation, less than 10% are confirmed to be allergic. Skin testing with a nonirritating concentration of macrolides may provide useful information in those patients with immediate reaction histories. However, in patients with an anticipated clinical need for macrolides, graded challenge without preceding testing is used most commonly, given the high likelihood of success and rare nature of anaphylaxis.

Antiretroviral Agents

There are several categories of antiretroviral drugs to treat HIV (reverse transcriptase inhibitors, protease inhibitors, entry inhibitors, and integrase inhibitors) and all have been implicated in hypersensitivity reactions, which usually present as delayed onset and range from mild self-limited maculopapular eruptions to life-threatening SJS/TEN or DRESS. Hypersensitivity to abacavir is a well-recognized, multiorgan, potentially life-threatening reaction that occurs in HIV-infected children and adults. Rechallenge is strictly contraindicated, because subsequent reactions may be more rapid and severe than the initial reaction. Importantly, these reactions have been associated with the presence of the MHC class I allele HLA-B*5701, and HLA testing has shown very high sensitivity and NPV. Therefore genetic screening for HLA-B*5701 is part of guideline-based therapy when abacavir is initially prescribed.

Chemotherapeutic Agents

Hypersensitivity reactions to chemotherapeutic drugs have been described, most notably to platinum agents and taxanes. The clinical pattern of immediate reactivity to platinum agents, along with skin test findings, is consistent with an IgE-mediated mechanism. Hence reactions occur after patients tolerated several previous treatments. In contrast, immediate reactions to paclitaxel and docetaxel usually occur with first exposure and the risk lessens with repeated exposure. They are believed to be due to emulsifying agents such as Cremophor-EL, which result in complement activation and generation of anaphylatoxins. Rapid desensitization (most typically a 12-step protocol) is effective for both IgE and non–IgE-mediated type reactions.

Biologics

An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of ADRs, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a black box warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 185).

Vaccines

Anaphylactic reactions to vaccines are very rare, occurring at a rate of approximately one event per million administrations, and they may be due to various vaccine components such as antibiotics, preservatives, stabilizers, virus-inactivating compounds, residual animal proteins, and latex. Measles mumps rubella (MMR) vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). Egg-allergic patients are not at higher risk of reacting to both inactivated and live influenza vaccine than those without egg allergy. Skin testing with the influenza vaccine is no longer recommended for egg-allergic patients but may be helpful if allergy to the vaccine itself is suspected. The American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI) Joint Task Force on Practice Parameters recommend that "Influenza vaccines should be administered to individuals with egg allergy of any severity, just as they would be to individuals without egg allergy." The incidence of anaphylactic reactions following mRNA COVID-19 vaccines may be higher (2.5-4.7 events per million). However, following evaluation by allergists/immunologists, most patients reporting immediate-type reactions to the first vaccine dose are able to tolerate the second dose, arguing against an IgE-mediated mechanism. Therefore the true rate of anaphylaxis is likely lower.

It is uncertain whether patients with underlying atopic conditions or other allergies are at increased risk of reacting to these vaccines. Although polyethylene glycol (PEG) (a component of mRNA COVID vaccines) has been proposed to be a possible culprit, there is limited evidence for the relationship.

Perioperative Agents

In North America, perioperative anaphylaxis is most frequently due to antibiotics, whereas in European series, neuromuscular blockers are the most common culprit. Other potential causes include induction agents, opioids, colloids and plasma expanders, chlorhexidine, sugammadex, and latex. The mechanism responsible may be IgE-mediated or non–IgE-mediated. Previous surgeries are a risk factor for IgE-mediated reactions because they require prior sensitization. Patients who have experienced perioperative anaphylaxis should be screened for possible mast cell disease. Skin testing with agents known to cause IgE-mediated reactions is useful and can help prevent recurrent reactions during subsequent surgeries. Sometimes, despite a thorough evaluation, an underlying cause for perioperative anaphylaxis is not detected.

Local Anesthetics

ADRs associated with local anesthetic agents are primarily nonallergic and include vasovagal, psychomotor, sympathetic stimulation, and toxic reactions. IgE-mediated reactions are exceedingly rare. Patients with suspected local anesthetic allergy should be referred to an allergist/immunologist for skin testing followed by a graded challenge. This procedure invariably finds a local anesthetic the patient is able to tolerate, in the rare individuals who are allergic to one of these agents. Although local anesthetics can be broadly grouped into esters (group I) and amides (group II), allergic cross reactivity within these groups is only relevant for delayed Gell and Coombs type IV reactions, not type I reactions.

Insulin

Insulin use has been associated with a spectrum of ADRs, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergenic than porcine insulin, which is less allergenic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergenic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly because of IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reinstitution of insulin therapy in sensitized patients.

Insulin therapy should not be interrupted if a systemic reaction to insulin occurs, and continued insulin therapy is essential. Skin testing may identify a less antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2- to 5-unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for >24-48 hours.

Radiocontrast Media

Immediate type allergic reactions to RCM may occur after intravascular administration, and during myelograms or retrograde pyelograms. The pathogenic mechanism has classically been thought to be non–IgE-mediated mast cell activation (anaphylactoid). However, there is growing evidence that some immediate reactions are IgE mediated. This may be because use of older high-osmolar RCM agents has been replaced by low- and iso-osmolar agents. One approach to patients with previous RCM reactions who require another diagnostic study is to choose an alternate agent and premedicate with prednisone and diphenhydramine. Another approach is to perform skin testing with the culprit and alternate RCM agents, with the results guiding the choice of treatment. The latter method appears to be more useful when the historical reactions are severe (i.e., anaphylactic). There is no evidence that seafood or iodine allergy is associated with or predisposes to RCM reactions.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Acetylsalicylic acid (ASA) and other NSAIDs have been associated with several types of allergic reactions. Reactions that are caused by modifying effects on arachidonic acid metabolism, namely respiratory reactions (in patients with underlying aspirin-exacerbated respiratory disease [AERD]) and urticarial reactions (in patients with underlying chronic idiopathic urticaria), show cross reactivity with other NSAIDs, as one would expect. Patients with AERD and aspirin-sensitive patients with chronic idiopathic urticaria tolerate drugs that selectively block the cyclooxygenase-2 (COX-2) enzyme, such as celecoxib. On the other hand, acute urticarial or anaphylactic reactions in otherwise normal individuals are medication specific. There are no skin or in vitro tests to identify patients allergic to ASA or other NSAIDs.

Except for respiratory reactions in asthmatics, there are no data on the incidences of reactions to ASA/NSAIDs in children; however, clinical experience suggests that it is much lower than in adults. Furthermore, only 20% of children reporting NSAID allergy are confirmed to be allergic when challenged. The incidence of AERD in children with asthma has been investigated in six prospective studies, the rate varied from 0% to 28%, and there was a trend for more respiratory reactions in adolescents compared with younger children. Overall, the data indicate that ASA sensitivity in asthmatic children under the age of 10 is rare and increases thereafter.

Patients with AERD whose nasal disease or asthma is poorly controlled with use of medications are candidates for ASA desensitization. This procedure, unlike antibiotic or chemotherapy desensitization, involves administration of the drug to cautiously induce a respiratory reaction (rather than prevent it), following which patients enter a refractory phase that can be maintained with continued administration of ASA. Long-term studies of adults maintained on chronic ASA desensitization demonstrated improved clinical outcomes for both upper and lower respiratory diseases. ASA desensitization is rarely performed in children because severe, poorly controlled AERD is encountered very infrequently in the pediatric population, and aspirin is not routinely recommended for children because of the risk of Reyes syndrome.

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