Allergic Diseases

Diagnosis and Treatment

THIRD EDITION

Edited by

PHIL LIEBERMAN, MD

JOHN A. ANDERSON, MD

HUMANA PRESS

Allergic Diseases

CURRENT ◊ CLINICAL ◊ PRACTICE

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To Barbara

P. L.

and

To Nicole

J. A. A.

Preface

Allergic Diseases: Diagnosis and Treatment, 3rd Edition is intended for the "front-line" physician who cares for the allergic patient. We have tried, once again, to make it as "user friendly" and clinically oriented as possible.

Our approach to the principles of pathophysiology is intended to allow them to be easily applied to the rationale for therapy. The major intent therefore is still to help the primary care physician deal with the day-to-day management of the allergic patient.

The arrangement of this text is similar to that of the first edition, with the major emphasis being on common allergic diseases and the pharmacologic tools we use to control them. To this end two new chapters have been added, one on antihistamines and the other on antileukotrienes. In addition, a new chapter has been added to help the physician deal with the child who experiences recurrent respiratory tract infections.

Many of the authors, because of the superb job they did with their first contributions, have been asked for an encore. However, to keep our approach fresh, some of these authors have been asked to write different chapters, and new contributors have been solicited.

Regardless of these changes, the thrust of the text remains the same—to disseminate the practical knowledge that we have accumulated in almost 70 years of practice and teaching in the field of allergy and immunology. As with the first and second editions of *Allergic Diseases: Diagnosis and Treatment*, our greatest hope is that the message has been delivered clearly, effectively, and in a manner that allows its easy application by the physician caring for those who suffer with allergic disease.

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1 Allergic Disease

Pathophysiology and Immunopathology

Gloria E. Akan, MD
and Robert F. Lemanske, Jr., MD

CONTENTS

SUMMARY

The incidence of asthma and allergic disease is rising. However, primary care physicians have dealt with allergic conditions far more often than they may expect even before the development of these recent epidemiological trends. Some examples of immunological disease that the primary care physician has encountered include asthma, allergic rhinitis, and atopic dermatitis.

This chapter will review the role of atopy in the development and clinical manifestations of allergy. The two-step process of sensitization will be described. The role of the mast cell, the primary cell involved in allergic disease, will be delineated on a molecular and clinical level. Examples of allergic sensitization and presentation of disease will be provided using an example of food allergy. Descriptions of the early- and late-phase responses will be provided using the nasal tissue and skin as examples. The overall goal is to give the reader a good foundation and understanding of the mechanisms involved in allergic sensitization and the presentation of allergic diseases in a genetically predisposed individual.

Key Words: Immunoglobulin E (IgE) antibody; mast cell; basophil; late-phase response; early-phase response; anaphylaxis; allergy; immediate hypersensitivity.

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INTRODUCTION

The incidence of asthma and allergic disease is rising. However, primary care physicians have dealt with allergic conditions far more often than they may expect even before the recent increase in allergic conditions. Some examples of immunological disease that the primary care physician sees include asthma, allergic rhinitis, and atopic dermatitis. To illustrate the importance of allergic disorders in clinical medicine, consider that physicians obtain an allergy history before prescribing any antibiotic because of the high incidence of drug reactions in the population.

Armed with the knowledge of the mechanisms mediating allergic reactions, a clinician can readily appreciate the pathophysiological changes caused by an exposure to a foreign antigen to a normally well-balanced system. This knowledge enables the physician to recognize and anticipate adverse reactions. Knowing that some asthmatics might experience a late-phase allergic response, for example, compels the physician to continue intensive therapy until the reaction has completely subsided.

Atopy, the genetic predisposition to the development of antigen-specific immunoglobulin E (IgE) antibody formation, involves complex genetic and environmental influences that are not fully understood. In other words, simple Mendelian inheritance patterns do not predict which individuals will develop allergies. Nevertheless, there appears to be a higher incidence of allergies among children of allergic parents.

One becomes "allergic" to a substance through a two-step process. The first step begins with sensitization and is outlined in Fig. 1. During the initial stage of sensitization, one develops significant amounts of IgE antibodies against an inhaled, ingested, or injected substance. Memory B-cells appear that are capable of immediately producing more specific IgE antibody when stimulated. The second stage involves adherence of this newly formed IgE antibody to circulating blood basophils or to tissue mast cells located in the mucosal surfaces of the skin, the gastrointestinal tract, and the respiratory system. These tissue mast cells were previously coated with IgE antibodies directed specifically against other potentially allergenic substances. The new exposure simply added to the existing population. There are millions of IgE molecules of different specificities (directed against different allergens) on the surface of each mast cell and basophil. An individual is "sensitized" only after IgE antibodies against a specific substance have been produced and are bound to the surface of mast cells and basophils. The process of sensitization does not produce any of the symptoms that we equate with allergic disease. In fact, a person is usually unaware of these initial molecular and cellular changes. It is not until re-exposure to the allergen that allergic symptoms begin to appear once this immunological response has been programmed to "target" a given organ system. Thus, the process of allergic sensitization does not necessarily equate with the development of allergic disease.

The second step in the two-step process of developing allergic disease involves the re-exposure of a sensitized person to the allergen. Symptoms range from negligible rhinorrhea to sudden death. Most cases lie somewhere in the middle of the two extremes. The biochemical events that lead to allergic symptoms will be discussed in some detail later, using an anaphylactic reaction to peanuts as an example. However, one should keep in mind that although the cellular and molecular events for all immediate hypersensitivity reactions are similar, differences in target organ responses ultimately dictate the clinical patterns of disease activity once a reaction has been induced. The mechanisms underlying differential target organ responses (i.e., rhinitis, atopic dermatitis, urticaria, asthma, and/

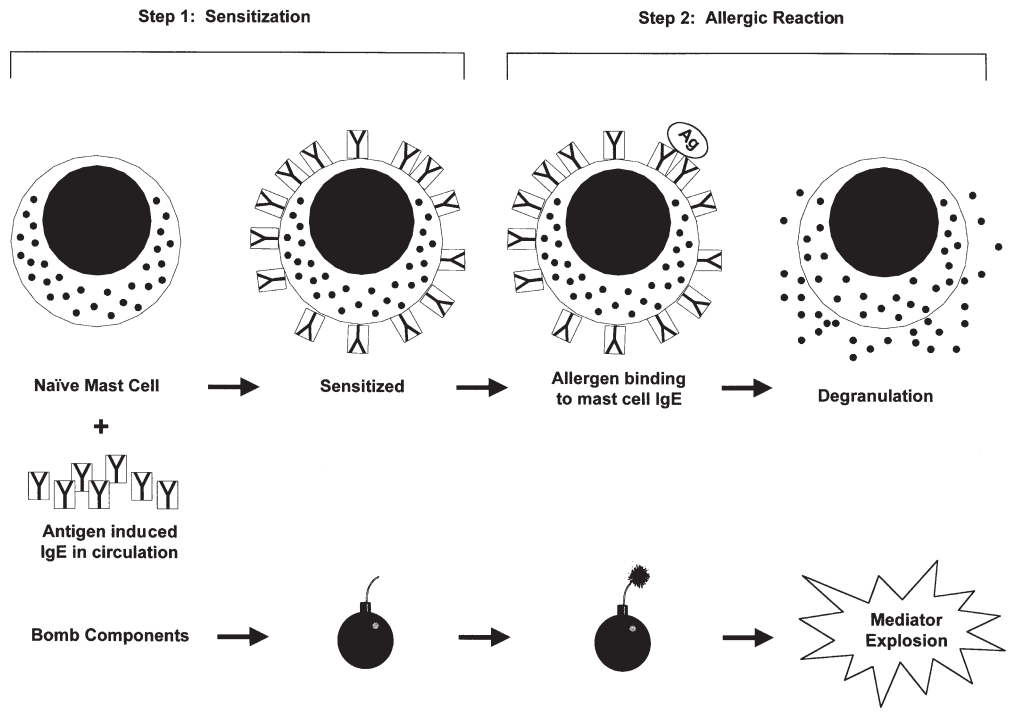

Fig. 1. Allergic sensitization and degranulation. The process of sensitization and degranulation in mast cells is analogous to the construction and detonation of a bomb. Initial binding of specific IgE to the naive mast cell surface "primes" the cell for activity, in effect building the bomb. Subsequent binding of allergen to the mast cell is akin to lighting the fuse of the bomb. Intracellular biochemical events lead to the ultimate "explosion"—a cellular degranulation leading to mediator release.

or anaphylaxis) in relationship to "atopic," immunological, genetic backgrounds, subsequent environmental exposures, and the development of these disease states have not been defined.

THE ALLERGIC REACTION: A SCENARIO

An 8-mo-old girl was in the care of her aunt. Unfortunately, peanut butter crackers were given to the girl as part of a snack. She ingested the crackers without incident. While she was enjoying playtime with her cousins, the peanut proteins were being absorbed in her gut and filtered through the bloodstream and lymphatics, and lodging in the regional lymph nodes. The antigens encountered T- and B-cells and were recognized as foreign proteins. The interaction with lymphocytes leads to IgE production in genetically predisposed or atopic individuals. This IgE was specifically directed against the peanut protein and circulated briefly through the bloodstream before binding to IgE receptors on the tissue mast cells and blood basophils. These receptors bound the antibody at the F_c end of the molecule, leaving the F_{ab} (antigen-binding) region exposed and free to bind circulation antigen. By this time the peanut protein had been cleared by the reticuloendothelial system. The only evidence that the girl was sensitized to the peanut protein was the presence of the specific peanut IgE on her mast cells and the presence of a few memory B-cells capable of producing more specific peanut IgE if they encounter the protein again.

One year later the girl attended a birthday party and ate a cookie containing peanuts. Within minutes, she developed urticaria around her mouth, wheezing, and cough. She was gasping for air as paramedics were summoned and was cyanotic by the time they arrived. Fortunately, prompt treatment allowed her to recover. At the molecular level, her immune system made her a living time bomb, ready to detonate when she came in contact with the peanut antigen "trigger." Despite the 12-mo gap, the immune system never forgot its initial exposure to the peanut. On being exposed to peanuts the second time, the peanut antigen circulated through the blood stream and lymphatics. This time, the antigen flowed past the IgE peanut-specific antibodies already situated on the surface of the mast cells. These IgE molecules, like hands, grabbed the antigen as it passed by. When the number of peanut antigen molecules bound to the IgE on the mast cell surface was sufficient, some IgE antibodies crosslinked and caused a chain reaction. The mast cells released preformed chemicals that were quiescent in their intracellular granules. These chemicals cause bronchoconstriction, vasodilatation, and upper airway edema. Additionally, the triggering and degranulation of mast cell caused the *de novo* production of other substances that also contributed to the reaction. The effect of the re-exposure to the peanut antigen in this girl's case is called anaphylaxis and represents the most severe type of allergic reaction. Fortunately, such a reaction is rare and can often be prevented, or at least attenuated. We will now explore the pathophysiology of such a reaction in greater detail, starting with the effector cell in immediate hypersensitivity, the mast cell. We will also mention the basophil, a granulocyte that releases mediators similar to those of the mast cell.

ASPECTS OF IgE PRODUCTION

The key intermediary in allergic conditions is IgE antibody. As discussed previously, it is the individual's propensity to produce IgE in response to an "allergic antigen" (also known as an allergen) that makes one atopic. The same allergen that stimulates B-cells to produce IgG or IgM in a nonallergic person may stimulate IgE antibody production in an atopic individual.

Why does the body respond to an allergen exposure by making IgE as opposed to other classes of antibodies? Antibody molecules consist of a variable region responsible for recognizing and binding the offending antigen and a constant region whose purpose is to dictate the fate of the antigen–antibody complex. For example, a person may make both IgA and IgG antibodies against a virus. Both are capable of binding to that virus, but the IgA is found mainly in secretions (as in the nasal mucosa), whereas the IgG predominates in the bloodstream. The mechanisms by which a particular antigen favors the production of one class of antibody over another are not firmly established; nevertheless, several factors that may favor IgE formation are worth discussing.

All antigens initially elicit the production of IgM antibodies against an injected or inhaled allergen. With repeated exposure, the antigen may stimulate an event known as class switching, whereby the constant portion of the antibody will "switch" to another class (i.e., IgG, IgA, or IgE). The new antibody will still have the same antigen-recognition region, but it will now be sitting on another constant region (e.g., IgG or IgA). IgE production by B-cells as a result of class switching is regulated by T-cells and macrophages, predominantly, and the cytokines they produce. Cytokines are small molecular-

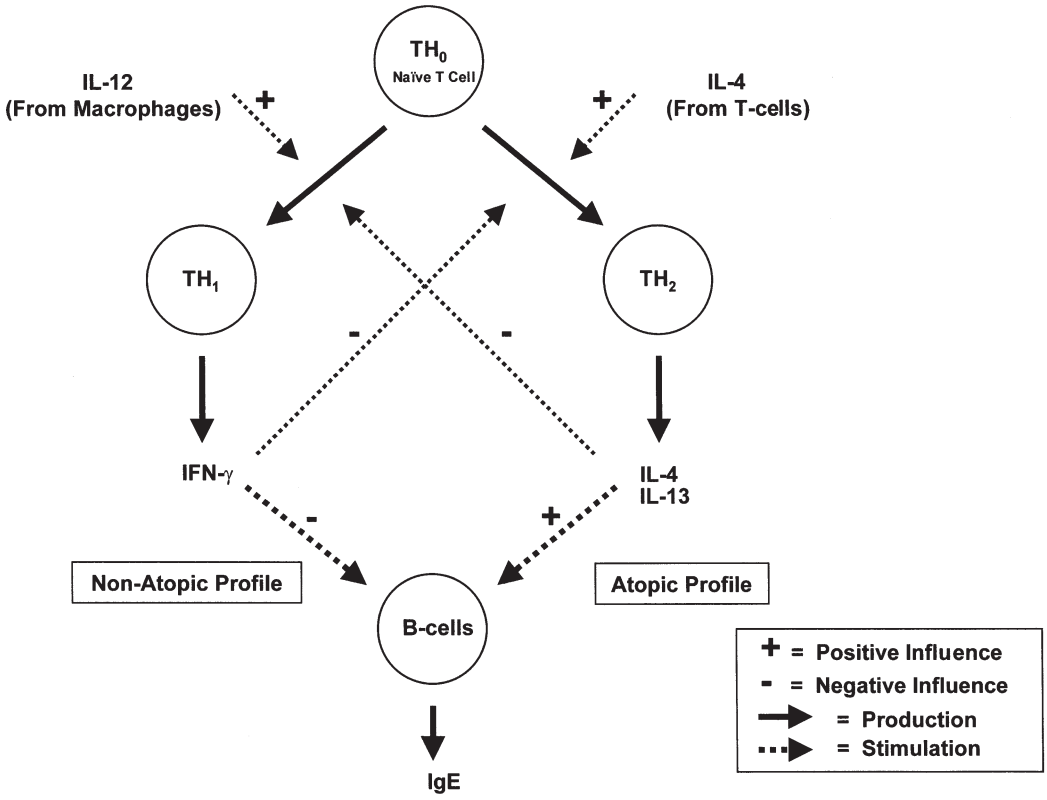

Fig. 2. The TH_1 and TH_2 paradigm. T-helper cells uncommitted to an atopic or nonatopic cytokine profile (TH_0) receive stimulation from cytokines IL-4 and IL-12 to polarize to a TH_1 or TH_2 phenotype. The TH_1 profile is consistent with a nonatopic phenotype, whereas the TH_2 profile is consistent with an atopic phenotype. TH_1 cells produce IFN-γ, which inhibits IgE production from B-cells and TH_0 differentiation into TH_2 cells. TH_2 cells, on the contrary, produce IL-4 and IL-13, both potent stimulators of IgE production from B-cells. IL-4 also feeds back to inhibit TH_0 differentiation into TH_1 cells; it can also further self-promote Th_0 differentiation into TH_2 cells to perpetuate the cycle of an atopic cytokine response.

weight molecules that affect cell function at the local level. Two primary cytokines that favor IgE class switching are interleukin (IL)-4 and IL-13. IL-4 and IL-13 are produced by a subset of $CD4^+$ T-cells, also known as T-helper 2 (TH_2) cells.

IL-4 is such an essential signal for IgE production that mice that have been genetically engineered to be devoid of IL-4 (IL-4 knockout mice) are unable to synthesize IgE. In contrast, the primary cytokine that inhibits IgE class switching is called interferon (IFN)-γ. IFN-γ is produced by a subset of T-cells that have a T-helper 1 (TH_1) cytokine profile. The cytokines produced by TH_1 and TH_2 cells reciprocally inhibit the other's development. These stimulatory and inhibitory interactions are outlined in Fig. 2. In atopic individuals the balance of TH_1 and TH_2 responses seems to favor the TH_2 response and IgE production. In nonatopic individuals, the balance between TH_1 and TH_2 favors a TH_1 dominant response.

The ability to produce polyclonal IgE antibody is present as early as 8–10 wk of gestation. Because IgE antibody cannot cross the placenta, any IgE present in cord blood has been produced entirely by the fetus. During the first year of life, antigen-specific IgE antibody is directed primarily against food antigens; by age 2–3 yr, aeroallergen sensitivity begins to become more prevalent.

The biochemical structure of an antigen appears to play a role in determining the isotype response. A polysaccharide antigen, from the surface of *Streptococcus*, for instance, will prompt B-cells to produce IgG but not IgE antibodies. In contrast, certain proteins from parasites can cause the B-lymphocytes (with help from the T-cells and IL-4) to cease production of IgG or IgM and to churn out vast quantities of IgE. However, exactly what it is about the structure of proteins that preferentially leads them to become allergens, thus stimulating IgE synthesis, remains unresolved.

THE MAST CELL

A medical student, named Paul Ehrlich, first described the mast cell in 1877. He chose the name *Mastzellen* (well-fed cells) based on the cells' characteristic cytoplasmic granules (he incorrectly thought that the mast cells were phagocytes and that the granules were ingested debris). We now recognize the central role that mast cells play in the immediate hypersensitivity response.

As with all hematopoietic cells, the mast cells are formed by the action of soluble factors on a pluripotent stem cell (progenitor cell) in the bone marrow. The cells emerge from the bone marrow and migrate to the connective tissues, where they mature, acquiring both cytoplasmic granules and a coating of high-affinity IgE receptors (called FcεRI-α) on their cell surface. Despite gross morphological homogeneity, it is now apparent that mast cells are a heterogeneous cell population. Most pulmonary mast cells contain primarily one neutral protease, tryptase. Skin mast cells, on the other hand, contain large amounts of both tryptase and another protease, chymase (described below). Mast cells in humans are divided and named on the basis of this biochemical difference and are termed MC_T (for mast cells containing tryptase) or MC_{TC} (for mast cells containing chymase). The tissue distribution of these subtypes of mast cells is shown in Table 1. The relative numbers of MC_T or MC_{TC} may change locally with tissue inflammation, fibrosis, or the cytokine microenvironment. There are no accurate means of discerning from what tissue an isolated mast cell population is derived, because mixtures of both MC_T and MC_{TC} cells are found in all tissues.

MEDIATORS OF THE ALLERGIC RESPONSE

The mediators released by mast cells and basophils can be grouped into two categories: (1) preformed substances contained within granules and (2) newly generated chemicals synthesized following cellular activation. These mediators comprise the effector function of the mast cell. Together they are able to increase vascular permeability, dilate vessels, cause bronchospasm, contract smooth muscle, and summon inflammatory cells, as summarized in Fig. 3. Few cells in the body produce compounds with such a large and varied spectrum of activity.

Histamine is a prominent preformed vasoactive amine contained within the mast cell granule. It is formed by the action of histidine decarboxylase on the amino acid histidine. Histamine is the only preformed mediator of the human mast cell with direct vasoactive

Table 1
Relative Distribution of the Two Predominant Human Mast Cell Phenotypes in Immunologically Relevent Tissues and Cell Population

Organ	*% MC_T Cells*	*%MC_{TC} Cells*
Skin	5	95
Intestinal mucosa	80	20
Intestinal submucosa	30	70
Alveolar wall	95	5
Bronchial subepithelium	40	60
Dispersed lung mast cells	90	10
Tonsils	40	60
Nasal mucosa	65	35

Adapted from Holgate and Church, Allergy. London: Gower Medical Publishing, 1993.

and smooth muscle spasmogenic effects. It can increase mucus production from airway epithelial cells and contract airway smooth muscle, thus contributing to both mucous plugging and bronchospasm. Histamine also acts to increase vascular permeability as well as to promote vasodilatation, thus causing extravasation of fluid into the tissues. In extreme cases, such intravascular fluid shifts can lead to hypotension and shock.

Neutral proteases are compounds that catalyze the cleavage of certain peptide bonds in proteins and facilitate protein degradation. Their activity is optimum at a neutral pH, hence the name. The two major proteases of human mast cells and basophils are tryptase and chymase. Basophils have negligible but detectable levels of proteases. Maintaining the interior of the granules at an acidic pH, thus inhibiting protease activity, controls the potentially dangerous proteolytic activity of these compounds.

Other accessory molecules have prominent roles in the allergic response. Proteoglycans, including heparin and chondroitin sulfate A, are important in mast cell and basophil biochemistry, respectively. Their exact function is unclear, although many believe that proteoglycans stabilize the enzymes to which they are bound until degranulation occurs.

Two predominant classes of mediators are synthesized *de novo* following activation of the mast cells and basophils: (1) lipid derivatives and (2) cytokines. The lipid derivatives include leukotrienes and prostaglandins. They represent byproducts of the metabolism of arachidonic acid formed upon activation of the mast cell. The mast cell is able to catabolize essential membrane components and convert them into biologically active mediators through a complex cascade of membrane-bound and soluble enzymes. The overall pathway is seen in Fig. 4. The leukotrienes, produced by the action of the 5-lipoxygenase system on arachidonic acid, demonstrate many different activities, of which the most prominent is immediate bronchoconstriction. They also can cause vasoconstriction in both the pulmonary and vascular beds. The primary leukotrienes made by human mast cells are B_4, C_4, D_4, and E_4. The leukotrienes, especially D_4, are greater than 10 times more potent than histamine.

Arachidonic acid is also broken down by the action of the cyclooxygenase pathway, resulting in the formation of prostaglandins, prostacyclins, and thromboxanes. These compounds generally function as local hormones and produce many of the same symptoms as the leukotrienes, such as bronchoconstriction, cough, and vasodilatation. The

MEDIATORS OF ALLERGIC REACTIONS

Molecules released from activated mast cells and basophils account for many allergic symptoms. This list includes a sampling of those chemicals and some of their effects, which can be redundant.

	CHEMICAL	ACTIVITY	SYMPTOMS
MEDIATORS FROM GRANULES	Histamine	Constricts bronchial airways	Wheezing; difficulty breathing
		Dilates blood vessels	Local redness at sites of allergen delivery· widespread dilation can contribute to potentially lethal hypotension (shock)
		Increases permeability of small blood vessels	Swelling of local tissue; if widespread, increased permeability can contribute to shock
		Stimulates nerve endings	Itching and pain in skin
		Stimulates secretion of mucus in airways	Congestion of airways
	Platelet-activating factor	Constricts bronchial airways	*Same as for histamine*
		Dilates blood vessels	*Same as for histamine*
LIPID MEDIATORS	Leukotrienes	Constricts bronchial airways	*Same as for histamine*
		Increase permeability of small blood vessels	*Same as for histamine*
	Prostaglandin D	Constricts bronchial airways	*Same as for histamine*

Fig. 3. Mast cell mediators and their effects. (Adapted from Lichtenstein L. Allergy and the immune system. Sci Am 1993;369:117–124, with permission.)

main prostaglandin produced by human mast cells is PGD_2, a compound at least 30 times as potent as histamine in causing bronchoconstriction. Thromboxane A_2 and prostacyclin (PGI_2) produce bronchoconstriction and bronchodilatation, respectively. Together they function as a mechanism to maintain bronchial and vascular tone.

Platelet-activating factor (PAF) is a phospholipid. PAF is produced by mast cells (as well as macrophages, neutrophils, and eosinophils) and functions to activate platelets and neutrophils and vasoconstrict smooth muscle. Perhaps most importantly, PAF stimulates chemoattraction of eosinophils to endothelial surfaces and eosinophil release of other cell mediators. PAF is rapidly inactivated in vivo, suggesting that it serves as a trigger of inflammatory events rather than a major mediator itself.

The identification of cytokines synthesized by mast cells and basophils is currently an area of intense investigation. Cytokines represent the primary mechanism by which cells

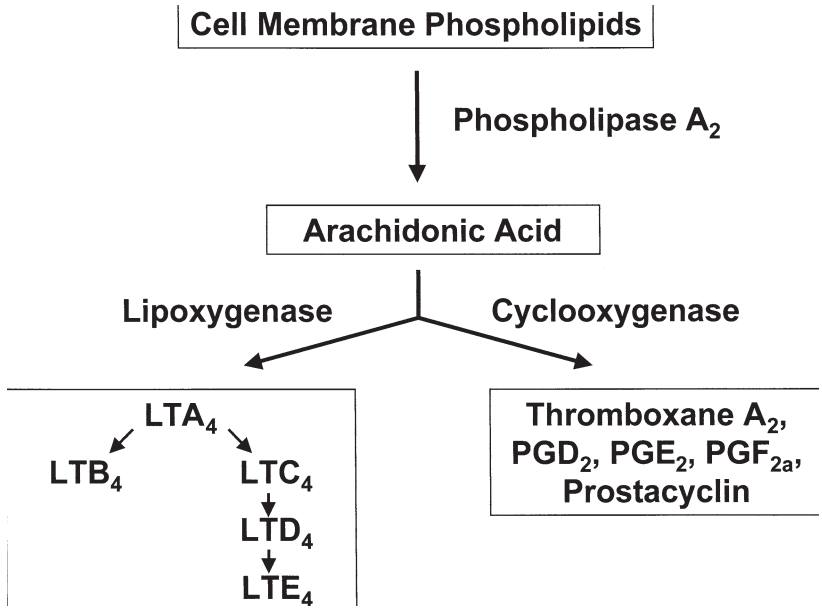

Fig. 4. Arachidonic acid metabolic pathways. Arachidonic acid, released as a result of phospholipase on the cellular membrane, is broken down by two distinct biochemical pathways: The lipoxygenase pathway results in formation of the leukotrienes (LT), whereas the cyclooxygenase pathway generates prostacyclin, thromboxane, and the prostaglandins (PG).

can influence the activity and development of unrelated cells and related cells in an exocrine and autocrine fashion. Human mast cells produce IL-4 and IL-5 as well as tumor necrosis factor (TNF)-α. The IL-4 stimulates mast cell differentiation and promotes immunoglobulin class switching to the IgE isotype. IL-5 is the most influential cytokine involved in eosinophil production and survival in humans. TNF-α increases vascular permeability and leukocyte migration.

Basophils have long been incorrectly viewed as the bloodborne equivalent of mast cells with analogous granules and functions. However, these cells represent a hematopoietic lineage distinct from mast cells, can also infiltrate tissues, and contain neither tryptase nor chymase. In addition, basophils seem to have a different role in the allergic reaction scenario. They tend to release abundant amounts of histamine but little, if any, PGD_2. This finding has been cited as evidence of their contribution to late-phase allergic inflammatory events in the nose, skin, and lung. The presence of increased histamine, but undetectable PGD_2, during late responses implies that basophils are recruited to sites of allergic inflammation (*see* Early- and Late-Phase Responses).

ACTIVATION OF THE MAST CELL

The mechanism by which the external signal of IgE crosslinking is translated into cellular activation, granule release, and *de novo* synthesis of new molecules is a fascinating tale of cellular adaptation and biochemistry. An overview of the reactions is illustrated in Fig. 5.

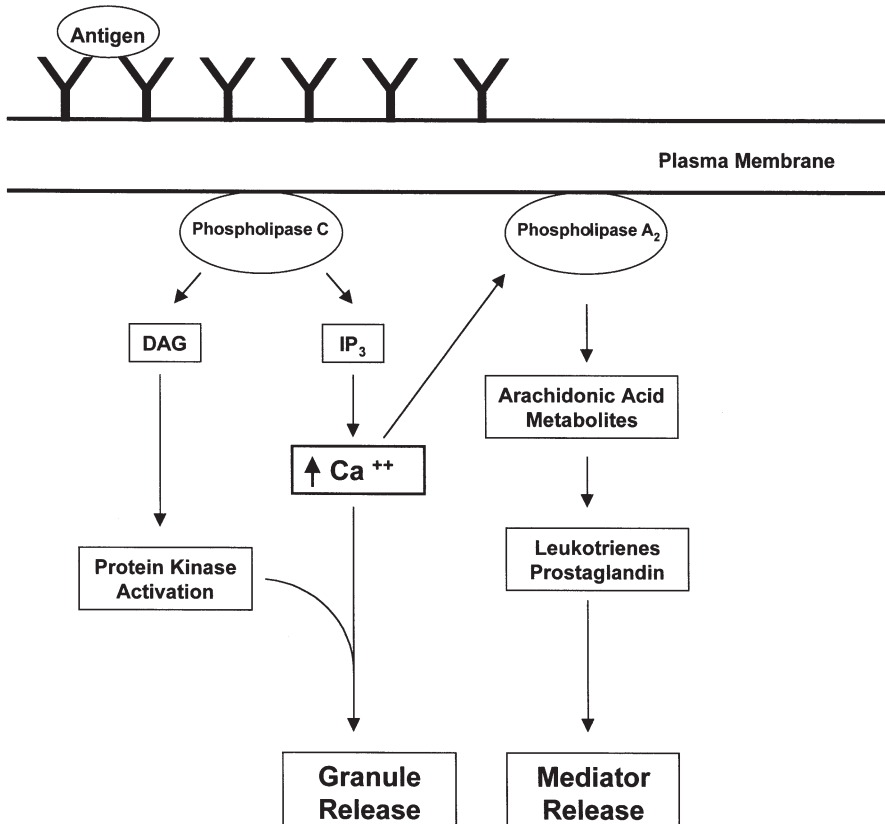

Fig. 5. Mast cell activation: biochemical reactions. Following IgE crosslinking by antigen, a series of protein kinase reactions culminate in the activation of phospholipase C, releasing diacylglycerol (DAG) and inositol triphosphate (IP_3) from the plasma membrane. The IP_3 releases calcium stores from the endoplasmic reticulum, which, along with DAG-stimulated kinases, leads to granule release. The intracellular calcium also activates phospholipase A_2, which generates arachidonic acid, a compound metabolized to form leukotrienes and prostaglandins.

The process begins with the crosslinking of two or more IgE molecules on the mast cell surface. This requires a multivalent antigen (i.e., more than one IgE-binding site on the same molecule). Monovalent antigens will not trigger mast cell activation. Once the antigen is attached to the mast cell by more than one IgE molecule, a series of cytoplasmic signals occur causing activation. This process is called signal transduction and is a method of cellular communication with the external environment. In this case, the signal enters the cell via a conformational change in the FcεRI-α receptor.

Once the antigen is bound to the mast cell via the IgE molecules, the cell begins a series of biochemical events that culminates in the release of its granules and the production of lipid mediators (arachidonic acid metabolites). The production of the lipid mediators requires effective intracellular scavenging by the mast cell. The principle is to cannibalize lipids from the membrane and transform them into potent mediators. PLA_2, activated by the calcium released from the endoplasmic reticulum, starts degrading phosphatidyl choline. In turn, arachidonic acid is formed and metabolized via the two pathways men-

tioned earlier: the lipoxygenase pathway (which produces leukotrienes) and the cyclooxygenase pathway (which produces prostaglandins). As stated previously, the main prostaglandin produced by mast cells is PGD_2. Leukotrienes B_4 and C_4 are the primary leukotrienes made. Leukotriene C_4 is subsequently converted to active compounds LTD_4 and LTE_4. The activities of these lipid mediators are described elsewhere.

In summary, the mast cell needs to accomplish two functions following activation: to release its granules with their associated biologically active compounds and to synthesize additional mediators of the allergic reaction using its cell membrane constituents as precursors. These activities utilize a great deal of cellular energy, most of which is obtained from the high-energy phosphate bonds generated by the action of protein kinases. The initiation of these cascades depends on interaction of the mast cell with antigen. The prerequisite crosslinking of the IgE molecules probably evolved as a safety mechanism to prevent premature activation of the cell. A sufficient quantity of specific IgE must be bound to the mast cell to achieve a crosslink, which is possible only if sensitization had occurred previously.

Allergic (IgE-mediated) activation of the mast cell was summarized earlier, but there is an alternate, IgE-independent mechanism of mast cell degranulation that should be mentioned. This degranulation is the result of mast cell membrane perturbation at a molecular level, often requiring calcium influx. This nonimmunological degranulation may be triggered by opioids, anaphylatoxins (complement components), and radiological contrast dyes. In fact, the majority of patients who report a history of "allergic reactions" to contrast dyes have experienced non-IgE-mediated reactions.

EFFECTS OF MAST CELL MEDIATORS ON TARGET ORGANS

The examination of the mechanisms contributing to the release of mast cell mediators is only half the story of allergic pathophysiology. The spectrum of symptoms that prompts a visit to the allergist begins only after these substances are released from mast cells and interact with resident and infiltrating cells in various target organs. In the case involving the 8-mo-old girl sensitized to peanut, these mediators combined to cause anaphylaxis. Histamine was liberated from the mast cell granules and was quickly dispersed through the bloodstream. Histamine receptors are located on many target organs, including the skin, the nasal mucosa, the smooth muscle of the lungs and gastrointestinal tract, and vascular epithelial cells. Once bound to its receptor, histamine causes such diverse effects as vasodilatation of small vessels with subsequent exudation of fluid into surrounding tissue; smooth muscle contraction, an effect of particular import when one is considering the muscles surrounding the bronchial airways; and increased glandular mucus secretion, an annoyance in the nasal mucosa but dangerous in the small bronchioles. Extremely high doses of histamine cause these effects to occur on a systemic level, possibly leading to hypotensive shock in the case of massive vasodilatation.

The lipid mediators cause symptoms that are very similar to histamine; however, their effects are more persistent. Histamine is rapidly degraded in the serum with a half-life of 1 min, but the lipid mediators are slowly metabolized. As you recall, both leukotrienes and prostaglandins are synthesized only after an allergic reaction has begun, thus accounting for the delay in onset of action. Historically, leukotrienes were collectively termed the slow-reacting substance of anaphylaxis because of this delay in activity. Once released in the serum, the prostaglandins bind to specific receptors and lead to bronchial smooth

muscle contraction in the lungs, vasodilatation in the skin, and nasal blockage. Leukotrienes are also highly potent bronchoconstrictors but utilize distinct receptors on the smooth muscle cells. They also increase permeability at postcapillary venules, leading to localized tissue edema.

ALLERGIC INFLAMMATION: A TH_2-MEDIATED RESPONSE

Just as IgE production and mast cell activation are key components to the initial allergic response, several other cells play a role in propagating this allergic inflammatory response. After the immediate release of mast cell mediators following allergen exposure, leukocytes influx into affected tissues. This occurs approx 2–8 hr after allergen exposure and has been termed the late-phase reaction (LPR) or the late allergic response (LAR). It is explained in detail later. The primary cell types recruited to sites of LPR include basophils, eosinophils, neutrophils, lymphocytes, and macrophages. The main attractants for these cells are cytokines secreted by mast cells, T-cells, and epithelial cells. Cells present during the initial allergic response, such as mast cells, as well as cells that migrate into tissues following an increase in vascular permeability, generate cytokines. Many cytokines contribute to this influx; however, IL-4, IL-5, TNF-α, and chemotactic cytokines termed chemokines play major roles. TNF-α and IL-4 attract basophils. IL-5 is a potent eosinophil activator, and C-C chemokines such as RANTES (regulated on activation, normal T-cell expressed and secreted) promote eosinophil migration into tissues. These responses collectively parallel the TH_2 cytokine profile shown in Fig. 2. In cases of perennial allergic rhinitis, perennial asthma, and acute atopic dermatitis, T-cells isolated from the affected tissues (nose, lung, or skin, respectively) exhibit a predominantly TH_2 cytokine profile. However, it is important to remember that any T-cell population will express heterogeneity and not uniformly possess one cytokine profile.

EARLY- AND LATE-PHASE RESPONSES

An important aspect of allergic disease, with scientific and clinical implications, is the concept of the late-phase IgE-mediated reaction. The mast cell activation pathway (described above) occurs within minutes of allergen exposure. All mechanisms and components of the system are designed for almost instantaneous responses. Once the initial surge of mediator release is completed, there is regeneration of the mast cell granules, although this process may take days to weeks to be completed. If one were to speculate that an allergic reaction represents an exaggerated host response to a foreign invader (or allergen), then it might make sense to have a backup system in place in case the immediate response is not completely successful. In the teleological sense, that is precisely what the late-phase response does.

The late-phase response is a delayed-in-time inflammatory response that occurs following mast cell activation. It may function to amplify an initial signal resulting from the first wave of allergen "attack." In response to a barrage of chemotactic and differentiative cytokines, multiple cell lineages (e.g., eosinophils, neutrophils) are summoned to the site of this breach of the immune system. Together, these summoned cells constitute the inflammatory or late allergic response (LAR). The LAR lacks the speed of the immediate response, but it more than makes up for this in terms of magnitude. The LAR typically occurs 2–8 h after initial allergen exposure. Subtle differences in the

nature and effect of the mediators involved in the LAR have been observed in each anatomical location in which it has been described. We will consider two such environments: the skin and the nose.

The cutaneous early reactions are well described: a characteristic wheal-and-flare reaction is seen with a positive skin test in an atopic individual. It resembles a mosquito bite in that it consists of a pale, circumscribed central area of edema surrounded by an erythematous diffuse border. This typical early-phase reaction will peak in 15 min and resolve in 30–60 min. In some cases, however, the early-phase response will persist for hours and progress into a late-phase response that peaks 6–8 h following allergen exposure and lasts up to 24 h. The cellular infiltrate observed 6–12 h after a cutaneous allergen challenge consists of a mixed population of neutrophils, eosinophils, and lymphocytes. Mediators produced in the cutaneous LAR reflect the nature of the cells summoned to the area and include various interleukins (IL-1, IL-4, IL-6).

The nasal late-phase response is characterized by a cellular infiltrate of eosinophils, mononuclear cells, and neutrophils and is often accompanied by fibrin deposition. The mediators produced in the nasal LAR are identical to those present in the early response with one exception: PGD_2 is absent. As mentioned earlier, the presence of histamine without PGD_2 suggests that basophils may play a prominent role in the nasal LAR. They characteristically produce negligible amounts of PGD_2 while maintaining a high histamine content. Nasal congestion is the predominant symptom associated with the nasal LAR (rhinorrhea and sneezing are generally associated with the early response).

CONCLUSION

Several generalities apply to all tissues in which an allergic reaction can occur. The immediate result of an interaction between a sensitized mast cell and a specific allergen, also known as the early-phase response, results in the release of preformed mediators. Both local and distal target organ effects are exhibited as a result of the early-phase response. Although the cellular effects of these mediators are similar on each tissue, the clinical symptoms produced may differ. For example, increases in vascular permeability may present as angioedema in the skin or as congestion in the nose. The presence of a late-phase response is also seen in various issues and represents the inflammatory response. Because the goal of the late-phase response is to attract inflammatory cells, the cytokine profile differs slightly from the immediate response.

How does this relate to the 8-mo-old girl with the allergy to peanuts? Her primary care physician wisely sent her to a specialist. The girl was skin-tested to peanuts and had a positive testing indicating sensitization. In combination with her history, this confirmed the suspected diagnosis of peanut allergy. Her family was instructed on avoidance measures, and Epipen Jr was prescribed and instructions given on its use. She diligently avoids peanuts without other sweeping food restrictions. As we will see in later chapters, there are many immunological and pharmacological interventions that may be useful in preventing both immediate and late-phase allergic reactions. An appreciation of the pathophysiology of the allergic reaction is essential to the proper use of these treatments.

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2 Approach to the Allergic Patient

Bruce L. Wolf, MD

CONTENTS

SUMMARY

Allergic disease is protean in its manifestations, affecting single or multiple organ systems. It may also mimic other conditions. The clinician must be prepared to take an in-depth history, make a comprehensive physical examamination, and seek appropriate objective measures in order to adequately consider the differential diagnosis and arrive at a proper diagnosis.

No less important is the conference with the patient once the diagnosis has been established. At that meeting, findings and impressions should be summarized in language understandable to the patient. Terminology should be carefully chosen and prognosis phrased optimistically whenever possible. Likewise, medication regimen (including inhaler technique) and rationale, environmental and lifestyle modifications, and/or follow-up may be discussed.

Key Words: Allergic; asthma; atopic; diagnostic; examination; history; rhinitis; skin testing.

INTRODUCTION

Although it often is remarked that everyone is allergic to something, in truth, only about 25–30% of the population is allergic to anything. This frequency is enough to make the allergic patient a common visitor in every medical setting. In addition, many disorders mimic allergy symptoms. Therefore, the differential diagnoses of various disease states must include allergy as a possibility.

Allergy can affect virtually any organ system. Common types of presentation include conjunctivitis (eyes), rhinitis (nose), urticaria and angioedema or atopic (allergic) dermatitis (skin), asthma (lungs), and anaphylaxis (multiorgan). Evaluation of suspected allergy must include a detailed medical history, comprehensive physical examination, and appropriate diagnostic tests.

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HISTORY

The most important component of the evaluation of a possible allergic problem is the patient's history. It is from the history that salient physical examination and tests follow. An allergy history is made up of a chief complaint, determination of seasonality or diurnal variation of symptoms, identification of triggers, occupational exposure, response to medication, family history, and other pertinent medical history. It may not be obvious to the patient what historical factors are important; thus, it is recommended that a questionnaire that screens for contributory factors be used (Fig. 1).

The history is the most important element in the evaluation of allergy. Key features of the history are:

- Worsening of symptoms on exposure to aeroallergens
- Seasonal variation in symptoms related to pollination of trees, grasses, and weeds
- A family history of atopic disease
- An environmental history assessing exposure at workplace and home
- The presence of associated allergic conditions

An allergy history seeks to define the patient's chief complaint(s) and focuses on the details concerning those complaints. If the chief complaint is narrow in scope, for instance, "I sneeze all the time," then the clinician may be tempted to direct the majority of the questions toward a given organ system. This approach should be avoided and the patient given ample opportunity to expound on the extent of the complaint.

There is a lexicon common to patients with allergy complaints. Many state that they have "sinus" or "hay fever." They describe a wide array of symptoms ranging from itchy nose, eyes, or palate to runny nose or postnasal drainage to nasal congestion. Sinus pressure and headaches are frequently cited as symptoms. "Popping or fullness of the ears," implying eustachian tube dysfunction, is an often heard complaint. Asthma symptoms may be overt and present as wheezing, but descriptions my be more subtle, such as cough, tightness in the chest, or inability to get a good breath or let all the air out of the lungs.

The history taker should be attuned to the patient's perspective as a potential allergy sufferer. Where and when do the symptome occur? Do they interfere with daily activities, school or work, or exercise? Is there seasonal variation to the symptoms, or are they of a perennial nature? Are the symptoms worse at a particular time of day? During sleep?

At first, questions searching for triggers should be open-ended. For instance, "What seems to trigger your symptoms?" rather than "Does this or that bother you?" If patients are reticent or rambling in their responses, direct questions may be appropriate. In most cases, the patient will stipulate if symptoms are worse inside the house or outdoors.

Increasingly, indoor allergens are recognized as important triggers and sensitizers of the allergic patient. Type of home and the presence of a basement may be important. For example, a wet environment tends to produce growth of molds and dust mites. House dust mite is likely the most common allergen in our society. It is found in greatest abundance in bedding, pillows, carpet, and upholstered furniture. Therefore, the kind of bedding and

type of flooring may be relevant to understanding a given patient. Mold sensitivity has been popularized in the press, but there is little scientific data to support the hysteria of mold causation. Cockroach is another allergen increasingly implicated with public housing, inner-city asthma, and allergic respiratory disorders. Particular attention should be given to any exposure to pets. Do the pets sleep in the bedroom or on the bed?

It may be difficult to distinguish between an irritant and an allergen. Irritants are often misconstrued as allergens because they can cause the same cascade of symptoms. Examples of irritants include cigarette smoke, perfume, cold air, strong odors, and cleaning solvents.

Outdoors, the allergic patient faces pollution (irritant) and pollens (allergens). Trees, grasses, and weeds can wreak havoc on an allergic sufferer. Likewise, different pollens may predominate in a particular region. For example, Bermuda grass may be prevalent in Florida but not in Montana. A given allergen can have its particular season, as in the case of pollen, or be perennial in its presence like the dust mite. One pollen season can also overlap another; that is, grass pollination can coincide with pollination of ragweed. This is often important because one allergen can prime a person to have heightened sensitivity to another. Growing seasons may vary according to residential area. In summary, the history taker is always confronted with the puzzle of microcosm vs macrocosm. Although television pollen counts may report elm pollen, those same reports do not anticipate which trees predominate outside a bedroom window or in a given neighborhood or in the courtyard where the patient takes a work break.

Occupational exposure must always be considered. If indicated, material safety data information sheets may be requested to better overview what the patient may be breathing in their work environment. Day-care facilities can be an insidious source of recurrent viral and bacterial exposure for children.

Family history of an allergic diathesis should be sought. The genetics of allergy are not entirely understood, but a parent with atopy roughly doubles a patient's chance of being atopic. Risk of atopy is increased from 25% in the general population to about 75% when both parents are atopic. In one study, 90% of allergic asthmatic children had one or both parents who were atopic.

In asthma, objective measures such as spirometry and peak flow measurements paint only part of the picture. History should help to delineate the asthma as mild, moderate, or severe. Questions to determine the extent of asthma control include type and amount of inflammatory medication used (type of delivery system and quality of inhaler technique), frequency of respiratory symptoms and need for β-agonists, interference with daily activities or sleep, and diurnal peak flow variability if known. In some practices, a quality-of-life survey is now employed to address subjective parameters that contribute to asthma severity.

Degree of severity will ultimately dictate choice and intensity of treatment. Emergency room visits or hospitalization for asthma in the past year or use of oral steroids in the last 6 mo identify the more severe asthmatic. Psychosocial problems, lower socioeconomic status, and history of previous intubation are potential risk factors for increased asthma morbidity and mortality.

Confounders of asthma must always be kept in mind. For instance, a history of recurrent use of antibiotics, frequent colds, or cough in a supine position may point to chronic sinusitis. Gastroesophageal reflux can present solely as cough and sometimes mimic or exacerbate asthma. Irritation of the skin presenting as pruritus or rash is frequently attributable to soaps that are too drying.

Primary reason for coming to Allergy & Asthma Specialists:

_____

Check your main symptoms - those that prompted your visit here:

Head or Nose	**Chest**	**Skin**	**Insect Stings**
☐ Sneezing	☐ Cough	☐ Eczema	☐ Hives
☐ Runny Nose	☐ Wheezing	☐ Itching	☐ Swelling
☐ Postnasal drainage	☐ Shortness of breath	☐ Swelling	☐ Shortness of breath
☐ Nose Blocking	☐ Hoarseness	☐ Hives	☐ Itching
☐ Sinus Infections	☐ Chest Infections		☐ Dizziness
☐ Sore Throat	☐ Voice Loss		☐ Fainting
☐ Ear Blocking			
☐ Headache			
☐ Snoring			
☐ Nosebleeds			
☐ Eye Symptoms			

How many years have you suffered from the chief complaints of:

Head or Nose symptoms _____ Chest symptoms _____

Skin symptoms _____ Insect Sting reactions _____

Please indicate pattern of symptoms:

	Head/Nose	**Chest**
Year round, no seasonal change	_____	_____
Year round, worse seasonally	_____	_____
Seasonally only	_____	_____

If seasonal, list months: _____

Are your symptoms worse at night? Yes ☐ No ☐

Do you note increased symptoms from any of the following?

Allergens	**Irritants**	**Ingestants**	**Weather**
☐ Mown grass	☐ Perfumes	☐ Alcoholic beverages	☐ Windy days
☐ Dead grass	☐ Soap	☐ Drugs	☐ Cold fronts
☐ Dead leaves	☐ Detergent	☐ Foods	☐ Temperature change
☐ Hay	☐ Cleaning agents	☐ Other (list):	☐ Damp weather
☐ House dust	☐ Smoke	_____	
☐ Cats	☐ Paint	_____	
☐ Dogs	☐ Hair spray	_____	

Please check the ones that best describe your home:

☐ House (Age:_____) ☐ Apartment ☐ City ☐ Country

Do you have a basement? ☐ Yes ☐ No

Type of heating system: ☐ Central ☐ Floor ☐ Electric ☐ Other:_____

Type of mattress: ☐ Conventional ☐ Waterbed

Type of pillow: ☐ Synthetic ☐ Down

Do you have stuffed animals? ☐ Yes ☐ No

Do you have carpet in your home? ☐ Yes Type: _____ ☐ No

Are your symptoms worse anywhere in your home? ☐ Yes Location: _____ ☐ No

Do you have pets at home? ☐ Yes What Kind: _____ ☐ No

Are your pets kept: ☐ Inside ☐ Outside

Fig. 1. Screening for contributory factors.

Are your symptoms worse at your workplace / school? ☐ Yes ☐ No
Have your symptoms been so severe as to cause you to miss work or school? ☐ Yes ☐ No
If so, how many days? _____
Has travel affected your symptoms? ☐ Yes ☐ No
Do you have hobbies that expose you to allergens or irritants? ☐ Yes ☐ No
If yes, explain briefly: _____

List medicines you use for the relief of allergy symptoms (including nose drops or sprays):

_____
_____

List other drugs you take for any reason (include all over-the-counter drugs, creams, suppositories, eye drops, etc.):

_____
_____

Can you take aspirin? ☐ Yes ☐ No
Are you allergic to any medications? ☐ Yes ☐ No
If yes, please list: _____
What type of reaction occurs? _____

Have you ever taken hypo-sensitization shots (allergy shots) before? ☐ Yes ☐ No

Have you ever had a chest x-ray? ☐ Yes ☐ No If yes, when? _____ Where? _____
Have you ever had a sinus x-ray? ☐ Yes ☐ No If yes, when? _____ Where? _____
Do you smoke? ☐ Yes ☐ No
If yes, how many packs per day? _____ How long? _____
Have you ever smoked? ☐ Yes ☐ No
If yes, how many packs per day? _____ How long? _____
Does anyone you live with smoke? ☐ Yes ☐ No
If yes, who? _____
Are you exposed to smoke at work or school? ☐ Yes ☐ No

Is there a history of any of the following in your family?
☐ Asthma ☐ Hay fever ☐ Nasal polyps ☐ Eczema ☐ Hives
If so, which family member? _____

Have you ever been treated in an emergency room? ☐ Yes ☐ No
If yes, how many times? _____
For what were you treated? _____
List all hospitalizations in order of most recent:

Cause of Hospitalization	Age
_____	_____
_____	_____
_____	_____
_____	_____

Circle any of the following that you might have had:
Stomach ulcer Diabetes Glaucoma High Blood Pressure
Circle any of the problems that you might have had with the following:
Blood Bones Heart Nervous system Urinary tract
List any medical problems you have not noted above: _____

Fig. 1. *(continued)*

A good drug history is necessary because medications often contribute to the allergic presentation. There are many examples. Frequent use of decongestant nasal spray can lead to rebound nasal congestion, also called rhinitis medicamentosa. Over-the-counter preparations (such as aspirin or nonsteroidal anti-inflammatory compounds, vitamins, and alternative remedies and herbal supplements), often not considered medication by the patient, may be causal factors in urticaria. Likewise, angiotensin-converting enzyme inhibitors and oral or ocular β-blockers may lead to cough or worsening of asthma.

The physical examination may be entirely normal at the time of the examination, because allergy symptoms and signs are often evanescent. The examination should emphasize the organs involved with allergy symptoms.

PHYSICAL EXAMINATION

An allergic patient's history may direct the clinician's examination to a particular area or organ system. A specific allergic symptom, however, should not divert the examiner's attention from the patient as a whole. Each patient should be approached in a systematic way. Often physical examination may be normal; lack of findings does not rule out allergy.

Vital signs are a starting point in any examination. Pulse rate and pulsus paradoxicus greater than 10 mmHg are two of the most sensitive indicators of severe airway obstruction. Respiratory rate is important as well, but hyperventilation is more a reflection of minute ventilation (respiratory rate × tidal volume) than respiratory rate alone. Fever (>100°F) is an infrequent manifestation of allergy and points the differential elsewhere.

With the worldwide increase in the use of inhaled corticosteroids for the treatment of allergic respiratory disease, growth in children has been more closely scrutinized. Height and weight should be measured in children on a periodic, at least annual, basis. Although growth in children may often occur in spurts, change in growth velocity or decremental change in height or weight percentile should alert the physician to consider reasons for change in growth with the knowledge that growth in atopic and asthmatic children is generally delayed and usually not strictly linear.

Clues to allergic propensity are often seen in the patient's face. Discoloration of the infra-orbital skin or "allergic shiners" may imply nasal congestion and subsequent lymph stasis. Extension of the mid-face or adenoid facies in children with adenoid hypertrophy, an infra-orbital crease or Dennie's line, and a transverse crease along the lower half of the nose are frequent but not absolute indicators of underlying allergy.

The eye examination is concerned principally with the state of the tarsal (lower lids) or palpebral (upper lids) and bulbar conjunctivae. Degree of injection is noteworthy. In vernal conjunctivitis and giant papillary conjunctivitis, the superior palpebral conjunctivae show papillary hypertrophy or cobblestoning and may be accompanied by a stringy, fibrinous secretion. Horner-Trantas dots, small white spots at the limbus, are sometimes seen in association with vernal conjunctivitis. Cataracts are found with increased incidence in atopic individuals; pingueculae are not.

Tympanic membranes should be visualized. Tympanosclerosis implies previous recurrent otitis and/or a history of myringotomy. If the light reflex is not well appreciated or

history suggests eustachian tube dysfunction, the tympanic membranes should be examined while the patient performs a Valsalva maneuver or with an insufflator to judge the functional patency of the eustachian tube. Sterile fluid behind the eardrum, a condition known as secretory otitis, is often seen. Assessment of hearing is ideal to establish a baseline.

The nose is best examined with an otoscope, head lamp with a nasal speculum, or a fiberoptic rhinoscope. Special attention should be directed to the degree of congestion and color of the nasal turbinates. A blue tint strongly points toward allergic etiology. Also, the condition of the nasal septum must be ascertained, especially the presence of deviation, bowing, spurs, or perforation. The integrity of Kesselbach's plexus—the most common source of epistaxis—can be compromised by intranasal steroids. To the best of one's ability, the examiner should rule out nasal polyps, other masses, and discharge. Many times, it may be necessary to shrink the mucosa with topical decongestants, oxymetazoline, or dilute cocaine to visualize the nasal passages adequately. Lastly, a history of anosmia calls for testing with various spices to assess function of the olfactory system.

The size and character of the tonsils should be noted. However, tonsils do not predict presence of hypertrophy of the adenoids. The oropharynx should be scrutinized for drainage or raised islands of lymphoid tissue (lymphoid hyperplasia) often seen in smokers or profound atopics. Finally, estimation of the depth and width of the oropharynx may lead to suspicion of obstructive sleep apnea. For those patients taking inhaled corticosteroids, thrush on the tongue and soft palate should be excluded at each visit.

The neck must be palpated to search for adenopathy. At the same time, the thyroid gland should be assessed, because thyroid hormone imbalance can confound allergic symptoms. In patients with wheezing, the larynx should be auscultated to rule out stridor as an upper airway origin. Accessory muscle use of the sternocleidomastoid muscles should not be missed because it is another sign of marked airway obstruction.

Lung examination is particularly relevant in the asthmatic. Configuration of the chest wall should be noted; in particular, pectus excavatum, kyphosis, lordosis, and scoliosis should be ruled out by inspection. Restrictive airways disease must always be considered along with obstructive airways disease. Intercostal retractions imply severe obstructive disease. Increased anterioposterior diameter may imply air trapping and hyperinflation. Wheezing should be listened for during basal breathing as well as on forced expiration, but absence of wheezing or a silent chest does not rule out bronchospasm. Extent of chest excursion and the inspiratory:expiratory ratio noted on presentation may represent important markers of change on serial examinations.

Finally, the skin is commonly affected by allergy, although skin findings are often falsely attributed to allergic disorders. Xerosis is unrelated to allergy *per se*; however, individuals with atopic dermatitis have, in general, exceedingly dry skin. In addition, in subacute atopic dermatitis the skin may contain erythematous, scaling papules. In patients with chronic atopic dermatitis, the skin is thickened with increased markings, known as lichenification. Both groups of patients may show signs of excoriation. Lesions of urticaria, or hives, are pruritic, raised, and erythematous, varying in size from pinpoint (cholinergic) to giant. They are protean: rounded or morbilliform or appearing as target lesions. Dermatographism, a transient wheal-and-flare reaction, when present, occurs within minutes after scratching the skin. The lesions of angioedema are indurated and usually not as well demarcated as urticarial lesions.

ALLERGY TESTING

Skin testing is the most sensitive and cost-effective way to screen for existing allergic sensitivity. Biological extracts of aeroallergens including trees, weeds, dust mites, cockroaches, molds, and animal danders are available for testing (Fig. 2). The most accepted way to test is by placing a drop of antigen on the surface of the patient's skin and scratching or pricking the skin with a lancet or sharp plastic. If tests are not reactive, an intradermal 1:1000 dilution of the concentrate may be applied to rule out any minor sensitivity of a given antigen. Reactions are immediate, and scoring of the tests, based on size of the wheal and flare of a given test, is done in 15 min. Negative (saline) and positive (histamine) controls are placed at the same time, the latter to ensure that antihistamines are not present and blocking reactions.

The most important ancillary test to confirm the diagnosis of allergy is the skin test, which is the gold standard in this regard.
The skin test results must be interpreted in light of the history to determine the importance of a positive test.

Age and chief complaint will help to determine the number of tests applied. For instance, a child younger than 4 years of age (not a candidate for immunotherapy) would likely receive only a few skin tests (including dust mite and relevant animal danders) to see if he or she might be able to avoid or minimize exposure to an antigen.

Other types of testing are also available. Food testing (prick testing only) is rarely indicated in the work up of urticaria, acute or chronic angioedema, or anaphylaxis unless history of food ingestion is strongly suggested as a trigger. Except for penicillin testing, skin testing to drugs is not well understood. Skin testing to penicillin is usually done in a hospital setting when acceptable substitutes for penicillin cannot be found. Patients may also be skin tested to hymenoptera, or stinging insect venom, to determine if anaphylactoid reactions may be IgE-mediated.

No matter how strongly a history suggests allergy, testing must be done to confirm atopy. An important caveat is that a positive skin test does not prove that allergy is causing the patient's symptoms. A positive skin test must be correlated with the history to postulate cause and effect.

DIAGNOSTIC STUDIES

Few blood abnormalities are found in an allergic patient. Eosinophils are often associated with allergy but are rarely increased in allergic rhinitis. More commonly, eosinophils are a peripheral marker of inflammation and are elevated in nonallergic as well as allergic asthma. Eosinophils can be measured by means of an automated complete blood count or a manual total eosinophil count. The number is considered abnormal if it is greater than 7% of the total white blood count or greater than 350/mm^3.

Nasal smears may be helpful in distinguishing an infectious process in the nose from an eosinophilic process. Predominance of segmented neutrophils implies underlying bacterial infection; more than10 eosinophils/high-power field as assessed by Wright's stain are frequent in allergic rhinitis. However, as in peripheral smears, eosinophils in the

ALLERGY & ASTHMA SPECIALISTS
ALLERGEN TESTING

Name: _____ **Date:** _____
DOB: _____ **Sex:** _____ **MEDICATIONS WHICH MAY AFFECT TESTING**

MEDICATION	DATE OF LAST DOSE

Location of Test(s): _____

TREES	PRICK	ID
Boxelder - Maple		
Sycamore		
Hackberry		
Walnut		
Elm		
Oak Mix		
Pecan		
Willow		
Ash		
Beech		
Cottonwood		
Birch Mix		
Cedar, Mountain		
Pine Mix		

GRASS	PRICK	ID
**Bermuda		
* Rye		
Johnson		
* Timothy		
Bahia		
* Kentucky Blue		
* Redtop		
* Orchard		
* Meadow Fescue		
* Sweet Vernal		

WEEDS	PRICK	ID
Ragweed Mix		
English Plantain		
Russian Thistle		
Lambs Quarter		
Careless Pigweed		
Marshelder-Poverty		
Dock, Sorrel		
Cocklebur		
Mugwort		

MOLDS	PRICK	ID
Alternaria		
Hormodendrum		
Heminthosporum		
Aspergillus Fumigatus		
Rhizopus		
Aspergillus Niger		
Fusarium		
Penicillium Notatum		

ENVIRONMENTALS	PRICK	ID
**Dust Mite F.		
**Dust Mite P.		
Cockroach		
**Cat 1 (Hair)		
**Cat 2 (Pelt)		
Dog		
Feathers		

COMMENTS _____

_____

_____

_____

_____

_____

_____

_____

_____

Control - Positive - Histamine _____
Control - Negative _____

TREES: GRASSES: WEEDS - 1:20
MOLDS: COCKROACH: DOG - 1:10
***STANDARDIZED - 100,000 BAU/ML**
****STANDARDIZED - 10,000 BAU/ML**

EXTRACTS - BAYER, INC.
HISTAMINE - CENTER LAB

#PRICKS _____ **TIME** _____
#IDS _____ **TIME** _____
EMPLOYEE INITIALS _____

Fig. 2. Allergen testing.

nose are not specific for allergy; they can also be seen in patients with nonallergic rhinitis with eosinophilia syndrome.

IgE is the antibody that accounts for allergic reactions. IgE is measured in international units (1 IU = 2.4 ng IgE). Umbilical cord levels greater than 1.0 IU are a good predictor of whether a newborn will develop allergic disease. Similarly, serum IgE levels greater than 20 IU/mL in infants predict allergic disease. On the other hand, total serum IgE (normal 0–100 U/mL) is rarely helpful in children or adults, as roughly only 75% of atopic individuals have IgE levels greater than 100 U/mL. In other words, 25% of allergic individuals have normal total IgE levels. Total IgE is useful in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. It is also elevated in active atopic dermatitis.

In vitro tests for specific IgE antibodies include the radioallergosorbent test (RAST) and other enzyme-linked immunosorbent assays. These tests are more expensive and less sensitive than skin tests. A disadvantage of RAST testing over skin tests is that their results are not immediately available to the clinician. Therefore, they are usually reserved for those patients with bad eczema or marked dermatographism that prohibit skin tests, patients who cannot forgo medications that block skin testing, or patients with a history of profound anaphylaxis when skin testing might be dangerous. These tests are usually scored on a class 0 (negative)–class 6 (highly positive) scale, with 0–2 scores being considered indeterminant.

Sinusitis is one of the most underdiagnosed conditions in the patient suspected of allergy. In fact, allergy and sinusitis are often concomitants. Radiographic imaging may be useful in establishing the presence or absence of sinus infection. A simple screening Water's view of the sinuses visualizes the maxillary and frontal sinuses fairly well. A Water's view is inexpensive but does not visualize the ethmoid and sphenoid sinuses with any certainty. Computed tomography is considered the gold standard for seeing all of the paranasal sinuses. Cost and X-ray exposure can be minimized with a limited scan, but this does not always detect the patency of the osteomeatal complex. Imaging during a viral infection may give spurious positive results and should be avoided.

CONCLUSION

Approach to the allergy patient has its culmination in the discussion of the findings with the patient. Effort should be made to express optimism that allergic conditions are almost always reversible and controllable. There is much myth and misconception among the general population concerning allergy. Adequate time should be allotted to explain in simple language the findings, plan, and prognosis for the patient.

Treatment of the allergic patient has three arms: avoidance of offending allergens, medication, and, when indicated, immunotherapy. All medications and, in particular, inhalers should be explained. Terminology such as "opener" or "controller or healer" may help the patient accept and understand the difference between and need for bronchodilators and anti-inflammatory agents. Delivery systems for use in the nose and lungs must be demonstrated and, in turn, the patient's technique observed. Side effects of drugs as well as risks and benefits of each treatment option should be explained in simple terms.

It is fundamental and imperative that a patient understand the premise of the treatment plan before accepting and adhering to avoidance steps and medication regimens. Thus, there should be no shortcuts on education concerning the patient's condition or treatment

plan. Questions should be welcomed and an open foundation of dialogue between patient and clinician/staff established. The patient should leave the office comfortable that the clinician and staff are willing partners in his or her care.

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3 Diagnostic Tests in Allergy

Dennis R. Ownby, MD

CONTENTS

SUMMARY

The diagnosis of allergic diseases depends first and foremost on a careful medical history taken by a suitably experienced clinician. An allergy history concentrates on the relationship between the consistency of the patient's problems with allergic diseases and the likelihood that the problems are the result of allergen exposure. The clinical suspicion of allergic disease is enhanced when the patient demonstrates IgE specific for the allergen or allergens identified by the history. Ultimately, the diagnosis is confirmed by the patient's response to allergen avoidance or other therapeutic trials. Both skin tests and blood tests for allergen-specific IgE can be very useful in diagnosis when the strengths and limitations of each are understood and appropriately used by the clinician.

Key Words: Allergy diagnosis; skin test; antibodies; serum test; in vitro test.

INTRODUCTION

The concept of "diagnostic" testing in allergy has been confusing for many years. Although there are many potential sources for the confusion, a major source has been commercial companies that market "diagnostic tests" as if a laboratory test could diagnose a patient with allergic disease. These companies imply that the diagnosis of allergic disease is as simple as drawing a blood sample and sending it to them. Allergic diseases can be diagnosed only from the patient's history of symptoms and compatible physical findings. Without a detailed history and physical, the results of skin tests or tests for allergen specific immunoglobulin (Ig)E are meaningless. For example, what does a positive test for cat-specific IgE mean? A patient with a positive test for cat-specific IgE may be asymptomatic, have rhinitis, have asthma, or have hives from exposure to cats. The test result is meaningless without the clinical history. If the patient has a consistent history of rhinitis every time he or she is exposed to cats and if the patient has physical

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Edited by: P. Lieberman and J. A. Anderson

Table 1
Criteria for Diagnosis of Allergic Disease

Absolute Criteria (The Gold Standard)

1. Reproducible symptoms occurring during double-blind, placebo-controlled, allergen exposure when the route, dose, and duration of allergen exposure are consistent with estimated or measured natural or occupational exposure.
2. The observed symptoms must be the direct result of the release of chemical mediators when the release of the mediators is triggered by the binding of IgE antibodies to the allergen.

Clinical Criteria

1. A history of signs and symptoms typical of allergic disease at a time and place when allergen exposure is probably occurring.
2. Demonstration that the patient has IgE antibodies specifi c for the allergen associated with the occurrence of symptoms.

findings typical of rhinitis after exposure, then a positive test for cat-specific IgE helps to confirm the suspected allergic nature of the patient's symptoms.

The combination of a typical clinical history, compatible physical findings, and a positive test result make a diagnosis of allergy probable. Two other important factors are the number of times the symptoms have been associated with allergen exposure and whether similar symptoms occur without allergen exposure. If the symptoms are exclusively related to allergen (cat) exposure and have occurred on multiple occasions, the diagnosis is relatively certain. Finding superficial conjunctivitis, nasal congestion, and rhinitis on examination would help confirm the history. The final step for confirming a diagnosis of cat allergy would be to demonstrate that the patient has cat-specific IgE antibodies.

To further clarify the role of allergy tests in allergy diagnosis, it is useful to define a "gold standard" for diagnosis (*see* Table 1). The critical elements of the gold standard are demonstration that exposure to the allergen under double-blind, placebo-controlled conditions reproduces suspected symptoms. It is also necessary to demonstrate that the symptoms are the result of IgE-mediated release of mediators from mast cells or basophils. This stringent definition of allergic disease is rarely met, even in research studies because of the difficulties of performing allergen challenges in a blinded fashion and of measuring mediator release.

Because of the difficulty in trying to satisfy the criteria of the gold standard, clinical criteria are usually accepted for diagnosis. Clinical criteria include a history of recurrent symptoms of allergic disease when allergen exposure is likely to be occurring and demonstration of corresponding allergen-specific IgE antibodies (Table 1). The application of clinical criteria must always be made in light of the potential risks and benefits of a diagnosis for the patient. Thus, allergy tests are only adjuncts to the clinical diagnosis of allergic disease.

SKIN TESTING FOR DETECTION OF ALLERGEN-SPECIFIC IGE

Physiology of Skin Tests

Skin tests are performed by introducing a small quantity of allergen into the epidermis by pricking, puncturing, or scratching the skin or by intradermal injection. This is usually

accomplished using a suitable concentration of an allergen extract. An allergen extract is an aqueous extract or solution of the allergen in question. Occasionally, some materials may be used directly for testing epicutaneous testing, e.g., the fresh juice of fruit. The immediate wheal-and-flare response resulting from a skin test is the result of a complex series of interactions. After the allergen has been introduced into the skin, it diffuses through the skin, where it binds to IgE antibodies (with specificity for the allergy), which are affixed to mast cells. When an allergen can crosslink two or more mast cell-bound IgE antibodies, a signal is generated for mediator release. Released mediators include preformed (histamine, tryptase, chymase, heparin) and newly synthesized (prostaglandins, leukotrienes, cytokines) cell products.

The central wheal of the skin response is principally a result of histamine-induced vasopermeability and secondary edema. The central erythema results from histamine-induced arteriolar vasodilation, and the circumferential erythema results from the stimulation of nerve receptors and resulting axon reflex vasodilation. The wheal-and-flare responses are typically maximal at 15 min after introduction of the allergen. Most of the skin response can be blocked by an H_1 receptor antagonist (antihistamine), but complete inhibition requires both H_1 and H_2 antagonists.

Following the immediate skin response, and depending on the dose of allergen and the sensitivity of the patient, there may be a late-phase reaction (LPR). These usually begin at 3–5 h, peak at 6–12 h, and resolve approx 24 h after the immediate response. Clinically, LPRs are characterized by pruritus and edema, often larger than the immediate reaction. Pathologically, LPRs are characterized by local infiltration of inflammatory cells, including neutrophils, monocytes, and eosinophils, into the involved site. Fibrin deposition also occurs. LPRs may follow immediate skin testing, especially if large reactions have occurred. Large local reactions following administration of allergen immunotherapy injections may also be LPRs.

Evaluation Prior to Skin Testing

Before skin testing is done, a patient must be examined by an experienced physician. Beyond establishing the likelihood of allergic disease, a patient's history and physical examination should alert the physician to any unusual risks of skin testing. Skin testing is generally safe, but there is always a small risk of inducing a systemic allergic reaction (anaphylaxis) that could be life threatening. Anything that might increase a patient's risk of an adverse outcome from anaphylaxis should be carefully considered and the potential risks weighted against the possible benefit for the patient before undertaking skin testing. A physician and emergency equipment for treatment of anaphylaxis must always be immediately available when a patient is skin tested. Because epinephrine is the drug of choice for treatment for all major allergic reactions, drugs altering the response to epinephrine, such as β-blocking agents, should be discontinued prior to skin testing. Pregnancy is a relative contraindication to skin testing because the fetus *in utero* is highly vulnerable to hypoxia, which might occur if the mother develops a systemic reaction. Patients with chronic medical problems, such as severe lung disease or unstable angina, should not normally be skin tested. Finally, patients with current, severe, allergic symptoms, especially unstable asthma, should not be skin tested until after their symptoms have been stabilized, because of an apparent greater risk of systemic reactions.

In addition to general medical concerns, the physician supervising the skin tests must be sure that the patient has an area of normal skin suitable for skin testing. The skin of patients who have recently recovered from an illness affecting the skin, such as chickenpox, or from illnesses with a high fever may not react normally for a few days or weeks. Patients must not be taking antihistamines or drugs with antihistamine actions, such as tricyclic antidepressants, because these agents can block skin-test responses. Patients with severe skin disease or with marked dermatographism are very difficult to reliably test. Both the very young and the very old have less reactive skin, and the criteria for grading skin-test reactions need to be adjusted in these individuals. Sunburns may alter skin reactivity for several weeks, and skin testing should be postponed.

Epicutaneous Skin Tests

Percutaneous or epicutaneous tests may be performed using a variety of methods, but the most common are the prick and puncture techniques. The prick test is performed on previously cleansed skin by passing a small needle (e.g., 25- or 26-gage) through a drop of allergen extract at approximately a 45° angle to the surface of the skin. The needle is lightly pressed into the epidermis and its tip lifted up, producing a pricking sensation. The skin pricks should not be deep enough to produce visible bleeding.

To test using a puncture technique, a drop of allergen extract is placed on cleansed skin. A puncture device is then pushed into the skin through the drop of extract into the skin. Commonly used puncture devices are constructed to allow a small point to penetrate no more than 1–1.5 mm into the skin. Further penetration is prevented by the instrument's shape. A variation on the puncture technique is the use of a bifurcated needle, originally designed for smallpox vaccination. For testing, the tip of the bifurcated needle is pressed firmly against the skin through a drop of extract and rocked back and forth or side to side.

Previously, many physicians would use a single needle or puncture device for multiple-prick skin tests on the same patient by cleaning residual extract from the device between each test site. The major risk of this procedure is that the person performing the tests will accidentally puncture his or her own skin while cleaning the device, creating the risk of infectious disease transmission. For this reason, most physicians have moved to using a single device for each allergen to be tested, properly discarding the device once the test has been placed. A second problem with using a single device for multiple tests is the possibility of not being able to clean all extract off the device between tests, resulting in contaminating the next test with residua from the preceding test. Tests can be applied to any area of normal skin, but the most commonly used sites are the back, volar forearms, and top of the thighs. Each test should be placed a minimum of 4 cm from other tests, and care should be taken to avoid smearing or mixing of the extracts. Tests placed too close together may interact, leading to difficulty when trying to interpret the reactions.

Intradermal Tests

Intradermal tests are generally more sensitive than prick or puncture tests, but they are more difficult to perform properly and produce more false-positive reactions. Intradermal tests are typically performed with 25-, 26-, or 27-gage needles. Some manufacturers provide needles with special intradermal bevels that help limit the depth of needle penetration. After drawing the allergen extract into the syringe and expelling all air, the tip of the needle is inserted into the superficial dermis and approx 0.02–0.05 mL of extract is injected. If the injection is performed properly, a distinct bleb, 2–3 mm in diameter and

1–2 mm high, will be produced. Extracts used for intradermal testing are normally diluted 1000-fold more than extracts used for epicutaneous tests. As with prick or puncture tests, intradermal tests should be placed at least 4 cm apart to prevent interactions leading to false-positive results.

The most common errors with intradermal tests are injecting too deeply, injecting too large a volume, and inducing excess bleeding. If extract is injected too deeply, little or no reaction will be visible on the surface of the skin. Injecting too large a volume may lead to false-positive reactions because of irritation, and a large volume increases the risk of a systemic reaction. Bleeding at the injection site may also cause false-positive irritant reactions. Intradermal skin tests are more likely to induce anaphylactic reactions than are epicutaneous tests. Because of the risks, technical difficulties, and problems of interpretation, intradermal testing is usually best left to an allergy specialist.

Positive and Negative Controls for Skin Testing

Because of the many variables present during skin testing, positive and negative controls must be included to allow accurate interpretation of test results, regardless whether the prick, puncture, or intradermal techniques is used. The negative control is either normal saline or the same buffer used to dilute the allergen extracts. The negative control must be applied in the same fashion as in all of the other tests. There is a tendency to apply the negative control more lightly because it is expected to be negative, thus diminishing its value.

Positive controls for skin testing are usually either histamine or a mast cell secretagogue, such as codeine. For epicutaneous tests, histamine is typically used at a concentration of 1 mg/mL, although a concentration of 10 mg/mL also has been recommended because some normal individuals do not respond to the 1 mg/mL concentration. For intradermal testing, histamine is most often used at a concentration of 0.01 mg/mL.

Recording and Scoring Skin-Test Results

Skin-test reactions to allergens are normally evaluated 15 min after the tests have been placed, when the reactions are typically maximal. Despite many years of use and many investigations, there is still great variation in the scoring and recording of skin-test results. The best method to record the results of skin tests is to measure the greatest diameter of the wheal and flare in millimeters and record these results for all tests and for the positive and negative controls. After measurement, the result of a test can be easily recorded as, for example, 5/21, meaning that the wheal was 5 mm in greatest diameter and the flare was 21 mm in diameter. Any epicutaneous test that produces a wheal at least 3 mm larger than the wheal of the negative control with a larger surrounding flare is normally considered positive for the presence of allergen-specific IgE. The advantage of measurements is that after being recorded they can be re-evaluated at any time by the original physician or by another physician.

Quality Control of Skin Testing

As with all diagnostic tests, persons supervising and performing skin tests should observe certain standards and quality controls. Quality control of skin testing should include making sure that the person performing the tests understands the testing procedure, the inter- and intra-operator reproducibility is acceptable, the procedures are consistent, the extract quality is maintained, and the results are consistently recorded. The

person performing the tests must be technically proficient in applying the tests and also understand factors that may affect the results of the tests, such as interfering drugs and skin abnormalities. Allergen extracts used for testing must be properly stored and discarded when their expiration date is reached.

Value of Epicutaneous vs Intradermal Skin Tests

Epicutaneous tests are adequate for most diagnostic work in allergy, but in some circumstances the higher sensitivity of intradermal tests is required, especially when dealing with those allergens associated with a high risk of death if sensitivity is missed, such as with penicillin or hymenoptera allergy. The increased sensitivity of intradermal tests comes at the expense of an increased risk of false-positive results and an increased risk of inducing anaphylaxis. Considering these risks, intradermal testing is best left to an allergy specialist.

MEASUREMENT OF ALLERGEN-SPECIFIC IGE

Basic Methods

Essentially all available assays for allergen-specific IgE antibodies utilize the principle of immunoabsorption illustrated in Fig. 1. The allergen of interest is first bound to a solid-phase support such as a paper disk, plastic microtiter well, or cellulose sponge. The patient's serum is then incubated with the allergen-coupled solid phase. If the patient has antibodies specific for the allergen, the antibodies will become bound to the allergen, and the remaining serum proteins, including unbound antibodies, can be washed away from the solid phase (this is immunoabsorption and separation). After washing, a labeled antihuman IgE antibody is incubated with the solid phase to allow binding of the anti-IgE to any IgE bound to the solid phase. After unbound anti-IgE is washed away, the quantity of anti-IgE bound to the solid phase is measured by quantitating the amount of label present and converting either to units of specific IgE by comparison to a standard curve or to a class score. The initial test for IgE antibodies used radiolabeled anti-IgE antibodies and was called the radioallergosorbent test (RAST). Because of its initial market dominance, RAST is often used as a generic term to mean any test for allergen-specific IgE antibodies, but in reality RAST is a brand name. In recent years other methods have largely supplanted RAST to avoid the problems associated with handling and storing radioactive materials. The major modification in newer assays is the use of enzyme labels in place of radiolabels. Thus, newer assays are specific applications of enzyme-linked immunosorbert assays. Despite the common use of enzyme labels, the term RAST is still commonly used to denote any test used to detect allergen-specific IgE antibodies. Both radiolabeled and enzyme-labeled assays are capable of detecting specific IgE at a concentration of less than 1 ng per mL of serum.

Reporting Results of In Vitro Tests

Currently there is no universally agreed-upon standard for reporting the results of tests for allergen-specific IgE antibodies. Modern assays for specific IgE are calibrated in terms of actual mass units of IgE, that is, nanograms or units of IgE per serum volume (1 U of IgE equals 2.4 ng). With these modern assays the lower limit of IgE detection is typically 0.35 U/mL, and all results of this value or higher are considered positive. The

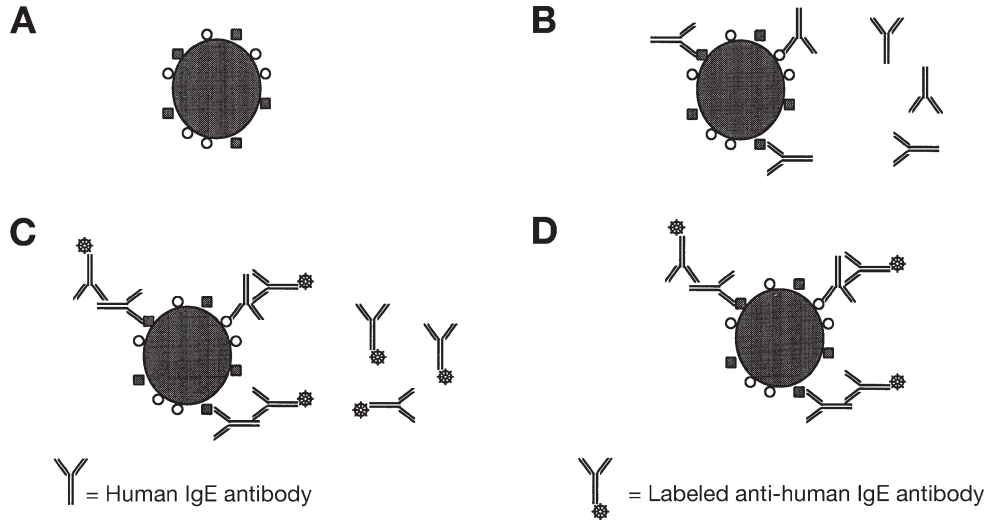

Fig. 1. Schematic presentation of an immunosorbent assay for allergen-specific IgE antibody. **(A)** Allergen represented by small circles and squares has been bound to solid phase. **(B)** Serum that may contain IgE antibodies specific for the allergen is incubated with the solid phase. Specific antibodies bind to the allergen, and nonbound antibodies are removed by washing. **(C)** Labeled antihuman IgE antibody is incubated with the solid phase, and the anti-IgE antibody binds to the immobilized IgE. Nonbound anti-IgE is washed away. **(D)** The amount of anti-IgE antibody on the solid phase is proportional to the concentration of allergen-specific IgE in the serum tested.

use of mass units allows a direct comparison of IgE levels between individuals or in the same individual over time. Calibration in mass units also provides useful clinical information in some circumstances, such as for predicting the likelihood that a person would have a reaction if challenged with a particular food.

Results from older assays are commonly reported as class scores, usually ranging from 0 to 4–6. Class 0 indicated undetectable IgE, whereas classes 1–4 or 6 represented increasing quantities of IgE. Some laboratories also report a class 0/1, or indeterminate class. Although physicians often interpret this indeterminate class as a very weak positive, the correct interpretation is that samples in this class have an equal probability of being positive or negative and should therefore not be considered positive.

Some laboratories report results using what is known as "modified" RAST scoring. The modified scoring system originally involved a number of technical details, but the net effect of the scoring system was to lower the point at which a result was considered positive. Lowering the decision point for a positive result increases the sensitivity but reduces the specificity of the test. Stated differently, allergic individuals are more likely to have positive test results (increased sensitivity), and nonallergic individuals are also more likely to have positive test results (reduced specificity).

When one is interpreting the results of in vitro assays, it is important to remember that the sensitivity and specificity of an in vitro test can vary markedly from one allergen to another. Although in vitro assays typically have sensitivities of 70–90% when compared to skin tests, much lower sensitivities are found with some allergens. It is important to remember that a test with a sensitivity of 75% will fail to detect 25% of truly sensitive individuals.

Table 2
Comparative Advantages of Skin Tests and In Vitro Tests in Allergy Diagnosis

Advantages of skin tests	*Advantages of in vitro tests*
Highest sensitivity	No risk of anaphylaxis
Results available in minutes	Medications do not affect results
Greater selection of allergens for testing	Not dependent upon skin condition
Less personnel and reagent expense per test	Better documentation of quality control
Minimal equipment required	May be more convenient for patients
Patient can see and feel the results of the test	Perceived as being more scientific

Advantages and Disadvantages of In Vitro and In Vivo Tests

Depending on the clinical situation, either skin tests or in vitro tests may be used to detect allergen-specific IgE. As listed in Table 2, there are certain advantages of each testing method. The most important advantage of skin testing is the high degree of sensitivity. When an intradermal skin test is properly performed, the risk of failing to detect allergic sensitization is extremely low. This degree of sensitivity is very important when the risk of failing to detect specific IgE may lead to the patient's death. Although not as sensitive as intradermal tests, epicutaneous tests are also very sensitive when properly performed with potent allergen extracts.

The most important advantage of in vitro tests is their safety. If an individual has had a life-threatening reaction to an allergen, an in vitro test offers the possibility of detecting specific IgE without the risk of inducing an allergic reaction in the patient. The patient should understand that if the in vitro test is positive and consistent with the patient's history, the diagnosis is relatively assured, but a negative in vitro test does not adequately exclude the possibility of sensitivity. In the face of a suggestive history and a negative in vitro test, the patient should still be skin tested before a final clinical judgment is made.

In routine allergy practice, skin testing has been found to be more cost-effective than in vitro testing. The cost-effectiveness is more pronounced because multiple allergens are tested. There are also advantages to the patient's being able to see the immediate allergic reaction on his or her skin and to having immediately available results. In comparison, in vitro tests offer the ability to test patients who do not have normal skin or who cannot discontinue certain medications. It may also be more convenient for both the patient and the physician to send blood samples to a reference laboratory for testing rather than for the patient to travel to another location, especially when testing is needed only for one or two allergens.

TOTAL SERUM IGE

Test Methods

Although a variety of assays have been used to measure the small concentrations of IgE normally present in human serum, the most frequently used method is a two-site immunometric assay using two different antihuman IgE antibodies. These assays are conceptually similar to the assays used for detection of allergen-specific IgE. The first antihuman IgE antibody is attached to a solid phase such as is used for detecting allergen-

Table 3
Total Serum IgE Levels in Skin-Test–Negative Children and Adults

Age (yr)	*N*	*Sex*	*Geometric mean*[a]	*Mean + 2 s.d.*[a]
6–14	69	M	40.9	2.0–824.1
	71	F	40.7	3.4–452.9
15–34	213	M	23.3	0.9–635.3
	201	F	16.5	0.8–349.1
35–54	145	M	20.4	0.9–443.6
	154	F	14.6	0.7-286.4
55–74	224	M	19.8	0.8–484.2
	348	F	10.7	0.6–198.6
75+	61	M	17.8	0.8–387.3
	83	F	28.9	0.4–208.9

From Klink M, Cline MG, Halonen M, et al: J Allergy Clin Immunol 1990;85:440.
[a]All values are International Units per milliliter.

specific IgE. An appropriate dilution of the serum to be tested is then incubated with the solid phase. IgE in the serum becomes bound by the anti-IgE coupled to the solid phase in proportion to the concentration of IgE in the serum sample. After unbound proteins are washed away, the quantity of IgE bound to the solid phase is determined by reacting the solid phase with the second, soluble, labeled anti-IgE antibody. After another wash to remove the unbound, labeled anti-IgE, the quantity of labeled IgE on the solid phase is measured and converted into units of IgE by comparison to a standard curve. A variety of commercial assays is available. Most are accurate to a concentration of less than 5 IU/mL (12 ng/mL) of IgE and reproducible within 10% or better.

Serum concentrations of IgE vary widely in normal individuals (Table 3). IgE levels are very low at birth and gradually increase, peaking in the second decade of life, followed by a slow decline into old age. Although the geometric mean values are relatively low, there is a very large 95% confidence interval at all ages (Table 3). Most laboratories report IgE concentrations as in IU or ng per mL (1 IU = 2.4 ng IgE). The Systeme International specifies that IgE be reported in micrograms per liter (μg/L), with two significant digits. Values in IU/mL can be converted to μg/L by multiplying by 2.4.

Relationship of Total IgE to Allergic Disease

Many studies have shown that total serum IgE concentrations are higher in allergic adults and children compared to nonallergic individuals of similar ages. There is, however, a relatively large overlap between serum IgE concentrations in allergic and nonallergic individuals, which limits the diagnostic value of total IgE measurements. When a high value of IgE is chosen to distinguish allergic from nonallergic individuals, the specificity of the test is often greater than 90%, but the sensitivity is low, 30–50%. Lowering the threshold level increases the sensitivity but lowers the specificity. For adults, the optimal IgE concentration for distinguishing allergic from nonallergic individuals is approx 100 IU/mL, whereas in children the threshold level varies with age.

Even though measurements of total serum IgE concentrations are not generally useful for diagnosis of allergic disease, total serum IgE measurements are valuable in the diagnosis and management of allergic fungal sinusitis (AFS) and allergic bronchopulmonary

aspergillosis (ABPA). (The term allergic bronchopulmonary mycosis [ABPM] is probably more appropriate than aspergillosis because organisms other than *Aspergillus* may be responsible.) Patients with ABPA (ABPM) and AFS typically have serum IgE levels greater than 500 IU/mL and often greater than 1000 IU/mL. With adequate glucocorticoid therapy, total serum IgE levels fall. When patients with these problems are followed over time, a sudden increase in serum IgE may herald disease exacerbation and allow time to alter therapy before symptoms increase or more lung or sinus damage occurs.

Some nonallergic conditions may be associated with abnormal total serum IgE concentrations. Among the more common nonallergic causes of elevated serum IgE are metazoan parasitic infections, smoking, and AIDS. IgE is grossly elevated in the rare cases of IgE myelomas that have been reported, but the levels of IgE may still be too low to be detected as a monoclonal spike on serum protein electrophoresis. IgE measurements are valuable in the evaluation of myelomas because IgE myelomas may be mistaken for light-chain disease. The distinction between light-chain disease and IgE myeloma is clinically important because the courses and responses to treatment differ. IgE is also elevated in patients with the hyper-IgE recurrent infection syndrome.

THE FUTURE OF ALLERGY TESTING

Currently, most allergy testing concentrates on IgE measurements, but some assays for the direct measurement of the mediators released during allergic reactions are available and may become more clinically relevant. Histamine can be measured during (serum) or after (urine) allergic reactions, but because it is difficult to collect and store proper specimens, histamine measurements are usually limited to research studies. Eosinophil cationic protein (ECP) can be measured in sputum or serum and correlates with the activation of eosinophils. ECP has been studied as a possible marker for monitoring anti-inflammatory asthma therapy with only modest success. Mast cell tryptase is elevated following massive release of mast cell mediators as during anaphylactic reactions. Tryptase levels usually peak 45–60 min after the onset of anaphylaxis and may remain elevated for several hours. Elevated tryptase measurements can help document that a reaction has resulted from mast cell mediator release. This distinction may be important during diagnostic evaluations and when counseling a patient about future risks. For as-yet-unknown reasons, tryptase does not appear to be increased during fatal or near-fatal anaphylactic reactions from foods in children. In the future, assays for histamine-releasing factor and other mediators may make the diagnosis of allergic disease easier and more precise.

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4 Environmental Allergens

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CONTENTS

SUMMARY

Airborne allergens in the outdoor environment are associated primarily with pollen grains and mold spores and usually induce seasonal symptoms. Exposure varies according to geographic location, season, and weather conditions. Indoors, allergenic proteins derived from house dust mites, furred pets, mold, and pests, such as mice and cockroaches, may induce perennial symptoms. A variety of factors determine the impact of these indoor allergens on disease manifestations. For example, cat allergen is carried on small particles that remain airborne for long periods. As a result, a person with cat allergy may develop symptoms promptly upon entering a home with cats and may have asthma symptoms as small particles freely reach the lower airways. In contrast, dust mite allergen is associated with larger particles that do not remain airborne and are concentrated in locations that support mite survival such as bedding that maintains high moisture for their survival. These features of dust mite allergen explain the lack of acute reactions upon exposure. This chapter describes a variety of features of environmental allergens and emphasizes those that are relevant to allergen avoidance and timing of medical management (e.g., seasonal use of medications) for improved care of individuals with allergic respiratory disease.

Key Words: Environmental allergen; pollen allergy; mold allergy; cockroach allergy; cat allergy; dog allergy.

INTRODUCTION

Respiratory and mucosal surfaces experience a constant barrage of particles that contain proteins of biological origin. Some of these low-molecular-weight proteins are capable of inducing immunoglobulin (Ig)E antibody and triggering an allergic response. There are usually several allergenic proteins derived from any specific allergenic source. For example, domestic cats, cockroaches, house dust mites, and pollens are common triggers of allergic responses, and several proteins from each source are recognized as allergens. When a particular protein is recognized by IgE antibody from more than half

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of individuals allergic to the source, it is termed a "major allergen." Allergens are named with the first three letters of the genus and then the first letter of the species name followed by a group designation. Examples include *Amb a 1* (*Ambrosia artemisiifolia*—ragweed), *Lol p 1* (*Lolium perenne*—ryegrass), and *Fel d 1* (*Felis domesticus*—domestic cat). For a growing number of allergenic proteins, DNA sequences are known and allergenic epitopes—sites on the protein binding IgE antibody and/or T-cell receptors—have been delineated. Molecular characterization of allergens has increased our understanding of the nature of the allergic response and has identified similar, or cross-reactive, structures among certain related allergens such as specific species of pollen, but has not identified a "typical" allergenic structure.

For individuals with an atopic predisposition, exposure to environmental allergens may cause not only the immunological sensitization required for the development of atopic disease, but also the provocation of acute symptoms and the maintenance of chronic ones. It has become evident that allergic sensitization and expression of a clinical allergy is the result of a complex interaction of environmental and genetic factors. The factors that may induce or modify an allergic response include dose of allergen, timing of exposure, and concomitant exposures (e.g., to environmental endotoxins that may modulate the immune response). In addition, genetic factors that determine a general disposition to, and expression of, atopic disease and genes that modulate immune responses to particular proteins, for example, human leukocyte antigen (HLA) molecules, determine the response to particular allergens and the clinical outcomes observed, such as asthma or rhinitis.

Environmental Allergen Exposure

Intermittent exposure, outdoors
- Pollens according to season
- Mold spores

Continuous exposure, indoors
- House dust mite
- Animal danders
- Mold spores
- Cockroach

Although there are many allergenic proteins on a variety of vectors in the environment, an understanding of just several classes of the major outdoor allergens that cause seasonal symptoms and indoor allergens responsible for perennial symptoms furnishes the physician with practical tools for the care of allergic individuals.

OUTDOOR ALLERGENS

To be clinically relevant, outdoor allergens, carried most often on plant pollens and mold spores, must reach a high airborne concentration. The level of exposure to these particles is determined by the vicinity of the flora to the patient, the density of production of the pollen or spores by its source, the seasonal and diurnal timing of pollen or spore release, weather conditions, and the aerodynamic characteristics of the vector carrying the allergenic proteins. Flora that are present in great numbers and produce large pollen

and mold spores occur in seasonal patterns, which will be detailed in the appropriate sections in this chapter.

Weather conditions greatly influence the airborne concentrations of these particles, sometimes in unexpected ways. Pollination and mold sporulation require warmth and are highest at midday and on warm days. However, some types of fungi release spores with active rainfall, whereas others suppress sporulation during precipitation. Pollen release is generally suppressed by humidity, but for some pollens water exposure may enhance availability of submicroscopic, allergen-rich particles that can become airborne and induce reactions. In fact, the brisk rainfall and wind patterns caused by thunderstorms may increase exposure, resulting, for example, in "thunderstorm asthma." Conversely, long periods of rainfall can act to scour particles and reduce exposure. Particle concentration increases with increasing wind speed, but in gusty winds these particles may be swept into the upper atmosphere, reducing ground exposure. In the cool, calm evening hours, these particles may resettle toward the ground, increasing exposure.

The aerodynamic characteristics of allergen-bearing particles play an important role in the degree and manner of exposure. Smaller particles remain airborne for longer periods, increasing exposure levels. Larger particles will settle more quickly, except in high winds. Particle size also determines the manner in which allergen exposure occurs. Particles larger than about 5 μm in diameter are deposited largely in the nose and are unlikely to penetrate to the lung. Despite the fact that most mold and pollen spores are 20–60 μm in diameter and impact mostly the eyes and nasal mucosa, lower airway symptoms can still be elicited by the allergenic proteins carried by these particles. These particles may exert their influence on the lung by reflexes elicited by nasopharyngeal stimulation or by hematogenous spread after the allergenic protein is eluted from vectors at mucosal surfaces, or the allergenic protein may become associated with smaller respirable particles in the environment, such as pollen fragments.

Pollen

About 60 families of higher plants in North America are implicated in pollinosis. Pollen contains the male genetic material of a plant and is released from mature anthers during specific weeks of the year. The pollen wall is composed of an outer exine, a middle layer termed the intine, and an inner protoplast. The exine has many micropores, but also larger pores or furrows through which the pollen tube emerges during successful pollination. Allergenic proteins dissolve through these pores onto mucosal surfaces, allowing hypersensitivity reactions. The overall shape of the pollen grain and the geometry and configuration of the pores makes speciation under light microscopy possible. Several examples of pollen morphology are shown in Fig. 1.

Plant Pollens

- Pollens responsible for seasonal allergies are light and transported by wind. They emanate from plants with small, nondescrite flowers.
- The "pollen season" varies by type of plant and geographic location but generally follows the order of trees, then grasses, then weeds.
- Airborne concentrations of pollen vary by weather conditions, with warm, dry, breezy conditions being favored for pollen dispersal.

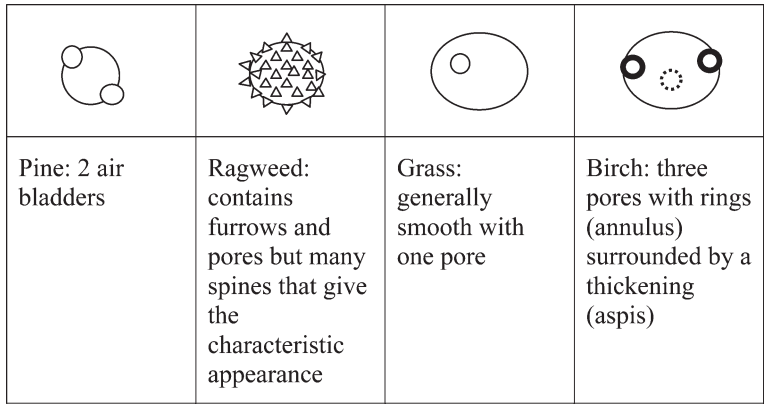

Fig. 1. Morphological features of several common types of pollen grains.

The manner in which a plant distributes pollen is relevant to allergy. Wind-dispersed (anemophilous) pollens achieve high airborne concentrations and are primarily responsible for clinical allergy. These plants tend to have small, nonaromatic flowers, little or no nectar, and produce large numbers of pollen grains that have aerodynamic properties to improve buoyancy. Many flowering plants, however, rely on animal or insect vectors for pollination (entomophilous), and these species—with their large, aromatic, colorful flowers—are generally not clinically relevant because their pollens are not airborne.

The aerobiology of pollens is of great public health interest. Pollens are counted after collection in a standardized fashion using machines that trap the pollen either actively with rotating arms coated with adhesive substances or by passive wind and gravitational force. After identification of the particular pollens to which the individual is sensitized, the published "pollen counts" can be a helpful guide in directing patients toward allergen avoidance and efficacious medication usage. However, the interpretation of these counts and their relevance to the individual patient must be considered. For example, daily variation may be extreme, making interpretation for daily symptom predictions difficult. In addition, symptom intensity depends on may factors, so reporting of a doubling in pollen count, for example, may not be clinically relevant to an individual whose threshold level of allergen that causes symptoms has not been reached. In addition, an individual's sensitivity to exposure may vary over a season, with increased reactivity following a period of exposure, termed "priming." In any event, knowing the patient's particular sensitivities, the yearly timing of their symptoms, the seasonal timing of pollination, and the characteristics of local fauna will help to guide patient care.

Pollen Seasons

In temperate regions, pollen seasons are traditionally grouped as trees, grasses, and weeds. In general, trees pollinate from late winter to late spring, grasses from late spring to midsummer, and weeds from midsummer to autumn. However, this delineation may vary widely depending on the yearly weather pattern and geographic location.

Tree Pollen

Tree pollination heralds the beginning of the allergy season in most climates in North America and begins in late February through April. In general, the greatest variety and

concentration of tree pollens occur in March through May, with the season ending in June. However, the tree pollen season may begin as early as December or January in areas of Arkansas, south Florida, and Texas, caused by pollen of cedar trees. Some examples of species that pollinate earlier in the tree season include red cedar and elm, while mid-season pollinating species include poplar, birch, ash, and willow, with late-season pollination by sycamore, oak, and mulberry. Table 1 shows five allergenically significant trees in each region of North America shown in the sequence in which they bloom. Trees on this list were selected to illustrate both significant species and the breadth of pollens that contribute to the span of the tree season in each area.

Grass Pollen

In most areas of North America, the grass pollen season overlaps and follows the close of the tree pollen season and runs from May to July, but there is much variation. Prominent grasses in temperature regions include orchard, timothy, ryegrass, and bluegrass. There is a significant allergenic overlap among the proteins of these regional species, and skin-test reactivity will often overlap. Because of this cross-allergenicity, differences in exposure to specific temperate grass species are not clinically significant, as they are for tree or weeds pollens. In the southern states and subtropical regions, Bermuda, Bahia, and Johnson grasses play a larger role in pollinosis. The allergens in these southern grass pollens are distinct. In some subtropical areas Bermuda grass and other species may produce almost perennial pollination. Table 1 shows examples of allergenically significant grasses by region in North America.

Weed Pollen

Weed pollination typically occurs in the late summer through October in most regions of North America. There are a tremendous variety of weeds, but ragweed species (*Ambrosia*) are responsible for the greatest amount of seasonal symptoms. Many species of ragweed have cross-allergenicity so sensitized individuals may experience symptoms "out of season" when visiting some regions where ragweed pollinates either perennially or in seasons outside of the usual mid-August to early October ragweed season, such as Coastal ragweed, which is prevalent in winter months in southern Florida. Other weeds responsible for significant regional allergy include pigweed, amaranth, marsh elder, dock, sorrel, plantain, and Russian thistle, among others. Allergenically significant weeds are listed by region in order of bloom within the weed pollen season in Table 1.

Fungi

Fungal spores (the term "molds" refers to fungi that lack macroscopic reproductive structures but may produce visible colonies) are responsible for both seasonal and perennial allergic symptoms. Most fungal forms grow best on a moist substrate, but fungi survive a variety of extremes in temperature and humidity. Outdoor varieties include *Cladosporium*, *Alternaria*, *Aspergillus*, *Penicillium*, and *Botrytis*. Allergenic proteins are found in the spores and in other fungal elements that may become airborne. Many of the allergenic proteins produced by these fungi have been characterized at the molecular level, such as *Alt a* 1 (*Alternaria alternata*) and *Cla h* 2 (*Cladosporium herbarium*). Measurements of fungal exposure include spore counts, immunoassay, semiquantitative culture and measurement of biochemical markers (such as mycotoxins or extracellular polysaccharides). Correlation of exposure levels to disease has been poor, possibly as a result of variations in measurement methods and disease definitions.

Table 1
Trees and Weeds of Allergenic Significance Shown in the Order of Bloom for Each Region[a]

Region	*Trees*	*Grasses*	*Weeds*
Northeast	Birch	Orchard	Sheep sorrel
(New England, NY, PA, NJ)	Elm	Timothy	Plantain
	Maple	June	Russian thistle
	Poplar	Sweet vernal	Giant ragweed
	Oak	Bluegrass	Short ragweed
Mid-Atlantic	Birch	Orchard	Plantain
(DE, MD, Washington DC,	Elm	Timothy	Dock
VA, NC, SC)	Maple	Bluegrass	Sage
	Hickory	June	Short ragweed
	Oak	Bermuda	Giant ragweed
Pacific Northwest	Alder	Timothy	Dock
(WA, NV, northern	Birch	Bluegrass	Plantain
California, OR)	Maple	Fescue	Russian thistle
	Oak	Rye	Nettle
	Walnut	Redtop	Sage brush
Plains	Elm	Timothy	Marsh-elder
(NE, KS, MN, eastern	Oak	Orchard	Russian thistle
Montana, Dakotas)	Box Elder	Bluegrass	Western hemp
	Willow	Bermuda	Short ragweed
	Maple	Redtop	Giant ragweed
Rocky Mountains	Cedar	Timothy	Sagebrush
(ID, WY, CO, UT,	Elm	Orchard	Russian thistle
western Montana)	Ash	Fescue	Short ragweed
	Birch	Redtop	Giant ragweed
	Oak	June	
Southern	Cedar	Bermuda	Dock
(FL, GA, TX, AK, southern	Elm	Orchard	Pigweed
Missouri)	Mulberry	Timothy	Russian thistle
	Poplar	Saltgrass	Giant ragweed
	Oak		Short ragweed
Southwest	Cedar	Bermuda	Sagebrush
(western Texas, NM, AZ)	Ash	Johnson	Russian thistle
	Mulberry		Saltbush
	Oak		Kochia
	Olive		Short ragweed
Southern California	Ash	Bermuda	Nettle
	Walnut	Saltgrass	Bur ragweed
	Elm	Brome	Russian thistle
	Oak		Sage
	Olive		Western ragweed

[a]Grasses listed by prevalence.

Table 2
Selected Allergen Sources in House Dust

House dustmites
Fungi
Furred pets
Cockroaches
Rodents (e.g., mouse, rat)
Pollens (from outdoors)
Miscellaneous debris (plant, food, etc.)

Alternaria species are more prevalent in dry, warm climates, whereas *Cladosporium* dominates temperate regions. Outdoor fungal particle levels peak seasonally, particularly in the mid-summer in temperate regions, but this is variable. Fungal spore exposure may also increase in the spring, when snow uncovers decaying vegetation, as well as immediately after rains. Patients may experience symptoms attributable to fungus exposure during outdoor activities that stir vegetation such as leaf raking, farming activities, grass cutting, or hiking. Although grass pollen, insect emanations, and other allergens can be stirred by these activities, the role of fungal allergens should not be overlooked.

INDOOR ALLERGENS

The house dust found in the indoor environment is a complex mixture that includes various levels of outdoor and indoor allergens (Table 2). In contrast to outdoor allergens that are typically implicated in episodic and seasonal allergic symptoms, perennial allergic symptoms are more commonly associated with indoor allergens. However, these distinctions are blurred by factors specific to each allergen source. Even the indoor environment may vary seasonally, resulting in different levels of exposure to the indoor allergens. For example, a dog-allergic patient may experience an increase in symptoms during the winter months when an outdoor pet spends more time indoors. Similarly, although pollen is typically thought of as an outdoor allergen, open windows and passive transfer on clothing and pets can result in significant levels of pollen exposure in the indoor environment. Furthermore, dust mite and indoor fungal allergens may vary seasonally because of variation in indoor humidity. Many atopic individuals experience perennial symptoms, such as rhinitis or asthma, because of allergens in the indoor environment. However, even perennial symptoms may wax and wane, making physician detective work and diligent history taking imperative. Indoor allergens have attracted much attention because epidemiological studies have linked elevated concentrations of house dust mite and cockroach with asthma severity in sensitized subjects.

Just as it is possible to count pollens by morphological characteristics, the measurement of indoor allergen concentrations is also possible but requires different methods. Determining the concentration of these indoor allergens is often helpful clinically because exposure levels are less predictable than seasonal outdoor allergens. Molds may be measured by colony counts, and dust mite numbers can be counted in measured dust samples using a light microscope. Monoclonal antibody assays to major allergens of dust mites, cat, dog, and cockroach, among others, have made analysis of exposure levels to a number of relevant allergens possible. This work provides data to support the notion that

there is a threshold level of a particular allergen that predisposes susceptible individuals to become sensitized, and that there is a higher threshold level above which symptoms may be elicited. Thus, steps taken to reduce levels of relevant indoor allergens may help to prevent the development of specific allergic sensitization as well as reduction of symptoms. This work has also helped to elucidate the aerobiological properties of these allergens and the steps needed to reduce exposure to them.

Fungi

Examples of common indoor fungi include *Penicillium, Aspergillus, Rhizopus,* and *Cladosporium.* Moisture is a key element in supporting the growth of indoor fungi. Colonies may be visible as dark stains in moist locations such as basement walls or grout between bathroom tiles and a "musty" odor may be noted. For example, *Penicillium* forms a greenish discoloration in damp areas. Various damp items including upholstered furniture, pillows, wet bathroom items, and even foods can support mold growth. For example, *Rhizopus* is the fluffy black growth seen on old bread. Humidifiers that use a cold water reservoir and duct systems that have become damp may also disperse fungal allergens. Because molds are ubiquitous, trying to culture them from a patient's home environment may not be as helpful as correlating symptoms, exposure risks, and skin-test or serum IgE antibody results in diagnosing their role in an individual's symptoms. Like pollens, outdoor airborne fungal allergens can become significant indoor allergens by virtue of entry through doors and windows.

Mold Spores

- Mold growth requires moisture.
- Mold spores can be found in the air year-round, but tend to peak in the spring, late summer, and fall during wet weather.
- Mold growth can be problematic in the home, especially in the basement, bathroom, and other damp areas.

Dust Mites

House dust mites are microscopic (approx 0.3 mm in length), eight-legged creatures that are in the same family as scabies. They do not bite, but they feed on human skin scales and other matter and rely on ambient humidity for water that they absorb through a hygroscopic substance on their legs. The most prominent species are *Dermatophagoides pteronyssinus* and *D. farinae*. They grow best at a relative humidity in excess of 75%, which may be easily achieved in, for example, a mattress, even when ambient humidity is lower. This requirement for humidity also results in a lower concentration of mites in surface dust as opposed to deeper areas such as in blankets, pillows, and furred toys. The optimal temperature for their growth is 18.3– 26.7°C. These requirements for growth explain why they are not as prevalent in cold, dry areas such as northern Sweden, central Canada, or at high altitudes as in Colorado.

The major source of mite allergen is derived from fecal particles that are 10–35 μm in diameter (similar to the size of pollen grains). The fecal particles can become airborne with disturbance but settle rapidly. The particles are surrounded by a membrane which allows contained allergen to elute when in contact with wet surfaces such as mucous

House Dust Mite

- The major allergen of the house dust mite derives from its fecal particles.
- House dust mite allergens may become airborne with disturbance, but they settle rapidly.
- Dust mites require a high relative ambient humidity to survive, so they are not usually found in surface dust but rather in thick items that hold moisture such as pillows, mattresses, and upholstered furniture.

membranes. Although a patient may give a history that is suggestive of dust mite allergy, such as acute symptoms occurring upon going to bed, frequently the role of this allergen may be more in the realm of chronic inflammation and chronic symptoms.

Animal Danders

An estimated 100 million domestic animals reside in the United States, with from one-third to one-half of homes having a pet, the most popular being cats and dogs. Animal dander carrying the allergenic proteins derive from emanations that include skin scales, urine, feces, and saliva. Exposure to a pet may elicit acute symptoms, but more often animal allergen in the home is responsible for chronic symptoms, often making the suspicion of an allergy to a household pet more difficult to diagnose. Lastly, it must be remembered that pets may act as a vector for bringing outdoor allergens, such as pollen, into the home environment.

Animal Danders

- Allergenic particles from furred animals may travel on small particles that remain airborne for long periods of time and induce symptoms through inhalation into the lower airways.
- Major allergenic proteins are common among cats and dogs of various breeds, so there is no nonallergenic breed.

Cats

The major allergen responsible for cat allergy is *Fel d* 1, although reactivity to other proteins including cat albumin play a role. Cats are among the most common household pets in urban areas, and survey data would indicate that 20–40% of the atopic population has sensitivity to cat allergen and about one-third of these people live with cats. All breeds, both long and short hair, produce *Fel d* 1 to varying extents, and males produce more than females. Even lions and tigers produce this allergen. The allergen is found in both saliva and sebaceous glands of the skin and is distributed by licking and grooming. The size of vectors that carry the allergen are generally less than 25 μm, and 10–30% are smaller than 2.5 μm. These small particles remain airborne for long periods of time and are not readily cleared by the nasopharynx. This ability of the particles to reach the lower airway may explain the sudden asthma symptoms some sensitive individuals experience upon entering a home with cats. Cat allergen has been found in low levels even in homes without cats or in schools; the allergen has been shown to be brought in by passive

transport from cat owners because these particles are adherent. In fact, particles carrying cat allergen are tenacious in that they have been detected not only in settled dust, but also on walls and fabrics, and can remain for months after a cat is removed from the home.

Dogs

The prevalence of sensitivity to a dog allergen is about half of that seen with cat sensitivity. The major dog allergen is *Can f* 1, which is detected on the coat and in saliva. The amount produced by different breeds varies, but all breeds produce the major allergen, so there is not truly an allergen-free breed. Some breeds do, however, produce breed-specific allergens, but the clinical relevance of this is not well understood. The airborne characteristics of dog allergen are not well described, but the allergenic proteins are carried on a variety of particle sizes, including small particles that can potentially reach the lower airways directly. Like cat allergen, the dog major allergen can be detected in homes without dogs or in schools showing that passive transport and persistence of allergen is possible.

Birds

IgE-mediated sensitivity to feathers has been found in canary fanciers and other bird breeders, but the prevalence of sensitization is not known. Positive skin tests to feather extract may be a result of contamination of the extract with dust mite allergen, leading to false estimates of the prevalence of sensitivity. Similarly, feather pillows may induce symptoms because of the growth of dust mites or mold in them rather than any avian proteins associated with the feathers. Interestingly, feather pillows may actually be less allergenic than other types (e.g., foam) because the cloth used to enclose the pillow is typically tight-woven and may exclude dust mite growth. Specific disease caused by bird exposure is, however, seen in pigeon breeders and budgerigar, canary, and other bird fanciers who may develop hypersensitivity pneumonitis. IgG antibody responses toward the avian serum γ-globulin is seen in these patients, although IgE-mediated sensitivity has also been demonstrated in some individuals with this disease.

Other Furred Animals

Allergy has been described to virtually all furred animals found in homes, schools, farms, and the workplace. Furred pets found in homes or schools include hamsters, gerbils, guinea pigs, rabbits, and many exotic pets. The allergens from these animals may be found in their fur, urine, and saliva. Farm animals such as pigs, cattle, and horses are also responsible for allergic disease, although little is known about the prevalence of disease activity from these sources in the United States. Sensitivity to these farm animals is a more common problem in northern Europe, presumably because of the closer proximity of these animals to the homes of their keepers.

Furred pests, such as mice and rats, should also be considered as a potential source of allergen. Mouse allergen (*Mus m* 1) has also been detected in many homes in the United States. The high concentrations found in urban homes are associated with higher sensitization rates in inner city children. Among laboratory workers exposed to animals, 11–30% show sensitivity, and most of these individuals become sensitive to more than one species. Rat allergen (*Rat n* I) is found in urban homes and is associated with more frequent sensitization in children and more severe asthma.

Insects

In addition to the allergic reactions that occur from insect stings, the fine wing scales, fecal pellets, and other emanations from moths, locusts, various beetles, flies, and other insects may be a source of inhalant allergens. The mayfly, for example, is responsible for allergic symptoms, especially in the area around the western end of Lake Erie. The allergen from the mayfly is carried on particles that are fragments of the insect's pellicle shed during molting.

Among the various insects that have been implicated in allergy, the cockroach is best studied. Three main species of cockroach inhabit buildings: *Blattella germanica, Periplaneta americana*, and *Blatella orientalis*. *B. germanica* is the most prevalent in crowded North American cities. Several allergens, including*Bla g* 1 and *Bla g* 2, derive principally from the saliva and fecal material. The larger American cockroach produces the allergen *Per a* 1, which cross-reacts with *Bla g* 1. Sensitivity to cockroach allergen has been shown to be associated with exposure levels and is more prevalent in urban as compared to suburban areas and has been associated as a risk factor for emergency room visits for asthma in the inner city. Although concentrated in kitchen and bathrooms, allergen is detectable in all areas of the home, including the bedroom, where levels are associated with risk of asthma hospitalization for sensitized asthmatic individuals. The allergen appears to settle from the air after disturbance, indicating an association with larger particle vectors.

Other Indoor Allergens

A number of other potential allergens are detectable in the indoor environment, but their role in disease is not well understood. These include indoor plant material, bacteria, protozoa, algae, food debris, and low molecular weight chemicals. Indoor plants do not usually produce pollen, but some may be allergenic, such as the airborne leaf particles of *Ficus benjamina* (weeping fig). Other plant materials, such as latex, and dust from cotton, coffee, and flour are probably only relevant in the industrial setting. Products such as enzymes secreted from bacteria and protozoa have been implicated in allergic disease, but the exact pathophysiology or epidemiology is not completely understood. Clinically relevant concentrations of food allergens may become aerosolized during cooking (especially egg, fish, and shellfish) or in industrial settings.

Low-molecular-weight chemicals, such as anhydrides, isocyanates, azo-dyes, and ethylenediamide, have been reported to cause allergic reactions in industrial settings. These chemicals are too small to evoke immune reactions unless they complex with proteins. Most exposures occur in industrial settings and not in domestic settings unless acrylic paints or glues are used without ventilation. Some of these chemicals may act as irritants rather than allergens. Again, the exposure history is important in considering these agents, and their significance in nonindustrial settings is unclear.

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5 Anaphylaxis

Lori Kagy, MD and Michael S. Blaiss, MD

CONTENTS

SUMMARY

Anaphylaxis is an acute allergic emergency that is potentially fatal. The treatment is epinephrine, which should be administered immediately. Anaphylaxis can be IgE mediated, but clinically indistinguishable events are mediated through other mechanisms, such as non-IgE-mediated mast cell degranulation episodes.

Key Words: Anaphylaxis; anaphylactoid reactions; epinephrine; shock; food allergy.

INTRODUCTION

Anaphylaxis is defined as an acute systemic allergic reaction that results from the sudden release of mast cell and basophil-derived mediators into the circulation. The reaction may vary in severity from mild to life-threatening or fatal and may be rapidly progressive.

The phenomenon itself is old, but it was recognized and named in the beginning of the 20th century by French physiologists Charles Robert Richet and Paul Portier. In 1902, Portier and Richet described the phenomenon that occurred when they injected dogs with venom from the sea anemone in an attempt to confer sting prophylaxis. Several days later, when they gave a second nonlethal dose of the venom to the dogs, the dogs quickly died. To describe this phenomenon, Portier and Richet proposed the term anaphylaxis, which was derived from the Greek words *a*-(against) and *-phylaxis* (immunity, protection). The

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Nobel Prize in Medicine or Physiology was awarded to Richet in 1913 for his collaborative research with Portier on anaphylaxis.

The list of agents that can trigger these life-threatening reactions in the population continues to grow. Common causes of anaphylaxis reactions are medications, foods, insect venoms, vaccines, and latex, with drugs and foods being the most frequent causes. The incidence of anaphylaxis is not clearly known, although there have been several studies and reviews of the literature. An analysis of published literature by Neugut et al. estimated that in the United States 3.3–4.3 million Americans were at risk for anaphylaxis and 1433–1503 were at risk for a fatality. They suggested that 12.4–16.8% of the U.S. population may suffer an anaphylactic reaction. Internationally, it is estimated that approx 154 fatal episodes of anaphylaxis occur per 1 million hospitalized patients. However, the true incidence of anaphylaxis is probably underestimated because it is underreported. Release of potent pharmacological mediators from tissue mast cells and peripheral blood basophils is the basis for the clinical manifestations seen in anaphylaxis and anaphylactoid reactions. Anaphylaxis and anaphylactoid reactions differ in that true anaphylaxis involves antigen response to immunoglobulin (Ig)E antibody, whereas IgE is not involved in anaphylactoid reactions.

PATHOPHYSIOLOGY

Anaphylaxis is a generalized, immediate IgE-mediated hypersensitivity reaction to a foreign antigen such as a protein, a hapten, or a polysaccharide. In susceptible persons, initial exposure to an antigen results in the formation of specific IgE antibodies to that antigen. These antibodies attach to receptors on the surface of mast cells and basophils. This leads to changes in the cell membrane with degranulation and release of preformed chemical mediators and generation of new potent mediators. It is these mediators that produce the clinical symptoms of anaphylaxis (Fig. 1).

Mast cells are marrow-derived, tissue-resident cells that are essential for IgE-mediated inflammatory reactions. These cells are scattered in connective tissues throughout the body, but are found in especially large numbers beneath mucosal and cutaneous surfaces such as the skin, the lung alveoli, the gastrointestinal (GI) mucosa, and the nasal mucous membranes. Mast cells express on their surfaces large numbers of high-affinity F_c receptors for IgE. Therefore, the surface of each mast cell is coated with IgE molecules that have been absorbed from the circulation and serve as receptors for specific antigens. When antigens bind to the mast cell's surface IgE molecules, it undergoes activation that leads to its subsequent degranulation and release of granule contents into the surrounding tissues. The granules contain large amounts of histamine and other inflammatory mediators.

Histamine is a major mediator of anaphylaxis, and histamine infusion has been shown to reproduce the majority of the manifestations of anaphylaxis. The activities of histamine are shown in detail in Table 1. The actions of histamine are mediated through four receptor types (H_1, H_2, H_3, and H_4). Two of these, the H_1 and H_2 receptors, are active in producing the symptoms of anaphylaxis. The H_3 receptor has been implicated in anaphylaxis in dogs, but its role in humans has not been elucidated at this time.

The overall effect of histamine on the vascular bed is to produce vasodilatation. This causes flushing and a lowering of peripheral resistance, resulting in a fall in systolic pressure. Vascular permeability also occurs, resulting from a separation of endothelial

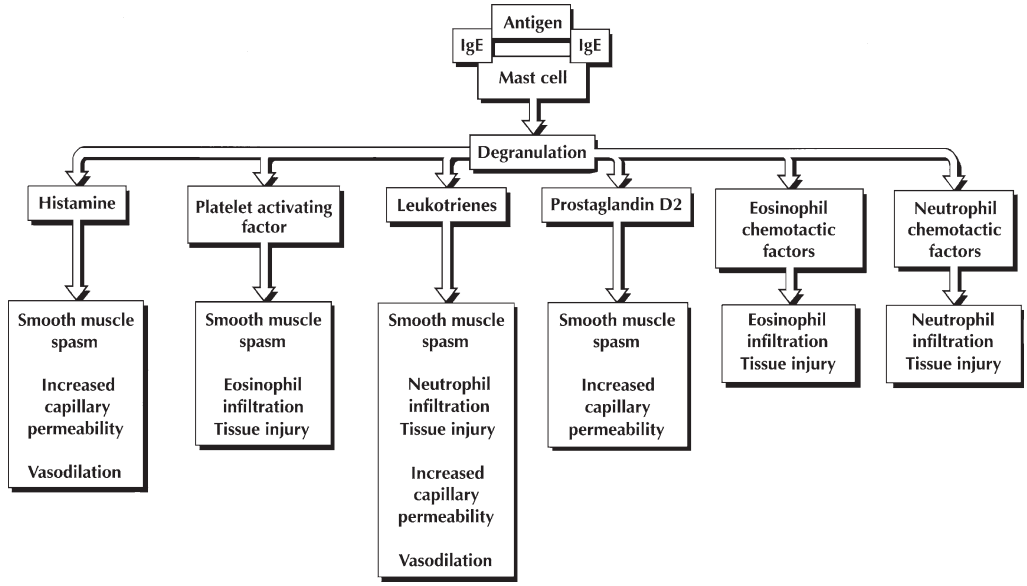

Fig. 1. Clinical manifestations of anaphylaxis.

cells at the postcapillary venule level. Both H_1 and H_2 receptors are operative in the production of vasodilatation.

Cardiac effects of histamine are mediated primarily through the H_2 receptor. H_2 receptor stimulation causes an increase in rate and force of atrial and ventricular contraction and decreases the fibrillation threshold. H_1 receptor stimulation can cause coronary artery vasospasm and an increased rate of depolarization of the SA node. Histamine leads to constriction of smooth muscle in the bronchial tree, uterus, and GI tract. Both H_1 and H_2 stimulation increase glandular secretion.

Like mast cells, basophils also bear high-affinity F_c receptors for IgE and contain histamine-rich cytoplasmic granules. The basophil participates in IgE-mediated reactions in a manner similar to that of the mast cell. Other chemical mediators involved in the IgE-mediated anaphylactic reaction include arachidonic acid metabolites, such as leukotrienes (LTC_4, D_4, E_4) and the prostaglandins (PGD_2, PGF_{2a}), as well as thromboxane A_2. These substances can cause contraction of airway smooth muscle, increased vascular permeability, goblet and mucosal gland secretion, and peripheral vasodilatation. Platelet-activating factor also contracts smooth muscle and enhances vascular permeability. Thus, histamine, arachidonic metabolites, and platelet-activation factor produce smooth muscle spasm, enhance vascular permeability, and cause vasodilatation. Also, these mediators stimulate sensory nerves, activate vagal effector pathways, and alter myocardial function. The results of these events are the classic symptoms of flushing, urticaria and angioedema, wheezing, hypotension and shock, myocardial ischemia, and GI smooth-muscle contraction with nausea, vomiting, and diarrhea. Other mediators such as tryptase, chymase, mast cell kininogen, and basophil kallikrein are involved and can activate secondary inflammatory pathways.

Table 1
Actions of Histamine Pertinent to Anaphylaxis Mediated Through H_1 and H_2 Receptors

H_1	*H_2*	*Requires H_1 and H_2 for maximum effect*
Smooth muscle contraction	Cardiac effects	Vasodilatation
	Positive chronotropic	Hypotension
	Positive inotropic	Headache
	Decreased fibrillation threshold	Flush
Vascular permeability	Vasodilatation	Increased amount mucous
	gland secretion	
Stimulation of nerve endings	Mucous glycoprotein	
Pruritus	Secretion from goblet cells	
Vagal irritant receptors	and bronchial glands	
Vasodilation		
Nitric oxide		
Direct effect		
Cardiac effects		
Increased rate of depolarization of SA node coronary artery		
Vasospasm		
Increased viscosity mucous gland secretion		

The role of nitric oxide (NO) has recently been recognized as a central mediator in immediate hypersensitivity reactions. It can cause smooth muscle dilation and increased vascular permeability leading to hypotension. On the other hand, the relaxation of the smooth muscle by NO can lead to improvement of bronchospasm and myocardial ischemia. In anaphylaxis, it appears that the harmful effects of NO outweigh its benefit.

It is also important to note that chemotactic factors are released from mast cells and basophils. These factors recruit other cells, which then degranulate and release a second wave of mediators. This second wave of mediators is thought to account for relapses of anaphylaxis that can occur after initial symptoms have resolved. These are termed "late-phase reactions." Additionally, these chemotactic mediators can result in protracted or prolonged episodes of anaphylaxis that persist long after the initial degranulation of mast cells and basophils. Biphasic anaphylactic responses have been reported to occur in less than 1% to a maximum of 20% of individuals experiencing an anaphylactic episode. They can also occur after both oral and parenteral administration of antigen. The time of occurrence of the second response can be anywhere from 1 to 72 h after successful treatment of the initial reaction. Corticosteriods do not seem to ablate the biphasic response, but an insufficient dosing of epinephrine and/or a delay in administration of epinephrine might predispose to a biphasic response.

Several mechanisms can lead to anaphylactoid reactions. One is the activation of the complement system, resulting in the formation of the potent anaphylatoxins, C3a and C5a. These proteins can directly trigger mast cell and basophil degranulation, releasing the same potent mediators. Another mechanism is the direct action of certain agents on mast cells and basophils, stimulating the release of mediators.

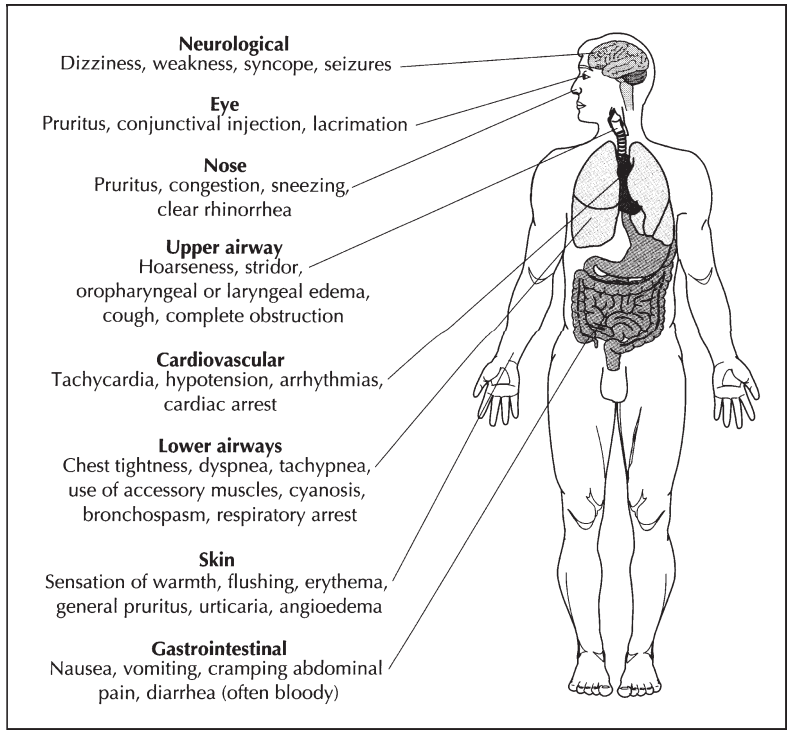

Fig. 2. Major chemical mediators of an anaphylaxis and their actions.

This mechanism is independent of IgE and complement. Anaphylactoid reactions can also occur in situations in which the mechanism is not clearly understood. These include systemic reactions initiated by exercise, aspirin, nonsteroidal anti-inflammatory drugs, and synthetic steroid hormones.

CLINICAL MANIFESTATIONS

The signs and symptoms of anaphylaxis vary greatly in onset, presentation, and course. The skin, the upper and lower airways, the cardiovascular system, and the GI tract may be affected solely or in any combination (Fig. 2). Symptoms of anaphylaxis usually begin within 5–30 min after exposure to the inciting agent. However, symptoms may be delayed for up to 1 h or more.

The clinical signs and symptoms of anaphylaxis can vary. Based on a compilation of 1784 patients from a review of published series, the most commonly affected organ is the skin. Cutaneous symptoms occur in more than 90% of individuals who suffer an anaphylactic reaction. Urticaria and angioedema were the most prevalent skin manifestations, occurring in approx 85–90% of the subjects. Flushing was seen in 45–55% of cases, whereas only 4–5% had generalized pruritus without a rash. The respiratory tract, involving both the upper and the lower airways, was the next most generally involved system, with 40–60% experiencing shortness of breath, dyspnea, wheezing, or upper airway angioedema. Rhinitis occurred in approx 15–20%.

Symptoms of hypotension or documented hypotension were frequent and were seen in 30–35% of the patients. The GI tract is also regularly involved. Diarrhea, abdominal

Clinical Manifestation Clinical Pearls

- Risk of anaphylaxis is higher if an agent is given by injection rather than orally.
- In general, the more rapid the onset of anaphylaxis after the inciting event, the more severe the manifestations in the patient.
- Patients with a significant anaphylactic episode should be observed in a hospital setting overnight for the possibility of biphasic anaphylaxis.

cramps, nausea, and emesis developed in 25–30% of the patients. Less frequent symptoms include headache, blurred vision, transient blindness, seizures, and substernal chest pain.

It is thought that there is a direct correlation between the immediacy of the onset of the symptoms after exposure to the triggering agent and the severity of the anaphylactic episode; the more rapid the onset, the more severe the event. In some patients, the episode may appear to resolve, and then the symptoms reoccur after several hours. This is called biphasic anaphylaxis. It can occur despite appropriate treatment of the initial event. Therefore, it is recommended that patients who have a significant anaphylactic event be hospitalized for overnight observation. The decision for prolonged observation should take into account the severity of the episode, the presence of concurrent medical problems, and whether the individual has other risk factors such as β-blocker use.

Death caused by anaphylaxis usually occurs as a result of respiratory obstruction and/or cardiovascular shock. In patients who die of anaphylaxis, the prominent pathological features are acute pulmonary hyperinflation, laryngeal edema, pulmonary edema, intra-alveolar hemorrhage, visceral congestion, urticaria, and angioedema. In some instances death occurs without any gross pathologicaal change and is presumed to be the result of profound cardiovascular collapse. Sudden vascular collapse is usually attributed to vasodilation or cardiac arrhythmia. Myocardial damage may occur in up to 80% of fatal cases.

RISK FACTORS

There are many factors that increase the risk of anaphylaxis in the population. Patients with atopy are at a higher risk of anaphylaxis from antigens administered by the mucosal route, such as food, compared with parenterally administered agents, such as vaccines. The longer the interval between doses for certain antigens, the less likely is a recurrence of anaphylaxis. Interruption of therapy may lead to predisposition to anaphylactic reactions, as has been documented with insulin treatment. Route of administration appears to be a risk factor, with a higher likelihood of anaphylaxis when an agent is given by injection rather than orally. Gender and age have been evaluated as potential risk factors. Women have a higher incidence of anaphylaxis in general compared to men and also have anaphylaxis more often in reaction to latex, muscle relaxants, and aspirin. Men have a higher rate of anaphylaxis in reaction to insects than do females. These higher rates based on gender may be more related to exposure than to a genetic difference. Adults tend to have a higher incidence of anaphylaxis to contrast medium, insects, plasma expanders,

Table 2
Etiological and Pathophysiological Classification of Anaphylaxis and Anaphylactoid Reactions

Anaphylaxis-IgE-mediated reactions
Drugs
Food
Insect bites and stings
Allergen immunotherapy
Latex
Exercise (some cases)
Anaphylactoid
Disturbances in arachidonic acid metabolism
Aspirin
Nonsteroidal anti-inflammatory drugs
Immune aggregates
γ-globulin
IgG–anti-IgA
Possibly protamine, dextran, and albumin
Director release of mediators from mast cells and basophils
Drugs
Idiopathic
Exercise
Physical factors (cold or sunlight)
Miscellaneous and multimediator activity
Nonantigen- antibody-mediated complement activation
Radiocontrast material
Possibly some cases of protamine reactions
Dialysis membranes

and anesthetics than children do. Again, this may be more a result of greater exposure to these agents in adults than children.

The route of administration of a particular agent can exert an effect on both the frequency of occurrence and the severity. Anaphylaxis can occur with any route, including oral, subcutaneous, intramuscular, intravenous, intranasal, intraocular, Cutaneous, intravaginal, intrarectal, and intratracheal. Attacks seem to be more severe and more frequent when the route of administration is injection.

ETIOLOGY

Although any substance has the potential to cause anaphylaxis, the most common causes of IgE-mediated anaphylaxis are medications, foods, insect bites and stings, latex, and allergen immunotherapy injections. Table 2 lists the etiological and pathophysiological classifications of anaphylaxis and anaphylactoid reactions. The following discussion is a review of some of the more common substances known to produce anaphylaxis.

Medications

Hundreds of agents have been documented as causes of anaphylaxis, and medications comprise one of the largest groups (Table 3). Penicillin and its derivatives are one of the

Table 3
Medicinal Agents Causing Anaphylaxis

Antibiotics	*Chemotherapeutic agents*	*Miscellaneous*
Penicillin and derivatives	Asparaginase	Aspirin
Cephalosporins	Vincristine	NSAIDs inflammatory
Tetracycline	Cyclosporine	Opiates
Sulfonamides	Methotrexate	Human gamma globulin
Ciprofloxacin	5-fluorouracil	Insulin
Nitrofurantion	Radiocontrast material	
Vancomycin	Heparin	
	Vaccines, (tetanus, measles, influenza, mumps)	
	Dextran	
	Protamine	
	Local anesthetics	
	Glucocorticosteroids	
	Antithymocyte globulin	

NSAIDs, nonsteroidal anti-inflammatory drugs.

most common causes of anaphylaxis to medication. Penicillin has been reported to cause fatal anaphylaxis at the rate of 0.002% in the general population, or 1 fatality per 7.5 million injections. Estimates of nonfatal anaphylaxis vary, ranging from 0.7 to 10%. Cross-reactivity exists between the various penicillins. All β-lactam antibiotics (penicillins, cephalosporins, monobactams, carbapenems, oxacephems, clavams, carbacephems) contain the main four-member β-lactam ring linked to a second five- or six-member ring, except for the monobactams, which lack the second ring. A list of β-lactam antibiotics can be seen in Table 4. There is much cross-reactivity with ampicillin, but only minimal cross-reactivity with methicillin and oxacillin. Cephalosporins also cross-react with penicillin in up to 30% of patients with allergy. Aztreonam, a β-lactam with a monobactam structure, can be used safely in patients with penicillin allergy. Anaphylaxis can occur from parenteral, oral, or topical drug administration, although the highest incidence is from parenteral administration.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are important causes of anaphylactoid events. These reactions are not IgE-mediated. They apparently produce anaphylactoid reactions through the aberrant mechanism of arachidonic acid, with inhibition of cyclooxygenase and subsequent increased production of leukotrienes. However, some episodes may be caused by the direct degranulation of mast cells. Adverse reactions to aspirin typically include urticaria, angioedema, asthma, chronic rhinosinusitis, and nasal polyps in sensitive individuals. Because the sensitivity persists for life, management entails strict avoidance. Acetaminophen is the alternative recommended drug. Studies have suggested that the cyclooxygenase-2 inhibitors are safe in aspirin-sensitive asthmatics, but they do not have Food and Drug Administration (FDA) approval at this time. Salsalate, choline salicylate, magnesium salicylate, and propoxyphene hydrochloride are the other drugs that can be used.

All NSAIDs may cross-react with aspirin to varying degrees. Desensitization can be considered in aspirin-sensitive patients with respiratory disease.

Table 4
β-Lactam Antibiotics

Penicillins	Cephalosporins
Penicillin G	Cephalothin
Penicillin V	Cefazolin
Methicillin	Cephalexin
Oxacillin	Cefadroxil
Carbenicillin	Cephalothin
Ticarcillin	Cefamandole
Mezlocillin	Cefuroxime
Piperacillin	Cefonicid
Cloxacillin	Cefpodoxime proxetil
Nafcillin	Cefaclor
Ampicillin	Cephalexin
Clavams	Cefotetan
Clavulanic Acid	Cefotaxime
	Cefitozime
	Ceftriaxone
Monobactams	Cefoperazone
Azteonam	Ceftazidime
	Cefixime
	Cefprozil
Carbapenems	Oxaceophems
Imipenem	Moxolactam
Meropenem	
Carbacephems	
Loracarbef	

Foods

Any food has the potential to cause anaphylaxis, but some foods are more allergenic than others. The most frequent causes of food anaphylaxis include peanuts, tree nuts, crustaceans, fish, eggs, and dairy products.

Table 5 gives a representative listing of foods reported to cause anaphylaxis. The incidence of anaphylactic reactions to foods is unknown, but may be more common than stinging insect anaphylaxis. A review of patients with a history of food-related anaphylaxis who had been instructed in epinephrine self-administration demonstrated that these patients required injections at a rate of 0.97 times a year, which was three times higher than that required in insect-allergic individuals. It appears that certain foods cause anaphylaxis more frequently in children than in adults and vice versa. The most common offender in adults is probably shellfish, whereas in children they are milk, eggs, and peanuts.

The peanut is responsible for allergic reactions in both children and adults. Over the last several decades the incidence of peanut allergy in children has dramatically increased. Now, about 1% of children in the United States have peanut allergy. Peanut allergy is probably the most common cause of death from food anaphylaxis in the United States. Peanut allergy, unlike other food allergies, is rarely outgrown, with only about

Table 5
Foods Causing Anaphylaxis

Legumes (peanuts, beans, peas, soybeans)
Shellfish (shrimp, lobster, crab, crawfish)
Milk
Eggs
Wheat
Fish
Nuts (cashews, almonds, pecans, walnuts)
Seeds (sesame, sunflower, poppy, cottonseed)
Spices (cinnamon, nutmeg, mustard, sage)
Fruits (apples, bananas, peaches, oranges, melons)
Chocolate
Potato
Corn

20% of patients losing their sensitivity over time. Once a diagnosis has been made, peanuts should be treated with strict avoidance. Patients with peanut allergy should be warned of "hidden" peanuts in many foods, including candy, chili, spaghetti sauce, and egg rolls.

If it is not apparent from the patient's history what food triggered the anaphylaxis, then skin testing with different food extracts may help in isolation of the cause. Although rare, it is important to note that prick skin testing with foods can itself cause an anaphylactic reaction. Therefore, using an in vitro test such as the radioallergosorbent assay (RAST) test, although less sensitive in determining the allergen, may be safer for verifying a particular food as the etiological agent when the history suggested a severe anaphylactic reaction to that food.

Insect Bites and Stings

Anaphylaxis occurs from stings of Hymenoptera insects, including bees (honeybee, bumblebee, and sweat bee), vespids (wasps, yellow jackets, and hornets), and imported fire ants. The importance of each of these insects as causes of anaphylaxis varies according to the geographic region. Bee and yellow jacket stings cause the most problems in the northern portions of the United States, with wasps and fire ants causing most problems along the Gulf Coast. As compared with Hymenoptera stings, anaphylaxis from insect bites is rare. Bites from kissing bugs and deerflies have been documented to cause IgE-mediated anaphylaxis.

Adults who have only skin manifestations of anaphylaxis or any other organ system involvement warrant skin testing with insect venoms. In contrast, it is recommended to skin test children for insect venoms only if they have skin manifestations along with involvement of one other organ system. Studies suggest that children with only skin reactions such as urticaria and angioedema after venom sting do not worsen on repeated stings and lose their sensitivity over time. If positive, appropriate venom immunotherapy should be instituted. In addition to venom immunotherapy, the individual should carry an autoinjector of epinephrine, wear a medical identification bracelet, and practice insect-avoidance procedures.

Latex

The incidence of latex allergy has increased dramatically in the past 10– 15 yr with the increased use of latex gloves in response to the universal precautions associated with AIDS and other infections. Latex is now a significant cause of anaphylaxis, with more than 1000 cases of latex anaphylaxis reported to the Food and Drug Administration between 1988 and 1992. Three groups appear to be at high risk for development of anaphylaxis to latex: health care workers, people with a history of pruritus from exposure to latex objects, and patients with spina bifida.

Many different latex proteins have been demonstrated to be allergenic. Some allergens have been isolated from natural latex, and others are produced from the processing of the rubber compound. Exposure to latex can be topical, inhalational, mucosal (from surgical and dental procedures), and intravenous. Patients with latex allergy also have a high incidence of anaphylaxis to certain foods, including bananas, kiwi fruit, chestnuts, and avocados. They should therefore be counseled regarding these foods.

Allergen Immunotherapy

Allergen immunotherapy is an important modality in the treatment of select patients with allergic rhinitis, asthma, and insect venom hypersensitivity. By giving increasing doses subcutaneously of the allergen(s) the patient is sensitive, increased tolerance to these allergens occurs. Unfortunately, immunotherapy has been associated with very low rates of anaphylaxis. Bernstein et al. in 2004 reported that fatal reactions to immunotherapy occurred every 1 per 2.5 million injections, with an average of 3.4 deaths per year in the United States. A number of risk factors are associated with such severe anaphylactic reactions to immunotherapy, including errors in dosage, failure to reduce the dosage after a longer than scheduled interval, administration of the wrong extract, inadvertent intravenous administration, failure to postpone injection because of asthma exacerbation, failure to observe patients for an appropriate length of time, and concurrent use of β-adrenergic blocking agents. All allergen immunotherapy should be given in a medical care setting and patients observed for at least 20 min after the injection for the possibility of anaphylaxis. No injections should be given if the patient is having asthma symptoms or is on β-adrenergic blocking agents.

Exercise-Induced Anaphylaxis

Exercise has been documented as a source of severe anaphylactoid reactions. Symptoms include angioedema, urticaria, abdominal cramping, diarrhea, laryngeal edema, bronchospasm, and respiratory distress. The reaction typically begins during exercise or shortly after exercise is completed. A special group of patients with exercise-induced anaphylaxis have symptoms only when they exercise within 2– 4 h of eating. This entity is called food-dependent exercise-induced anaphylaxis. Some patients with this condition have symptoms with exercise only after eating certain foods, such as celery, wheat, shellfish, and oysters. Others have symptoms in association with any food and exercise. All individuals with these conditions should exercise with a companion capable of administering epinephrine. Individuals with food-dependent exercise-induced anaphylaxis should not exercise within 2–4 h of eating. About two-thirds of individuals with exercise-induced anaphylaxis have a family history of atopy, and about one-half have a personal history of atopy. The exact mechanism is unknown, and it has been speculated

that the release of endogenous opioid peptides with vigorous exercise may release mediators in susceptible individuals. There is also evidence for mast cell activation in skin biopsy from patients with exercise-induced anaphylaxis.

Plasma Exchange

Patients undergoing plasma exchange can experience anaphylaxis from multiple causes. The reported incidence is as high as 12%. Reactions can be from the plasma or the apparatus used during the plasmapheresis procedure. Changing the plasmapheresis equipment may help to prevent subsequent reactions. Pretreatment with prednisone and diphenhydramine can also be helpful.

Hemodialysis

Anaphylaxis and anaphylactoid reactions during hemodialysis have been attributed to a number of different factors. Ethylene oxide used for sterilization can produce an IgE-mediated event. Other reactions have been related to the procedure used in processing the hemodialyzer. The type of hemodialysis membrane can be important. Severe reactions have been reported with the use of hollow-fiber membranes made of cuprammonium cellulose. The use of angiotensin-converting enzyme(ACE) inhibitors during dialysis seems to predispose to anaphylactoid events. When a patient experiences anaphylaxis during hemodialysis, the type of membrane should be changed, no reprocessed membrane should be used, and ACE inhibitors and β-blockers should be discontinued if possible.

Insulin

Reactions to insulin include local or systemic reactions and insulin resistance. Although human recombinant DNA insulin appears to be less antigenic than bovine-type insulin, it can cause allergic reactions. Local reactions are the most common and are generally encountered during the first 1–4 wk of therapy. They are usually IgE-mediated and consist of mild erythema, swelling, burning, and pruritus at the injection site. These local reactions usually disappear in 3–4 wk with continued administration of insulin. Dividing the insulin dose into two or more sites or switching to a different preparation is generally helpful. If not, antihistamines may be given until the reaction disappears. Local reactions may precede anaphylactic reactions. Therefore, epinephrine should be available to these patients. Systemic reactions include urticaria, angioedema, bronchospasm, and hypotension. Most of these reactions occur upon re-starting of insulin after an interruption in therapy. In treatment of the systemic reactions it is very important that the insulin therapy not be discontinued. If the last dose is given within 24 h, the subsequent dose should be decreased by one-third and then subsequently increased slowly by 2–5 units until the desired dose is reached. If it has been more than 24 h since the onset of anaphylaxis, a serious reaction with re-administration of insulin is more likely to occur. The least allergenic insulin is selected by skin testing using several different preparations of insulin. Desensitization of a patient with a history of a systemic reaction to insulin should be carried out in an intensive care unit setting.

Radiocontrast Media

Generalized reactions to radiocontrast media that occur immediately after administration are encountered in 0.5–3% of patients who receive the substance. The majority of

patients who experience a reaction have urticaria. Reactions to radiocontrast media are not IgE-mediated but probably involve mast cell activation with release of histamine and other mediators. Use of nonionic, lower osmolarity agents reduces the risk of a reaction. Unfortunately, their use is limited because of higher expense. In patients who receive β-adrenergic blocking agents, the reactions may be more severe and less responsive to treatment. There is no association between reaction to radiocontrast media and topical iodine solution or shellfish allergy.

The risk of subsequent reactions is substantially reduced by pretreatment regimens of corticosteroids, antihistamines, and adrenergic agents or by use of low-osmolarity nonionic radiocontrast material.

Local Anesthetics

IgE-mediated reactions to local anesthetics are extremely rare. The adverse reactions most commonly seen with these agents are vasovagal or hyperventilation episodes, toxic reactions, or epinephrine side effects. The preservatives in local anesthetics, which include sulfites and parabens, may be responsible for allergy-type reactions. Skin prick testing can be done with a local anesthetic, which does not contain epinephrine. If the result of the test is negative, graded subcutaneous injections of diluted and full-strength doses of that local anesthetic are given at 15-min intervals. If the patient tolerates that local anesthetic, it may be used for future procedures.

Idiopathic Anaphylaxis

In up to one-third of patients, no identifiable factor can be found for their anaphylaxis. These individuals are labeled as having idiopathic anaphylaxis. Patients who are victims of frequent and life-threatening episodes of idiopathic anaphylaxis may need prophylactic treatment with oral H1 antihistamines and prednisone.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anaphylaxis and anaphylactoid events is listed in Table 6. The most common condition mimicking anaphylaxis is the vasodepressor (vasovagal) reaction. Most of these events precede emotional trauma or a threatening event.

Hypotension, pallor, diaphoresis, weakness, nausea, vomiting, and bradycardia are classically seen in these reactions. Patients lack the urticaria, pruritus, angioedema, tachycardia, and bronchospasm that are commonly seen in anaphylaxis. The characteristic bradycardia can be used as a differential diagnostic factor to distinguish these episodes from anaphylaxis. Symptoms are almost immediately reversed by recumbency and leg elevation. Other forms of shock, such as hemorrhagic, cardiogenic, and endotoxic shock, must be included in the differential diagnosis of anaphylaxis. These forms of shock, however, are usually not difficult to distinguish from anaphylaxis.

A number of reactions involving the "restaurant syndromes" have been observed that can mimic anaphylaxis. These include reactions to monosodium glutamate (MSG), sulfites, and saurine. MSG ingestion can cause chest pain, facial burning, flushing, sweating, dizziness, paresthesias, headaches, palpitations, nausea, and vomiting. In children, screaming, chills, irritability, and delirium have been reported. Symptoms typically begin no later than 1 h after ingestion, although they can be delayed in some instances for up to 14 h. The exact mechanism is unknown; however, it has been postulated that a transient

Differential Diagnosis Clinical Pearls

- The most common condition mimicking anaphylaxis is the vasodepressor (vasovagal) reaction. It is distinguished from anaphylaxis by lack of urticaria, pruritus, angioedema, tachycardia, and bronchospasm.
- A helpful clue in distinguishing scombroidosis from a true anaphylactic event is that usually everyone who ate the spoiled fish in sufficient quantities will also have symptoms of scombroidosis.
- Measuring serum mast cell β-tryptase level is more useful than measuring serum histamine levels in diagnosing anaphylaxis because of its longer half-life, approx 2 h.

acetylcholinosis occurs. Approximately 15–20% of the population is thought to be susceptible to MSG reactions, but these reactions can occur in anyone if the dose is large enough.

In some individuals the ingestion of sulfites can produce a reaction that can be confused with anaphylaxis. Sulfites can be found in many foods, including dried fruits, gelatin, wine, sausage, shellfish, and pickles. After ingestion of a food containing sulfites, certain patients may experience flushing, hypotension, and bronchospasm. Bronchospasm is typically the most prominent symptom of this syndrome, and it can be very severe.

Ingestion of saurine, which is contained in spoiled fish, can result in scombroidosis. Saurine is a histamine-like chemical that is produced by bacterial decarboxylation of histidine. Symptoms of scombroidosis can be very similar to those seen in true anaphylactic events, and at times it can be difficult to distinguish unless a careful history is taken. Symptoms typically include flushing, urticaria and angioedema, pruritus, headache, nausea, and vomiting. A helpful clue in distinguishing scombroidosis from a true anaphylactic event is that usually everyone who ate the spoiled fish in sufficient quantities will also have symptoms of scombroidosis. Patients who are taking isoniazid seem to be particularly susceptible to this reaction.

There are several syndromes that produce flushing that can be mistaken for anaphylaxis. These include carcinoid tumors, postmenopausal flush, chlorpropamide/alcohol-induced flush, medullary carcinoma of the thyroid, autonomic epilepsy, and idiopathic flush. Individuals with carcinoid tumors can have symptoms similar to those seen during anaphylaxis. These tumors can secrete histamine, neuropeptides, kallikrein, and prostaglandins, in addition to 5-hydroxytryptamine (serotonin). In reaction to these substances, patients with carcinoid tumors can exhibit flushing, abdominal pain, diarrhea, and occasionally wheezing. Postmenopausal flush typically occurs over the face, neck, upper chest, and breasts. The flush may last anywhere from 3 to 5 min and can occur several times throughout the day. Stress and alcohol can aggravate it. There is no associated urticaria, angioedema, hypotension, or GI involvement. The ingestion of alcohol while taking chlorpropamide (a sulfonylurea agent) can cause flushing with hypoglycemia and its associated symptomatology. The flush usually begins 3–5 min after alcohol ingestion and peaks in about 15 min. Patients with medullary carcinoma of the thyroid can have a protracted flush of the face and upper extremities. These patients typically have telangiectasias, mucosal neuromas, and a family history of the disease. These thyroid tumors

Table 6
Differential Diagnosis of Anaphylaxis

Vasodepressor reactions
Other forms of shock
Hemorrhagic shock
Cardiogenic shock
Endotoxic shock
Adrenal insufficiency
"Restaurant syndromes"
MSG
Sulfites
Saurine (scombroidosis)
Flush syndromes
Carcinoid flush
Postmenopausal flush
Chlorpropamide/alcohol-induced flush
Medullary carcinoma of the thyroid
Autonomic epilepsy
Idiopathic flush
Excess endogenous production of histamine syndromes
Systemic mastocytosis
Urticaria pigmentosa
Basophilic leukemia
Acute promyelocytic leukemia (tretinoin treatment)
Hydatid cyst
Nonorganic diseases
Panic attacks
Munchausen's stridor
VCD syndrome
Globus hystericus
Miscellaneous conditions
Hereditary angioedema
"Progesterone anaphylaxis"
Urticarial vasculitis
Pheochromocytoma
Hyperimmunoglobulin E, urticaria syndrome
Neurological (seizures, stroke)
Pseudoanaphylaxis
"Red man syndrome"
Recurrent syncope of unknown cause

MSG, monosodium glutamate; VCD, vocal cord dysfunction.

can secrete histamine, prostaglandins, substance P, and serotonin. Autonomic epilepsy is a rare disorder caused by the release of paroxysmal autonomic discharges. Individuals with this disorder may have tachycardia, flush, and syncope, as well as hypotension or hypertension.

Idiopathic flush occurs primarily in women. It can be associated with diarrhea, syncope, palpitations, and hypotension. Bronchospasm, urticaria, and angioedema are absent from this disorder. Several syndromes are characterized by excessive endogenous pro-

duction of histamine. These include systemic mastocytosis, urticaria pigmentosa, basophilic leukemia, acute promyelocytic leukemia, and hydatid cyst. Anaphylactic events can occur in such patients. Patients with systemic mastocytosis can experience anaphylactic episodes after the ingestion of opiates. Patients with promyelocytic leukemia can experience episodes after treatment with tretinoin. Human infection with the larval stage of the canine tapeworm *Echinococcus granulosus* causes hydatid cysts. If the hydatid cyst ruptures, the contents are released and an IgE-mediated anaphylactic reaction can occur.

Patients with emotional disturbances can also have episodes that may be confused with anaphylaxis. Flushing, tachycardia, GI symptoms, and shortness of breath often accompany panic attacks. Two other conditions, which can sometimes be confused with anaphylaxis, are Munchausen's stridor and vocal cord dysfunction. They have similar presentations; however, one is consciously self-induced and the other is involuntary. Vocal cord dysfunction is caused by an involuntary adduction of the vocal cords, which produces obstruction in both expiration and inspiration. The patient is not aware of the process and is unable to reproduce the event. In Munchausen's stridor, the laryngeal spasm is self-induced. In both, the patients will present with symptoms mimicking laryngeal edema with stridor. However, these patients will lack urticaria, angioedema, or other cutaneous symptoms.

Several other miscellaneous conditions can be included in the differential diagnosis of anaphylaxis: hereditary angioedema, urticarial vasculitis, pheochromocytoma, and "red man syndrome." Hereditary angioedema is an autosomal-dominant disorder that can be mistaken for anaphylaxis. This condition is associated with painful swellings, laryngeal edema, and abdominal pain. This disorder usually has a slower onset, lacks urticaria and hypotension, and is often accompanied by a family history of similar reactions. Obtaining a C4 level, which is decreased in this condition, can confirm the diagnosis.

At times it may not be clear whether or not a patient has had an anaphylactic reaction. The reaction may be verified by measuring a serum mast cell β-tryptase level. In the mast cell, β-tryptase is stored in granules and released with activation of the mast cell, in contrast to α-protryptase, which is secreted constitutively. Unlike plasma histamine, which usually declines within 30 min of the anaphylactic reaction, the mast cell β-tryptase level peaks at 60– 90 min and then declines, with a half-life of approx 2 h. Ideally, β-tryptase level should be ascertained with 15 h of the initial event to determine if it is anaphylaxis.

PREVENTION

Once the diagnosis of anaphylaxis has been established and a cause has been identified, prevention of future episodes by avoidance is the cornerstone of therapy. Measures to reduce the incidence of anaphylaxis and anaphylactic deaths can be seen in Table 7. In the case of drug or food allergy, the offending agent as well as those agents that may cross-react must be avoided. If an individual has a history of an allergic reaction to a drug, such as penicillin, a drug that does not cross-react with the penicillin family should be used. When medications must be given, oral administration is preferable to parenteral administration because reactions are usually less severe after oral administration. If an in-office parenteral administration of a drug is required, the patient should remain for observation for at least a 20- to 30-min period. Insect-allergic patients should avoid flowers, garbage, mowing the lawn, and walking barefoot outdoors. Latex-allergic indi-

Prevention Clinical Pearls

- A complete history taken from the patient about reactions to medication is paramount in the prevention of prescribing a cross-reacting drug.
- All patients with food and insect anaphylaxis should carry an autoinjector of epinephrine on their body and not left in a car or at home.
- All patients who receive an in-office parenteral injection should remain for observation at least 20–30 min for the possibility of anaphylaxis

Table 7
Measures to Reduce the Incidence of Anaphylaxis

Steps for the physician:
Take a detailed medical history noting past anaphylactic reactions
Mark all medical records regarding past anaphylactic reactions
Require clear indication of a drug's use
Avoid drugs with immunological or biochemical cross reactivity with any agents to which the patient is sensitive
Administer medication orally if possible
Keep patient in office 20–30 min after injections
Be prepared to treat anaphylaxis
Have emergency equipment available
Use pretreatment and desensitization protocols when indicated
Specific measures for patients at risk:
Patients should be instructed on self-administration of epinephrine
Patients should avoid beta-adrenergic blocking agents, ACE inhibitors, and monoamine oxidase inhibitors
Patients should discard all unused medications
Patients with food-induced anaphylaxis need to check all labels for the offending agent

ACE, angiotensin-converting enzyme.

viduals should avoid contact with all latex products and should use only nonlatex gloves. If these patients require surgery or dental procedures, the procedures should be performed only in a latex-free area.

Patients at risk for anaphylaxis should carry appropriate identification, such as a Medic-Alert bracelet or necklace or an identification card, in a wallet or purse. All patients should carry a preloaded syringe of epinephrine or an autoinjector of epinephrine (Epi-pen®) at all times and should be instructed in its use. Any individual who has had an anaphylactic reaction should not take β-adrenergic blocking agents, ACE inhibitors, monoamine oxidase inhibitors (MAOIs), or certain tricyclic antidepressants (TCAs), such as amitriptyline. β-Blockers inhibit the therapeutic action of epinephrine and can also increase the severity of an attack. ACE inhibitors prevent the conversion of angiotensin I to angiotensin II. This is turn prevents a compensatory response to hypotension. MAOIs and some TCAs are dangerous in some situations because they interfere with the degradation of epinephrine.

Table 8
Initial Management of Anaphylaxis

Immediate action
Assessment
Secure and maintain airway
Rapid assessment of level of consciousness
Vital signs
Treatment
Epinephrine 1:1000, 0.01 mL/kg up to 0.3 mL im preferred in thigh or sc; repeat every 5 min as necessary
Supine position, legs elevated
Oxygen
Tourniquet proximal to injection site
H_1 antihistamine (diphenhydramine 1–2 mg/kg im or iv up to 50 mg/kg every 4–6 h
Corticosteroids (hydrocortisone 5–10 mg/kg up to 500 mg iv every 4–6 h)
H_2 antihistamine (ranitidine 12.5–50 mg iv every 6–8 h)
Monitor vital signs frequently
Peripheral iv fluids
If hypotension persists, norepinephrine bitartrate, 208 mg/min, or dopamine, 2–10 mg/kg/min, to maintain blood pressure
If hypotension caused by β-blocker, administer glucagon, 1–5 mg iv over 1 min, and begin continuous infusion 1–5 mg/h
Administer specific antiarrhythmic agents in indicated
For persistent bronchospasm, administer aminophylline, 5 mg/kg over 20 min, then continue iv aminophylline drip at 0.9 mg/lg/h; aerosolized β-agonist as needed
Keep patient in observation for at least 24 h in use of a protracted course

MANAGEMENT

Anaphylaxis has a highly variable presentation; therefore, rapid recognition with immediate treatment is essential. The treatment of anaphylaxis should follow established principles for emergency resuscitation (Table 8). This approach is required to counteract the effects of mediator release, prevent further release of mediators, and support vital functions. The drugs used in the treatment of anaphylaxis are shown in Table 9.

At the first sign of anaphylaxis, epinephrine should be administered. Simultaneously, a rapid assessment of the patient's airway status and state of consciousness should be assessed. An airway should be secured immediately if there is any compromise. The patient should be placed in a supine position with the legs raised. If the patient is upright, there is a risk of insufficient venous return to the heart leading to circulatory collapse and cardiac ischemia. Supplemental oxygen should be administered if there is any question about the cardiopulmonary status.

Epinephrine is the single most important agent in the treatment of anaphylaxis. Delaying administration or failure to administer the drug can result in a fatal outcome. The dose and route of administration of epinephrine depend on the severity of the reaction. In most instances, intramuscular is preferred, although the subcutaneous route can be used. The dose for an adult is 0.3–0.5 mL (0.3–0.5 mg) of 1:1000 preparation, whereas the dose for a child is based on body weight (0.01 mL/kg). The initial dose may be repeated every 5 mins as needed—although one should watch for toxicity. Recently, studies have sug-

Treatment Clinical Pearls

- Epinephrine is the drug of choice in the treatment of anaphylaxis. Delaying or failing to administer epinephrine can result in a fatal outcome.
- The patient with anaphylaxis should be placed in a supine position with the legs raised. If the patient is upright, there is a risk of insufficient venous return to the heart leading to circulatory collapse and cardiac ischemia.
- If anaphylaxis is from an injection or an insect sting, a tourniquet should be place proximal to the site of the injection or sting and a half-dose of epinephrine should be injected in the area of the inciting injection or insect sting.

Table 9
Equipment for Treatment of Anaphylaxis

Medications
Epinephrine 1:1000 for sc, im
Epinephrine 1: 100,000 for iv
Corticosteroids (methylprednisolone, hydrocortisone)
H_1 Antihistaminew (diphenhydramine, hydroxyzine)
H_2 Antihistamines (cimetidine, ranitidine)
β_2 Agonists (albuterol)
Aminophylline
Glucagon
Dopamine
Norepinephrine bitartrate
Oxygen, face mask, nasal cannula
iv fluids (normal saline, albumin)
Airway kit, Ambu bag, laryngoscope, scalpel, and 11-gauge needle for cricothyroidotomy
Electrocardiograph
Sphygmomanometer ans stethoscopes
Tourniquets

sc, subcutaneous; im, intramuscular; iv, intravenous.

gested that epinephrine should be administered intramuscularly into the thigh (vastus lateralis) instead of intramuscularly or subcutaneous in the arm (deltoid) because intramuscular injection in the thigh gives more complete and rapid absorption of epinephrine. Rarely, severe refractory anaphylaxis will require intravenous epinephrine. The amount administered depends on the severity of the episode. Generally a 1:10,000 aqueous preparation can be prepared by diluting 1.0 mL of a 1:1000 aqueous epinephrine solution in 9 mL of normal saline. This 1:10,000 solution can then be administered in doses of 0.1–0.2 mL every 5–15 min depending on the response of the patient. Of course, lower doses may be needed for patients with underlying cardiac disease.

If the reaction is from an injection or an insect sting, a tourniquet should be placed proximal to the site of the injection or sting. The tourniquet should then be released every 10 min for 1–2 min. If anaphylaxis resulted from an injection or sting, as long as the sting is not in the head, neck, hands, or feet, a second injection of epinephrine 1:1000, one-half

dose(0.1–0.2 mg), can be given at the site of the injection or sting to reduce the antigen absorption.

Other medications can be given to supplement the effect of epinephrine. Antihistamines can be used after administration of epinephrine; however, they should not be used as a sole form of therapy. Diphenhydramine may be administered intravenously or intramuscularly. The dose in adults is 25–50 mg, and in children the dose is 1–2 mg/kg. The dose of diphenhydramine may be continued thereafter every 6 h for 48 h to help reduce the risk of recurrence. Other rapidly absorbed antihistamines may be substituted, as well as the addition of H_2 antagonists to the previous therapy. Ranitidine is administered in a dose of 1 mg/kg intravenously. The dose of cimetidine is 4 mg/kg, given intravenously. H_2 antagonists should be administered slowly because rapid administration of these agents has been associated with hypotension.

If the patient does not respond to the above measures and remains symptomatic with either hypotension or persistent respiratory distress, admission to the intensive care unit is essential. In these instances, intravenous fluids and vasopressors should be considered for administration. Intubation and tracheostomy may be necessary if upper airway obstruction is severe enough to impair adequate ventilation. Corticosteroids are not helpful in the acute management of anaphylaxis; however, they should be administered in moderate or severe reactions in order to prevent protracted or recurrent anaphylaxis. Hydrocortisone can be administered in a dose of 5 mg/kg up to 1 g intramuscularly or intravenously. Methylprednisolone may also be used at a dose of 80–125 mg intravenously in adults and 40 mg intravenously in children. For milder episodes, oral prednisone may be given at a dose of 60 mg in adults and 30 mg in children. Glucagon may be given to patients who are taking β-adrenergic blocking agents because of its positive inotropic and chrontropic effects on the heart. The dose is administered as an intravenous bolus of 1–5 mg followed by a 5–15 μg/min titration. Atropine may also be beneficial if the patient has bradycardia. The dose is 0.3–0.5 mg subcutaneously, repeated every 10 min to a maximum of 2 mg. Wheezing unresponsive to epinephrine can be managed with an aerosolized β-adrenergic agent. An example is albuterol, 0.5 mL of a 0.5% solution in 2.5 mL of normal saline. When a compressor nebulizer is not available, a metered-dose inhaler is acceptable. Aminophylline 5 mg/kg over a 30-min period intravenously may be beneficial if there is no response to inhaled β-adrenergic agents.

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6 Insect Sting Allergy

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CONTENTS

SUMMARY

Anaphylaxis resulting from insect stings is estimated to affect 0.3–3% of the population and is responsible for at least 40 deaths a year in the United States. In addition, increasing numbers of reactions are caused by stings of the fire ant, a nonwinged Hymenoptera present primarily in the southeastern United States. Anaphylactic symptoms are typical of those occurring from any cause. The majority of reactions in children are mild, with dermal (hives, angioedema) symptoms only. The more severe reactions, such as shock and loss of consciousness, can occur at any age, but are relatively more common in adults. After an initial anaphylactic reaction, about 60% of unselected people will continue to have reactions from subsequent re-stings. The natural history of this disease process is influenced by age and severity of anaphylaxis. Children who had dermal reactions only have a very benign course and are unlikely to have recurrent re-sting allergic reactions. People who have had severe symptoms are more likely to have re-sting reactions, usually of similar intensity. People with a history of sting anaphylaxis and positive venom skin tests should have epinephrine available and are candidates for subsequent venom immunotherapy (VIT), which provides almost 100% protection against re-sting reactions. Recommendations for the duration of VIT are still evolving. VIT can be stopped if skin-test reactions become negative; for most people, 3–5 yr of VIT appears adequate, despite the persistence of positive tests. Individuals who have had life-threatening reactions, such as loss of consciousness, and retain positive skin tests should receive VIT indefinitely.

Key Words: Stinging insects; venom allergy; venom skin tests; venom immunotherapy.

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INTRODUCTION

Allergic reactions to insect stings are a very common and, occasionally, serious medical problem. The incidence of anaphylaxis in the general population has been estimated to range from 0.3 to 3%. Vital statistic registry data document at least 40 deaths per year as a result of insect sting anaphylaxis, with the likelihood that other episodes of unexplained sudden death are also the result of insect stings. Individuals at risk are often very anxious about further stings and, as a result, make significant changes in their lifestyles.

In recent years, particularly since the availability of purified venoms for diagnosis and therapy, major advances have occurred. The natural history of insect sting allergy is now understood, and tools are available for appropriate diagnosis and for treatment of individuals at risk for insect sting anaphylaxis. For many individuals, this is a self-limited disease, and for others treatment results in a permanent "cure."

INSECTS

The stinging insects are members of the order Hymenoptera of the class *Insecta*. They may be broadly divided into two families; the vespids, which include the yellow jacket, hornet, and wasp; and the apids, which include the honeybee and bumblebee. Individuals may be allergic to one or all of the stinging insects. The identification of the culprit insect responsible for reactions is thus important in terms of specific advice and specific venom immunotherapy (VIT; discussed later).

The presence of the different stinging insects varies in different parts of the country. For example, the wasp is most common in Texas, and honeybees may be more common in farm areas, where they are used for plant fertilization.

The yellow jacket is the most common cause of allergic reactions resulting from insect stings. These insects primarily nest in the ground and are easily disturbed in a course of activity, such as lawn mowing and gardening. They are also attracted to food and are thus commonly found around garbage and picnic areas. Yellow jackets are particularly present in the late summer and fall months of the year. Hornets, which are closely related to the yellow jacket, nest in shrubs and are easily provoked by activities such as hedge clipping. Wasps are found in nests, usually hanging from eaves. In general, there are few wasps per nest, and thus stings are relatively uncommon in most of the country. The honeybee hive may contain thousands of honeybees. As a rule, these insects are quite docile, as exemplified by the common picture of the beekeeper handling thousands of bees on his face or other parts of the body. However, if the honeybee hive is disturbed, multiple stings may occur. The bumblebee, which is a solitary bee, is a rare cause for an insect sting reaction.

The problem of multiple insect stings has been intensified by the introduction of the "Africanized" honeybee, the so-called killer bee, into the southwestern United States. The African honeybee was introduced into Brazil from Africa in 1956 for the purpose of providing a more productive bee in tropical climates. These bees are much more aggressive than domesticated European honeybees, which are found throughout the United States. The African honeybee has interbred with the European honeybee, but unfortunately the aggressive characteristics have persisted. These bees are extremely aggressive, and massive stinging incidents have occurred, resulting in death from venom toxicity. The Africanized honeybees entered south Texas in 1990 and are now present in Arizona and California. It is anticipated that these bees will continue to spread through the southern United States. They are unable to survive in colder climates but may make periodic forays into northern United States during the summer months.

The fire ant, which is a nonwinged stinging insect, is found in southeastern and south central United States primarily near the Gulf Coast. These insects are gradually spreading northward and westward. It is anticipated that they will extend as far north as Virginia and have now reached California. The fire ant is increasingly responsible for allergic reactions. It attaches itself by biting with its jaws. It then pivots around its head and stings at multiple sites in a circular pattern. Within 24 h a sterile pustule develops, which is diagnostic of the fire ant sting.

In contrast to stinging insects, biting insects, such as the mosquito, rarely cause serious allergic reactions. These insects deposit salivary gland secretions, which have no relationship to the venom deposited by stinging insects. Anaphylaxis has occurred from bites of the deerfly, kissing bug, and bedbug. Isolated reports also suggest that on rare occasions mosquito and black fly bites have caused anaphylaxis. It is much more common, however, for insect bites to cause large local reactions, which may have an immune pathogenesis.

REACTIONS TO INSECT STINGS

Normal Reaction

Insect stings, in contrast to insect bites, always cause pain at the sting site. The usual or "normal" reaction is localized pain, swelling, and redness. This reaction usually subsides within a few hours. Little treatment is needed other than analgesics and cold compresses.

Large Local Reactions

Extensive swelling and erythema, extending from the sting site over a large area, is fairly common. The swelling usually peaks in 24–48 h and may last 7–10 d; a sting on the hand may cause swelling extending as far as the elbow. On occasion, when the reaction is severe, fatigue, nausea, and malaise may be present. If mild, these large local reactions can be treated with aspirin and antihistamines. When a reaction is severe or disabling, steroids such as prednisone, 40 mg daily for 2–3 d, are very helpful in diminishing the swelling. There is no documentation that the application of papain (meat tenderizer) or "mud" alleviates local swelling. These large local reactions have been confused with infection and cellulitis. Insect sting sites are rarely infected and antibiotic therapy rarely indicated. Tetanus prophylaxis is unnecessary.

The natural history of reactions that occur following subsequent re-stings in individuals who have had large local reactions has been well studied. After subsequent stings large local reactions tend to reoccur in about 80% of individuals. The risk for subsequent insect anaphylaxis is very low, less than 5% Thus, individuals who have had large local reactions are usually not considered candidates for VIT (discussed later) as treatment to prevent anaphylaxis and do not require venom skin tests. There are conflicting reports regarding the efficacy of VIT to minimize large local reactions. The use of VIT might be a consideration for people frequently stung who develop significant local reactions despite appropriate medical therapy.

Anaphylaxis

There are no clinical criteria or risk factors that identify individuals at potential risk for insect sting anaphylaxis other than a history of a prior anaphylactic reaction. The clinical features of anaphylaxis following an insect sting are similar to anaphylaxis from

other causes. The most common symptoms are dermal, generalized urticaria, flushing, and angioedema. The most severe symptoms, which may be life-threatening, include respiratory distress as a result of asthma and upper airway swelling, circulatory collapse, and shock. Other symptoms include nausea, bowel cramps, diarrhea, rarely uterine cramps, and a feeling of "impending doom." Anaphylactic symptoms usually start immediately after a sting, within 10–30 min. On rare occasions reactions have started after a longer time interval.

Estimates of the incidence of anaphylaxis in the general population range as high as 3%. The majority of reactions have occurred in individuals under the age of 20, with a 2:1 male to female ratio. These prevalence data probably reflect exposure rather than any specific age or gender predilection for anaphylaxis. Although the majority of insect sting reactions occur in younger individuals, severe anaphylaxis may occur at any age. Most deaths have occurred in older individuals, many of whom had cardiovascular disease.

The natural history of insect sting anaphylaxis has been the subject of fairly intense investigation. In individuals who have had insect sting anaphylaxis, the recurrence rate after subsequent stings is approx 60%. Viewed from a different perspective, not all individuals presumed to be at risk react to re-stings. The incidence of these re-sting reactions is influenced by age and severity of the initial anaphylactic reaction. In general, children are less likely to have re-sting reactions as compared with adults. The more severe the anaphylactic reaction, the more likely it is to reoccur. For example, children who have had dermal symptoms as the only manifestation of anaphylaxis have a remarkably low re-sting reaction rate. On the other hand, in individuals of any age who have had severe anaphylaxis, the likelihood of repeat reactions is approx 80%. When anaphylaxis does reoccur, the severity of the reaction tends to be similar to the initial reaction. No relationship has been found between the occurrence and degree of anaphylaxis and the intensity of venom skin-test reactions.

Unusual Reactions

Serum-sickness-type reactions, characterized by urticaria, joint pain, and fever, have occurred approx 7 d after an insect sting. Individuals who have this reaction are subsequently at risk for acute anaphylaxis after repeat stings and thus are considered candidates for VIT.

There have been isolated reports of other reactions such as vasculitis, nephritis, neuritis, and encephalitis, occurring in a temporal relationship to an insect sting. The specific etiology for these reactions has not been established and in general VIT is not indicated.

Toxic Reactions

Many simultaneous insect stings, for example, 100 or more, may lead to toxic reactions owing to venom constituents. The clinical symptoms that characterize these reactions are primarily cardiovascular and respiratory in nature. Immediate treatment is directed to cardiovascular and respiratory support. Following toxic reactions, individuals may develop immunoglobulin (Ig)E antibody and may then be at risk for subsequent allergic sting reactions. Thus, individuals who have had toxic reactions should be tested for the possibility of potential sensitization and need for specific therapy. The frequency of these toxic reactions has increased because of the Africanized honeybees.

ALLERGY TESTS

Acute allergic reactions from insect stings result from IgE antibodies reacting with insect venoms. These antibodies are best detected by the immediate skin test reaction. Individual insect venoms—yellow jacket, honeybee, white-faced hornet, yellow hornet, and wasp—are commercially available for diagnostic skin tests. A positive skin test is defined as an immediate wheal-and-flare reaction occurring within 10 min after an intradermal skin test with venom doses up to 1.0 μm/mL. Higher venom doses cause nonspecific irritative reactions. IgE antibodies in the serum can also be measured by the radioallergosorbent test (RAST). This in vitro test is more expensive and generally less sensitive than the simple immediate skin test. It is estimated that approx 20% of individuals with positive venom skin tests will not have a positive RAST. Thus, the RAST is not recommended for routine diagnosis unless a skin test cannot be performed.

There have been isolated observations of people who have had systemic allergic reactions from an insect sting after negative venom skin test reactions. Some of these people have had detectable serum venom-specific IgE (RAST). As a result of these observations, measurement of serum venom-specific IgE is recommended if an individual has a history of moderate-to-severe venom anaphylaxis and has a negative venom skin-test reaction.

Individuals with systemic mastocytosis may have anaphylaxis, usually moderate to severe, from an insect sting, which is a result of nonimmunological release of mediators as the result of the pharmocological properties of venom. These people have elevated baseline serum tryptase levels. It is therefore advisable to search for the possibility of systemic mastocytosis as the explanation for venom-induced anaphylaxis in people with undetectable venom-specific IgE (skin test and RAST).

At the present time, fire ant venom is not available. The commercial whole-body fire ant extract is reasonably reliable for skin-test diagnosis and immunotherapy for fire ant-allergic individuals.

THERAPY

Acute Reaction

The immediate medical treatment for acute anaphylaxis resulting from insect stings is the same as that for anaphylaxis from any other cause. This treatment is detailed in Chapter 5.

If the insect stinger remains in the skin, it should be gently flicked off, with care being taken not to squeeze the sac. Unfortunately, the majority of the venom is deposited very quickly after the sting, and removal of the sac will only be helpful if done immediately.

Prophylaxis

Individuals who have had insect sting anaphylaxis and have positive venom skin tests are at risk for further reactions after re-stings. Prophylactic measures include minimizing potential exposure, keeping medication for immediate treatment of anaphylaxis available, and consideration of VIT.

Measures that might minimize insect stings include wearing protective clothing when outside, such as shoes, slacks, long sleeves, and gloves. Cosmetics, perfumes, and black

or drab clothing, which attract insects, should be avoided. Great care should be taken when eating outdoors because food and garbage do attract insects.

The primary medication for treatment of anaphylaxis is epinephrine. Individuals at potential risk should be given epinephrine, available in preloaded syringes, (Epi-Pen, Center Laboratories, Port Washington, NY; Twinject, Verus Pharmaceuticals Inc., San Diego, CA). Antihistamines, such as diphenhydramine, are also recommended and may be helpful for treatment of hives and edema.

VENOM IMMUNOTHERAPY

Injection of purified venoms (VIT) is extremely effective treatment for individuals at risk for venom anaphylaxis. The overall success rate in preventing subsequent anaphylaxis is more than 98%. VIT reduces the risk for anaphylaxis from approx 50–60% in untreated individuals to about 2% after 3–5 yr of treatment. The guidelines for selection of individuals for treatment and VIT dosing are now well established and are outlined in Tables 1–3.

Selection of Individuals

All individuals who have severe symptoms of anaphylaxis and have positive venom skin tests should receive VIT (Table 1). Children who have had very mild reactions with dermal symptoms only do not require therapy. Their families should be advised to keep epinephrine and antihistamines available. Adults who have had similar mild anaphylaxis can probably be treated in a similar fashion, but there is less evidence to support this practice in adults than in children. Currently VIT is still recommended for these adults. Those individuals who have had reactions of moderate intensity such as mild asthma, nausea, and urticaria, without serious life-threatening reactions, might also be treated without immunotherapy and with the availability of emergency medication. They are likely to have similar moderate reactions to subsequent stings. This decision is influenced by other factors such as risk of exposure, other disease processes, such as cardiac disease, and medication use.

Following serum sickness reactions, individuals usually have positive skin tests and are then at risk for subsequent anaphylaxis. These observations are similar to the classic horse-serum-induced serum sickness. If skin tests are positive, these individuals should then receive immunotherapy. Because venom is a highly sensitizing agent, individuals who have had toxic reactions may develop IgE antibody and then are at potential risk for anaphylaxis. In that situation, immunotherapy is indicated. As already noted, individuals with large local reactions usually are not candidates for VIT.

Venom Selection

The product brochure, which has not changed since the availability of commercial venoms in 1979, recommends VIT with each venom that elicits a positive skin-test reaction. Studies of venom antigenic crossreactivity explain the common observation of multiple positive venom skin tests despite only one insect sting reaction. For example, an individual who has had an allergic reaction following a yellow jacket sting will almost always have positive skin tests to both yellow jacket and hornet venoms and possibly to wasp venom. Awareness of this crossreactivity allows for more selective venom treatment. The selection of venom for therapy is based on a history of the culprit insect responsible for the reaction and the degree of skin-test reactivity. This approach utilizing

Table 1
Indications for Venom Immunotherapy in Patients With Positive Venom Skin Tests [a]

Insect sting reaction	*Venom immunotherapy*
"Normal" — transient pain, swelling	No
Extensive local swelling	No
Anaphylaxis	
Severe	Yes
Moderate	Yes[b]
Mild; dermal only	
Children	No
Adults	Yes[b]
Serum sickness	Yes
Toxic	Yes

[a]Venom immunotherapy is not indicated for individuals with negative venom skin tests.
[b]Patients in these groups might be managed without immunotherapy (see text).

Table 2
General Venom Immunotherapy Dosing

Initial dose	0.01–0.1 μg, depending on degree of skin test reaction
Incremental doses	Schedules vary from "rush" therapy administering multiple venom injections over several days to traditional once weekly injections
Maintenance dose	50–100 μg of single venoms 300 μg of mixed vespid venom.
Maintenance interval	4 wk year 1 6 wk year 2 8 wk year 3
Duration of therapy	Stop if skin test becomes negative Finite time; 3– 5 yr (*see* text)

single venoms despite multiple positive skin tests is less expensive, requires fewer injections, and is therapeutically as very effective.

Dosing Schedule

VIT is initiated with injection of small doses of venom followed by increasing doses until the recommended maintenance dose has been reached (Tables 2 and 3). The initial dose of venom is based on the degree of skin-test reactivity, not the severity of the anaphylactic reaction. Incremental doses are given according to a number of schedules ranging from once-weekly single doses to rush immunotherapy, which utilizes multiple doses over a 2- to 3-d period. A typical dose schedule is shown in Table 3. Maintenance doses of 100 μg of single venoms or 300 μg of a mixed vespid preparation (yellow jacket, white-faced hornet, yellow hornet) is the traditional recommendation. Our studies indicate that top doses of 50 μg of individual venoms are effective. Once the maintenance

Table 3
Representative Examples of Venom Immunotherapy Dosing Schedules[a]

	Traditional	*Modified rush*	*Rush*	
Day				
1	0.1	0.1	0.1[b]	3.0
		0.3	0.3	5.0
		0.6	0.6	10
			1.0	
2			20	
			35	
			50[c]	
			75	
3			100	
Week				
1	0.3	1.0		
		3.0		
2	1.0	5.0	100	
		10	Repeat every 4 wk	
3	3.0	20		
4	5.0	35		
5	10	50[c]		
6	20	65		
7	35	80		
8	50[c]	100		
9	65			
10	80	100		
11	100	Repeat every 4 wk		
12				
13	100			
	Repeat every 4 wk			

[a]Starting dose may vary depending on patients' skin test sensitivity. Subsequent doses modified by local or systemic reactions. Doses expressed in micrograms.
[b]Sequential venom doses administered on same day at 20- to 30-min intervals
[c] 50 µg may be used as top dose.

dose is reached, injections are usually given at 4-wk intervals through the first year and then 6- and 8-wk intervals after the second and third years, respectively.

Reactions to Venom Immunotherapy

Systemic Allergic Reactions

Systemic allergic reactions resulting from VIT are relatively uncommon, as compared with reactions that follow other types of allergen immunotherapy. However, because of the possibility of such reactions, it is important that VIT, as with other allergenic extracts, only be administered in the setting in which personnel and equipment are available for treatment of an anaphylactic reaction. Following such a reaction, the venom dose is

usually decreased about 25–33% and subsequent doses given at lesser increasing increments. If the patient is receiving several different venoms, it is prudent to give only one venom at each treatment time or separate the time of administration. Inability to ultimately tolerate a maintenance venom dose is rare.

Local Reactions

Large local reactions following VIT are more common. When other types of allergenic extracts are administered, doses are decreased and a smaller dose might be maintained to avoid such reactions. In the case of venom, however, it is necessary to administer a maintenance dose (50–100 μg) in order to assure protection from insect stings. Measures to minimize these local reactions include splitting the venom dose into two injection sites and the addition of a small amount of epinephrine, such as 0.05–0.1 mL, with the venom, a commonly used procedure, although its efficacy has never been documented. When these local reactions are extensive and particularly somewhat delayed in onset, there may be accompanying nausea and fatigue. In this situation, the addition of a small amount of steroid, such as betamethasone 0.05–0.1 mL, to the venom may markedly reduce such reactions.

Fatigue, Malaise

Fatigue, nausea, malaise, and even fever are unusual symptoms that have been reported after venom injections and also after injection of other types of allergenic solutions, such as dust and mold. These symptoms usually start several hours after the venom injection and may last 1–2 d. The concomitant administration of aspirin with the venom injection and then further aspirin doses for the next 24 h may eliminate these reactions. If the reactions persist despite aspirin, then a small dose of oral steroids, such as prednisone 20 mg, given with the venom dose and repeated once in 6–8 h has been very helpful.

Long-Term Therapy

There have been no reported adverse reactions from long-term VIT.

Pregnancy

Venom injections appear to be safe for use during pregnancy.

Monitoring During Venom Immunotherapy

Venom Skin Tests

In a minority of venom-treated patients the venom skin test becomes negative. The loss of skin test reactivity indicates that venom-specific IgE is not present and, thus, the need for continued venom treatment is unnecessary (discussed later). As a general rule it is reasonable to retest individuals with venom every 1–2 yr to examine this possibility.

Measurement of Serum Venom-Specific IgG

Venom-specific IgG has been associated with immunity to insect stings. During the course of VIT, venom-specific IgG is stimulated. It has been suggested that individuals receiving VIT should have serial monitoring of this antibody titer and those individuals who have failed to develop adequate titers should have a modification in dosing. In my opinion, careful review of these data does not support that recommendation. Because VIT is 98% effective in preventing subsequent sting reactions, it does not seem reasonable to

Table 4
Cessation of Venom Immunotherapy

Suggested criteria for stopping venom immunotherapy:
Conversion to a negative venom skin test
Persistence of positive venom skin test: 3– 5 yr of therapy
Factors that may influence decision to stop therapy:
Severe anaphylactic symptoms, such as loss of consciousness, caused by insect sting
Systemic reactions to venom immunotherapy
Unchanged venom skin test sensitivity during venom immunotherapy
Honeybee venom allergy (compared with vespid venom allergy)
Presence of significant medical problems, such as cardiovascular disease
Access to emergency medical care

monitor any type of immune parameter looking for possible treatment failures. In addition, published data do not indicate that for an individual patient there is that close a correlation between absolute antibody titers and the success of VIT.

Treatment Failures

Persistent allergic reactions following insect stings in individuals receiving VIT are most uncommon. As noted previously, the success rate of VIT exceeds 98%. When these reactions do occur, it is first necessary to determine whether the patient has been treated with the correct venom. This might require reassessment by history and repeat skin tests. If other insects are suspect, then VIT should be modified. If it appears that the patient is receiving the correct venom, then the dose of the venom must be increased. For example, if the individual is receiving 100 µg of venom, the dose should be increased to 150–200 µg.

Cessation of Venom Immunotherapy

Definitive criteria for safe cessation of VIT are still evolving. These include immunological criteria and a specific period of treatment unrelated to the persistence of IgE antibody (Table 4).

Conversion to a Negative Skin Test

In my opinion, conversion to a negative skin test is an absolute criterion for stopping therapy, indicating that the IgE antibody, the immune mediator of this reaction, is no longer present. In my experience approx 20% of individuals will convert to a negative skin test after 3–5 yr of VIT.

Specific Time Period

Three to five years of VIT appears adequate for the large majority of individuals who have had mild-to-moderate anaphylactic reactions, despite the persistence of a positive venom skin test. The re-sting reaction rate after cessation of VIT is low, generally in the range of 5–10%. Individuals who have had severe anaphylactic symptoms such as hypotension, laryngeal edema, or loss of consciousness have a higher risk of a repeat systemic reaction, often of similar severity, if therapy is discontinued. For this reason, I currently recommend that individuals who have had severe symptoms and retain positive venom skin tests, receive VIT indefinitely, which at this point can be administered every

8–12 wk. Other risk factors associated with the occurrence of re-sting reactions after cessation of VIT include systemic reactions to VIT, persistence of significant skin-test reactivity, and honey bee venom allergy as compared to vespid venom allergy. These decisions regarding cessation of therapy should include consideration of other medical problems, concomitant medication, patient lifestyle, and patient preference.

CONCLUSION

Although problems remain, such as prediction or selection of individuals at potential risk for initial anaphylaxis and issues regarding duration of treatment, the understanding and approach to treatment of individuals with insect sting allergy have been defined and effective treatment is available for the majority of individuals.

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7 The Child With Asthma

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CONTENTS

SUMMARY

This chapter is dedicated to my dear friend and mentor, Gail Shapiro, w ho died while undergoing cardiac surgery in August 2006 at the age of 59. Gail was a pediatric allergist who contributed to important studies of drug treatments for asthma and allergies and helped develop widely used standards for managing childhood asthma. She had an infectious enthusiasm for treating patients and was a powerful advocate for improving care for children with asthma and allergic diseases. Although she was diminutive in size, her intelligence, grace, and kindness were larger than life. She will long serve as a role model for those who aspire to excellence.

Key Words: Airway inflammation; asthma action plan; exacerbation; inhaled corticosteroids; intermittent asthma; mild persistent asthma; moderate persistent asthma; remodeling; severe persistent asthma; spirometry.

EPIDEMIOLOGY

Asthma is a major public health problem in the United States. In 2001, 6.3 million children under the age of 18 yr were reported to have asthma, and approximately one-fourth of these children were younger than 5 yr. Asthma is the third ranking cause of hospitalizations and is responsible for more than 200,000 hospitalizations per year for children under age 15. In 2000 there were 4.6 million asthma-related outpatient visits to private physician offices and hospital clinics and more than 700,000 asthma-related visits

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to emergency departments. Asthma mortality nearly doubled between 1980 and 1993 (17 and 32 asthma deaths per 1 million population, respectively), and in 2000, 4487 people died from asthma. Asthma affects 1 of every 13 school children and is the leading causes of school absenteeism, accounting for 14 million school days annually. Poor school attendance has an adverse effect on grades, academic success, self-esteem, and future life accomplishments. The economic impact of asthma is enormous, approaching $3 billion per year for directs costs and $1 billion per year for indirect costs (parents and caregivers taking time away from work to take care of their ill children).

Asthma disproportionately affects urban minority populations, including both African American and Hispanic children as compared with non-Hispanic whites. They experience more emergency department visits, more hospitalizations, and more deaths as a result of asthma.

The National Heart, Lung, and Blood Institute (NHLBI) has developed and published asthma guidelines relying on evidenced-based medicine when possible. These guidelines are an important tool that provides a template for the clinician but also allows the clinician to use his or her own judgment as the clinical situation dictates. The science of medicine is combined with the art of medicine when taking care of children with asthma.

PATHOGENESIS

Asthma is a chronic inflammatory disease of the lungs. Even young patients with mild asthma have inflamed airways. This process involves a complex orchestration of inflammatory cells (mast cells, eosinophils, T-lymphocytes, and neutrophils), chemical mediators (histamine, leukotrienes, platelet-activating factor, bradykinin, etc.), and chemotactic factors (cytokines, eotaxin, etc.). This inflammation increases airway hyperresponsiveness, which is the tendency of the airway smooth muscles to constrict in response to allergens, irritants, viral infections, and exercise. It also results in airway edema, increased mucus production in the lungs, an influx of inflammatory cells into the airway, and epithelial cell denudation.

Chronic airway inflammation can lead to a proliferation of extracellular matrix proteins and vascular hyperplasia called airway remodeling. This begins relatively early in the asthmatic disease process and may lead to irreversible structural changes and a progressive loss in lung function. Exactly when the child is most at risk for remodeling and whether therapeutic intervention can prevent this is still unknown. Significant airway remodeling can begin despite normal pulmonary function and high-dose inhaled corticosteroid therapy in patients with difficult-to-control asthma. One of the goals of long-term asthma therapy is prevention and/or reversal of this disease process.

Clinical management tends to emphasize controlling the symptoms of coughing, wheezing, shortness of breath, and chest tightness. However, recent studies have shown that treatment based on markers of inflammation and airways hyperresponsiveness is more effective in reducing exacerbations than therapy based on symptom control. Future diagnostic testing will use such biomarkers to assist the physician in decisions on therapeutic intervention to decrease airway inflammation and hyperresponsiveness.

DIAGNOSIS

The evaluation of a child suspected of having asthma has three components: a thorough history, physical examination, and objective measurements. Important components of

the history include a detailed description of both symptoms and aggravating factors. Symptoms may include cough, wheezing, shortness of breath, rapid breathing, and/or chest tightness, and the history should also elicit the frequency and severity of symptoms. Aggravating factors that may worsen the child's symptoms include viral infections, exposure to allergens and irritants (smoke, strong odors, and fumes), exercise, emotions, and change in weather/humidity. Nighttime symptoms are common, often awakening the child and/or parent, particularly during asthma flare-ups. Age of onset can also be an important clue as 50–80% of patients with asthma experience symptoms within the first 5 yr of life. An environmental history should also be obtained and should include not only questions about the home environment but also exposures to potential aggravating factors at school, day care, and homes of friends and family. Because allergic diseases tend to occur in families, obtaining a family history of allergy and/or asthma can be useful. In addition, asking about the child's response to asthma medications, such as bronchodilators and corticosteroids, should also be included in the history. If symptoms do not improve with these therapies, evaluation for other disease processes is warranted.

For many infants and young children, it is common to wheeze with viral respiratory infections. For some of these children, the symptoms may subside in the preschool years, whereas others will have more chronic symptoms. There are prognostic indicators that may help the clinician in identifying preschool-aged children with recurrent wheezing who are at risk for developing persistent asthma. These prognostic indicators include having a parent with asthma or the wheezing child having eczema, allergic rhinitis, wheezing episodes apart from colds, and/or eosinophilia greater than 4%. Children and their parents often ask whether they will outgrow asthma and whether asthma will return after remission. Sensitization to house dust mite; airway hyperresponsiveness, female sex, smoking, and early age of asthma onset are associated with asthma persistence and relapse, as shown in Table 1.

On physical examination, findings may be subtle or absent. Wheezing may or may not be present. Evidence of other atopic diseases such as eczema or allergic rhinitis may be noted.

During acute episodes, the child may demonstrate tachypnea, tachycardia, cough, wheezing, accessory muscle use, and a prolonged expiratory phase. As the attack progresses, cyanosis (especially perioral), decreased air movement, retractions, agitation, inability to speak, tripod sitting position, diaphoresis, and pulsus paradoxus (decrease in blood pressure of >15 mmHg with inspiration) can be observed.

Objective measurements of pulmonary function (e.g., spirometry) are helpful for confirming the diagnosis of asthma, monitoring the patient's response to the treatment plan, and documenting the severity of an asthma exacerbation. In general, children older than 5 yr can perform spirometry maneuvers. For younger children, several practice sessions may be needed for them to master spirometry technique. The best of three forced expiratory tracings should be used as the best estimate of a patient's pulmonary function.

Spirometry measurements include the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), ratio of FVC/FEV_1, and forced expiratory flow from 25 to 75% of the FVC ($FEF_{25/75}$). Comparing these values to predicted norms (based on age, height, gender, and race) provides critical information that guides both short -and long-term treatment. The FEV_1 is most commonly used as a reproducible index of airflow obstruction resulting from asthma, whereas $FEF_{25/75}$ can be more variable. The FVC to FEV_1 ratio is also an indicator of airflow obstruction and may be helpful diagnostically, espe-

Table 1
Risk Factors for Persistent Asthma

Allergy
Atopic dermatitis
Allergic rhinitis
Elevated total serum IgE (first year of life)
Peripheral blood eosinophilia >4% (2–3 yr of age)
Food and inhalant allergen sensitization
Gender
Males
Transient wheezing
Persistent allergy-associated asthma
Females
Asthma associated with obesity and early-onset puberty
"Triad" asthma (adulthood)
Parental asthma
Lower respiratory tract infection
Respiratory syncytial virus, parainfluenza
Severe bronchiolitis (requiring hospitalization)
Pneumonia
Environmental tobacco smoke exposure (including prenatal)

From Liu et al., 2003.

cially in those children who maintain normal FEV_1 readings. Performing spirometry before and 15–20 min after a short-acting bronchodilator treatment is a straightforward test that can confirm the diagnosis of asthma. Significant airway reversibility is demonstrated by an increase of at least 12% and 200 mL in FEV_1 and is considered diagnostic for asthma. However, a lack of improvement in FEV_1 does not necessarily rule out asthma. In some cases, a 1- to 2-wk course of oral corticosteroids may be necessary to demonstrate a reversible component to airway obstruction, especially when there is severe airway inflammation.

The majority of children older than 5 yr with asthma have concomitant allergic sensitization, and ongoing exposure to relevant allergens is believed to play an important role in asthma persistence. Therefore, it is important to establish which allergens should be avoided, especially in children with chronic asthma. This evaluation is best performed by a qualified allergist (one who has completed a 2- to 3-yr period of concentrated study in the field of allergy and immunology after completing a pediatric or internal medicine residency). He or she offers the special skill of administering and interpreting allergy skin tests to identify allergic sensitivities and to instruct families in environmental control measures that may provide clinical benefit. Testing is performed with commercial extracts of relevant allergens based on the child's history and known or potential allergen exposure. Antigen applied to the skin via percutaneous or intracutaneous method reacts with specific mast-cell-bound allergic antibodies, inducing histamine release and a resultant wheal-and-flare response. Skin test results are known within 15–20 min, and studies demonstrate that positive skin test results correlate strongly with bronchial allergen

provocative challenges. In vitro tests, such as radioallergosorbent test and enzyme-linked immunosorbent assay, are alternative methods to measure levels of antigen-specific immunoglobulin (Ig)E. In general, in vitro testing is less sensitive and more expensive than skin testing, and the results are usually not available for several days.

A chest radiograph (anterioposterior and lateral views) should be obtained in children with recurrent episodes of cough and/or wheeze to aid in excluding other diagnoses. It also should be considered for every patient admitted to a hospital with asthma, depending upon the presentation and severity of asthma, and any suspicion of complications, such as pneumonia or pneumothorax. Radiographic findings in asthma may range from normal to hyperinflation with increased peribronchial markings and/or atelectasis.

Newer objective measures, such as impulse oscillometry and exhaled nitric oxide measurement, are currently being investigated in clinical research trials. In the future, these tests may provide additional information for asthma diagnosis and assessment of disease severity.

DIFFERENTIAL DIAGNOSIS

Establishing the diagnosis of asthma in children can be difficult. In early childhood, asthma is often underdiagnosed, especially in infants and young children who wheeze and cough only with respiratory illnesses. Also, in this young age group the diagnosis is based primarily on clinical grounds and symptom reporting by a caregiver as there is a lack of tools to objectively measure lung function. It is also important to note that not all wheeze and cough is due to asthma, and alternative diagnoses should be excluded. Misdiagnosis can expose children to inappropriate prolonged asthma therapies. Other conditions that can masquerade as asthma include cystic fibrosis, gastroesophageal reflux, foreign body aspiration, bronchopulmonary dysplasia, congenital heart disease, congenital airway anomalies such as laryngeal webs, vascular ring, and tracheoesophageal fistula. In older children and adolescents, vocal cord dysfunction can masquerade as asthma, especially for those patients who fail to respond to appropriate therapy (Tables 2 and 3). A practical approach for a young child who is suspected of having asthma is an empiric trial of asthma controller therapy while other evaluations are being pursued.

ASTHMA MANAGEMENT

Current asthma guidelines emphasize environmental control, pharmacological therapy, and patient/family education promoting adherence and effective self-management.

Environmental Control

Because children with asthma tend to have coexistent allergies, steps to reduce allergen exposure should be implemented (Table 4). A long-term commitment is necessary. Exposure to higher house dust mite concentrations in childhood has been associated with more severe asthma. However, there are conflicting reports as to whether house dust mite avoidance is both achievable and associated with subsequent clinical improvement.

For the motivated family, house dust mite avoidance includes encasing the pillow, mattress, and box spring with dust-mite-impermeable, zippered encasements, washing bed linens weekly in hot water (>130°F), and limiting the number of stuffed toys with which the child sleeps. Dust mites and mold thrive in high-humidity areas. To minimize

Table 2
Mnemonic of Causes of Cough in the First Months of Life

Cystic fibrosis
Respiratory infections
Aspiration—(swallowing dysfunction, gastroesophageal reflux, foreign body, trachaeoesophageal fistula)
Dyskinetic cilia
Lung and airway malformations—(laryngeal webs, laryngotracheomalacia, tracheal stenosis, vascular rings and slings, etc.)
Edema—(heart failure—congenital heart disease)

Adapted from Schidlow, 1994.

Table 3
Differential Diagnosis of Cough and Wheeze in Infants and Children

Upper respiratory tract	*Middle respiratory tract*	*Lower respiratory tract*
Allergic rhinitis	Bronchial stenosis	Asthma
Adenoid/tonsillar hypertrophy	Enlarged lymph nodes	Bronchiectasis
Foreign body dysplasia	Epiglottitis	Bronchopulmonary *Chlamydia trachomatis*
Infectious rhinitis	Foreign body	Chronic aspiration
Sinusitis	Laryngeal webs	Cystic fibrosis
	Laryngomalacia	Foreign body aspiration
	Laryngotracheobronchitis	Gastroesophageal reflux
	Pertussis	Hyperventilation syndrome
	Toxic inhalation	Obliterative bronchiolitis
	Tracheoesophageal fistula	Pulmonary hemosiderosis
	Tracheal stenosis	Toxic inhalation
	Tracheomalacia	Tumor
	Tumor	Viral bronchiolitis
	Vascular rings	
	Vocal cord dysfunction	

Adapted from Lemanske et al.,1998.

dust mite and mold growth, humidity should be kept below 50%; dehumidifiers and air conditioners can help remove the excess moisture from the air.

For those children who are pet allergic, a candid discussion with the family needs to occur about removing the pet from the home. Pet removal can result in major improvement in asthma symptoms for these children, but doing so can be quite difficult, especially after an emotional bond has been made. Families are often unable to deal with the loss of a pet, putting asthma lower on the priority list than other psychosocial issues. Also, it is important to discuss with families that immediate benefit may not be observed after the pet is removed because dander levels slowly decline over several months. If the pet cannot be removed from the home, at minimum, the pet must be kept out of the bedroom, doors closed, and a high-efficiency particulate air (HEPA) filter can be used to decrease the amount of airborne dander.

Table 4
Controlling Factors Contributing to Severity

Major indoor triggers for asthma	*Suggestions for reducing exposure*
Dust mites	Essential actions: • Encase pillow, mattress, and boxspring in allergen-impermeable encasement • Wash bedding in hot water weekly Desirable actions: • Avoid sleeping or lying on upholstered furniture • Minimize number of stuffed toys in child's bedroom • Reduce indoor humidity to <50% • If possible, remove carpets from bedroom and play areas. If not possible, vacuum frequently
Animal dander	• Remove the pet from the home or keep outdoors; if removal is not acceptable, then (a) keep pet out of bedroom, (b) use a filter on air ducts in child's room, and (c) wash pet weekly
Cockroach allergens	• Do not leave food or garbage exposed • Use boric acid traps • Reduce indoor humidity to <50% • Fix leaky faucets, pipes
Indoor mold	• Fix leaky faucets, pipes • Avoid vaporizers • Reduce indoor humidity to <50%
Tobacco smoke, wood smoke	• No smoking around the child or in child's home • Help parents and caregivers quit smoking • Eliminate use of wood stoves and fireplaces
Viral upper respiratory infections	• Limit exposure to viral infections (e.g., smaller day-care groups)
Influenza	• Influenza vaccinations for children with persistent asthma (if not egg allergic)

Adapted from American Academy of Allergy, Asthma & Immunology, Inc., 1999.

Cockroach allergen sensitivity has been linked with higher rates of asthma morbidity in inner-city children. Attempts at environmental control are difficult at best but include removing food sources and water leaks, exterminating these insects, and repairing squalid and dilapidated conditions that support infestation.

Allergy-avoidance measures are limited for those patients who suffer from pollen allergies. Keeping bedroom and car windows closed and using air conditioning or HEPA filters while indoors may be beneficial.

For all children with asthma, exposure to irritants such as tobacco and wood smoke should be limited. Tobacco smoke exposure has been linked to lower birthweights, sudden infant death syndrome, chronic otitis media with effusion, decreased lung growth,

and childhood respiratory infections. It has also been associated with earlier onset of asthma, more frequent and severe asthma symptoms, increased need for asthma medication, and more emergency department visits and hospitalizations. In the United States, 43% of children, aged 2 mo to 11 yr, live in a home with at least one smoker. Health care professionals have an obligation to counsel family members to quit smoking; if that is not possible, smoking should be restricted to a specific location, preferably outside of the home.

Annual influenza vaccination for asthmatic children 6 mo of age and older is strongly urged except for those children with severe, anaphylactic reactions to egg. Influenza vaccine is produced in embryonated eggs and does contain appreciable amounts of egg protein. On rare occasions, vaccine administration may induce immediate allergic reactions.

Pharmacological Management

Asthma pharmacotherapy can be divided into categories: long-term control medications and quick-relief medications.

Long-Term Control Medication

Long-term control medications are used on a daily basis to lessen airway inflammation and/or maintain control of asthma.

Inhaled Corticosteroids. Inhaled corticosteroids (ICSs) are the most effective anti-inflammatory medications for the treatment of chronic, persistent asthma and are the cornerstone of asthma treatment. Numerous studies have shown that regular use of ICSs reduces airway hyperreactivity, the need for reliever medications, the risk of hospitalization, and risk of death from asthma. They have also been shown to improve pulmonary function, exercise tolerance, and quality of life. They are available as pressurized metered-dose inhalers (pMDIs), dry-powdered inhalers (DPIs), and nebulizer solutions. ICSs available in the United States include beclomethasone, budesonide, fluticasone, mometasone, and triamcinolone. Clinical trials are proceeding with the next generation of ICS, including ciclesonide.

In general, if ICSs are used in doses of less than 400 micrograms/day (beclomethasone or budesonide equivalent), there is little risk of systemic corticosteroid activity. The greatest concern raised about the use of ICS in children is their potential effect on growth. The published data in this area are confusing. Studies consistently report a growth delay of approx 1 cm in the first year of therapy. However, this delay appears to be short-lived because growth velocity reverts to pretreatment levels when children are followed longitudinally. The Childhood Asthma Management Program (CAMP) trial is the largest and longest prospective clinical trial of ICSs in children between the ages of 5 and 12 yr with mild-to-moderate asthma. The results demonstrated a decrease in growth velocity in the first year of ICS therapy without additional growth effects as therapy continued for 4–6 yr. The measured difference in height between children receiving ICSs as compared to those assigned placebo was 1.1 cm. An ongoing CAMP Continuation Study is monitoring these children until they reach their final adult height. In addition, untreated asthma can result in growth delay. The practitioner should monitor all pediatric asthma patients for potential growth suppression by measuring heights with a stadiometer at regular intervals (e.g., every 6 mo). A discussion of the potential growth risks should also take place with the parents in all children treated on a long-term basis with ICSs.

Additional safety concerns regarding ICSs include effect on bone mineral density (BMD) and hypothalamic–pituitary–adrenal (HPA) axis. The CAMP trial also examined the interaction between BMD and the use of low to moderate doses of ICS in growing children and found no effect on BMD. There is conflicting information in the literature whether ICSs lead to HPA axis suppression. However, when low to moderate doses of ICSs are used, there appears to be little effect on HPA axis. For both BMD and HPA axis, the long-term effects of higher doses of ICS in growing children are unresolved.

Local side effects of hoarseness and candidiasis sometimes occurs with ICS therapy but can be reduced by using spacer devices and rinsing the mouth after inhalation. These techniques can also help decrease absorption of ICSs from the gastrointestinal tract. To minimize side effects, the goal is to use the lowest effective dose that controls the child's asthma. For children with severe asthma, higher doses of ICS may be needed to taper the oral steroid dose. The benefits of ICSs consistently outweigh their side effects, and longitudinal studies offer reassurance that at conventional doses, ICSs do not have significant long-term adverse effects.

Leukotriene Modifiers. Leukotrienes are chemical mediators that are synthesized via the arachidonic acid pathway and have a wide range of biological activities, including airway edema, mucus secretion, eosinophil migration into the airways, and smooth muscle bronchoconstriction. Leukotriene modifiers are daily, oral, long-term controller medications that are designed to counteract these biological effects in the airways. There are two classes of leukotriene modifiers, defined based on their site of action: cysteinyl leukotriene receptor antagonist (e.g., montelukast and zafirlukast) and leukotriene synthesis inhibitor (e.g., zileuton). Montelukast is dosed once daily at night as 4-mg granules or a 4-mg chewable tablet for children aged 12 mo to 5 yr; as a 5-mg chewable tablet for children aged 6–14 yr; and as a 10-mg tablet for adolescents older than 15 yr. Zafirlukast has been approved for use in children older than 7 yr of age and is dosed twice daily. Zileuton, a 5-lipoxygenase inhibitor, is approved for use in children 12 yr of age and older. The use of zileuton has been limited by the need to regularly monitor liver enzymes, the possibility of drug interactions, and a dosing regimen of four times per day.

Pediatric clinical research studies have shown that leukotriene modifiers are effective for the treatment of mild asthma, the attenuation of exercise-induced bronchospasm, and as steroid-sparing agents in patients with more difficult to control asthma. Recent asthma guidelines refer to leukotriene modifiers as "alternative" controller therapy for asthma. However, montelukast has emerged as a popular first-line therapy for selected children with mild persistent asthma because of its ease of administration and excellent safety profile for children as young as 12 mo of age. In addition, leukotriene modifiers do not provoke "steroid phobia" in families or physicians, which can be a reason for the undertreatment of asthma.

Long-Acting β_2-Agonists. Two inhaled long-acting β_2-agonists (LABAs) (formeterol and salmeterol) and one oral LABA (oral albuterol) are approved for use in asthma. They exert their effects by relaxing the bronchial smooth muscles for several hours (up to 12 h), relieving airflow obstruction. It is important to recognize that these agents do not possess any significant anti-inflammatory effects. Several studies have demonstrated that the adding a LABA to ICS is more beneficial than doubling the dose of ICS. Formoterol, available in the DPI form, is approved for use in children older than 5 yr. Salmeterol is approved in DPI form for children older than 4 yr. Both agents are beneficial in preventing exercise-induced bronchospasm and as a maintenance bronchodilator. Formoterol has a

rapid onset of action akin to albuterol (15 min), whereas salmeterol begins dilating the airways within 30 min. Recently, the FDA has noted that while LABAs decrease the frequency of asthma episodes, these agents are associated with risk of worsening bronchospasm; death and life-threatening episodes have occurred.

A less preferred LABA is albuterol, as a 4-mg sustained-release oral tablet. Compared with inhaled LABA, oral albuterol is a less effective bronchodilator with a higher incidence of β-agonist side effects such as tremors, irritability. and tachycardia.

Combination ICS/LABA. A fluticasone/salmeterol combination product, Advair®, is available in three strengths, varying by the amount of fluticasone delivered with each inhalation (100 μg, 250 μg, 500 μg). Each strength delivers the same amount of salmeterol (50 μg). Advair is administered one inhalation twice daily. Advair 100/50 is approved for use in children aged 4 yr and older, whereas Advair 250/50 and 500/50 are approved for children older than 12 yr. Studies have shown that combination therapy resulted in a significant reduction in the fluticasone dose while maintaining or improving asthma control in children 12 yr of age and older.

Anti-IgE Therapy. In 2003, a humanized monoclonal anti-IgE antibody, omalizumab, received US Food and Drug Administration (FDA) approval for the treatment of moderate to severe persistent allergic asthma in patients 12 yr of age and older. Clinical trials have reported reduced emergency department visits, hospitalizations, and doses of corticosteroids in patients treated with omalizumab. This medication is administered subcutaneously every 2 or 4 wk depending on the total serum IgE and weight of the patient. Omalizumab is the first "biotech" agent approved for use in asthma, and its high cost relative to other therapies has so far limited its use to just a small subset of asthma patients.

Older Therapeutic Agents. Cromolyn sodium and nedocromil sodium are inhaled medications that can be used as alternative therapies for the management of management of mild persistent asthma and can be used intermittently to prevent exercise or allergen-induced asthma exacerbations. They possess anti-inflammatory activity, although their exact mechanisms of action are unknown. Both are available as pMDIs, and cromolyn is also available in nebulizer solution. The usual recommended dosage for cromolyn by pMDI (1 mg per actuation) is two puffs four times per day; although it is often prescribed two to three puffs two to three times per day. The nebulizer solution contains 20 mg/mL and probably provides more therapeutic benefit; however, no comparative studies have been published. Cromolyn does not add steroid-sparing effect and should be discontinued when patients requires ICS for asthma control. Nedocromil sodium may have a faster onset of action as compared to cromolyn and appears to have some steroid-sparing capability. Nedocromil is dosed by pMDI (1.75 mg per actuation) two puffs four times a day, often tapering to twice daily after an adequate clinical effect is attained. The safety profile for both drugs is excellent and they are generally well tolerated. For approx 15–20% of patients, nedocromil is associated with an unpleasant taste, resulting in poor compliance.

In the past, theophylline was more widely used, but with current management aimed at inflammatory control, theophylline's popularity has declined. In the guidelines, it is considered an alternative add-on therapy for patients with moderate to severe persistent asthma. Theophylline is available in syrup, tablet, and capsule formulation. It is effective as a mild bronchodilator. Serum levels must be routinely monitored and typically maintained between 5 and 15 μg/mL. Serum levels can be affected by febrile viral illnesses,

diet, and medications, such as macrolide antibiotics, cimetidine, and antifungal agents. Nausea, insomnia, headaches, anorexia, and hyperactivity are adverse side effects associated with theophylline. Seizures can occur if recommended serum levels are exceeded. Theophylline may be an option for children who have poor compliance with inhaled therapy and as a useful adjunct for the child with severe chronic asthma. One advantage to using theophylline is that serum levels can be monitored to assess compliance in individuals.

Quick-Relief Medications

Quick-relief medications include short-acting inhaled or oral β_2- agonists, ipratropium bromide, and short courses of oral corticosteroids.

Short-Acting β_2-Agonists. Short-acting inhaled β_2-agonists, such as albuterol, levalbuterol, and pirbuterol, are the most effective bronchodilators, relaxing bronchial smooth muscle within 5–10 min of administration and lasting for 4–6 h. Patients are prescribed a short-acting inhaled β_2-agonist to alleviate acute symptoms and as prophylaxis prior to allergen exposure or exercise. Short-acting inhaled β_2-agonists are available as pMDI or nebulizer delivery systems. Oral and parenteral preparations are also available, although the inhaled route is preferred in most situations because of its faster onset of action and fewer side effects of tremor, prolonged tachycardia, and irritability. To limit the side effects of inhaled short-acting β_2-agonists and achieve bronchodilitation at lower doses, the stereoisomer of albuterol, levalbuterol, was created and is currently available as a pMDI and in a nebulizer solution in three doses.

Overuse of β_2-agonists suggests that asthma may not be adequately controlled and indicates a need for further evaluation. The definition of "overuse" depends on the child's asthma severity; however, use of more than one MDI canister per month or more than eight puffs per day are signs that asthma is uncontrolled.

Anticholinergic Agents. Ipratropium bromide is an anticholinergic bronchodilator that relieves bronchoconstriction, decreases mucus hypersecretion, and counteracts cough-receptor irritability by binding acetylcholine at the muscarinic receptors found in bronchial smooth muscle. It is available as pMDI and in nebulizer solution. The literature does not support the use of anticholinergic medications for long-term asthma control in children. Ipratropium appears to have additive benefits to inhaled β_2-agonists for children with acute exacerbations, especially those children with severe exacerbations.

Oral Corticosteroids. Short bursts of oral corticosteroids (3–10 d) are administered for use in children with acute asthma exacerbations. The initial starting dose is 1–2 mg/kg followed by 1 mg/kg over the next 24–48 h. There is no significant difference in efficacy between oral and parenteral formulations of corticosteroids because gastrointestinal absorption is rapid. Parenteral corticosteroids can be used in those children unable to tolerate oral corticosteroids because of emesis. Oral corticosteroids are available in various liquid or tablet formulations: prednisone, prednisolone, and methylprednisolone. No evidence exists that tapering the dose following improvement prevents relapse or that tapering the dose is necessary if the course is less than 10–14 d. Prolonged use of oral corticosteroids is associated with systemic effects, including HPA axis suppression, weight gain, cataracts, hypertension, stomach ulcers, osteoporosis, and growth suppression. Rarely, patients with severe asthma may need oral corticosteroids for extended periods. When possible, these medications should be tapered to the lowest effective dose, preferably on alternate days.

Table 5
Recommendation for Initiating Long-Term Controller Therapy in Infants and Young Children

Consider long-term controller therapy if

- Symptoms more than twice per week or more than two nights per month, or
- Severe exacerbations less than 6 wk apart, or
- More than three episodes of wheezing within past year plus the following risk factors:
  - Either parental history of asthma or atopic dermatitis, or
  - Two of the following:
    - § allergic rhinitis
    - § wheezing not concurrent with respiratory infection
    - § peripheral blood eosinophilia ≥4%

From Szefler, 2004.

APPROACHES TO CARE

Current therapy is based on the concept that inflammation is a key feature of asthma. The National Heart, Lung and Blood Institute's National Asthma Education and Prevention Program (NAEPP), updated in November 2002, published guidelines on classification and treatment based on asthma severity. Asthma severity can be classified as intermittent and persistent, with gradations of persistent ranging from mild to moderate to severe. Unfortunately, not all children fit nicely into the guidelines.

A child with intermittent asthma experiences asthma symptoms less often than twice a week. To determine if a child is having persistent asthma, the "rule of twos" can be helpful. The presence of daytime symptoms more often than twice a week or nighttime awakening more often than twice a month indicates persistent asthma and a need for long-term controller medications. For infants and younger children who have severe exacerbations less than 6 wk apart or have had three episodes of wheezing in the previous year as well as risk factors for the development of asthma (e.g., parental asthma, peripheral blood eosinophilia, wheezing between upper respiratory tract infections, personal atopy), long-term controller medications are recommended (Table 5).

From there, the choices can be influenced by the age and maturity of the child, the severity of disease, the needs of the family/caregiver, and insurance restrictions. The stepwise approach for management of infants and young children is found in Fig. 1 and for older children in Fig. 2.

For all children with asthma, a quick-relief medication (inhaled short-acting bronchodilator) should be prescribed. For infants and young children, wheezing most commonly occurs with viral respiratory infections. Typically, inhaled albuterol via nebulizer or MDI with face mask/spacer device is used every 4–6 h. If the episode becomes severe or the child has a history of severe acute exacerbations, a burst of oral corticosteroids may be needed.

The NAEPP guidelines recommend ICSs as preferred long-term controller medication for all levels of persistent asthma and in all age groups, including young children. In clinical trials comparing ICSs to cromolyn, nedocromil, leukotriene modifiers, or theophylline, ICSs are the most effective medications in improving long-term asthma control. The benefits of ICS treatment generally outweigh the potential risks, and a more favorable cost–benefit ratio is particularly apparent for treatment of more severe asthma with these agents. Once control of asthma is accomplished, further reduction of risk is possible by titrating to the lowest effective dose.

For children of all ages with mild persistent asthma, the preferred therapy is low-dose ICS. Currently in the United States, administration of ICS via pMDI to children younger than 5 yr and by DPI to children younger than 4 yr is not FDA approved. Although fluticasone pMDI with a spacer is commonly prescribed in young children, this product lacks FDA approval for use in children younger than 12 yr of age. Budesonide inhalation suspension via jet nebulizer is the only approved ICS for the treatment of asthma in children 12 mo to 8 yr of age. Alternative therapies for children with mild persistent asthma include the use of cromolyn, leukotriene modifiers, nedocromil, or theophylline.

For children younger than 5 yr of age with moderate persistent asthma, the guidelines recommend low-dose ICS plus LABA or moderate doses of ICS. However, the options for LABA are limited in children younger than age 4 as only salmeterol in DPI form has been approved for children 4 yr or older. Also, the DPI delivery device may be difficult for some young children to perform. The evidence for adding a leukotriene modifier, theophylline, or doubling the dose of corticosteroid has not been as well studied in this age group. It is recommended that children older than age 5 with moderate persistent asthma use low-to-medium doses of ICS with LABA. Alternative treatments include combining ICSs with leukotriene modifiers or theophylline.

For children with severe persistent asthma, high-dose ICS and LABA are the preferred therapy. Theophylline and leukotriene modifiers may also be used as add-on therapy. Oral corticosteroids may also be needed and should be used at the lowest possible dose and on an alternate-morning regimen if possible. Omalizumab became available after the national guidelines were published. Children older than age 12 yr with significant allergy-induced asthma may be considered for this treatment.

The guidelines also recommend that children be seen every 1–6 mo so that medications can either be reduced (step-down) or increased (step-up), depending on the child's asthma control.

Administering medications to children can be challenging. For infants and young children, nebulizer or spacer/holding chamber with face mask can be used. Whenever a face mask is used, regardless of the delivery device or drug, a tight seal between the mask and the child's face must be maintained. The looser the mask, the less medication is delivered to the lungs. "Blow-by" technique is not effective and carries a potential safety risk by allowing the drugs to have direct contact with the eyes.

As children grow, inhalers are favored because they are less time-consuming and may allow the child more independence. Many children between the ages of 2 and 5 can learn to effectively use a pMDI with a spacer/holding chamber with mask. The spacer/holding chamber with mask is held in place for 20–30 s after each pMDI actuation, allowing the child to take in at least six breaths per puff. For school-aged children, pMDIs with spacer devices with mouthpieces rather than face masks and DPIs are generally used.

PATIENT EDUCATION

The success of long-term management of asthma is clearly linked to education of patients and their families. Education must begin at the time of diagnosis and includes teaching basic asthma facts, an explanation of exacerbating triggers, environmental control measures, the role of medications, and improving patient skills in how to appropriately take medications and use peak flow meters. Families should have an asthma action plan, as shown in Fig. 3, for daily care as well as for exacerbations. The asthma action

Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	Daily Medications
Step 4 Severe Persistent	Continual Frequent	■ Preferred treatment: – **High-dose inhaled corticosteroids** AND – **Long-acting inhaled beta$_2$-agonists** AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	■ Preferred treatments: – **Low-dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists** OR – **Medium-dose inhaled corticosteroids.** ■ Alternative treatment: – Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – **Medium-dose inhaled corticosteroids and long-acting beta$_2$-agonists.** ■ Alternative treatment: – Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	■ Preferred treatment: – **Low-dose inhaled corticosteroid (with nebulizer or MDI with holding chamber with or without face mask or DPI).** ■ Alternative treatment (listed alphabetically): – Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	■ No daily medication needed.

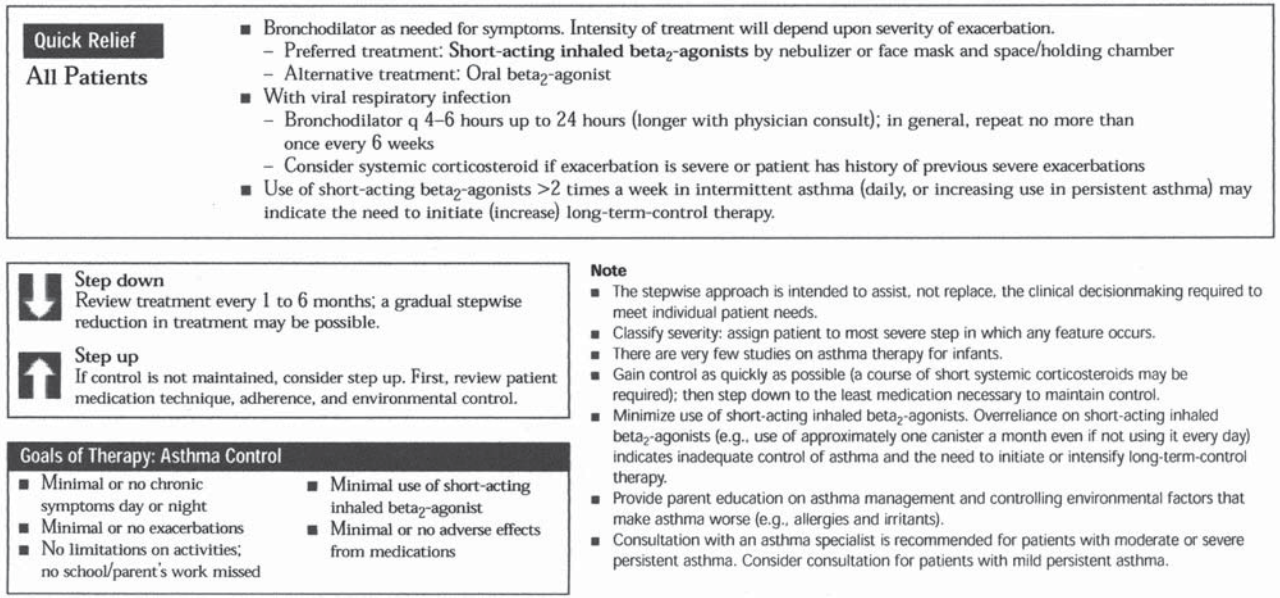


Fig. 1. Stepwise approach for managing infants and young children (≤5 yr) with acute or chronic asthma.

Classify Severity: Clinical Features Before Treatment or Adequate Control			Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	PEF or FEV_1 PEF Variability	Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	■ **Preferred treatment:** – **High-dose inhaled corticosteroids** AND – **Long-acting inhaled beta$_2$-agonists** AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	> 60% – < 80% > 30%	■ **Preferred treatment:** – **Low-to-medium dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists.** ■ Alternative treatment (listed alphabetically): – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ **Preferred treatment:** – **Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled beta$_2$-agonists.** ■ Alternative treatment (listed alphabetically): – Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	≥ 80% 20–30%	■ **Preferred treatment:** – **Low-dose inhaled corticosteroids.** ■ Alternative treatment (listed alphabetically): cromolyn, leukotriene modifier, nedocromil, OR sustained-release theophylline to serum concentration of 5–15 mcg/mL.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	≥ 80% < 20%	■ No daily medication needed. ■ Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

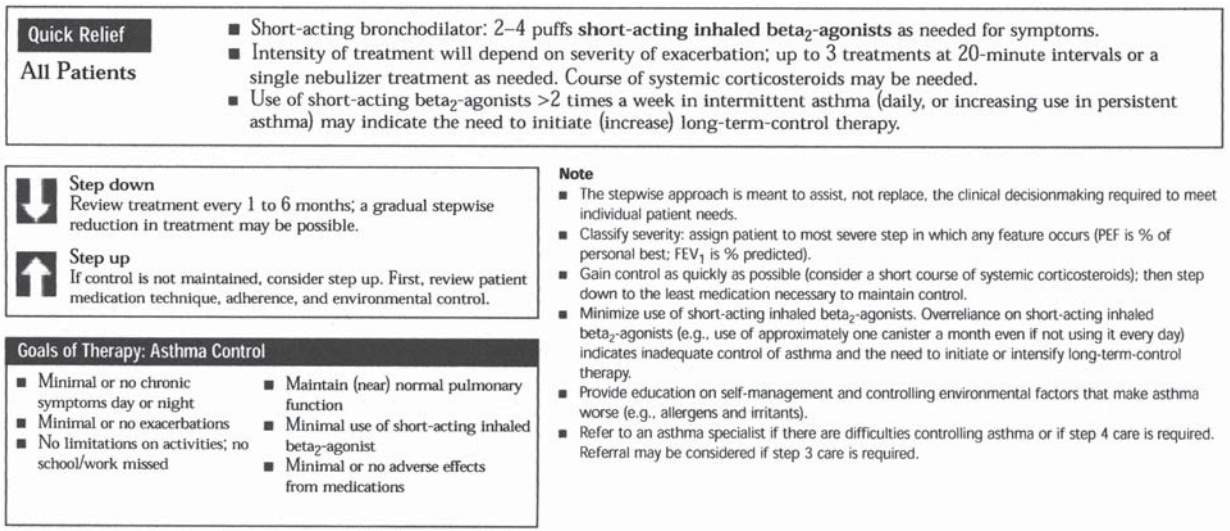
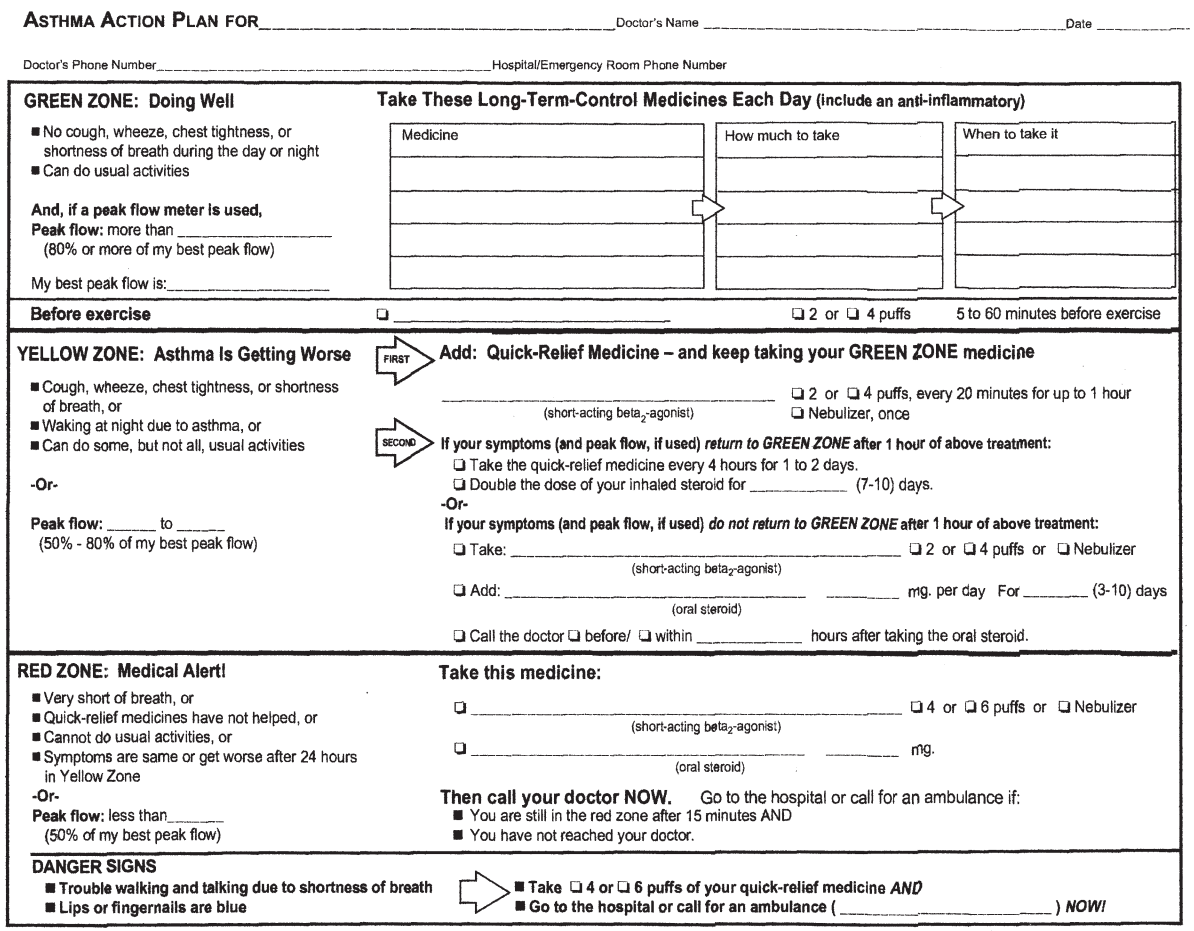


Fig. 2. Stepwise approach for managing asthma in adults and children >5 yr: treatment.



ASTHMA ACTION PLAN FOR_____ Doctor's Name _____ Date _____

Doctor's Phone Number_____ Hospital/Emergency Room 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% 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 to 60 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% - 80% of my best peak flow)

FIRST **Add: Quick-Relief Medicine – and keep taking your GREEN ZONE medicine**

_____ ❑ 2 or ❑ 4 puffs, every 20 minutes for up to 1 hour
(short-acting $beta_2$-agonist) ❑ Nebulizer, once

SECOND **If your symptoms (and peak flow, if used) *return to GREEN ZONE* after 1 hour of above treatment:**
❑ Take the quick-relief medicine every 4 hours for 1 to 2 days.
❑ Double the dose of your inhaled steroid for _____ (7-10) days.

-Or-

If your symptoms (and peak flow, if used) *do not return to GREEN ZONE* after 1 hour of above treatment:
❑ Take: _____ ❑ 2 or ❑ 4 puffs or ❑ Nebulizer
(short-acting $beta_2$-agonist)
❑ Add: _____ _____ mg. per day For _____ (3-10) days
(oral steroid)
❑ 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% of my best peak flow)

Take this medicine:

❑ _____ ❑ 4 or ❑ 6 puffs or ❑ Nebulizer
(short-acting $beta_2$-agonist)
❑ _____ _____ mg.
(oral steroid)

Then call your doctor NOW. Go to the hospital or call for 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 (_____) *NOW!***

Fig. 3. Asthma action plan. (From National Asthma Education and Prevention Program. Practical Guide for the Diagnosis and Management of Asthma. NIH Publication 97-4053. Bethesda, MD: U.S. Department of Health and Human Services, 1997. www.nhlbi.nih.gov/health/prof/lung/asthma/practgde.htm)

plan should help families be informed about the early warning signs of asthma deterioration, how to manage an asthma exacerbation, when to add or increase medications, and when to call for help. Outside resources such as the Asthma and Allergy Foundation of America, the American Lung Association, or AAN/Mothers of Asthmatics provide additional educational material for families.

Peak flow monitoring is a self-assessment tool that can be helpful for children older than 4 or 5 yr and can help promote the patient or parent to become an active manager of the disease. It is particularly suited for children with moderate to severe asthma who are "poor perceivers" of airway obstruction or who have a history of severe exacerbations. Peak flow monitoring can also be useful for children recently diagnosed with asthma who are still learning to recognize asthma symptoms.

A peak flow meter measures pulmonary airflow in a forced expiration. To use a peak flow meter, the child should be standing with the indicator placed at the bottom of the scale. The child inhales deeply, places the device in the mouth, bites down on the mouthpiece, seals his or her lips around the mouthpiece, and blows out forcefully and rapidly. The indicator moves up the numeric scale. The peak expiratory flow rate (PEFR) is the highest number achieved. The test is repeated three times to obtain the best possible effort. Peak flow meters are available as low-range (measurement up to 300 L/s) and high-range (measurement up to 700 L/s). For children, it is important to provide the appropriate range meter so accurate measurements can be obtained and the child does not get discouraged because their blows barely move the indicator.

A child's personal best is the highest peak flow number he or she can achieve over a 2-wk period when stable. Based on the child's personal best, a written action plan can be established. The asthma action plan is divided into three zones similar to a stoplight. The green zone indicates a PEFR between 80 and 100% of the child's personal best value. In this zone, the child is likely asymptomatic and should continue medications as usual. The yellow zone indicates a PEFR between 50 and 80% of the child's personal best value, which generally coincides with the child's asthma becoming more symptomatic. Rescue medications (short-acting inhaled bronchodilators, e.g., albuterol) are administered every 4–6 h, and the physician should be notified if PEFR are not returning to the green zone within the next 24–48 h or if asthma symptoms are deteriorating. The red zone indicates a PEFR below 50% and is a medical emergency. Rescue medications should be used immediately. If the PEFR remains in the red zone or the child is having significant airway compromise, the physician should be notified and evaluation in an emergency department may be warranted.

An important message for families is that children with asthma should be seen not only for exacerbations but also periodically when they are doing well. Regular office visits allow the health care team to review adherence to medication and environmental control measures and to determine if doses of medications need adjustment. The therapeutic regiment should be simplified when possible to encourage adherence.

ASTHMA EXACERBATION/STATUS ASTHMATICUS

Most asthma exacerbations can be successfully managed at home, as shown in Fig. 4. However, if the child is not responding to outpatient therapy, hospital admission may be needed. Management of asthma exacerbations in the emergency room and hospital-based care is shown in Fig. 5. Exacerbations may progress over several days or occur suddenly

Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	Daily Medications
Step 4 Severe Persistent	Continual Frequent	■ Preferred treatment: – High-dose inhaled corticosteroids AND – Long-acting inhaled beta$_2$-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	■ Preferred treatments: – Low-dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists OR – Medium-dose inhaled corticosteroids. ■ Alternative treatment: – Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – Medium-dose inhaled corticosteroids and long-acting beta$_2$-agonists. ■ Alternative treatment: – Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	■ Preferred treatment: – Low-dose inhaled corticosteroid (with nebulizer or MDI with holding chamber with or without face mask or DPI). ■ Alternative treatment (listed alphabetically): – Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	■ No daily medication needed.

Fig. 4. Management of asthma exacerbations: home treatment. (From National Asthma Education and Prevention Program. Practical Guide for the Diagnosis and Management of Asthma. NIH Publication 97-4053. Bethesda, MD: U.S. Department of Health and Human Services, 1997. www.nhlbi.gov/health/prof/lung/asthma/practgde.htm)

and can range in severity from mild to life-threatening. Significant respiratory distress, dyspnea, wheezing, cough, and a decrease in PEFR signify deterioration in asthma control. During severe episodes of wheezing, pulse oximetry is helpful in monitoring oxygenation. In status asthmaticus, arterial blood gases may be necessary for measurement of respiratory ventilation. As airway obstruction worsens and chest compliance decreases, CO_2 retention can occur. In the face of tachypnea, a normal P_{CO2} (40 mmHg) indicates impending respiratory arrest.

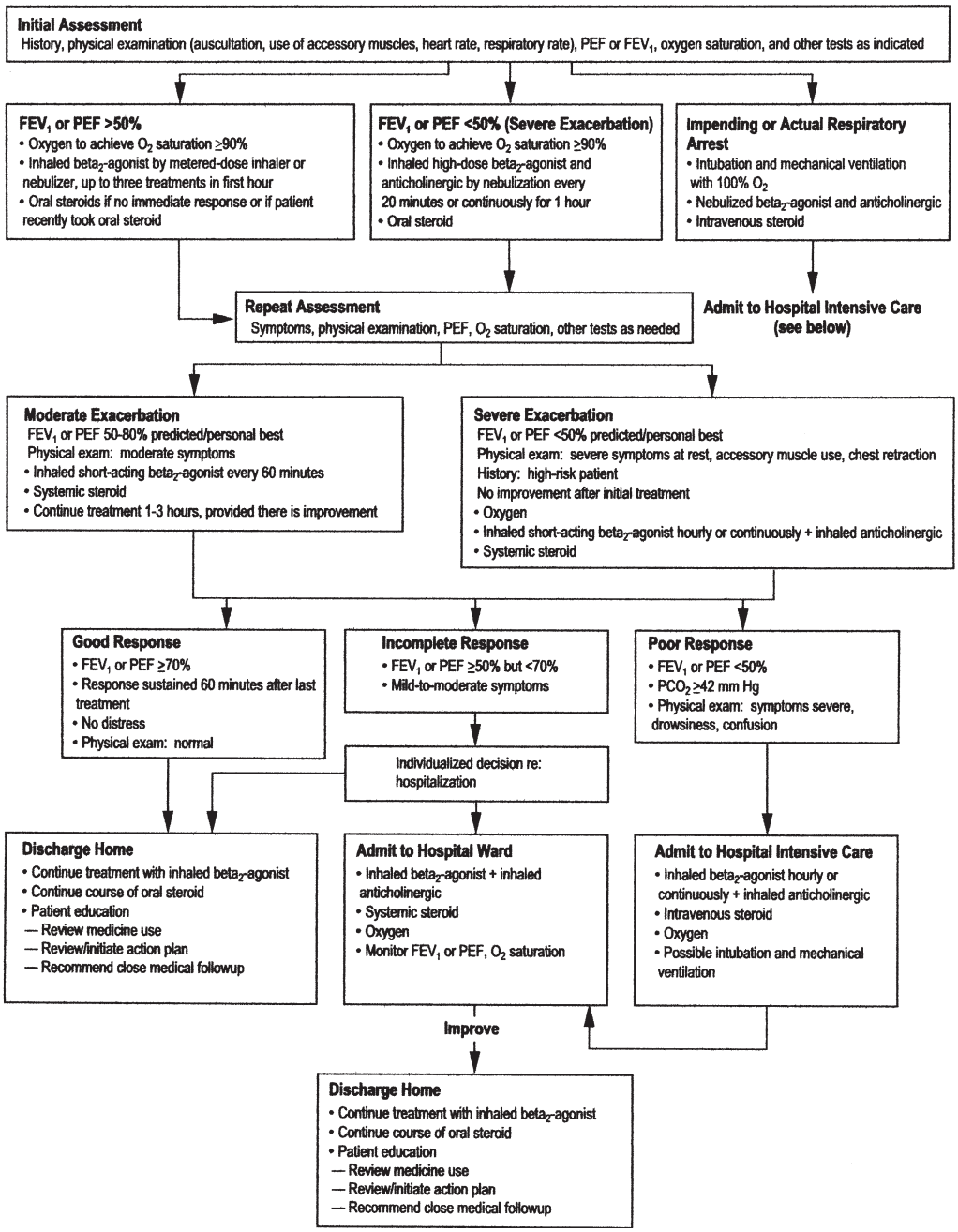


Fig. 5. Management of asthma exacerbations: emergency department and hospital-based care. (From National Asthma Education and Prevention Program. Practica lGuide for the Diagnosis and Management of Asthma. NIH Publication 97-4053. Bethesda, MD: U.S. Department of Health and Human Services, 1997. www.nhlbi.gov/health/prof/lung/asthma/practgde.htm)

First-line therapy includes supplemental oxygen, repetitive or continuous administration of short-acting bronchodilators, and corticosteroids (oral or intravenous). Co-administration of anticholinergic medications (ipratropium) with short-acting bronchodilators

Table 6
Referral to an Asthma Specialist

- Child has had a life-threatening asthma exacerbation
- Goals of asthma therapy are not being met after 3- to 6-mo period of treatment—earlier if child appears unresponsive to treatment
- Signs and symptoms are atypical. Consider other diagnoses
- Other conditions complicate asthma or its diagnosis: rhinitis, sinusitis, gastroesophageal reflux
- Additional diagnostic testing is indicated: pulmonary function testing, allergy skin testing
- Child or family needs additional education and guidance on complications of therapy, problems with adherence or avoidance of triggers
- Child is being considered for immunotherapy.
- Child has severe persistent asthma.
- Child is under age 3 yr and has moderate or severe persistent asthma
- Child has used prolonged courses of oral corticosteroids, high doses of inhaled corticosteroids, or more than two bursts of oral corticosteroids in 12 mo

From American Academy of Allergy, Asthma & Immunology, Inc,1999.

has been shown to decrease rates of hospitalization and duration of time spent in the emergency department. Early administration of corticosteroids is important to treat the underlying inflammation. Intramuscular epinephrine is rarely used with the exception of severe asthma associated with anaphylaxis or unresponsive to continuous administration of short-acting bronchodilators.

WHEN TO REFER

Guidelines for when a child should be referred to an asthma specialist are found in Table 6. Most importantly, the specialist should work closely with the primary care physician to optimize the child's asthma control.

CONCLUSION

Childhood asthma is a major public health problem in the United States, with an increasing prevalence over the past 20 yr. The reason for this increasing trend is not clear, but it is the topic of research for many investigators. The prevailing concept that asthma is a chronic inflammatory disorder of the airway has led to a revision in the management of asthma in the last decade. Early intervention with inhaled corticosteroids significantly improves asthma management and is the preferred agent for long-term control of persistent asthma in children of all ages. Also now being identified are prognostic factors for asthma development that assist the health care professional in assigning the asthma diagnosis. Future research will be needed to examine if early intervention with inhaled corticosteroids can prevent irreversible airway remodeling, identify objective measures that best determine asthma control, and develop therapies that could revolutionize asthma treatment. Managing asthma in children is dynamic, ever-changing, challenging, and rewarding.

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8 Asthma in Adults

Diagnosis and Management

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CONTENTS

SUMMARY

Asthma affects more than 15 million adults in the United States. The incidence of asthma has risen in the past few decades. It is a significant health concern and a tremendous economic burden in modern societies. In this chapter we discuss the etiologies and pathogenesis of asthma. We also describe the current concepts and guidelines of asthma intervention and treatment.

Key Words: Asthma; allergy; asthma treatment; inhaled steroids; bronchodilators.

INTRODUCTION

It is estimated that 20.3 million Americans had asthma in 2001. The incidence has increased by about 60% in the past decade, not only in the United States but worldwide (Table 1). From 1999 to 2001, the lifetime prevalence rate of asthma increased 27%. The asthma attack rate increased 12% during the same period of time. On the other hand, the number of deaths and hospitalizations resulting from asthma has decreased slightly in recent years. Asthma was estimated to cost approx $14 billion in 2002. It accounts for approx 14.5 million lost workdays annually.

From: *Current Clinical Practice: Allergic Diseases: Diagnosis and Treatment, Third Edition*
Edited by: P. Lieberman and J. A. Anderson

Table 1
Asthma Epidemiology: United States, 2001

31.3 million lifetime prevalence
20.3 million current sufferers
15.1 million adults (7.1%) with current asthma
465,000 hospitalizations (year 2000)
14.5 million lost workdays
1.8 million emergency visits
~5000 deaths per year (14 people per day)
$14 billion costs

The word *asthma* was derived from the Greek word for panting, or breathlessness, and thus might be considered a description of the primary symptom of this disease. Asthma can be defined clinically as recurrent airflow obstruction causing intermittent wheezing, breathlessness, chest tightness, and sometimes cough with sputum production. The National Asthma Education Panel, developed in conjunction with the National Heart, Lung and Blood Institute, defined asthma as having three components:

1. Airflow obstruction that is reversible (or nearly completely so), either spontaneously or in response to therapy
2. Airway inflammation
3. Increased airway responsiveness to a variety of stimuli

CAUSES OF BRONCHIAL ASTHMA

Allergic Asthma

About 90% of asthmatics between the ages of 2 and 16 yr are allergic, 70% less than 30 yr are allergic, and about 50% of patients older than 30 yr are concomitantly allergic (Table 2). Thus, coincidental allergies are far and away the most common underlying condition associated with the development of asthma. One should suspect allergy as a contributing factor when (1) there is a family history of allergic diseases, (2) the clinical presentation includes seasonal exacerbations or exacerbations related to exposures to recognized allergens, (3) there is concomitant allergic rhinitis or other allergic disease, (4) a slight-to-moderate eosinophilia is present (300–1000/mm^3) or eosinophilia in the sputum is observed, or (5) the patient is less than 40 yr old. Skin testing can be used to confirm immunoglobulin (Ig)E directed against incriminated allergens but does not establish a cause-and-effect relationship. Thus, patients may have a positive skin test but not have clinical symptoms of allergy or asthma when exposed to the incriminated allergen. Thus, skin testing (or radioallergosorbent test [RAST]) is only used to confirm the history and physical examination that suggest allergy. Levels of total IgE are of limited usefulness; only about 60% of allergic asthmatic subjects have elevated IgE levels.

Because limiting exposure to allergens and allergy immunotherapy are both specifically helpful in treating allergic asthmatic subjects, a careful search for possible allergies is indicated in nearly all asthmatics. Current recommendations are that all asthmatics who wheeze more than 2 d per week should be evaluated by an allergist or other physician skilled in identifying allergic disease in order to institute prophylactic allergen-avoidance measures.

Table 2
Conditions That Cause and Worsen Asthma

Conditions that cause asthma:
Allergic disease
Allergic asthma
Allergic bronchopulmonary aspergillosis
Infections
Bronchiolitis
Upper respiratory tract infections
Bronchitis
Industrial–occupational or environmental exposure
Irritants
Allergens
Chemical or drug ingestion
Aspirin or other nonsteroidal anti-inflammatory drugs
Sulfiting agents
β-Adrenergic antagonists
Vasculitis (Churg and Straus allergic granulomatosis)
Idiopathic (intrinsic)
Conditions that may worsen asthma:
Sinusitis
Gastroesophageal reflux
Pregnancy
Hyperthyroidism
Psychological stress

It was once thought that allergic asthma was associated with a milder form of disease, but this contention has not been borne out. Allergic asthma is as severe as any other cause of asthma. Onset of asthma between the ages of 2 yr and puberty generally has a good prognosis, whereas asthma appearing before age 2 may be of a more severe nature. Moreover, childhood asthma was once considered a transient disease, which might be "outgrown." This philosophy is a serious error in judgment for many reasons, including the availability of excellent effective treatment plans, the impairment of body image that an asthmatic child may develop, which lasts throughout life, the long-range effects of restricted physical activity on mental and physical health, and the loss of school and recreation time because of a treatable problem. Current recommendations include conditioning of the asthmatic to better prepare him for strenuous exercise, selecting swimming or biking in place of running as an exercise of choice, and using prophylactic medications to prevent exercise-related airflow obstruction.

Mast Cells and Asthma

The essential components of allergic reactions include allergens, IgE antibodies directed at antigenic determinants on the allergen, and activated mast cells, which generate and release mediators and cytokines. In order to initiate allergic responses, exposure to an appropriate antigen and a genetically determined capacity to respond with IgE production are required. Antigen presentation requires access of antigens to the mucous membrane, uptake by antigen-presenting cells, antigen processing, and stimulation of local antibody production. IgE production occurs in the same local environment

as antigen presentation, probably in the draining lymph nodes. IgE production is regulated by locally produced helper factors, thought to include cytokines produced by local TH_2 helper cells. The IgE produced sensitizes mast cells in the same environment by binding to high-affinity receptors for IgE on the cell surface. Although no one is certain of the precise time involved, the production of sufficient IgE to render a subject allergic is thought to take several years or more. However, children less than 1 yr old with unquestionable allergic diseases are not uncommon.

Once sensitized, mast cells may degranulate upon subsequent allergen exposure. The bridging of IgE receptors by aggregation of IgE molecules bound to multivalent allergens initiates a biochemical reaction, which leads to the secretion of a range of chemical mediators from mast cells. These mediators then stimulate the surrounding tissues to elicit the allergic response.

In humans, the mast cell is found in the loose connective tissues of all organs, most notably around blood vessels, nerves, and lymphatics. Mast cells in the lung are found beneath the basement membranes of airways, near blood vessels in the submucosa, adjacent to submucosa glands, scattered throughout the muscle bundles, in the intra-alveolar septa, and in the bronchial lumen. Mast cells appear in increased numbers in the epithelium after allergen exposure and are predominant in biopsies obtained during the allergy season. In the airways, there are about 20,000 mast cells/mm^3, and the mast cells represent 1–2% of alveolar cells.

Mediators of Anaphylaxis

Three categories of mediators are released during the process of mast cell degranulation: preformed soluble molecules stored within the cytoplasmic granules, newly formed lipid mediators, and cytokines (Table 3). The consequences of mediator release occur within minutes (immediate hypersensitivity) or take hours to develop (late-phase allergic reactions). Research has revealed an expanding list of mediators whose actions may contribute to the pathological changes seen in asthma (Table 4).

In addition to the granule-derived mediators, the process of degranulation leads to transcription, synthesis, and secretion of potent cytokines over several hours, which likely contribute to the late-phase allergic response. Thus, mast cells synthesize and release interleukin (IL)-3, IL-4, IL-5, and IL-6 in addition to tumor necrosis factor and other inflammatory cytokines. IL-4 helps regulate IgE production and mast cell activation, and release of IL-4 might actually upregulate IgE production.

Allergens in Asthma

Inhalant allergens are most frequently involved in allergic respiratory diseases such as allergic rhinitis and asthma. These antigens, which directly impact on the respiratory mucosa, are usually derived from natural organic sources such as dust mites, pollens, mold spores, and insect and animal emanations. Chemicals and irritants from the workplace have been increasingly recognized as a cause of rhinitis, asthma, or both. These chemicals can act as allergens or irritants or could influence the mucosal environment in such a manner as to predispose the individual toward developing an allergic response. Data suggest that diesel particulates can affect some patients toward becoming allergic. Inhalant allergic diseases may be episodic, seasonal (such as hay fever), or perennial. The most important seasonal allergens are pollens. Despite popular belief, the heavy, sticky pollens of brightly colored flowers seldom cause allergy symptoms, as these pollens are

Table 3
Mast Cell-Derived Mediators

Preformed mediators
Histamine
Serine proteases
Tryptase
Chymase
Cathepsin G
Carboxypeptidase A
Proteoglycans (heparin, chondroitin sulfate E)
Newly synthesized lipid mediators
Leukotriene C_4
Prostaglandin D_2
Platelet-activating factor
Superoxide
Cytokines
Interleukins-1α, 2, 3, 4, 5, 6, 8, 10, 13, 16
GM-CSF, TGF-β
Macrophage inflammatory proteins 1α and 1β
Monocyte chemotactic and activating factor
TNF-α (both preformed and newly synthesized)
TCA-3
Endothelin-1
MARC, I-309
SCF
VPF/VEGF
β-FGF

GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF, transforming growth factor; TNF, tumor necrosis factor; TCA, tricarboxylic acid; SCF, stem cell factor; VPF, vascular permeability factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor.

spread by insects and not by wind currents. Exposure to nonseasonal allergens, mainly through inhalation but in some instances by ingestion, accounts for year-round allergies. Among the inhalants, dust mites, mold allergens, cockroaches, and animal emanations are responsible for most perennial allergic asthma.

Diagnosis of Allergy

Despite the development of in vitro methods of detecting IgE antibodies, skin testing (prick or intradermal) with appropriate allergens is the least time-consuming, most sensitive, most useful and also the least expensive method to confirm the presence of allergen-specific IgE. Skin testing can be performed on infants as young as 1–4 mo of age, although age dictates both the choice of allergens used and the clinical conditions for which they can be used. Under the age of 1 yr, food antigens are the likely offenders, causing eczema or asthma. Inhalant allergens are more likely to be involved after 2–4 yr of exposure, although sensitization to indoor allergens can occur much more quickly. In exceptional cases, such as in patients with extensive eczema or marked dermatographism that negates use of skin tests, in vitro assays for serum IgE antibodies by radioallergosorbent, fluorescent-allergosorbent, multiple-thread allergosorbent, or enzyme-linked immunosorbent

Table 4
Pathological Changes in Asthma and the Putative Mediators Responsible

Pathological changes	*Mast cell mediators responsible*
Bronchial smooth muscle contraction	Histamine Leukotrienes C_4, D_4, E_4 Prostaglandins and thromboxane A_2 Bradykinin Platelet-activating factor
Mucosal edema	Histamine Leukotrienes C_4, D_4, E_4 Prostaglandin E_2 Bradykinin Platelet-activating factor Chymase Reactive oxygen species
Mucosal inflammation	Inflammatory factors Cytokines(IL-1, IL-6, TNF-α,etc.) Eosinophil and neutrophil Chemotactic factors Leukotriene B_4 Platelet-activating factor
Mucus secretion	Histamine Prostaglandins HETEs Leukotrienes C_4, D_4, E_4 Chymase
Desquamation	Reactive oxygen species Proteolytic enzymes Inflammatory factors and cytokines

IL, interleukin; TNF, tumor necrosis factor; HETE, hydroxyeicosatetraenoic acid.

assay techniques might be substituted for direct testing. With either in vitro testing or skin tests, however, it is essential that the relevance of the results be correlated to the patient's current clinical problems and their detailed history.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) was described in England as a progressive form of asthma leading eventually to pulmonary fibrosis. It was thought that the damp climate in England was responsible for the relatively frequent occurrence there and infrequent occurrence elsewhere. However, recent studies in the United States have revealed the presence of ABPA in the midwestern portion of this country as well.

Compared to other forms of asthma, ABPA is seen infrequently and may be heralded by its specific clinical characteristics. There are five pulmonary disease patterns elicited by exposure to *Aspergillus* species: (1) allergic asthma induced by exposure to mold spores in subjects with IgE antibodies directed at *Aspergillus* antigens; (2) hypersensitivity pneumonitis in response to mold spore inhalation in nonatopic individuals who

Table 5
Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

Primary criteria	Asthma
	Eosinophilia (>1000/mm^3)
	Positive immediate skin-test reactions to *Aspergillus* antigen
	IgG antibodies to *Aspergillus* antigens
	Marked increase in IgE level
	Pulmonary infiltrates, often transitory
	Central, saccular bronchiectasis
	Elevated serum IgE and IgG to *A. fumigatus* compared to control groups
Secondary criteria	*Aspergillus* in sputum
	History of expectorated brown plugs or specks
	Late-phase (or Arthus) skin-test results to *Aspergillus* antigen

develop IgG-class antibodies and cellular immunity to *Aspergillus* antigens; (3) a fungus ball or aspergilloma, which is a saprophytic colonization of a pre-existing cavity (as in old tuberculosis or sarcoidosis); (4) invasive aspergillosis, which is an overwhelming diffuse pneumonia in reaction to *Aspergillus* in an immunocompromised host; and (5) ABPA, which is a subacute inflammatory reaction elicited by both IgE- and IgG-mediated immune responses directed at *Aspergillus* species growing in the respiratory track. The precise incidence of ABPA in the United States is not known, but although the disease is not rare, it is seen uncommonly. Diagnostic criteria for ABPA have been established and are summarized in Table 5.

There are five stages of ABPA: stage 1 is the form of ABPA when the diagnostic criteria listed in Table 5 are met. Generally, the patient exhibits moderate-to-severe asthma, with purulent mucus production, eosinophilia, abnormal chest X-ray, and high IgE levels. Skin testing to *Aspergillus* produces a positive immediate (and often late) reaction. The possible presence of bronchiectasis is analyzed by computed tomographic scans, and serological testing for IgG antibodies directed at *Aspergillus* is performed. At this point patients should generally be treated aggressively with corticosteroids (CCS), with a resultant remission (stage 2).

Once the patient has had a remission, CCSs are reduced to either every-other-day use or are removed entirely. At this stage most experts continue patients on moderate doses of inhaled CCSs. Stage 3 occurs if an exacerbation eventuates and may lead to the stage where chronic CCSs (either daily or every other day) are necessary (stage 4). Diffuse pulmonary fibrosis (stage 5) can develop or be the presenting stage at which ABPA is recognized. The importance in making the diagnosis of ABPA rests on the aggressive use of oral and inhaled CCSs in order to try to prevent the development of pulmonary fibrosis.

For patients with CCS-dependent ABPA, the addition of itraconazole 200 mg twice a day for 16 wk and then 200 mg/d for another 16 wk can lead to significant improvement of clinical response. This treatment is generally well tolerated. The toxicity and adverse reactions induced by itracanazole are not significantly higher than those observed in patients receiving steroid treatment alone.

Infections

All patients with asthma may experience a worsening of their symptoms concurrent with upper respiratory tract infections, bronchitis, or influenza-type illnesses. Moreover, children may experience their initial asthma as a consequence of viral bronchiolitis, which commonly develops into chronic asthma. Finally, some patients have no clinical asthma except during concurrent respiratory infections. Some adult asthmatics trace their chronic asthma to a viral respiratory infection that led directly to chronic and often severe, nonallergic asthma.

Bronchiolitis is an acute viral infection of the bronchioles, generally seen only in children less than 2 yr old. It is usually accompanied by upper respiratory tract symptoms, which may precede the lower respiratory tract involvement by 2–3 d. Patients experience cough (sometimes croup), dyspnea, rapid respirations, fever, and sometimes prostration. Physical examination reveals retractions, rapid respiration, occasional rales, and wheezing. Respiratory syncytial virus (RSV) is the most frequent etiological agent, but adenoviruses, rhinovirus, parainfluenza virus, and others may also cause the disease.

RSV-related bronchiolitis has a mortality risk of 1%. Several studies suggest that atopic children develop IgE antibodies directed at the RSV, which converts the infection into an allergic reaction. About 50% of children with bronchiolitis in whom a family history of either allergies or asthma exists develop recurring wheezing. In most instances, postbronchiolitis asthma is mild in nature and largely under control or in remission by the age of 8 yr. Current studies suggest that some patients with asthma may have an underlying bronchitis caused by *Mycoplasma* or *Chlamydia* infection. Such patients generally have adult-onset disease, associated with an initial infection and some persistent cough and mucus production. In such patients, a 1- to 2-mo trial of appropriate antibiotics (such as Clarithromycin, 500 mg bid) might be helpful. Information of the possible relationship between a low-grade infection and asthma is suggested by increased antibody titers against *Mycoplasma* and/or *Chlamydia* or the presence of bacterial RNA in lung biopsy.

Occupational Asthma

The air we breathe may contain allergens of natural origin or generated as a consequence of industrial or environmental processes. In addition, chemicals in the air may irritate the airways and lower the threshold for airway responsiveness. These same irritants may in addition be allergens for susceptible individuals. Besides industrially related exposure, modern life generates pollutants that linger in the air, generally in or around cities, which may damage the lungs. Thus, everyone is at risk of breathing potentially harmful substances, but asthmatics are at much greater risk to react adversely to them. Certain pollutants such as ozone increase airway reactivity even in normal subjects, and asthma may be exacerbated during pollution with either industrial or photochemical smog. Approximately 2–15% of all cases of adult-onset asthma in men are of occupational origin (depending on the level of airway irritants and allergens in any working area).

Suspicion of occupational lung disease should be raised by the history of cough or chest tightness in relationship to the workplace. In asthmatics, worsening of symptoms every week, especially early in the week, may be noted. Such suspicions can be strengthened by evidence of wheezing or abnormal pulmonary function after occupational exposure. Only a few appropriate antigens are available for skin testing, so provocation with

Table 6
Some Agents Capable of Causing Occupational Asthma

Category	*Active substance*
Metal salts	Salts of platinum, nickel, chrome
Wood dusts	Oak, western red cedar (plicatic acid),redwood, mahogany
Vegetable dusts	Grain (mite, weevil), flour, castor bean, green coffee, gums, cottonseed, cotton dust
Industrial chemicals	Toluene diisocyanate, polyvinyl chloride, phthalic and trimelletic anhydrides, ethylenediamine
Pharmaceutical agents	Penicillin, phenylglycine acid chloride, ethylenediamine
Biological enzymes	*Bacillus subtilis*, pancreatic enzymes
Animal and insect materials	Rodent urine protein, canine or feline saliva or secretions

the suspected airborne chemical or particulate may be the only confirmatory test available. Some of the more common occupational exposures leading to asthma are listed on Table 6.

The prevalence of occupational asthma varies with the exposure and the provocative agent. Although only about 5% of workers regularly exposed to toluene diisocyanate develop asthma, 10–45% of workers exposed to relatively high concentrations of proteolytic enzymes in laundry detergent in the past were affected. The pattern of response may be immediate, late, or both. The underlying mechanism involves direct irritation and/or the induction of immunological processes, including IgE- or IgG-type responses. Removal of the worker from the workplace may reduce or reverse the airways disease, although there are many exceptions.

Chemical or Drug Exposure

Aspirin and Nonsteroidal Anti-Inflammatory Drugs

It is estimated that 3–5% of asthmatics will reliably worsen after the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Ingestion of aspirin or other NSAIDs may provoke either of two responses: respiratory responses, including bronchorrhea, rhinorrhea, bronchospasm, conjunctivitis, lacrimation, and flushing; or urticaria and angioedema. Rarely, combinations of the two patterns are seen. Aspirin-sensitive patients may be recognized by the presence of nasal polyps, nonallergic rhinitis, persistent sinusitis, and asthma associated with moderate eosinophilia (>1000/mm^3). The frequency of NSAID sensitivity increases with age, although children and families have been described with clear-cut reactivity. There may be a wide range of associated allergies, but many subjects (about 50%) are not allergic.

The mechanism responsible for NSAID sensitivity appears to involve an abnormal modulation of eicosanoid production (increased production of leukotrienes C and D). NSAIDs inhibit the cyclooxygenase (COX) enzyme system responsible for prostaglandin formation, thereby reducing prostaglandin production and leading to increased production of lipoxygenase products. It has been suggested that NSAIDs cause asthma by reducing the formation of prostaglandins such as PGE, that help maintain normal airway function while increasing the formation of asthma-provoking eicosanoids, including

hydroxyeicosatetraenoic acids (HETEs) and leukotrienes C and D. Recent work in humans has confirmed this suspicion, demonstrating that sensitive subjects exposed to NSAIDs secrete excessive quantities in leukotrienes in their respiratory tract and develop both rhinitis and asthma.

Aspirin sensitivity should be suspected in any asthmatic with nasal polyposis, chronic sinusitis, and eosinophilia. The polyposis and sinusitis may precede the onset of recognized NSAID sensitivity by years. Under some circumstances, selected patients with this syndrome can be "desensitized" to NSAIDs by repeated oral challenges with aspirin and may remain unresponsive to subsequent NSAID exposure if oral NSAIDs are given daily. Many asthma investigators believe that leukotriene antagonists are indicated in these patients. Generally, aspirin-sensitive patients can safely take COX-2 inhibitors without developing asthma.

Sulfiting Agents

Sulfiting agents include sulfur dioxide (SO_2) and any of its five sulfite salts, which are added to foods to prevent nonenzymatic browning, to inhibit growth of microorganisms, to inhibit enzymatic activity, and to act as antioxidants and reducing agents, as bleaching agents, as processing aids, as pH controls, and for stabilization. In 1986, in response to the recognition that sulfites could precipitate asthma, the US Food and Drug Administration (FDA) banned their use on fruits and vegetables served fresh. Other products, like beer and wine, are now labeled as containing sulfites. Sulfites are generally converted under acid conditions to sulfur dioxide and are largely liberated during the processing and cooking of foods. It is thought that ingestion of sulfites leads to the liberation of SO_2 in the mouth and stomach, which is then inspired. In very sensitive asthmatics, inhalation of SO_2, even in small amounts, provokes asthmatic attacks. It may be anticipated that only the most hyperresponsive asthmatics will react to ingested sulfites.

Sulfite sensitivity should be suspected in asthmatics who worsen in relationship to eating processed foods containing sulfites (e.g., dried fruit, fruit juices, or processed potatoes) or wine and beer. Sulfite-sensitive asthmatics should be advised to have a Medi-Alert bracelet and to carry a bronchodilator metered-dose inhaler (MDI) and injectable epinephrine.

β-Adrenergic Antagonists

The β-adrenergic blocking agent propranolol hydrochloride was introduced in 1964, and it was immediately recognized that asthmatics were adversely affected by this drug. β-Adrenergic blocking agents are being used in diverse diseases such as glaucoma, migraine, hypertension, myocardial infarction, and tremor. The underlying mechanism by which β blockade induces asthma is thought to involve prevention of the normal β-adrenergic inhibitory influences on the parasympathetic ganglia in the airways. The reduction in β -adrenergic inhibitory influences at this level thereby allows relatively unimpaired cholinergic constrictor influences to develop. In the opinion of most specialists, asthmatics should not take β -adrenergic blocking agents in most situations. Of note, worsening of the status of a previously stable asthmatic should provoke inquiries as to other medications given by practitioners, in search of possible β -adrenergic blocking agent administration. There is an ever-widening use of β –blockers, and some β -blockers are now "hidden" in combination tablets, along with diuretics.

Vasculitis

In 1951, Churg and Strauss described a vasculitic process that had pathological findings and clinical features warranting the designation of a separate disease entity, allergic angiitis and granulomatosis. The disease is characterized pathologically by necrotizing vasculitis, tissue infiltration by eosinophils, and extravascular granulomas. The disease has three phases, beginning with a prodrome of allergic asthma and allergic rhinitis that may exist for many years. The second phase includes eosinophilia along with the development of pulmonary eosinophilic infiltrates resembling Löffler's syndrome, eosinophilic pneumonia, or eosinophilic gastroenteritis. The third phase is the vasculitic phase involving pulmonary vessels (96%), skin (67%), peripheral nerves (63%), the gastrointestinal tract (42%), heart (38%), and kidney (38%).

The syndrome affects males and females equally; the onset of first stage involving allergic rhinitis and asthma occurs around the age of 30 yr, while the vasculitis becomes apparent by the age of 38 and is suggested by the development of eosinophilia greater than 1500/mm^3, infiltrates in chest roentgenogram, hypertension, abdominal pain, purpura, urticaria, subcutaneous nodules, mononeuritis multiplex, general malaise, persistent low-grade fever, and weight loss. Many patients have an increased IgE level and the presence of rheumatoid factor. The prognosis in untreated patients is poor. Treatment generally consists of CCSs alone or combined with cytotoxic therapy.

Although this is a rare disease (approx 1:30,000–50,000 asthmatics has Churg-Strauss syndrome), the recent introduction of leukotriene antagonists has led to an increased recognition of this disease. Thus, asthmatics who are weaned off oral CCSs and develop a flu-like syndrome with eosinophilia should be suspected of having Churg-Strauss syndrome. In that circumstance, a chest X-ray is indicated to search for pulmonary infiltrates.

Idiopathic or Intrinsic Asthma

Up to 30% of asthmatic patients, particularly those over 30 yr of age, have no apparent cause for their asthma. Often their disease begins with a severe upper or lower respiratory tract infection or sinusitis and progresses to asthma in short order. Such patients often have coexistent sinusitis and nasal polyposis, as well as vasomotor rhinitis. It has been thought that such patients have a worse prognosis than other types of asthmatics, but this is certainly not predictable. In such patients it is necessary to search for factors that might worsen asthma. Many patients with idiopathic asthma regularly produce mucus and have a history of tobacco smoking; such patients may have an asthmatic form of bronchitis. In some patients a trial of antibiotics for low-grade infectious bronchitis might be appropriate.

CONDITIONS ASSOCIATED WITH EXACERBATIONS OF ASTHMA

Several clinical conditions are closely associated with and may worsen asthma by diverse mechanisms.

Sinusitis

An association between asthma and concomitant sinus disease has been recognized since the early part of the century and has been reconfirmed repeatedly both in children and adults. It is estimated that 60–75% of severe asthmatics have concomitant sinusitis

and that 20–30% of sinusitis patients have asthma. Slavin treated 33 adults with asthma and concomitant sinusitis medically or surgically. After therapy, 28 of 33 subjects believed their asthma was improved, and 15 of 18 reduced their steroid requirement by 85%. Anecdotal observations suggest that the difficulty of treating asthmatics with sinusitis is proportional to the degree of sinusitis present. Physicians treating asthmatics should be alert to the possibilities that sinusitis frequently coexists in their patients and that the severity of the sinusitis may influence the course of the bronchial asthma. Although the precise mechanism by which sinusitis worsens asthma is not known with certainty, there is substantial evidence that a naso-sino-bronchial reflex exists which increases airway irritability and airflow obstruction.

In both children and adults, symptoms from acute sinusitis include purulent nasal discharge, persistent coughing (especially at night), and the presence of purulent mucus in the nasal vault and pharynx. Facial pain, headache, and fever occur less frequently. Most acute episodes of sinusitis follow upper respiratory infections, while some then develop into chronic or recurrent problems. Chronic sinusitis is associated with persistent or recurrent purulent nasal discharge, cough, headache or facial pressure, hyposmia, fetor oris, occasion temperatures, and worsening of asthma.

The physician should consider diagnostic studies for sinusitis whenever symptoms of upper respiratory infection or rhinitis are more protracted than expected, the patient has dull to intense throbbing pain over the involved sinus area, the patient's asthma is not responding appropriately to medications, or the patient has prolonged or persistent bronchitis that has failed to respond to appropriate therapy. On physical examination, edema and discoloration below the eyes may occasionally be observed. The nasal mucosa is inflamed, and a purulent discharge frequently is seen on the floor of the nose, beneath the middle turbinate, or draining down the throat.

Generally, roentgenograms with the findings of opacification, noticeable membrane thickening, or air-fluid levels within one or more sinuses confirm the suspicion of sinusitis. Computed tomography scans are much more sensitive than X-rays, provide better images, and are the currently recommended diagnostic procedure of choice.

Gastroesophageal Reflux

The presence of gastroesophageal reflux (GERD) is suggested by heartburn, especially postprandial, that is increased on bending over, lying down, or straining. Confirmatory tests include roentgenographic demonstration of reflux, the finding of acid in the esophagus after instilling hydrochloric acid into the stomach, 24-h monitoring of intraesophageal pH, or Bernstein's test, in which hydrochloric acid is dripped onto the lower esophagus and symptoms are elicited.

It has been reported that as many as 45–65% of adults and children with asthma have GERD. The mechanism by which GERD produces asthma appears to involve triggering intraesophageal reflexes by acid stimulation, resulting in cholinergic reflexes into the airways and resultant bronchial constriction. While GERD may be asymptomatic in asthmatics, the strongest association is with nighttime asthma symptoms— especially night cough and nocturnal wheezing. GERD should be highly suspect in patients (especially children) with nocturnal exacerbations (especially cough) and recurrent heartburn. Effective management of GERD may concomitantly reduce asthma in some, but not all patients.

Pregnancy

Asthma complicates 4% of pregnancies and is the most common chronic disease to do so. About one-third of pregnant asthmatics will improve during pregnancy, one-third will be unchanged, and one-third will worsen. Pregnancy is associated with an increase in tidal volume and a 20–50% increase in minute ventilation. This change has been attributed to a response to increased circulating progesterone, which acts as a respiratory stimulant. Arterial blood gases reflect a compensated respiratory alkalosis as a result of overventilation. Characteristic blood gases are a pH of 7.40–7.47, a partial arterial carbon dioxide pressure of 25–32 mmHg, and a partial arterial oxygen pressure of 100–106 mmHg.

Earlier studies suggested that the likelihood of prematurity and low-birthweight infants and both perinatal and maternal death rates were increased in asthmatic women, but current studies do not confirm these problems in properly treated patients. The clinical course of asthma during pregnancy may be predicted by the behavior in the first trimester, and most patients have the same pattern of response with repeated pregnancies. When a pregnant asthmatic worsens, one should always consider pulmonary emboli as a possible cause.

The management of asthma in pregnancy involves the extensive use of inhaled medications and careful avoidance of any medication that might adversely affect the fetus. Because the uterus compromises the thoracic space late in pregnancy, it is very important to keep pregnant asthmatic under excellent control throughout the pregnancy in order to avoid exacerbations during the last trimester.

DIFFERENTIAL DIAGNOSIS OF ASTHMA

Not all that wheezes is asthma! Diseases in which wheezing is a component are listed in Table 7. Asthma, chronic bronchitis, and emphysema affect the airways diffusely, cause airway obstruction, and may coexist in the same patient. Generally, chronic bronchitis occurs in cigarette smokers who develop chronic cough that persists for years before airflow becomes symptomatically obstructed. The bronchorrhea may vary in intensity in relation to infectious or irritant exposure, for example. Chronic bronchitis involves hyperplasia and hypertrophy of the submucosal glands, inflammation of the small airways, and hypersecretion of mucus. Emphysema may also be heralded by longstanding cough and mucus production, but this is a diagnosis confirmed only histologically. Emphysema is suggested by the presence of a reduced diffusing capacity and obstructing airways disease. Most adults have some degree of emphysema at autopsy, but severe emphysema is seen only in about 10%. Emphysema is another disease that usually develops in smokers.

A small number of patients with emphysema and bronchitis have a congenital absence of α-antitrypsin and present with bronchitis and wheezing and may develop emphysema and cirrhosis of the liver.

In children, most conditions likely to be confused with asthma begin in infancy, so it is in the wheezing infant that the differential diagnosis of asthma is important. The most common differential is an aspirated foreign body. A history of aspiration, findings of unilateral wheezing or hyperinflation on physical examination, or a persistent infiltrate on chest radiology suggests the need for further evaluation. Other illnesses encountered

Table 7
Differential Diagnosis of Asthma

Nonasthmatic conditions associated with wheezing
Pulmonary embolism
Cardiac failure ("cardiac asthma")
Foreign bodies[a]
Tumors in the central airways
Aspiration (gastroesophageal reflux)[a]
Carcinoid syndrome
Laryngo-tracheo-bronchomalacia[a]
Löffler's syndrome
Bronchiectasis
Tropical eosinophilia
Hyperventilation syndrome
Laryngeal edema
Vocal cord dysfunction
Laryngeal or tracheal obstruction[a]
Factitious wheezing
α_1-Antitrypsin deficiency
Immotile cilia syndrome, Kartagener's syndrome[a]
Bronchopulmonary dysplasia[a]
Bronchiolitis, croup[a]
Overlapping diseases
Chronic bronchitis and emphysema
Cystic fibrosis[a]

[a]Especially important in differential diagnosis in children.

in wheezing infants include bronchopulmonary dysplasia, cystic fibrosis, GERD, and immunoglobulin deficiency.

PATHOPHYSIOLOGY

Pathologically, the airflow obstruction of asthma is a result of combinations of bronchial smooth-muscle contraction, mucosal edema and inflammation, and viscid mucus secretion. The disease involves large and small airways but not alveoli. Pathological examination of asthmatic lungs reveals that small bronchi and bronchioles are principally involved, there is extensive airway denudation resulting from loss or thinning of the epithelium, and the goblet cells are often markedly hyperplastic. The basement membrane is thickened because of the deposition of subbasement membrane collagen, and the lamina propria is infiltrated with $CD4^+$ lymphocytes, mast cells, eosinophils, and neutrophils. The smooth muscle is hyperplastic and contracted. The submucosal glands are hyperplastic and are actively secreting mucus. The airway lumen is often filled with secretions containing mucus, edema fluid, eosinophils, inspissated mucus plugs, Charcot-Leyden crystals, and Curschmann's spirals.

The pathophysiological event causing asthma is a reduction in small-airway diameter. This abnormalities leads to an increase in airway resistance, which makes it difficult for inspired air to escape the lungs, leading to a reduction in forced expiratory volumes and

flow rates and hyperinflation of the lung with air trapping. The increase in the work of breathing creates a sense of breathlessness and generates inequities of alveolar ventilation and perfusion, which causes hypoxemia. Initially blood gases exhibit reduced CO_2 levels, reflecting overventilation in an attempt to maintain O_2 levels. Associated with the dynamics of air trapping are electrocardiographic changes reflecting cor pulmonale and, with hypoxemia, increases in pulmonary arterial pressures. These changes may lead to pulsus paradoxus. The presence of pulsus paradoxus and the need to use the accessory muscles of respiration reflect the severity of the airflow obstruction and may be useful clinical signs.

Bronchial Smooth Muscle Contraction

Because airway obstruction occurs within minutes of an inciting event and can reverse itself within minutes of treatment with β-adrenergic agonists, it is likely that airway smooth-muscle constriction contributes significantly to airflow obstruction. Of the recognized factors capable of causing bronchial smooth muscle contraction, mast cell mediators, and several neuropeptides are probably the most important (Table 4).

Mucosal Edema

Edema of airway mucosa is a result of increased capillary permeability with leakage of serum proteins into interstitial areas. In the earliest careful descriptions of asthmatic lungs, the presence of edema was the most striking abnormality. More recently, mucosal edema has been directly observed by bronchoscopy after airway antigen challenge, and plasma protein exudation after antigen challenge has been documented. These observations combine to support the growing appreciation of the importance of airway mucosal edema in asthma.

Vascular permeability occurs within several minutes of allergen challenge and persists for 30–60 min. It is not surprising that edema would occur as a consequence of allergic reactions, as swelling is the primary response to allergen exposure in sensitized individuals in all other parts of the body. The late-phase allergic reaction is thought to be a result of a combination of edema of the airways and the presence of increased inflammatory cells.

Airway Inflammation

The mucosa of patients who have died in status asthmaticus contains mixed cellular infiltrates consisting of eosinophils, neutrophils, macrophages, lymphocytes, mast cells, and plasma cells. In the airway lumen, admixed in the abundant secretions are eosinophils and eosinophil-derived "Charcot-Leyden crystals," neutrophils, and desquamated clumps of epithelial cells ("Creola bodies"). The same pathological changes are found in the lungs of allergic or nonallergic asthmatics, suggesting that there is a commonality in the pathophysiological events.

Recent biopsy studies of the airways of asthmatics after allergen challenge have shown the following observations: Within minutes of allergen exposure mast cells degranulate (and release mediators detectable in the broncho-alveolar lavage fluid), the superficial vessels swell and become permeable, and mucosal edema forms. Biopsies done several hours later reveal persistent edema, the increased expression of adhesion molecules on blood vessels, and increased cells in the mucosa-expressing molecules, which can bind

to the adhesion molecules. The mucosa becomes infiltrated initially with neutrophils and after 12–24 h with eosinophils. The eosinophils release granule contents, as reflected in the presence of major basic protein in airway biopsies or pathological specimens. Eosinophil-derived proteins can cause epithelial denudation, mucus secretion, and irritability of the airway. Of all the infiltrating cells, the eosinophil is the most specific, being seen rather exclusively in asthma and not with other inflammatory diseases of the airway.

Biopsies have also indicated that the lymphocytes in the asthmatic mucosa are primarily $CD4^+$, express genes for the production of IL-4 and IL-5 (suggesting that they are of the TH_2 phenotype associated with increased inflammation, prolonged eosinophil survival, and increased IgE production), and become activated after allergen challenge. The cytokines produced by TH_2 lymphocytes can not only enhance IgE production, but also support many of the pathological events that occur in the airways of asthmatics. It is this population of lymphocytes that appears to be specifically expanded in atopic subjects. Moreover, allergen exposure in allergic individuals is the stimulus for TH_2 expansion during the late-phase allergic reaction and in airways of asthmatics. Thus, there is a growing body of evidence that allergy and asthma are associated with an expanded TH_2 population of lymphocytes, which act to support the events occurring in the asthmatic airway (Table 8).

Mucus Secretion

Pathological examinations of patients who have died in status asthmaticus almost always reveal diffuse collections of mucus, which appear to contribute significantly to obstruction of the airways. The precise mechanisms responsible for increased mucus production have been partly defined (Table 4).

Bronchial Hyperresponsiveness

One of the absolute features of asthma is exaggerated nonspecific airway reactivity to a variety of irritating stimuli. Thus, asthmatics develop airway obstruction in response to natural exposures (cold air, exercise, irritating chemicals, laughing, and coughing) or to provocations in the laboratory (histamine, methacholine, cold air hyperventilation) (Table 9). Airway hyperresponsiveness is found universally in asthmatics, in a portion of subjects with chronic bronchitis, in some subjects with allergic rhinitis, and in 3–8% of otherwise normal subjects. There is a close correlation between the degree of increased responsiveness and disease severity: patients with the most reactive airways often require oral CCSs for control, whereas milder degrees of abnormality predict the requirement for fewer medications. Hyperresponsiveness increases after allergen exposure, late-phase allergic reactions, viral infections (especially influenza-type infections), and ozone exposure. Conversely, airway hyperresponsiveness may return toward normal after allergen avoidance, allergy immunotherapy, or treatment with cromolyn or inhaled or oral CCS. In recent years, airway hyperresponsiveness and airway inflammation have become prime targets in asthma therapy, leading to the use of anti-inflammatory agents to reduce airway reactivity.

Other Pathological Events

Denudation of airway epithelial surfaces with the appearance of epithelial clumps in expectorated secretions accompanies severe asthma. The denuded epithelial surfaces

Table 8
Pathology of Asthma

Denudation of airway epithelium
Subbasement membrane fibrosis and collagen deposition
Airway wall edema
Mast cell activation
Inflammatory cell infiltration
Neutrophils
Eosinophils
Lymphocytes (TH_2 cells)
Mucus hypersecretion
Goblet cell hyperplasia
Mucus gland hyperactivity

Table 9
Airway Hyperresponsiveness

Exaggerated broncho-constriction to a variety of stimuli
Histamine, methacholine, cold air, exercise
Induced by mast cell and lymphocyte mediators, cytokines, and chemokines
Associated with eosinophil and neutrophil infiltration
Improved but not eradicated by anti-inflammatory therapy

may be replaced by goblet cells, resulting in goblet cell hyperplasia and increased mucus secretion. The mechanism for epithelial desquamation has not been systematically examined, although several mediators might participate. Edema of the airway results in movement of edema fluid between epithelial cells and into the airway lumen. This process may also contribute to weakening the epithelial bond. Lymphocyte-derived cytokines may also contribute to these phenomena.

FACTORS PREDISPOSING TO ASTHMA

Genetic Factors

When differentiating asthma from other obstructive airways disease, it is always relevant to ask if family members experience the same symptoms. It is well recognized that asthma is the result of both genetic and environmental influences. Asthma, as with many other medical conditions, such as hypertension and diabetes mellitus, is a complex genetic disorder. It cannot be classified as an autosomal-dominant, recessive, or sex-linked pattern of inheritance. At the present time, several chromosomal regions have been identified to be strongly associated with asthma, such as 5q31, 6, 11q13, 12q, 13q14, and so on. The 5q31, for example, is on chromosome 5. It influences total IgE production, eosinophil count, IL-4, IL-5, and IL-13 production, CD14 expression, and so on. The completion of human genome sequencing will certainly help facilitate the process of identifying genes involved in asthma.

Autonomic Dysfunction

An imbalance of the autonomic nervous system with a blunted β-adrenergic response and hyperresponsiveness of the " β-adrenergic and cholinergic systems have been documented in asthmatics, although this defect is not unique for asthma. The exact contribution of the disarray of autonomic imbalances found in asthmatic subjects is not clear. Some of the abnormalities are also found in allergic subjects and in patients suffering from cystic fibrosis. These data suggest that asthmatics have an inherently reduced ability to sustain open airways and a tendency for airflow obstruction based on an inherent defect in their autonomic balance.

CLINICAL ASTHMA

Symptoms

The classic symptoms of asthma include intermittent, reversible episodes of airflow obstruction manifested by cough, wheezing, chest tightness, and dyspnea (Table 10). When the clinical situation permits, a detailed history (Table 11) should be taken that includes the following: (l) family and personal history of atopic disease; (2) age of onset of asthma, frequency and severity of attacks; (3) times (including seasons) and places of occurrence of asthmatic attacks; (4) known provocative stimuli and any previous correlating skin-test reactions; (5) the severity of the disease as reflected in the wheezing episodes per day, the number of missed school or work days per year, whether sleep is interrupted, the necessity for emergency room visits, and the number of hospitalizations for asthma; and (6) previous pharmacological or immunological therapy and its efficacy.

Early symptoms often include a vague, heavy feeling of tightness in the chest, and, in the allergic patient, there may be associated rhinitis and conjunctivitis. The patient may experience coughing, wheezing, and dyspnea. Although the cough (if present) is initially nonproductive, it may progress to expectoration of a viscous, mucoid, or purulent and discolored sputum. There appears to be a subgroup of asthmatics whose asthma is characterized solely by cough without overt wheezing, the "cough variant of asthma." (Just as all that wheezes is not asthma, all that is asthma does not necessarily wheeze.) If this syndrome is suspected, patient's airways should be examined by spirometry before and after bronchodilator inhalation or after receiving a methacholine inhalation challenge.

Patients who appear to have allergic asthma, as demonstrated by seasonal exacerbations or clearly recognized allergen-related triggering events, may be sensitive to pollens, dust mite, animal dander, mold spores, occupational dusts, or insects. Less frequently, children may also be allergic to certain foods. If the offending allergen can be identified from the patient's history and avoided, further workup may not be necessary. However, the fact that atopic patients may be allergic to many allergens or may react to such small amounts of crude allergens (i.e., dust mite) indicates that the association is not clear-cut. Moreover, allergic asthmatics may respond to many nonallergic conditions (such as cigarette smoke, noxious fumes, upper respiratory tract infections, or weather conditions) by wheezing.

All patients should be asked if they can take aspirin or NSAIDs without ill effects, and this line of inquiry is even more important in patients with sinusitis or nasal polyps. Occupational asthma should be suspected if patient worsens early each week and then improves during the course of the week, or if asthma is worse during the week as com-

Table 10
Asthma Diagnosis: Episodic Symptoms of Airflow Obstruction (Determine Frequency)

Wheezing
Shortness of breath (with or without exercise)
Chest tightness (below sternum)
Cough (throat vs chest, quantity and quality of sputum)
Nocturnal awakenings
Morning vs evening symptoms
Emergency room visits
Hospitalizations

Table 11
Initial History (Determine Days/Week/Month for Each)

Do you wheeze?
Shortness of breath?
Tightness in the chest (inability to take a full breath)?
Exercise? Need pretreatment with bronchodilator?
Cough? Throat vs chest, sputum quality/quantity?
Use of bronchodilator?
Nocturnal awakenings
Peak flow meter use; average, best and worst reading?
Emergency room visits, hospitalizations?

pared to weekends or during travel. It may be necessary to have the patient use a peak flow meter at work during the course of a week to help determine what exacerbates the disease, or to conduct a bronchial challenge with materials to which the patient is exposed at work.

Chest X-rays should be repeated every 3–5 yr, and a yearly complete blood count is a reasonable precaution in most patients. Some subjects worsen reliably with every upper respiratory infection, and it may be necessary to treat them prophylactically with antibiotics and/or CCSs to prevent these exacerbations.

Many subjects are unaware of their chest disability and benefit from frequent peak flow readings (Table 12). We routinely provide a peak flow meter to all asthmatics and request that readings are taken twice a day, in the morning and at night. These readings are an invaluable adjunct to the management of most asthmatics.

Physical Findings

In the completely asymptomatic patient, results of chest examination will be normal, although head, eye, ear, nose, and throat examination may disclose concomitant serous otitis media, allergic conjunctivitis, rhinitis, nasal polyps, paranasal sinus tenderness, signs of postnasal drip, or pharyngeal mucosal lymphoid hyperplasia. Clubbing of the fingers is extremely rare in uncomplicated asthma, and this finding should direct the physician's attention toward diseases such as bronchiectasis, cystic fibrosis, pulmonary neoplasm, or cardiac disease. With an acute exacerbation, patients may be restless, agitated, orthopneic, tachypneic, breathing through pursed lips with a prolonged expiratory

Table 12
Peak Flow Meter Characteristics

Inexpensive
Easy to use
Accurate
Provide "real-life" measurements at worst and best time of day
AM and PM, monitor range between the measurements
Obtain "personal-best" measurement

phase, using accessory muscles of respiration, diaphoretic, coughing frequently, or audibly wheezing and cyanotic. Cyanosis occurs only with profound arterial oxygen desaturation and is a grave sign that appears late in the course of severe asthma. Vital signs will confirm the physician's impression that the patient is tachypneic, and evaluation of the blood pressure may show that the patient has a widened pulse pressure and a pulsus paradoxus. The latter sign, when present, is a relatively reliable indicator of severe asthma. Although a low-grade fever may be of viral origin, the presence of an elevated temperature should alert the physician to search for a possible bacterial infection requiring antibiotic therapy.

Examination of the chest will often show signs of hyperinflation, such as hyperresonance on percussion and low, immobile diaphragms. In milder stages of asthma, wheezing may be detected only on forced expiration, but with increasing severity, wheezing may also be heard on inspiration. In some episodes of severe asthma, wheezing may be heard early in the course of disease, but with increasing obstruction of the airways, the wheezing may seem to "improve" as increasing difficulty in ventilating develops. This abatement of wheezing may, unfortunately, be taken as a clinical sign of improvement and result in less than optimal treatment. As the patient does improve, one may notice the reverse situation; namely, that wheezing may increase in intensity. Again, this finding should not be erroneously interpreted as worsening of the asthma. The major point is that in judging the severity of asthma, the physician must rely on many physical findings (such as the use of accessory muscles and the presence of paradoxical pulse) as well as the degree of wheezing. As the patient recovers, the improvement takes place most often in reverse order of the appearance of symptoms,that is, there is a sequential loss of mental status abnormalities, cyanosis, pulsus paradoxus, use of accessory muscles, dyspnea, tachypnea, and, finally, wheezing. It is important to note, however, that when the attack appears to have ended clinically, abnormal pulmonary function test results are still present and may persist for several days. At this point in the course of the illness, there is usually a residual volume twice that of normal, an FEV_1 60% of that predicted, and a maximum mid-expiratory flow rate 30% of that predicted. Such findings support the contention that treatment should be continued well past the symptomatic period and that close outpatient follow-up is indicated.

Classification of Asthma

Asthma may be divided into four clinical phases, based on symptoms and pulmonary function testing. These stages allow physicians to communicate about asthma severity and provide general guidelines on treatment. The four categories include mild intermittent asthma, mild persistent asthma, moderate persistent asthma, and severe persistent

Table 13
Classification of Asthma Severity

Category	*Symptoms*	*Nocturnal symptoms*	*Pulmonary function*
Mild intermittent	Less than twice weekly Normal between attacks Attacks brief and usually mild	Less than twice monthly	Both FEV_1 and PEFR >80% predicted
Mild persistent	More than twice a week, less than daily Attacks limit activity monthly	More than twice weekly	Both FEV_1 and PEFR >80% predicted
Moderate persistent	Daily symptoms Daily use of medications Attacks affect activity Attacks usually more than twice a week and may be severe and last days to weeks	More than weekly	FEV_1 and PEFR 60–80% predicted
Severe persistent	Continuous symptoms Limited physical activity Frequent exacerbations	Frequent, up to every night	FEV_1 and PEFR <60% predicted

PEFR, peak expiratory flow rate.

asthma. These categories advance in severity and a patient may move from one to another depending on various circumstances. Table 13 shows details of the current classification scheme.

Mild intermittent asthma occurs less than twice weekly, and the patient is asymptomatic otherwise. Pulmonary function is normal except during periods of disease, and exacerbations are brief and usually easily treated.

Mild persistent disease occurs more than twice a week, but less than once a day. Symptoms are severe enough to interfere with daily activities and may interrupt sleep up to twice a month. Moderate persistent disease occurs on a daily basis and requires regular use of medications. This stage of asthma is moderately inconvenient, with patients constantly aware of their disease, requiring medications on a daily basis, having their sleep interrupted at least weekly, and having to accommodate their lifestyle to the disease.

Severe asthma has continuous symptoms despite medications, which limit activity and are associated with frequent exacerbations and sleep interruptions.

A patient with mild persistent disease can be exposed to allergens or develop a cold and have a severe exacerbation of his asthma symptoms, which places him in the severe persistent classification until the attack is resolved. Conversely, a patient with severe persistent symptoms can be treated effectively and have resolution of symptoms, with reclassification to a mild persistent category while he or she takes medications.

Exercise-Induced Asthma

Exercise is a well-established nonspecific stimulus to airflow obstruction, and this phenomenon can be demonstrated in most patients with asthma. Thus, exercise-induced

asthma might better be thought of as a reflection of increased nonspecific airway hyperresponsiveness than as a distinct form of asthma. It is most common in children and adolescents (probably because they exercise more strenuously than do most adults). The problem is clinically important in at least two-thirds of adolescents with asthma because it interferes with school and recreational activities.

The mechanisms by which exercise causes bronchial obstruction is unknown, but a fall in the temperature and humidity of the intrathoracic airways is a critical initiating event. The exact roles of mast cell mediator release and reflex responses (perhaps regulating blood flow in response to the temperature change) in this syndrome are unclear. Exercise asthma usually begins after about 6–10 min of exercise or after the exercise is completed. Exercise asthma can be reproduced by having subjects hyperventilate cold, dry air.

Swimming and activities that necessitate only brief intervals of exercise are likely to be best tolerated. Breathing warm and humidified air (as in jogging with a face mask) and the use of prophylactic drug therapy (β-agonists usually) generally afford adequate protection against exercise-induced asthma.

TREATMENT

Over the past decade, the treatment of asthma (Table 14) has changed remarkably, largely because of our increased understanding of the pathophysiology of the disease, with recognition of the importance of airway inflammation. Recognizing that the airflow obstruction in asthma is due to a combination of airway wall edema, increased mucus secretion, increased inflammation, bronchial smooth muscle contraction and increased airway irritability and not just bronchospasm (as was once thought) has led to a fundamentally altered approach to asthma therapy. One way to summarize this approach is based on a classification of treatments into specific (long-term controlling) and symptomatic (short-term relieving) agents: specific treatments are agents that reduce the underlying causes for asthma and thereby reduce the need for symptomatic agents. Symptomatic treatments act only by reducing symptoms of airflow obstruction and have no effect on the underlying causes of asthma. Thus, we can separate the treatments used for asthma into the following.

Specific treatments (long-term controlling) include the following:

- Allergy avoidance
- Allergy immunotherapy
- Inhaled CCS
- Cromolyn or nedocromil
- Oral CCS
- Leukotriene modifiers
- Combination of inhaled LABA and CCS
- Humanized monoclonal anti-IgE (Omalizumab, Xolair)

Symptomatice treatments (short-term relieving) include the following:

- β-agonists
- Theophylline
- Anticholinergics
- LABA

Table 14
Goals of Asthma Treatment

1. Prevent chronic and troublesome symptoms
2. Maintain (near) normal pulmonary function
3. Maintain normal activity levels
4. Prevent recurrence of the disease and any need for emergency treatment or hospitalization
5. Provide optimal treatment with minimal side effects
6. Meet patients and family's expectations for asthma control

All patients should receive one or more specific treatments and may also receive symptomatic treatments as needed. As a patient's symptoms move him or her into one of the more severe categories of asthma, the patient generally will receive more medications, both specific and symptomatic. Thus, the general approach is to treat initially with combinations of specific and symptomatic therapies in order to totally control the symptoms and then to reduce the treatments to the least amount required to maintain remission. For example, mild intermittent asthma is only treated with inhaled bronchodilators on an as-needed basis. At the next level, mild persistent asthma requires more chronic dosing, and the usual approach is to use a low to moderate dose of inhaled CCS and/or a leukotriene modifier, plus a bronchodilator on an as-needed basis. Moderate asthma is usually treated with a higher dose of inhaled CCS and/or a LABA or a leukotriene antagonist. The combination of LABA and CCS, for example, fluticasone/salmeterol (Advair), is usually more effective than other modalities of treatment in this group of patients. Oral theophylline may be used in addition to or in place of the LABA or leukotriene antagonist. For the severe persistent asthmatic patients, the combination of higher doses of inhaled CCS and LABA is the preferred treatment option. These patients may also require leukotriene antagonists and, if symptoms persist, oral CCS. Monoclonal anti-IgE can be given to moderate to severe persistent asthmatics to reduce exacerbation, lower CCS requirement, and reduce disease severity.

In all patients, symptomatic therapies are also given, to be used on an as-needed basis. The goal in all of these patients is to tailor the medicines and their doses to control the level of the disease, always trying for optimal control with the lowest effective dose of medications. These principles are summarized in Table 15. The comparative dose of inhaled steroids is shown in Table 16.

To summarize, the basic concepts of asthma management include the following:

1. Daily use of specific treatments (long-term control treatments), often used in combination. Allergy management is superimposed on other treatment modalities for long-term control.
2. Symptomatic use of bronchodilators (quick-relief medications) used only on an as-needed basis.
3. Step therapy:
   a. Use whatever dose or combination of therapies required to totally control symptoms and achieve a maximum (personal best) peak flow.
   b. Once completely controlled, step down the treatment plan while maintaining symptom control and personal best peak flow to the lowest effective doses of medication.

Table 15
Stepwise Approach to the Treatment of Asthma

Category	*Specific, long-term controller medication*	*Symptomatic medication*
Mild intermittent	No daily medication required Allergy treatment as indicated	Inhaled β-agonist PRN
Mild persistent	Inhaled CCS (low dose) or leukotriene antagonist or cromolyn or nedocromil Allergy treatment as indicated	Inhaled β-agonist PRN
Moderate persistent	Inhaled CCS (moderate dose) and LABA (salmeterol or formoterol) or combination of CCS + LABA, such as Advair May add leukotriene antagonist and/or theophylline Allergy treatment as indicated Monoclonal Anti-IgE	Inhaled β-agonist PRN Ipratropium or tiotroprium for mucus secretion or cough
Severe persistent	Inhaled CCS (high-dose) and LABA (salmeterol, or formoterol) or combination of CCS + LABA, such as Advair May add leukotriene antagonist and/or theophylline Allergy treatment as indicated Monoclonal anti-IgE	Inhaled β-agonist PRN Ipratropium for mucus secretion or cough

PRN, as needed; CCS,corticosteroid; LABA, long-acting β-agonist.

4. Regular follow-up visits.
5. Written management plan (including emergency treatment plan).
6. At-home monitoring with peak flow meters.

Specific Therapies

Allergen Avoidance

Allergies are the major underlying cause of asthma, particularly in the pediatric to young adult populations. Avoidance of allergens, therefore, represents a simple yet important approach to asthma management (Table 17). The allergy status of any patient who wheezes more than 2 d a week should be evaluated by an allergist (or other physician trained and competent to do allergy assessment) early in the disease process. Although almost three-fourths of asthmatics are reported to have positive skin test reactions to common inhalant allergens, only significant skin test reactions that closely correlate with clinical symptoms should be targeted for treatment.

There is substantial (although not entirely consistent) evidence supporting the benefits of allergen avoidance as a strategy in asthma care. Avoidance of allergens in dust-mite-allergic asthmatic children leads to an improvement in both airflow obstruction and airway reactivity. Similarly, dust-sensitive asthmatic children whose bedrooms are made

Table 16
Estimated Comparative Daily Dosages for Inhaled Corticosteroids

Medicine	*Low dose (μg)*	*Medium dose (μg)*	*High dose (μg)*
Beclomethasone HFA, 40 or 80 μg/puff	80–240	240–480	>480
Budesonide DPI 200 μg/inhalation	200–600	600–1200	>1200
Flunisolide, 250 μg/puff	500–1000	1000–2000	>2000
Fluticasone			
MDI:44,110,220 mg/puff	88–264	264–660	>660
DPI:50,100,250 μg/inh	100–300	300–600	>660
Triamcinolone, 100 μg/puff	400–1000	1000–2000	>2000

dust-free experience less wheezing, require less medication, and have higher peak expiratory flow rates than do their counterparts with unmodified bedrooms.

Compliance in preparing allergy-free environments is an issue. Our experience has shown that patients are more likely to comply with written instructions about allergen avoidance than to oral instructions and that these recommendations should be reasonable. For instance, requesting the purchase of allergen encasements for the pillow, mattress, and box springs along with weekly washing of linens in hot water (>130°F) are reasonable, whereas asking for a carpet to be removed may not be. Thus, we are careful to only advise allergen-control measures that the patient can actually do.

Immunotherapy

In immunotherapy (Table 18), increasing doses of allergen vaccines are injected subcutaneously over time. The use of immunotherapy for the treatment of asthma has generally been accepted as useful. Data clearly indicate that immunotherapy works well in the treatment of relatively pure allergic asthmatics, such as those with cat-, dog-, or pollen-induced asthma. In a large meta-analysis of immunotherapy of asthma, the evidence was considered overwhelming that immunotherapy is helpful. Moreover, current findings support earlier observations that immunotherapy of allergic rhinitis may prevent the development of asthma.

When successful, treatment with immunotherapy reduces bronchial reactivity, asthma symptoms, skin-test reactivity, and the need for medications. As such, immunotherapy is the only modality available in asthma treatment that has the chance of making the patient asymptomatic on less or no medication. Asthmatic patients most likely to benefit from immunotherapy are those who also have concomitant allergic rhinitis, unequivocal immediate sensitivity, a history of asthma with allergen exposure, and an inadequate response to allergen avoidance.

Pharmacological Therapies

Inhalers. The use of MDIs in asthma has revolutionized asthma treatment. Traditionally, an inhaler is a canister containing pressurized chlorofluorocarbons (CFCs or Freon), in which powdered medications can be suspended. Upon actuation, a metered dose is expelled, containing particles of various sizes. Only those particles less than 5 μm

Table 17
Allergy Advice

1. All patients who wheeze more than 2 d a week should undergo an allergy evaluation
2. Allergen avoidance is fundamental to allergy management.
3. Try allergen avoidance plus pharmacotherapy before you consider immunotherapy
4. Be reasonable in regards to allergen avoidance; advise patients to do what can be done (appropriate dust controls, pets out of the bedroom), not what is impossible
5. Provide practical advice on pollens, molds, dust, dander.

Table 18
Allergy Immunotherapy

1. Indicated if the patient does not respond to avoidance and pharmacotherapy. In some circumstances (dust, dander)avoidance may not be possible.
2. Do not use unless there is a positive history and significantly positive confirmatory skin tests.
3. Use for 2 yr and, if no improvement, stop!
4. Data supporting its use in asthma in both adults and children are substantial, and it is the only treatment with the long-term chance of remission of asthma.
5. Can be used as an inhaled cortocosteroid-sparing agent

in diameter enter the airstream and reach the lower airways. It is estimated that 5–15% of a metered dose actually reaches the lung; the rest is deposited in the mouth and throat. The propellant CFC has become recognized for its contribution to the depletion of the earth's ozone shield. CFC-containing inhalers are being gradually replaced by inhalers using a new propellant, hydrofluoroalkane-134a (HFA), or dry powder inhalers (DPIs) without any propellant.

Teaching a patient proper inhaler use techniques is critical to the usefulness of these products. Table 19 shows one of the most effective techniques.

The current crop of Freon-propelled MDIs will shortly be replaced with HFA-driven inhalers. These new inhalers will not deplete ozone as does Freon and will have a softer plume, which will facilitate deeper penetration of the dose of medication. Some asthma medications are soluble in HFA, allowing for the generation of smaller particle sizes and much greater deposition of the inhaled dose into the lungs.

The use of spacers can be employed to facilitate better inhaler technique. A spacer is a reservoir into which the metered dose is expelled and from which the patient breathes. The major advantage of spacer use is that hand–eye coordination is not necessary and most large particles impact on the wall of the spacer and are not inhaled. Thus, the relative fraction of medicine that the patient breathes that actually gets into the lungs is enhanced. Unfortunately, although spacers are an important improvement on inhaler administration, only a small fraction of the total medicine dispelled from the MDI through the spacer actually reaches the lungs.

Another Freon-free choice is DPIs, which have recently been introduced to the market. DPIs reduce the eye–hand coordination problem and are very convenient. However, they also suffer from a relatively small respirable fraction.

Anti-Inflammatory Therapy. CCS are the most potent of the available pharmacological agents for the specific treatment of asthma and airway hyperresponsiveness.

Table 19
Proper use of Metered-Dose Inhalers (Chlorofluorocarbon or Hydrofluoroalkane-134a)

- Shake metered-dose inhaler
- Breathe out
- Place metered-dose inhaler two finger breadths in front of open mouth (or place in mouth with lips loosely around mouthpiece)
- Aim at back of throat
- Activate inhaler while breathing in slowly (over 3–4 s)
- Hold breath 10 s
- Wait 30–60 s between actuations

Table 20
When to Use an Inhaled Corticosteroid

1. For all asthmatics who:
   a. wheeze more than 2 d/wk
   b. use a bronchodilator on a frequent basis
   c. have nocturnal awakenings with asthma (all persistent asthmatics!)
2. Not indicated for the mild intermittent asthmatic who wheezes less than 1-2 d/wk and is otherwise asymptomatic

These agents have many actions that make them valuable in the treatment of asthma, including the ability to reduce airway inflammation, mucus secretion, edema, and airway hyperreactivity. Despite their proven value in asthma therapy, CCS are often withheld from patients who could benefit from their use because of the fear of major side effects. In order to reduce unwanted systemic effects, the pharmaceutical industry has created highly specific molecules with topical activity but limited systemic effects. It is safe to say that when used properly, inhaled CCS need not cause additional problems for the asthma patient (Table 20).

Inhaled CCS is the first-line treatment of persistent asthma and is indicated for all patients who wheeze more than twice a week. The dose of CCS is modified for each patient, aiming for the appropriate minimal dose effective for the patient's level of severity (Table 16). To minimize the potential adverse effects associated with inhaled CCSs use, several precautions should be taken, as shown in Table 21.

CCS are not equal nor interchangeable. Many factors go into the individual choice of CCS. For example, fluticasone is somewhat more potent than several of the other CCS, but we usually do not prescribe more than a total of 880 µg/d (Flovent 220, two puffs bid, maximum dose). On the other hand, many patients respond to fluticasone better then they do other CCS preparations. For more severe asthmatics who require higher doses of CCS, the choices are flunisolide (Aerobid, 250 µg per puff), budesonide (Pulmicort, 200 µg per puff; a DPI), and fluticasone (220 µg per puff).

For lower dose requirements, there is a wide choice of products, and the choice may be dictated by the availability of a built-in spacer (Azmacort), the desirability of using a DPI (Pulmicort), or the wish to avoid using a Freon-propelled MDI (Qvar).

Triamcinolone, flunisolide, and beclomethasone each have long safety records, whereas both fluticasone and budesonide have received enormous attention in recent

Table 21
Cautions in Using Inhaled CCSs

1. Rinse mouth after each use (brush teeth, use mouthwash).
2. Use to reach personal best peak flow rate. Consider using high doses until the peak flow readings have plateaued. Then back off to lower dose while maintaining personal best peak flow.
3. Use spacer or dry powder inhaler.
4. Maximum of twice-daily dosing.
5. Try to use "minimal effective dose."

years. In general, daily doses below 660 μg/d for fluticasone are safe over the long term. Sustained use of higher doses can be associated with glaucoma, cataracts, increased bone mineral loss, minimal linear growth rate suppression in children, and adrenal suppression, among other unwanted side effects. It is possible to minimize the systemic absorption and side-effect profile of these products by using a spacer (which reduces pharyngeal deposition and may enhance the relative fraction actually reaching the lungs in some patients), rinsing the mouth with mouthwash after each use, administering the medications on either daily or twice daily dosing frequencies, and using the lowest effective dose possible.

Beclomethasone in HFA (a substitute for Freon that is ozone-friendly) is a novel MDI that generates an aerosol consisting of smaller particle sizes than are generated by currently available CCS preparations. This new product, Qvar (40 and 80 μg per puff), achieves extraordinary deposition rates into the lungs, deep into the small airways.

A DPI, such as Diskhaler (Fluticasone/Salmeterol, Advair) and Turbohaler (Budesonide, Pulmicort), does not have propellent. In most studies, the efficacy of this delivery system is comparable to the conventional pressurized MDI. The DPI does not require a spacer.

Budesonide (Pulmicort Respule) is also available in a liquid form for nebulization. It is primarily used in young children. It can also be used in patients who have trouble using an MDI or DPI form of CCS.

One objective way to decide if the dose of inhaled CCS is adequate is to monitor the morning peak flow rates. Thus, a patient is started on a chosen dose of inhaled CCS and the peak flow is followed until it peaks and plateaus. The initial dose of CCS is either maintained or increased until the peak flow increases and plateaus at the "personal best" level. Thereafter, the dose of CCS can be reduced while monitoring the peak flow. The aim is to achieve the lowest dose of CCS that maintains the personal best peak flow.

Peak flows are also useful in the management of emergency situations by helping the physician estimate the degree of severity of an asthma attack. Finally, peak flows allow patient self-management. Each patient is shown his or her "personal best" peak flow (plateau number), and alerted as to what to do if the peak flow falls 10–20, 20–50, or more than 50% (*see* Table 22). Thus, proper use of peak flows substantially enhances the management of asthma, and many asthma specialists routinely provide peak flow meters to each of their patients.

Oral CCS therapy is used to achieve control during exacerbations, when the peak flow falls to 50% or less from the patient's personal best. Oral CCSs are also useful at the first sign of a cold or sinusitis in patients known to exacerbate under these conditions. Oral CCSs are usually considered as a treatment of last resort for those asthmatics who have

Table 22
Patient "Self-Management"

Based on personal best peak flow measurements
Peak flow falls 10-20%: double dose of inhaled CCS
Peak flow falls >20%: add short-acting bronchodilators every 4-6 h; call office (determine if infection is present)
Peak flow falls 40-50%: add oral CCS; call office
Peak flow falls greater than 50%: emergency visit
Provide written emergency management plan

CCS, cortocosteroid.

Table 23
When to Use Cromolyn or Nedocromil

1. Most useful in younger, allergic asthmatics
2. Best if used for prophylaxis. Might add after patient is well controlled with CCS, as a means to reduce CCS dose
3. Try for coughing patient
4. Try prophylactically for exercise-induced asthma
5. Try larger doses if standard dose fails (more than two puffs at a time)
6. Try nedocromil in the office. If taste is a problem, do not prescribe
7. Use nebulized form for younger asthmatics

CCS, corticosteroid.

failed to respond to other drugs, largely because of concern over the risk of serious adverse effects. Despite these concerns, if oral steroids are to be used, clinicians must be sure to give adequate doses—often 20–30 mg or more per day—for a sufficient period of time to achieve a meaningful effect. The initial daily dose can be given in single or divided doses, recognizing that divided doses are both more effective and more dangerous. Patients should be given a written schedule of their individualized treatment plan. As soon as possible after a remission is achieved, the dosing schedule should be either reduced to an alternate-day regimen or tapered off entirely.

If a patient requires frequent bursts of daily CCS, it might be more efficient to treat with alternate-day CCS—a dose one day and then none for 48 h. This alternate-day schedule reduces most of the untoward side effects of oral CCS.

Nonsteroidal Drugs: Cromolyn and Nedocromil. The nonsteroidal agents cromolyn sodium (Intal) and nedocromil sodium (Tilade) can be used to reduce the inflammatory response and mast cell reactivity in patients with asthma (Table 23). They are more useful in younger, allergic asthmatics and best used for prophylaxis. In addition, prophylactic use of these agents can prevent allergen-induced early asthmatic responses, late asthmatic responses, and the increased airway reactivity associated with these reactions. Cromolyn is used to maintain control in cases of mild-to-moderate asthma. Although the exact mechanism of action is not fully understood, cromolyn appears to stabilize the mast cell, preventing the release of mast cell mediators, and to protect against bronchospasm. Cromolyn is particularly beneficial in the younger allergic asthmatic but can also be used in adults and children with nonallergic asthma. Cromolyn causes only minimal side effects. A 4- to 6-wk trial may be required to determine efficacy in individual patients.

Table 24
When to Use Leukotriene Modifiers

1. Leukotriene receptor antagonists: Zafirlukast (Accolate, 20 mg bid on empty stomach) and Montelukast(Singulair, 10 mg qhs)
2. Try in persistent asthmatics
3. Try in aspirin-sensitive patients and patients with sinusitis, polyposis,urticaria
4. Must adjust warfarin doses (Accolate)
5. Experience indicates that about 30-50% of patients will improve with each product, some dramatically
6. May allow reduced CCS requirement

Nedocromil is similar in action to cromolyn and may be somewhat more effective. Evidence suggests that nedocromil is safe and effective in decreasing asthma symptoms and bronchial reactivity in allergic and nonallergic adult asthma patients. Both agents are categorized as pregnancy category B. Both agents can be used as first-line treatment of mild persistent asthma, especially in children, and both agents could be added to inhaled CCS in more moderately affected patients.

Cromolyn is often given to small children through nebulization and has been useful in preventing exercise-induced asthma.

Nonsteroidal Drugs: Leukotriene Modifiers. Zileuton was withdrawn from the market in 2004; leukotriene receptor antagonists will be the only leukotriene modifiers available. These products have been on the market for a few years, and experience suggests that Accolate and Singulair can be tried as monotherapy in mild disease, with about 30–50% of patients responding. Because these are oral medications and patients tend to prefer pills to inhalers, they may be worth a try in mild patients. These agents exhibit some anti-inflammatory actions and bonchodilator capacity, and they are generally quite safe. In moderate and severe asthma, both Accolate and Singulair can be added to inhaled CCS in order to allow reduction in the dose of CCS.

These products should be tried in all patients with aspirin sensitivity, and they are useful in some patients with sinusitis, polyposis, or urticaria. Because of drug–drug interactions, coumadin (Accolate) doses may need adjustment (Table 24).

Nonsteroidal Drugs: Humanized Murine Recombinant Anti-IgE (Omalizumab, Xolair). IgE is implicated as a fundamental participant in allergic asthma. Anti-IgE is a new treatment approach for asthma, especially for moderate-to-severe persistent asthma. The antibody is directed against the binding site on IgE for its high-affinity Fc receptor. Free IgE in serum will not be able to attach to the mast cells, basophils, and other inflammatory cells bearing high-affinity IgE receptors. Consequently, anti-IgE blocks the IgE medicated inflammatory processes and immune responses to allergen exposure. Omalizumab does not trigger any immune response by itself. After binding to IgE, the complexes formed as a result of treatment are small and circulate in plasma for months. No clinical evidence of complement activation or immune complex-mediated reactions has been observed in clinical trials.

Omalizumab can reduce free-serum IgE by 98–99% after intravenous or subcutaneous administration. The use of Omalizumab reduced inhaled steroid dose by at least 50%. In addition, Omalizumab can also reduce the chance of asthma exacerbation, emergency room visits, and hospitalizations. It has also been shown to improve the quality of life in

Table 25
When to Use a β-Agonist (Short-Acting)

1. With symptomatic disease, *as needed*
2. With exacerbations, at a peak flow 20% below personal best
3. Prior to exercise
4. *Do not use on a regular basis*
   Do not prescribe qid; Instead, use "as often as qid"

chronic asthmatic patients. Omalizumab is in general well tolerated. However, at the present time, because of concern about drug-related reactions, especially anaphylaxis, the administration is usually done in a physician's office. We usually observe the patients for 30 min after subcutaneous administration. The safety profile of Omalizumab may require longer-term assessment. The FDA recommends that Omalizumab be given to patients over 12 yr of age, with moderate to severe persistent asthma, who have positive skin (or blood) tests for perennial aeroallergens and whose symptoms are not adequately controlled by inhaled CCS.

Symptom Relief Agents

Short-Acting β-Adrenergic Agonists

β-Agonists (Table 25) have been available for three decades and are now the most commonly prescribed medications for asthma. This class of agents is selective for the β_2-receptor of the airway, resulting in relaxation of the airway smooth muscle and, possibly, modulation of mediator release from mast cells and basophils.

The role of β-agonists in the treatment of asthma has undergone a significant change in recent years. Once formerly considered the first-choice asthma treatment, experts now agree that these agents should be used only on an as-needed basis. This change came about in part because of concern that regular and heavy use of β-agonists might lead to increased mortality; a contention that has not been confirmed by carefully conducted prospective studies. Nonetheless, it is now recommended that β-agonists be used only when symptoms require prompt bronchodilation and that the dose and frequency of administration be as low as possible.

Generally, one canister a month (about 200 puffs, or 7 puffs per day) should be adequate for any patient (Table 26). Patients using one or more canisters a month should be considered to be inadequately controlled and should be aggressively treated with anti-inflammatory agents. β-Agonists are excellent pretreatments for the prevention of exercise-induced asthma and should be administered 10–20 min before exercise. Some patients respond better to bronchodilation with MaxAir (a breath-activated MDI) because of easier coordination between breathing and activation of the product.

There are a variety of inhaled β-agonists on the market, although albuterol is the most popular. Although albuterol is relatively fast-acting, it still takes up to 15 min to have its maximal effect. Oral β-agonists are also available, with actions that may last 4 to 8 h. In general, inhaled β-agonists are preferred because they have fewer side effects and work more quickly than do oral preparations. An alternative is the breath-activated MDI, Maxair, which removes part of the hand–eye coordination problems seen with ordinary MDIs. Proventil and Ventolin are available in the ozone-friendly propellant, HFA. A novel form of albuterol (levalbuterol, Xopenex) is available as a nebulized treatment of

Table 26
Cautions with Short-Acting β -Agonists

1. Be aware of canister use. Aim for less than one canister per month. (one canister per month is 200 puffs of albuterol, which means patient is using inhaler multiple times, every day).
2. Always ask how many times per day the β-agonist is being used before refilling prescription.
3. Consider MaxAir for patients with difficulty using a MDI.
4. Consider Proventil or Ventolin HFA, which is albuterol in HFA, an ozone-friendly propellant.

HFA,hydrofluoroalkane-134a.

asthma. The conventional albuterol has equal amounts of R- and S-albuterol. Levalbuterol is a single isomer (R-albuterol). R-Albuterol is the major bronchodilator in albuterol. When compared with racemic albuterol (a mixture of R- and S- forms), levalbuterol can achieve comparable bronchodilatory effect at much lower dose and subsequently less β-agonist-associated adverse reactions. It is claimed to be better than albuterol itself, but there are only sparse data supporting this claim. Currently, levalbuterol is only available in nebulizing solutions. It is likely a MDI form of levalbuterol will shortly become available.

Long-Acting β-Agonists

The long-acting inhaled β-agonists salmeterol xinafoate (Serevent) and formoterol fumerate (Foradil) offer 12-h duration of bronchodilation and have been shown to be effective in the treatment of mild, moderate, and severe asthma. They are indicated for patients who require multiple doses of a short-acting β-agonist despite concomitant use of inhaled CCS at appropriate doses (Table 27), for nocturnal wheezing despite appropriate treatment, and, in some cases, for prevention of exercise-induced asthma. They may also have a role in some cases of occupational asthma, as prophylaxis for patients who are intermittently exposed to irritants in the workplace. Addition of a long-acting bronchodilator to the treatment plan in moderate or severe asthma may allow reduction in the dose of inhaled CCS required.

Formoterol has a relatively faster onset of action compared to salmeterol and may be as useful as albuterol in emergency treatments. As a prophylactic bonchodilator, formoterol is quite effective. Both Serevent and Foradil are DPIs. Generally, Serevent is added to the treatment plan that includes inhaled CCS and other specific therapies. Preferred use is in the moderate or severe asthmatic to both provide symptomatic bronchodilation and reduce the need for inhaled CCS. Serevent is also available in combination with fluticasone (Advair). Recent studies indicate that the fluticasone plus salmeterol combination (Advair) offers the potential for increased clinical efficacy over concurrent use of the same doses of the same two drugs. After administration from a single inhaler, fluticasone propionate and salmeterol might codeposit in the airways. It is hypothesized that this codeposition offers an increased opportunity for synergistic interaction to occur. Budesonide and formoterol combination inhaler (Symbicort) is under investigation.

The recent results from the Salmeterol Multi-center Asthma Research Trial showed a small but significant increase in asthma-related death in patients receiving salmeterol. African Americans appeared to have a higher risk than Caucasians. The risk is higher when salmeterol is not used with an inhaled steroid. We do not recommend the use of

Table 27
When to Add a Long-Acting β-Agonist

1. When patient requires multiple inhalations of short-acting β-agonist per day despite appropriate therapy
2. When patient is experiencing nocturnal wheezing despite appropriate therapy
3. To prevent exercise-induced asthma when use of short-acting β-agonist is inconvenient
4. When patient is intermittently exposed to irritants in the environment (work exposures, fumes) as prophylaxis
5. Consider as an inhaled CCS-sparing agent, especially combined with an inhaled CCS
6. Not advisable to use without the concurrent use of inhaled steroid in persistent asthmatics
7. Can enhance the effectiveness of inhaled CCS

CCS, cortocosteroid.

Table 28
Cautions in Use of Salmeterol or Formoterol

1. Never start during exacerbations or when patient is worsening, add when patient is stable
2. Start cautiously in older patients (>60 yr old)
3. Advise patients not to carry this product, it is for prophylaxis only. Recommend that it be used in the bathroom, not when needed for emergency(except for exercise-induced asthma, when it may be used before exercise)

Serevent or Foradil alone in patients with persistent asthma, especially in African Americans (Table 28).

Theophylline

Although declining in popularity, theophylline has been used for many years as both emergency and routine therapy and is still an extremely useful symptomatic agent to treat chronic asthma. Theophylline is often recommended for patients who are not adequately controlled on other medications, those who have nocturnal diseases, and those in whom a long-acting oral bronchodilator is needed (Table 29). The recommended dose for most patients aims to achieve a blood level of 5–15 μg/mL.

Although a staple for the treatment of asthma for many years, theophylline is associated with several drawbacks. Side effects that are dose related include gastrointestinal discomfort, headache, insomnia, and seizures. In addition, use of theophylline is thought to affect behavior, mood, and learning in both adults and children; however, these possible actions are controversial. Drug–drug interactions are also of concern, with some agents increasing theophylline levels and others reducing it (Table 30). Some of the agents implicated include allopurinol, cimetidine, ciprofloxacin, erythromycin, birth control pills, and others. Despite these drawbacks, theophylline should be considered an important third-line agent in the treatment of moderate-to-severe asthma, to be used in conjunction with specific treatments and β-agonists.

Theophylline is a category B product in pregnancy and can prove very useful in asthmatics who worsen significantly during pregnancy. Appropriate serum levels of theophylline in pregnancy are 5–12 μg/mL. Studies have shown that compliance is higher with oral theophylline than with inhaled agents, especially with teenagers. Theophylline is available as once- or twice-daily sustained-release tablets.

Table 29
When to Use Theophylline

1. When patients are not adequately controlled symptomatically with short- or long-acting β-agonists plus inhaled cortocosteroid
2. With persistent nocturnal awakening
3. When a long-acting oral bronchodilator is preferred
4. Consider as an inhaled cortocosteroid-sparing agent
5. In pregnancy, when a safe long-acting bronchodilator is necessary

Table 30
Cautions With Theophylline

1. Yearly blood levels (5-15 mg/mL; <12 μg/mL if pregnant)
2. Agents that affect theophylline metabolism

Decreased clearance (*elevated blood levels*):
liver failure, >55 yr old, heart failure, high fever, <1 yr old, allopurinol, cimetidine, ciprofloxacin, erythromycin, TAO, BCP, propranolol, ketoconazole, chlorethromycin, and others

Increased clearance (*reduced blood levels*):
cigarette or marijuana smokers, phenytoin, rifampin, charcoaled foods, and others

TAO, troleandomycin.

Anticholinergics

Ipratropium bromide (Atrovent) and atropine sulfate have been the only short-acting anticholinergic drugs available in the United States for treatment of asthma. An inhaled formulation of ipratropium may be beneficial in the treatment of asthmatics with excessive mucus secretion (the asthmatic bronchitis patient) (Table 31). The availability of nebulized ipratropium has led to its increased use in emergency treatment of asthma and in patients (many of whom are children) who use nebulizers. Ipratropium is also available in combination with albuterol (Combivent MDI, or Duoneb), and the combination has more bronchodilating properties than either agent alone. Tiotropium (Spiriva), a new inhaled anticholinergic agent, has just become available for treatment of chronic obstructive pulmonary disease; its use in asthma has not been approved yet.

Treatment of Concomitant Diseases and Conditions

Many asthmatics will only respond once their concomitant sinusitis, GERD, thyroiditis, emotional stress, or pregnancy is under control. Moreover, the treatment of asthma requires close attention to concomitant colds, flu, bronchitis, environmental irritant or pollutant inhalation, recreational drug use, and emotional changes. Compliance is a significant problem, both with medication use and allergen avoidance and inhaler techniques. Thus, the physician who treats asthma needs to keep the whole patient in focus, as well as his work and family environment. On the other hand, proper treatment is nearly always effective and can be extraordinarily gratifying. It is common to convert "pulmonary cripples" into totally functioning humans in a matter of weeks.

Table 31
Anticholinergics

1. Most useful in the asthmatic with bronchitis to help reduce mucus production
2. Atrovent solution adds to β-agonist inhalation in emergency settings
3. Combivent (a metered-dose inhaler combining albuterol with ipratropium) may be useful for asthma and bronchitis (DuoNeb is one nebulized form)

The proper treatment of asthma involves a close partnership between primary care physicians (PCPs) and specialists. Referral to specialists should result in significant insights into the cause and treatment of this disease, and the patient should receive important education in allergen avoidance and medication use, as well as written emergency treatment plans. The role of immunotherapy in allergic asthmatics as a useful long-term controlling (specific treatment) influence is gaining popularity again. In today's market, most immunotherapy is started by the allergist and provided in the PCP's office. Thus, immunotherapy and allergen-avoidance techniques, much like other approaches to asthma, can be started and explained by the specialist and supported and provided by the PCP.

SUGGESTED READING

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9

Allergic Rhinitis

Diagnosis and Treatment

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Contents

SUMMARY

Allergic rhinitis is a common condition with a diverse differential diagnosis and multiple therapeutic options. Optimizing treatment by verifying the diagnosis and directing therapy to the most bothersome symptoms will result in improved quality of life.

Key Words: Nasal polyp; antihistamine; corticosteroid rhinitis; allergic rhinitis; nonallergic rhinitis; immunotherapy.

INTRODUCTION

Rhinitis is a syndrome defined by the symptoms of nasal congestion, postnasal drip, rhinorrhea, sneezing, and nasal itching, usually with physical findings of turbinate edema and increased secretions. The term implies inflammation as an essential component of the pathophysiology, but inflammation may not always be evident or confirmed in the pathophysiology of all rhinitis syndromes. Nevertheless, rhinitis is generally used to describe the constellation of symptoms listed. Classification of severity is generally based on symptom intensity and duration rather than physical examination or laboratory findings. Rhinitis may be subdivided into more than nine groups based on probable etiology or associations. These include allergic, idiopathic perennial nonallergic (sometimes referred to as vasomotor rhinitis), infectious, medication-related (medicamentosa), hormonal,

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atrophic, polypoid or hyperplastic rhinitis, and rhinitis associated with systemic diseases (Table 1). Some authorities divide nonallergic rhinitis into subgroups based on triggers,for example, weather, odor, alcohol ingestion, or irritants, but the symptoms and physical findings of these rhinitis subgroups tend to be more alike than dissimilar, prompting others to classify all into one category. Occupational rhinitis is a classification sometimes used, referring to irritant, nonallergic rhinitis or allergic rhinitis related to work environments. This chapter will focus on allergic rhinitis and includes the differential diagnosis of other rhinitis syndromes (Table 1).

PATHOPHYSIOLOGY AND SPECIFIC IGE

The pathophysiology is well defined for allergic, infectious, some medication-related, and select systemic disease-associated rhinitis syndromes. The pathophysiology of allergic rhinitis stems from the degranulation of mast cells and the subsequent mucosal recruitment of inflammatory cells, particularly eosinophils (Table 2, Fig. 1). Mast cell degranulation has been established by nasal allergen challenge, nasal lavage with analysis of mediators, nasal cytology, and nasal biopsy. Inflammation, characterized by recruitment of eosinophils into the nasal mucosa, is an essential component of the pathology of allergic rhinitis.

The symptoms of allergic rhinitis are a composite of the effects of mediators on receptors, for example, histamine with H_1 receptor or leukotrienes (LTD_4 specifically) with cysteinyl-leukotriene receptor 1, and of cell recruitment with inflammation. The mediators released from mast cells are responsible for the acute symptoms of allergic rhinitis, primarily itching and sneezing (Table 3, Fig. 2). The inflammation is primarily a result of eosinophil immigration, activation, and persistence, largely due to factors released by the mast cell. The mast cell degranulates when high-affinity immunoglobulin (Ig)E receptors are crosslinked by antigen (allergen). IgE specific for a causal allergen is bound to the mast cell, enabling the triggering of degranulation on exposure to the allergen. The production of specific IgE is a result of the complex interaction of genetic predisposition and the environment. Exposure to environmental allergens, which is a risk factor for sensitization, does not result in uniform immune responses, even in subjects with similar, or even identical, genetic backgrounds. Modulation of the IgE response is dependent on variables such as the type of allergen, the route and dose of exposure, the timing of exposure (e.g., childhood vs adulthood), and concomitant or preceding exposure to infectious organisms or adjuvants, such as endotoxin. Genetic factors affect the epitope or specific portion of the antigen to which the individual responds (some epitopes are more likely to evoke an IgE response) as well as the immunological regulation that modulates the tendency to produce IgE. Interaction between antigen-presenting cells, such as dendritic cells and B-lymphocytes, T-regulatory cells, and TH_1- and TH_2-like cells (types of helper T-cells) affect the probability of IgG antibody formation vs IgE antibody formation vs tolerance to a specific allergen. To further complicate the understanding of this process, individuals may simultaneously be sensitized and tolerant to different allergens, for example, dust mite and cat, emphasizing that antigen properties and genetic factors regulate individual antigen responses. Finally, neither the blood concentration of specific IgE nor the size of the skin test response for a selected allergen does not generally correlate with the severity of symptoms upon exposure to that allergen. Thus, a simple unifying explanation of the allergic response or a measurable parameter that will consistently predict symptoms is not available.

Table 1
Differential Diagnosis of Rhinitis

- **Allergic rhinitis**
  - Seasonal or intermittent
  - Perennial or persistent
- **Infectious rhinitis**
  - Viral
    - Adenovirus
    - Influenza virus
    - Parainfluenza virus
    - Respiratory syncytial virus
    - Rhinovirus
  - Bacterial
    - *Streptococcus*
    - *Haemophilus*
- **Structural nasal disorders**
  - Nasal septal deviation
  - Nasal polyps (Fig. 4)
  - Adenoid hyperplasia or cyst
  - Concha bullosa (Fig. 5)
  - Choanal atresia
  - Neoplasm
    - Squamous cell carcinoma (more common in cigarette smokers)
    - Angiofibroma (more common in adolescent boys)
    - Esthesioneuroblastoma (resembles a benign nasal polyp)
    - Lymphoma
    - Sarcoma
    - Inverted papilloma
  - Foreign body
  - Encephalocele
  - Ciliary defects
  - Cerebrospinal rhinorrhea
- **Other Forms of Rhinitis**
  - Atrophic rhinitis
  - Perennial nonallergic rhinitis (vasomotor rhinitis)
  - Nonallergic rhinitis with eosinophilia (NARES with or without polyps)
  - Rhinitis medicamentosa
    - Topical decongestants
      - Oxymetazoline
      - Cocaine
      - Neosynephrine
    - Systemic therapies
      - Beta blockers
      - Alpha antagonists
      - Estrogen supplements or oral contraceptives
      - Nonsteroidal antiinflammatory drugs
  - Systemic diseases
    - Endocrine/hormonal
      - Hypothyroidism
      - Pregnancy or breast feeding
      - Diabetes mellitus
    - Inflammatory
      - Sarcoidosis
      - Wegener's granulomatosis
      - Relapsing polychondritis
      - Reticular histiocytosis (lethal midline granuloma)
    - Infiltrative
      - Amyloidosis
  - Irritant rhinitis
  - Gastroesophageal reflux
  - Fungal hypersensitivity sinusitis

NARES, nonellergic rhinitis with eosinophilia.

Table 2
Mast Cell Mediators of Allergy

Mediator	*Acrion*
Preformed	
Histamine	Increases vascular permeability, Increases mucous production, Anti-inflammatory effects via H_2 receptors
Neutral proteases Tryptase(s) Chymotryptase(s) Carboxypeptidase(s)	Protein degradation and activation of protein precursors
Synthesized during cellular activation	
Leukotriene C4,D4 (LTC_4, LTD_4)	Increases vascular permeability, Increases mucous production
Leukotriene B_4 (LTB_4)	Increases neutrophil chemotaxis
Prostaglandin D_2 (PgD_2)	Smooth muscle contraction
Thromboxane A_2	Platelet aggregation, vasoconstriction
Platelet-activating factor (PAF)	Platelet aggregation, Increases neutrophil and eosinophil chemotaxis and activation, Increases vascular permeability, Smooth muscle contraction
Cytokines	
Interleukin-4	Increases endothelial expression of VCAM-4 Increases IgE production, Stimulation of TH_2 and inhibition of TH_1 lymphocytes
Tumor necrosis factor	Increases endothelial ICAM-1 expression
Interleukin-5	Activates eosinophils and basophils
Interleukin-3	Activates esoinophils and basophils, growth factor for mast cells
Granulocyte-monocyte colony-stimulating factor	Activates eosinophils and basophils, growth factor for mast cells
Select chemokines	Neutrophil, eosinophil and basophil chemotaxis, Enhance mast cell and basophil mediator release

The importance of specific IgE in the development of allergic rhinitis is confirmed by nasal challenge with allergen in subjects with specific IgE, correlation of symptoms with the level of allergen exposure, the predictive value of specific IgE in determining response to specific allergen immunotherapy, evidence of mast cell degranulation with allergen contact, and the improvement of allergic rhinitis with anti-IgE monoclonal therapy. Local production of IgE, which would not be recognized by blood or skin tests, and non-

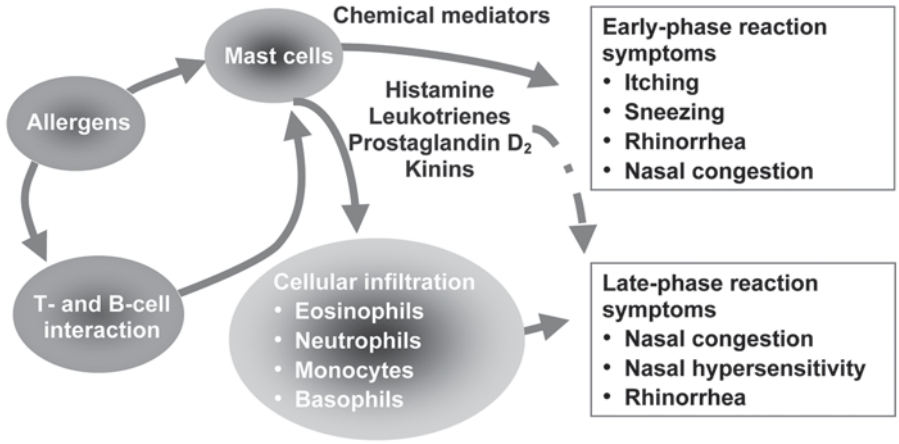

Fig. 1. Mechanisms of allergic reaction: Allergen is processed and presented to T-cells via dendritic cells or macrophages or B-cells. The T-cell response is regulated by a network of regulatory T-cells and by the concentrations of a variety of cytokines secreted by cells involved in the immune response. In allergy-prone subjects (atopic subjects), the tendency to produce IgE specific for the allergen is increased. The IgE is made by B-cells, which transform into plasma cells. The IgE is bound to mast cells and basophils via a high-affinity receptor for IgE. Upon subsequent exposure to allergen, the mast cells degranulate and release chemical mediators responsible for the early-phase reaction and recruit inflammatory cells, which are largely responsible for the late-phase reaction. The dashed arrow indicates that some of the mediators released or created by the mast cell during degranulation, particularly leukotrienes and kinins, contribute to the late-phase reaction. Itching, sneezing, and watery rhinorrhea are the predominnt symptoms in the early-phase reaction, whereas congestion and mucoid nasal discharge or rhinorrhea are the predominant symptoms in the late-phase *reaction*. (From Fineman S. In: Lieberman PL, Blaiss MS, eds. Atlas of Allergic Diseases. Philadelphia: Lippincott Williams & Wilkins; 2002:113.)

IgE mechanisms of mast cell degranulation are hypotheses offered to explain allergic-like rhinitis in subjects without measurable specific IgE.

EPIDEMIOLOGY

The prevalence of atopic disease in general and of allergic rhinitis in particular has increased during the past century. Currently, the prevalence of allergic rhinitis is approx 30%, increased from approx 10–15% at the mid-point of the 20th century. The increase is more apparent in affluent socioeconomic circumstances, particularly western Europe, North America, Australia, and New Zealand. Explanation for this increase remains elusive, with a variety of hypotheses (summarized in Table 4). The hygiene hypothesis, as first suggested by Salzman and colleagues in 1979, is probably the most widely accepted explanation. This hypothesis proposes that reduced infections and endotoxin exposure in infancy diminishes the stimuli to convert the TH_2-like immune response (allergic-like with a predominance of interleukin [IL]-4 and IgE production) present at birth to a TH_1-like response (nonallergic with interferon-γ production and reduced IgE). The endotoxin association suggests that the innate immune system and Toll-like receptors are important in the conversion of TH_{2-} to TH_1-like immune responses. The data supporting this are

Table 3
Allergy Symptoms and Responsible Mediators

Symptom	*Mediator*
Itching/sneezing	Histamine
	Prostaglandins
Nasal blockage/	Histamine
microvascular leakage	Prostaglandins
	Leukotrienes
	Platelet-activating factor
	Kinins
	Chymase
	Substance P
Mucous secretion	Histamine
	Leukotrienes
	Platelet-activating factor
	Kinins

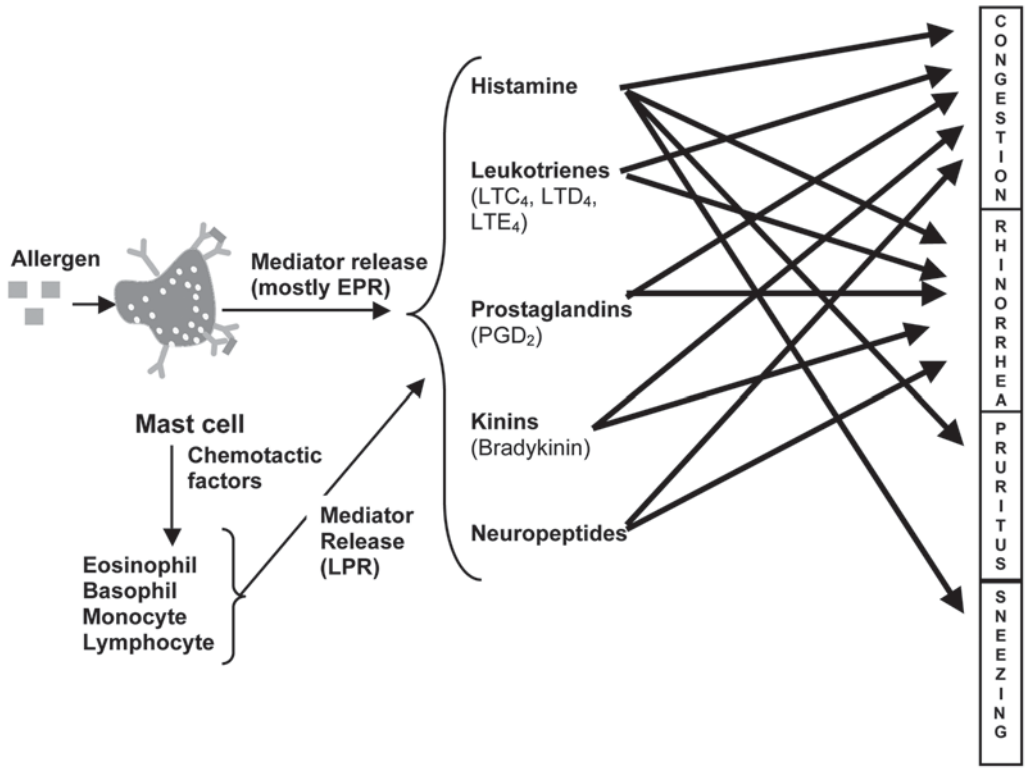

Fig. 2. Meditors responsible for symptoms of allergic rhinitis. Symptoms result from a variety of mediators and the inflammatory effects of cell recruitment from chemotactic factors. The redundancy of causal mediators and mechanisms is one explanation for the failure of single mediator inhibitors, such as antihistamine therapy, to control the complex symptoms of allergic rhinitis, particularly congestion and rhinorrhea, which result from multiple mediators. In contrast, pruritus and sneezing are more dependent on histamine, and therefore antihistamine therapy is more effective for these symptoms. LPR, late-phase reaction. EPR, early-phase reaction.

Table 4
Proposed Explanations for the Increase in Atopic Disease During the Twentieth Century

- Reduction in family size with fewer older siblings
- Urbanization with reduced exposure to farm animals and endotoxin
- Fewer serious infectious illnesses in infancy due to cleanliness, antibiotics and vaccination
- Change in enteric bacterial colonization because of diet or urbanization
- Modification of diet with either increase in calories or decrease in protective nutrients
- Increased exposure to diesel particles or other pollutants common in urban environs
- Stress
- Increased time indoors with greater exposure to potent indoor allergens
- Increased exposure to prenatal and/or postnatal passive cigarette smoke
- Reduced breast-feeding and earlier age of introduction of solid foods
- Obesity

found in both epidemiological studies as well as experimental work. For example, urban children with similar ethnic and genetic backgrounds to those in rural, farming areas have a higher occurrence of allergic rhinitis. Furthermore, the occurrence of allergic rhinitis correlates inversely with exposure to farm animals and to endotoxin in early childhood. Conflicting data are a reminder that the hygiene hypothesis is not proven, and additional explanations for the increased prevalence of allergic rhinitis are likely.

There is a bimodal variation in the prevalence of allergic rhinitis with age, with one peak occurring in either the mid- to late teenage years or late childhood and the second peak occurring in the mid-20s. Most affected subjects initially develop symptoms prior to adulthood. However, approx 20% of individuals with allergic rhinitis report symptom onset after the age of 30 yr. The prevalence of allergic rhinitis diminishes progressively as the population ages.

The importance of allergic rhinitis is its impact on the quality of life in up to 30% of the population. Individuals with symptomatic allergic rhinitis do not learn or process information as well as those unaffected. Sleep quality and sense of vitality are also commonly adversely affected. The treatments utilized, particularly sedating or first-generation antihistamines, may compound these problems. Allergic rhinitis is also associated with a variety of other airway diseases or symptoms, including otitis media, sinusitis, cough, and asthma, and with other allergic conditions, including atopic dermatitis and food allergy. Treatment of allergic rhinitis improves asthma and may reduce the development of asthma in those predisposed. Treatment of rhinitis may also decrease other associated conditions, including sinusitis, otitis media, and sleep disturbance. Thus the importance of diagnosing and treating allergic rhinitis extends beyond the simple relief of nasal complaints.

CLASSIFICATION OF ALLERGIC RHINITIS

Traditionally, allergic rhinitis has been separated into perennial allergic rhinitis (responsible allergens found indoors, such as dust mites, dogs, and cats) with year-round symptoms or seasonal allergic rhinitis (responsible pollen allergens found seasonally outdoors, such as trees in the spring, grass in the summer, and weeds in the fall in temperate climates in the Northern Hemisphere). The Allergic Rhinitis and its Impact

on Asthma (ARIA) Workshop, in collaboration with the World Health Organization, recommended a different classification, using the terms intermittent and persistence and the severity classifications of mild, moderate, and severe. Intermittent is defined as having symptoms for less than 4 wk of the year. Mild is defined as not affecting quality of life. Most subjects who seek medical care are expected to be in the moderate to severe persistent category, because over-the-counter products are available for treatment of less severe disease. Published studies report that the ARIA classification is more useful in clinical assessments than the seasonal and perennial terminology, suggesting that persistent rhinitis as defined is not equivalent to perennial rhinitis and intermittent is not equivalent to seasonal. Both classifications are used clinically and in the medical literature.

DIFFERENTIAL DIAGNOSIS

Allergic Rhinitis

Allergic rhinitis is the most prevalent form of rhinitis and should be considered in any individual presenting with nasal complaints. Other possible diagnoses are listed in Table 1. The principal factors utilized in distinguishing allergic rhinitis from the other conditions are summarized in Tables 5 and 6, with history being the most important. The diagnosis of allergic rhinitis is presumptive until specific allergic sensitivity is identified by epicutaneous or percutaneous testing or in vitro specific IgE testing. Immediate wheal and flare skin tests remain the most cost-effective means of identifying specific IgE. The value of intradermal allergy testing is primarily to exclude the diagnosis with negative results, with positive intradermal results providing only tenuous support of a diagnosis of allergic rhinitis. The evidence of specific IgE should be correlated with exposure and symptoms to support the diagnosis. Identifying environmental factors that trigger nasal symptoms is important in distinguishing allergic rhinitis from nonallergic or mixed rhinitis (components of both allergic and nonallergic rhinitis). For example, worsening symptoms from odor would be attributed to nonallergic rhinitis, rather than allergic. If odor affects symptoms in a subject with allergic rhinitis, the individual has mixed rhinitis (i.e., coexistence of two rhinitis syndromes).

Congestion is the most common symptom prompting physician evaluation of nasal complaints but is nonspecific (Fig. 2, Table 6). Itching, particularly with rubbing of the nose vertically, is typical of allergic disease. The repetitive rubbing results in the characteristic "nasal crease" of allergic rhinitis (Fig. 3). Additional supportive historical features for allergic rhinitis include rubbing the tongue on the roof of the mouth producing a "clucking" sound and paroxysmal or episodic sneezing, particularly four or more in succession. Itching and sneezing are more common with intermittent or seasonal than with persistent or perennial allergic rhinitis. The less frequent, discriminating symptoms of itching and sneezing in perennial or chronic allergic rhinitis result in more difficulty in distinguishing persistent allergic rhinitis from other nasal disorders. The secretions in allergic disease typically are clear or white, but severe disease may result in cloudy mucus. Allergic rhinitis symptoms should be bilateral, with lateralizing complaints or findings suggesting an alternative diagnosis or a complication. The presence of other allergic diseases, particularly allergic conjunctivitis or atopic dermatitis, would also be strong support for the diagnosis of allergic rhinitis. Finally, family history is important, since one immediate family member increases the likelihood of allergic rhinitis to approx

Table 5
Factors Utilized in Identifying and Diagnosing Allergic Rhinitis

- History of seasonal or situational environments with suspected allergens triggering symptoms
- Positive family history of atopic disease in first-degree relatives
- Personal history of atopic dermatitis or asthma or food allergy
- Onset prior to middle age of adulthood
- Evidence or history of allergic conjunctivitis
- Predominance of itching and sneezing, particularly vertical rubbing of face and cluster sneezing (four or more)
- Clear nasal discharge, often copious, and usually watery
- Nasal mucosa pale or at least nonerythematous
- Nasal crease reflecting the constant rubbing of the face (Fig. 3)
- Identification of specific IgE for allergens associated with symptoms (skin testing or in vitro IgE testing)

Table 6
Distinguishing Allergic Rhinitis From Nonallergic Rhinitis

Feature	*Allergic rhinitis*	*Nonallergic rhinitis*
Age of onset	Usually prior to 20 yr (20% after the age of 30 yr)	Usually after 30 yr
Family history	Positive for atopic disease	May or may not be positive for "sinus," negative for asthma and allergic rhinitis
Seasonal pattern	Variable but may be related to major seasonal changes particularly dependent on predominant pollinating plants	No specific seasonal pattern, but weather change or barometric pressure changes may affect symptoms, which may be confused with seasonal pattern
Primary triggers	Allergen exposure	Odor, irritants, body position change, weather change, alcohol ingestion
Primary symptoms	Sneezing paroxymsms (4 or more in succession), itching, congestion, clear rhinorrhea	Congestion, mucoid to watery nasal discharge, postnbasal drip, facial pressure, sneezing 2–3 times in succession (not more than 4)
Other atopic features	Allergic conjuctivitis, atopic dermatitis, or history of same	None, althought dry eye or blepharitis may be reported and confused with allergic conjunctivitis, nonspecific dry skin confused with atopic dermmatitis
Physical exam	Transverse nasal crease, mucosa variable but classically pale and watery or boggy	Erythematous with turbinate edema and mucoid or watery secretions
Confirmatory tests	Nasal eosinophilia, specific IgE for allergens which correlate symptoms, blood eosinophilia, increased blood IgE (normal in 20–30% of affected subjects)	Negative tests for specific IgE or no correlation with positive tests and symptoms, eosinophilia only in nonallergic rhinitis with eosinophilia

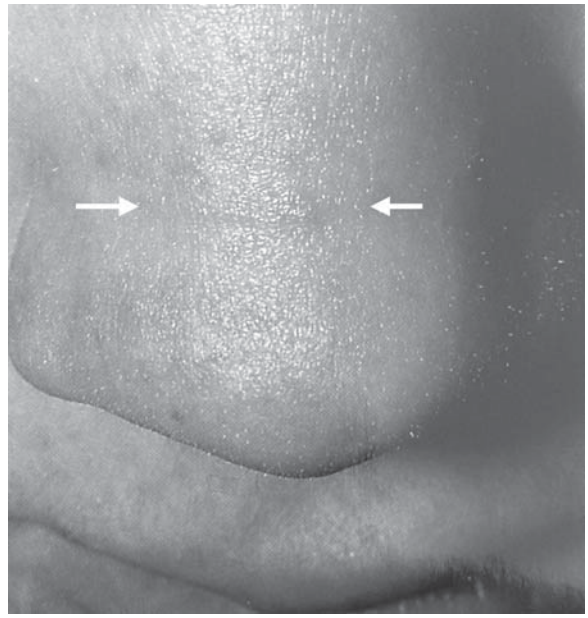

Fig. 3. The transverse nasal crease (arrows) characteristic of allergic rhinitis. This linear change results from repetitive rubbing of the nose vertically, pushing the tip of the nose cephalad. Identifying such a crease in a family member of a patient is a useful feature supporting a positive family history of allergy.

40–50%. Having two affected immediate family members makes the probability of having allergic rhinitis greater than 60%.

Treatment of allergic rhinitis will be reviewed in the next section.

Perennial Nonallergic Rhinitis

Perennial nonallergic rhinitis (PNAR) is a term used to designate a heterogeneous group of disorders that share clinical features. The pathophysiology is not completely defined, and nasal histology does not correlate with symptoms. PNAR is common, representing 30–60% of subjects referred to an allergy/immunology or otolaryngology clinic for evaluation. PNAR coexists with allergic rhinitis in more than 50% of adults with allergic rhinitis, a condition referred to as mixed rhinitis. Mucosal inflammation is less evident in PNAR than in allergic rhinitis, making the term rhinitis sometimes a misnomer. However, the symptoms are consistent with other inflammatory nasal disease, and inflammation may be present in a subset of PNAR.

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

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

The diagnosis of PNAR is suggested by the symptom history, the nature of provoking stimuli, and absence of a family history of allergy. The nasal mucosa is variable in appearance but generally is congested with normal to erythematous color. The secretions are usually clear and do not contain a significant number of eosinophils or neutrophils. Other causes of nasal symptoms should be excluded because of the lack of a confirmatory diagnostic test for PNAR. The exclusion of perennial allergic rhinitis is particularly important since the symptoms of the two are similar and some subjects have both conditions (Table 6). Sinusitis should also be considered because many symptoms are common to both.

The treatment of PNAR is symptomatic in that the pathophysiology is usually unknown. The physician should focus the therapy on the primary symptom. Decongestants, nasal saline to lavage irritants from the mucosa or dilute secretions, and topical ipratropium bromide 0.03% (Atrovent® Nasal) for rhinorrhea are often helpful. Oral antihistamine therapy offers limited benefits, although the anticholinergic effects of first-generation sedating antihistamines may be helpful for rhinorrhea. Topical antihistamine therapy with azelastine is efficacious and approved for treatment of PNAR, contrasting with the lack of any oral antihistamines being approved. Topical, nasal corticosteroid therapy relieves symptoms of PNAR, probably by reducing glandular secretion and blood flow to the nose, since mucosal inflammation is not consistently present. The response to topical nasal corticosteroids is variable and not as predictable as with allergic rhinitis. Although only select nasal corticosteroids have a US Food and Drug Administration (FDA) indication for nonallergic rhinitis, most likely all work and all are generally used. Nasal corticosteroids with a detectable odor,for example, beclomethasone (Vancenase AQ®) or fluticasone (Flonase®), may aggravate symptoms, suggesting a preference for sprays without smell. Regular aerobic exercise, 20–30 min two to three times a week, may help reduce symptoms, at least temporarily, and is good for general health. Nasal congestion and sinus pressure are often the most bothersome symptoms, so emphasis on avoidance of regular, topical decongestants is important as this may lead to rhinitis medicamentosa. Oral lozenges containing menthol may affect the perception of nasal congestion but have no measurable effect on congestion. Finally, affected subjects need reassurance and sensitive care to reduce "doctor shopping," unnecessary surgery, overuse of antibiotics, and overinterpretation of allergy tests.

Nonallergic Rhinitis with Eosinophilia

Nonallergic rhinitis with eosinophilia (NARES) is a syndrome that is generally distinguished from PNAR by the presence of eosinophils in the nasal secretions or mucosa. The symptoms cannot be distinguished from PNAR, and the family history is generally negative, increasing the clinical confusion between NARES and PNAR. Affected subjects are

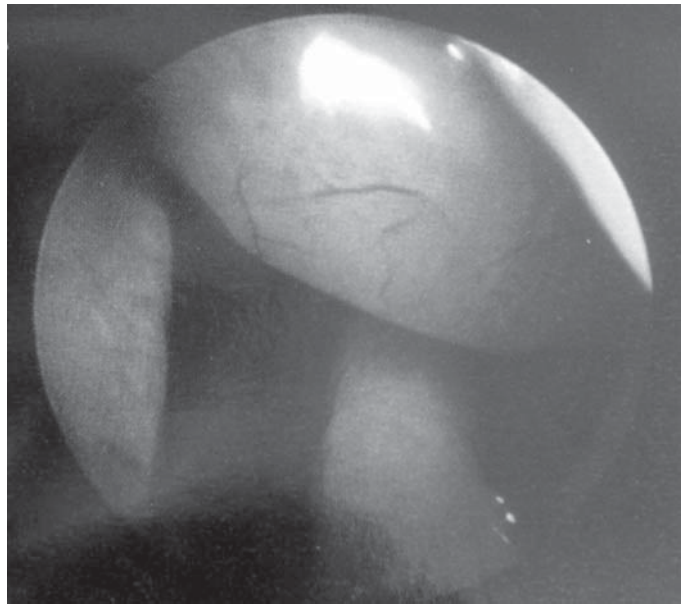

Fig. 4. Nasal polyp: view from the rhinoscope in the left nostril. The septum is on the left and the polyp is the pale soft tissue between the middle and inferior turbinate. Nasal polyps are associated with chronic inflammatory sinus disease, usually eosinophilic. Nasal polyps are not consistently found in subjects with allergic rhinitis but could explain persistent congestion. Cystic fibrosis is also associated with nasal polyps, although not generally with eosinophilic inflammation.

described as suffering from perennial nasal congestion, rhinorrhea, sneezing, and pruritus but do not have specific IgE for allergens, an increase in total IgE, or a personal or family history of atopy. The nasal secretions contain eosinophils, which distinguishes this condition from other forms of PNAR. The lack of an atopic personal and family history in NARES makes an undefined allergy unlikely as the cause. The condition may be part of the spectrum of eosinophilic rhinitis and nasal polyposis. Subjects with aspirin triad (nasal polyps with eosinophils, asthma, aspirin sensitivity) experience eosinophilic rhinorrhea and nasal congestion prior to the development of nasal polyps, suggesting a spectrum of eosinophilic nasal disease (Fig. 4). However, most subjects with NARES do not develop aspirin triad.

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

Rhinitis Induced by Drugs or Hormones (Rhinitis Medicamentosa)

Topical use of α-adrenergic decongestant sprays for more than 5–7 d in succession may result in a rebound nasal congestion upon discontinuation of treatment or after the immediate effects have waned. Continued use of the decongestant to control withdrawal

congestion can lead to an erythematous, congested nasal mucosa termed rhinitis medicamentosa. Regular intranasal cocaine use will have the same effect and should be considered in the differential diagnosis. Other systemic medications or hormone changes may also be associated with nasal symptoms, although the nasal mucosa may not always appear the same with each medication.

The mechanisms responsible for nasal symptoms associated with medications or hormones are variable. Antihypertensive therapies with β-blockers and α-adrenergic antagonists probably affect regulation of nasal blood flow. Oral α-adrenergic antagonists are also commonly utilized for symptom relief of prostate enlargement. Topical ophthalmic β-blocker therapy may also result in nasal congestion by the same mechanism. Nasal congestion and/or rhinorrhea may also result from changes in estrogen, and possibly progesterone, either from exogenous administration, pregnancy, or menstrual cycle variations. Hypothyroidism is associated with nasal congestion, rhinorrhea, and a pale, allergic-like nasal mucosa. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may result in congestion and rhinorrhea, primarily in subjects with aspirin triad. Subjects with intermittent symptoms associated with aspirin or NSAIDs may be part of the evolving spectrum of chronic, eosinophilic rhinosinusitis with nasal polyps (*see* NARES). The primary treatment of rhinitis medicamentosa is discontinuation of the offending agent or correction of the hormonal imbalance, if possible. Symptomatic treatment may be helpful. Treatment of rebound nasal congestion associated with topical decongestant use may require 5–7 d of oral prednisone or equivalent, 20–30 mg/d, followed by topical intranasal corticosteroid therapy. Reassurance that the nasal symptoms are the result of the medications or hormonal changes may be sufficient to discourage other unnecessary investigations if the treatments causing the rhinitis are essential.

Atrophic Rhinitis

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

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

Symptomatic treatment of atrophic rhinitis with low-dose decongestants and nasal saline lavage is minimally effective. Individuals with confirmed sicca complex, or Sjögren's syndrome (Table 7), may benefit from oral cevimeline 30 mg three times a day, keeping in mind that bronchospasm and arrhythmias are potential side effects. Oral antibiotic therapy is necessary for ozena. Topical antibiotic therapy, such as gentamycin or tobramycin 15 mg/mL or ciprofloxacin 0.15 mg/mL in saline, may offer some benefit for subjects with atrophic rhinitis and recurrent mucosal infections or sinusitis, although there are no studies to validate this treatment. An over-the-counter topical treatment

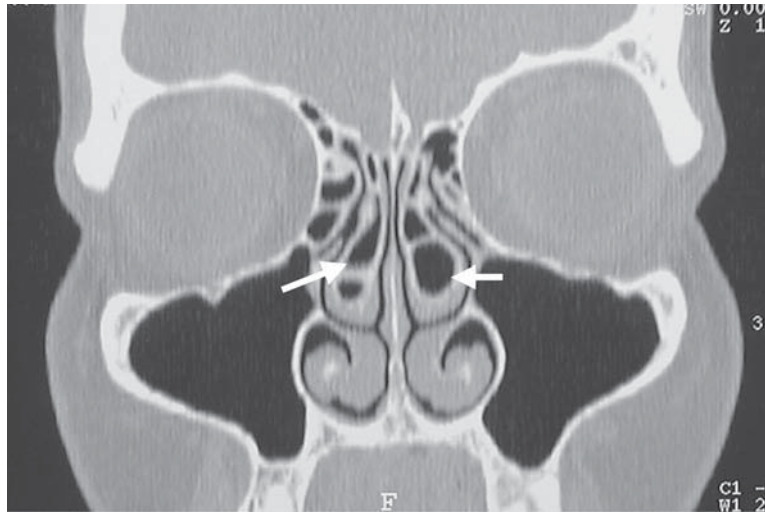

Fig. 5. Concha bullosa: coronal computed tomography scan image of the paranasal sinuses. The arrows point to the concha bullosa in each middle turbinate. In this case, septae divide the concha bullosa into more than one air space. The usual result of the cocha bullosa is enlargement of the turbinate, usually resulting in chronic nasal congestion. Infection may occur in the concha bullosa. Frequently the septum is deviated away from a unilateral concha bullosa. Therefore, this entity should be considered in a patient complaining of chronic congestion.

reported to reduce bacterial colonization, Sino Fresh®, is another consideration. No clinical trials support this agent in atrophic rhinitis; thus, a treatment trial is in reality a trial and benefits may be the result of the lavage, at a much greater cost than saline. The addition of proplylene glycol, 3–15%, or glycerin to nasal saline may prolong the benefits of topical moisturization by reducing the water's surface tension or reducing the irritation from irrigation. Application of petrolatum or petrolatum with eucalyptus/menthol (Vicks® ointment) to the nasal mucosa at night may help reduce nasal bleeding. Topical shea butter (Butterbar), an over-the-counter herbal therapy, also may be of some benefit but is unproven.

Rhinitis Associated With Systemic Diseases or Anatomical Defects

The presence of systemic findings or the persistence of nasal symptoms despite treatment should prompt consideration of systemic diseases or anatomical problems resulting in nasal symptoms. Structural problems typically will present with a predominance of unilateral symptoms or initially unilateral symptoms. Nasopharyngoscopy, paranasal computed tomography, and/or otolaryngological consultation are major considerations with lateralizing nasal complaints or bleeding noted from one nasal airway or unremitting congestion (Fig. 5). Nasal septal deviations are the most common anatomical nasal variants noted, but often septal deviation is not primarily responsible for the symptoms unless very severe or coupled with mucosal disease such as allergic rhinitis or PNAR. Profuse rhinorrhea should prompt testing of the secretions for glucose or for β_2-transferrin (β-trace protein) to exclude cerebrospinal fluid rhinorrhea.

Table 7
Laboratory Tests for Systemic Diseases Associtated with Nasal Symptoms

Test	*Diagnoisis*
Erythrocyte sedimentation rate	Wegener's granulomatosis Relapsing polychondritis Sarcoidoisis
Delayed-type hypersensitivity testing	Tuberculosis
VDRL test	Syphilis
Sweat chloride	Cystic fibrosis
Cystic fibrosis transmembrane regulator genotyping	Cystic fibrosis
Antineutrophil cytoplasmic antibody	Wegener's granulomatosis Churg Strauss vasculitis
Angiotension-converting enzyme level	Sarcoidosis
Quantitative immunoglobulins	Common variable immunodeficiency IgA deficiency
Thyroid-stimulating hormone	Hypothyroidism
ANA, anti-Ro (SSA), anti-La (SSB)	Sjögren's syndrome
Schirmer tear test[a]	Sjögren's syndrome
Saccharine Taste Test[b]	Immotile cilia syndrome

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

[b]Saccharine is placed with a cotton swab on the inferior turbinate, at the junction of the anterior and middle thirds of the turbinate. The time required for tasting is recorded, with normal usually less than 20 min. Greater than 30 min before tasting is considered indicative of dysfunction of ciliary motility. The patient must be instructed to not sniff, blow the nose or use any toopical nasal therapies during the test. (Stanley P, MacWilliam L, Greenstone M, et al. Efficacy of a saccharine test for screening to detect abnormal mucociliary clearance. Br J Dis Chest 1984;78:62. Corbo GM, FGoresi A, Bonfitto P, et al. Measurement of nasal mucociliary clearance. Arch Dis Child 1989;64:546.)

Wegener's granulomoatosis may present initially with upper airway complaints, particularly hearing loss, intractable sinusitis, and persistent nasal congestion associated with purulent or bloody nasal discharge. Sarcoidosis of the nasal airway may appear similarly, although not usually as necrotizing. Persistent sinusitis or recurring infectious complications should prompt consideration of cystic fibrosis, partially cleft or submucosal cleft palate, humoral immunodeficiency, or ciliary dysfunction. Table 7 lists potentially useful tests to discriminate among the systemic possibilities.

TREATMENT OF ALLERGIC RHINITIS

The treatment of allergic rhinitis is three-pronged—allergen exposure modification or avoidance, allergen immunotherapy (allergy shots), and/or pharmacotherapy (Fig, 6, Table 8). Clinical studies confirming efficacy of various therapies utilize symptoms as primary outcome variables. More objective means of assessing allergic rhinitis have been somewhat useful but have not supplanted symptom scores in clinical trials. These other methods include acoustic rhinometry, rhinomamometry, nasal peak flow, nitric oxide

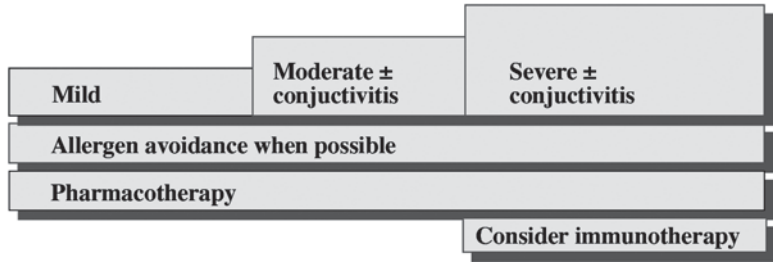

Fig. 6. Treatment strategies for allerigic rhinitis based on severity of rhinitis.This approach is suggested by the World Health Organization ARIA (Allergic Rhinitis and Its Effect on Asthma) report. Pharmacotherapy and allergen avoidance are the initial approach to allergic rhinitis, with the severity of the rhinitis usually modifying the pharmacotherapy. Oral antihistamine therapy is used for mild disease and topical nasal corticosteroid therapy, with or without oral antihistamine therapy, in moderate to severe disease. Topical azelastine, oral montelukast, or oral decongestants are considered either as add-on treatment or occasionally as monotherapy in the case of azelastine. Specific immunotherapy is generally reserved for more severe, persistent disease. (Adapted from WAO ARIA report.)

levels in exhaled air, concentration of mediators in nasal lavage, nasal cytology, and nasal histology. These objective methods show promise but difficulties with reproducibility, necessity of patient cooperation or mastering technique, sampling error, and cost combine to reduce their utility. Using symptoms scores as the primary outcome variable limit the ability to compare treatments as the magnitude of response is not always consistent from study to study.

Allergen Avoidance

Avoidance is primarily helpful for indoor, domestic allergens, although occasionally modifiable occupational exposures, such as animal contact or colophony fumes during soldering, may be effective. Indoor avoidance focuses primarily on dust mite allergen reduction (encasing the pillow, mattress, and box springs with a material that does not allow dust mite migration) and washing all bedding in water at a temperature greater than 130°F (Table 9). Washing removes the allergen, which is primarily digestive enzymes present in dust mite excrement. The hot water is essential to control dust mite populations, the source of the allergen. Studies to show benefit of dust avoidance have failed when hot water washing was not assured. Air filter systems probably do not have a significant role in allergen avoidance, although high-efficiency particulate air (HEPA) filters may be helpful for homes with animals and possibly help with indoor mold spore reduction. Very little data support the use of filtration.

Allergen Immunotherapy

Specific allergen immunotherapy provides a 50% reduction in medication and symptoms if sufficient doses of the major allergens are administered to significantly (epicutaneous or percutaneous positive skin tests) allergic subjects. This improvement is confirmed by the majority of controlled trials with immunotherapy in both seasonal and perennial allergic rhinitis. Laboratory tests and challenge studies, in general, correlate with the clinical findings. The most consistent humoral change is an increase in specific IgG, with some studies showing a switch from specific IgG1 to IgG4 (Table 10). However, the many exceptions indicate that there is not a specific confirmatory test to

Table 8
Stepwise Approach to the Treatment of Seasonal Allergic Rhinitis

Allergen avoidance and pharmacological therapy	
Mild disease or with occasional symptoms	• Oral nonsedating H_1-antihistamine when symptomatic (desloratidine, fexofenadine, loratidine, or possibly cetirizine)[a] OR • Topical nasal azelastine when symptomatic or sodium cromoglycate to eyes, nose, or both/alternative for intermittent eye symptoms is topical ocular antihistamine or topical nonsteroidal antiinflammatory (ketoroloac tromethamine)[b]
Moderate disease with prominent nasal symptoms	• Intranasal corticosteroid daily (start early in season) PLUS • Antihstamine or topical eye therapy with sodium cromoglycate or lodoxamide tromethamine or olopatadine hydrocholoride[b]
Moderate disease with prominent eye symptoms	• Oral nonsedating H_1-antihistamine daily[a] OR • Intranasal corticosteroid and topical eye therapy with sodium cromoglycate or lodoxamide tromethamine or olopatadine hydrocholoride/topical nonsteroidal antiinflammatory (ketoroloac tromethamine) additional therapy for exacerbations[b]
If above ineffective	• Review possibility of coexisting disease or complications (e.g., sinusitis) • Consider immunotherapy • Systemic corticosteroid therapy for a few days for severe symptoms • Topical ipratropium bromide if rhinorrhea a major problem
Perennial allergic rhinitis in adults	• Allergen avoidance • Intranasal corticosteroids if long-term exposure
Intermittent disease	• Oral nonsedating H_1-antihistamine therapy[a] • Oral decongestants

[a]Sedating, traditional (first-generation) antihistamine therapy is a consideration because of cost of second-generation antihistamines. However, functional impairment occurs with first-generation antihistamine therapy even if treated subjects do not perceive impairment. Therefore, it is difficult to evaluate the risk–benefit ratio, and a treating physician may be at legal risk if any accident occurs while a patient is being treated with a sedating antihistamine without first trying nonsedating antihistamine therapy. Fexofenadine, loratidine, and desloratidine are safe, effective, nonsedating antihistamine therapies that have almost no side effects. There is no concern with combining these treatments with other therapies, including macrolide antibiotics and azole antifungals. Cetirizine is mildly sedating, with clinical trial results variable as to the importance of this sedation. Oral antihistamine therapy achieves approx 30% improvement in 50% of treated subjects. Azelastine (a topical antihistamine therapy for rhinitis) is also mildly sedating, but some authorities debate the clinical significance of this effect. Azelastine topical is indicated for nonallergic rhinitis, an indication not shared by any oral antihistamine. This point supports a mechanism of action that may be unique for azelastine topical.

[b]Topical ocular therapy is not recommended with contact lens use.

Table 9
Allergen Avoidance Measures

Avoidance measures for mite allergen
Bedrooms
• Cover mattresses and pillows with impermeable covers
• Wash bedding regularly at 130° F
• Remove carpets, stuffed animals, and clutter from bedrooms
• Eliminate wall-to-wall carpet
• Vacuum clean weekly (wear a mask or use a high-efficiency particulate air (HEPA) filtered vacuum cleaner
Rest of house
• Minimize carpets and upholstered furniture (particularly in basements or overlying concrete)
• Reduce humidity below 45% relative humidity or 6 g/kg (may not be feasible in many climates)
• Consider treatment of carpets with benzyl benzoate powder or tannic acid spray (questionable efficacy)
Avoidance measures for cat allergen
Remove cat from the house (allergen reduction sufficient to affect symptoms may take >12–16 wk)
Measures to reduce allergen if cat remains in home (limited if any efficacy)
• Minimize cat contact with carpets, upholstered furniture, and bedding
• Use vacuum cleaners with an effective filtration system
• Increase ventilation
• Consider a HEPA system to remove small airborne particles
• Consider washing cat every 2 wk

demonstrate clinical benefit. Symptom improvement remains the standard response variable.

Advantages of allergen immunotherapy in addition to symptom improvement are that the treatment may reduce the future development of additional sensitivities and minimize the occurrence of asthma in subjects with allergic rhinitis. Pharmacotherapy is not likely to achieve these goals. Finally, immunotherapy offers the potential of treating allergic airway disease beyond the nose with improvement in allergic conjunctivitis and/or asthma. Duration of allergen immunotherapy is based on clinical experience and limited evidence. In general, 3–5 yr of maintenance treatment, usually administered every 3–4 wk, is necessary to minimize reoccurrence of symptoms after discontinuation.

The major impediments to allergen immunotherapy are the inconvenience and cost of the therapy and risk of anaphylaxis. Analyses have shown that high-dose allergen immunotherapy is cost-effective because of the reduction of regular medication use. Anaphylaxis following immunotherapy occurs in 0.1–3% of treated subjects. This risk, which is minimized by identification and treatment of anaphylaxis, requires that allergen immunotherapy be administered under the immediate supervision of a physician or provider trained in the treatment of anaphylaxis. Treated subjects should remain under

Table 10
Mechanisms of Action of Immunotherapy

- Increase in T-suppressor activity
- Modulation of T-regulatory cells
- Decrease in histamine-releasing factors
- Increase in specific IgG
- Decrease in specific IgE
- Decrease in mediator release from basophils

observation for 20–30 min after receiving subcutaneous allergen immunotherapy to minimize risk after departure.

The indications for allergen immunotherapy include severe symptoms, poor response to medications, intolerance to, or side effects from medications or reluctance to take medications (Fig. 6). Relative contraindications include uncontrolled asthma, β-blocker therapy, autoimmune disease, and malignancy. Immunotherapy should be initiated and supervised by a trained specialist but can be administered by any physician who is prepared to treat anaphylaxis, the most serious adverse effect of the treatment.

The risk and inconvenience of allergen immunotherapy have stimulated the study of oral allergen immunotherapy. This technique has been utilized in the past but the dose of allergen administered was inadequate for double-blind, controlled trials to demonstrate efficacy. In the past 10 yr, a series of investigations have shown clinical improvement with high-dose oral immunotherapy. Side effects do occur, but these tend to be less severe than with injection immunotherapy and localized to the mouth and gastrointestinal tract. The advantages of home administration, the minimized risk of anaphylaxis, and the relatively rapid attainment of the maintenance dose and clinical improvement make this treatment attractive. The disadvantages are the requirement for a very large dose of allergen vaccine, probable reduced efficacy compared to injection treatment, less evidence of efficacy in children, and limited evidence for long-term disease modification. Nevertheless, sublingual allergen immunotherapy may be a consideration for select patients at risk for anaphylaxis or in circumstances not permitting regular visitation with a physician to administer immunotherapy. This treatment is not currently approved in the United States.

Pharmacotherapy

Pharmacotherapy may be divided into two broad classes—topical or oral (Table 8). Advantages of topical therapy are greater efficacy for nasal complaints and limited toxicity. Patient nonacceptance because of nasal irritation or taste is the major objection. Advantages of oral therapy include the potential to address the systemic nature of the allergic response and greater patient acceptance compared to sprays.

Topical Therapy of Allergic Rhinitis

Topical corticosteroids offer 70% improvement in approximately three-fourths of treated subjects with allergic rhinitis, making this option statistically the most efficacious (Table 8). In addition, topical nasal corticosteroids will improve nonallergic rhinitis and subjects with nasal polyps, conditions that typically do not respond to oral therapy other than corticosteroids and decongestants. Response with topical corticosteroids may occur

within 7–12 h, but maximum effect requires days to weeks. Differences among the various products are minimal, although the newer agents (fluticasone, mometasone) have a greater first-pass clearance of swallowed drug, making these treatments inherently safer. Almost 80% of a nasally administered drug is swallowed, but the relatively low dosage used in nasal therapy limits potential systemic side effects. However, a study with beclomethasone diproprionate (Vancenase AQ® or Beconase AQ®) at recommended dosage demonstrated a reduction in 1-yr growth of children. This is a reminder that systemic side effects may occur with topically applied medications. Mometasone has the youngest approved age indication, 2 yr, and budesonide has the safest FDA classification for pregnancy, class B, with other agents being class C. The most common side effect with nasal corticosteroid therapy is nasal bleeding. Bleeding is minimized by instructing the patient to administer the spray in a lateral direction, or toward the ipsilateral ear, to minimize septal deposition. Mucosal atrophy does not occur with topical corticosteroids, but the anterior nasal septum has a squamous epithelium, with a possibility of irritation, ischemia, and rarely perforation with topical corticosteroid application.

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

Oral Therapy of Allergic Rhinitis

Oral antihistamines, with or without decongestants, are the most commonly utilized approach in allergic rhinitis (Table 8). The newer second- and third-generation antihistamines offer excellent relief of itching and sneezing without the side effects of excessive sedation, dryness, constipation, or bladder dysfunction. Thirty percent improvement in 50% of treated subjects is the approximate expected clinical response. The explanation for the reduced magnitude of response with oral antihistamine therapy, compared to

topical nasal corticosteroids, is the general lack of improvement in congestion and limited, if any, effect on nonallergic rhinitis. Nonallergic rhinitis may coexist with allergic rhinitis in up to 50% of affected adults. In addition, symptoms of allergic rhinitis are the result of a variety of mediators, limiting the benefits of a single inhibitor (Table 3, Fig. 2).

Selecting a non- or less sedating antihistamine is often predicated on formulary coverage, previous therapeutic trials, or personal bias. Cetirizine, desloratidine, fexofenadine, and loratidine are the second- and third-generation oral antihistamines available in the United States. Levocetirizine, the active stereoisomer of cetirizine, is due on the US market in 2007. Distinguishing these agents is somewhat of a challenge and subject to individual opinion more than evidence. Loratidine, which is available without prescription, probably is the least potent and may not be effective for a full 24 h. Fexofenadine has the least potential for sedation, but absorbtion is most affected by food. Cetirizine may have mild somnolence as a side effect but is considered to be the "strongest" antihistamine by many physicians. This is based on little clinical evidence but upon experience, which could be clouded by the mild sedating effect of cetirizine. Desloratidine and cetirizine have an indication for both seasonal and perennial allergic rhinitis. Loratidine and cetirizine have a class B rating in pregnancy; fexofenadine and desloratidine are class C. Cetirizine, desloratidine, and loratidine have the youngest approved age indication, 6 mo. One study shows some benefit in 50% of subjects after changing oral antihistamine therapy in individuals who have noted declining benefit with chronic antihistamine treatment. This supports the commonly reported phenomenon of "resistance" to oral antihistamine therapy, without evidence of measurable change in the histamine receptor. Cetirizine is unique in having been shown to minimize the development of asthma resulting from dust mite or grass allergens following chronic cetirizine therapy of atopic dermatitis in children. A similar study is currently underway using levocetirizine.

The first-generation antihistamines are equal or superior in efficacy compared to the newer agents but result in a variety of side effects from central nervous system and anticholinergic complications. These result from the first-generation antihistamines readily crossing the blood-brain barrier and interfering with other receptors, such as serotonin, acetylcholine, and dopamine receptors, among others.

Adding an oral decongestant to an antihistamine may improve the clinical response, particularly by reducing nasal congestion, but also may result in side effects of nervousness, sleep disturbance, increase in blood pressure, and bladder dysfunction. This is a popular alternative because of the primal importance of nasal congestion among affected subjects.

Oral montelukast is also effective for seasonal, allergic rhinitis and is associated with minimal side effects. The degree of improvement is difficult to compare to oral antihistamine therapy but is probably slightly less effective. An advantage of oral montelukast is a greater effect on asthma than current oral antihistamines. Montelukast may be particularly useful in a subject with cough attributed to upper airway disease, but who may have a component of asthma as well. Combining oral antihistamines and montelukast may or may not offer any clinical advantages, but from a theoretical standpoint it is appealing. The combination of oral second- or third-generation antihistamine and montelukast may increase treatment costs significantly.

Oral corticosteroid therapy of relatively short duration is effective for severe rhinitis associated with congestion such that topical therapy is limited by inability to deliver the treatment to the affected mucosa. Oral corticosteroid therapy is also helpful for nasal

polyps and rhinitis medicamentosa. Treatment is generally limited to 5–7 d to minimize side effects, and the dose is generally 0.5 mg/kg/d of prednisone or equivalent.

Future Therapeutic Options for Allergic Rhinitis

Future therapies for allergic rhinitis may include immunomodulators such as monoclonal anti-IgE (omalizumab), inhibitors of inflammatory cell immigration into the nasal mucosa, and anti-inflammatory therapies. Omalizumab binds to soluble IgE and also results in a reduction in the high-affinity receptor for IgE on mast cells and basophils and possibly on select dendritic cells. If dosed according to the recommendation of 0.16 mg/kg/U IgE, the free plasma IgE concentration is reduced to approx 15 U/mL. This results in reduced allergic rhinitis symptoms and improvement in asthma. The necessity for injecting this compound and the cost are the major limitations on the eventual application of omalizumab for allergic rhinitis. A variety of anti-inflammatory therapies or immunomodulators have been considered or tried for rhinitis. Syk-kinase inhibitor is an example of such therapeutic approaches. Syk-kinase is a signaling protein important for mast cell and basophil degranulation. By applying a topical inhibitor of syk-kinase to the nasal mucosa, allergic rhinitis symptoms are improved. Other similar targets of intervention are being explored as bench research is applied to the inflammation of allergic rhinitis. The potential of more rapid application of this cutting edge science to allergic rhinitis is greater than other diseases because of the relative ease of applying these therapeutics to the nasal mucosa.

CONCLUSION

Allergic rhinitis is a common condition that significantly impacts the quality of life of affected subjects and occurs coincidentally with a variety of other airway, systemic, or allergic conditions. The application of an appropriate differential diagnosis and targeting therapy to the predominant symptom of the patient will allow the physician to make a major difference in the lives of affected subjects. Nasal disease is complex in scope, but the two most common examples, allergic rhinitis and perennial nonallergic rhinitis, can be assessed with a modest degree of investigation. As with most medical conditions, the history is paramount because the physical findings in rhinitis are somewhat limited or nonspecific. Consideration should always be given to systemic diseases other than allergy, particularly if the clinical data are inconsistent. Appropriate allergy testing is essential to confirm the diagnosis of allergic rhinitis. Knowledge of the environment and the important allergens in a particular area are critical to understanding the results of allergy testing. Many of the "panels" offered by commercial laboratories are not targeted to specific environments. Allergists/immunologists have a unique advantage in the assessment of affected subjects because their training encompasses the immunological and environmental factors that affect the upper airway.

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10 Sinusitis and Otitis Media

Jonathan Corren, MD and Gary Rachelefsky, MD

CONTENTS

SUMMARY

Sinusitis occurs in both acute and chronic forms. The acute form is usually a result of bacterial complications secondary to a viral upper respiratory tract event. Approximately 1 in 200 viral upper respiratory tract events results in a secondary bacterial infection of the sinuses, with the ethmoids and maxillary deemed the most frequently involved. Chronic sinusitis may be a complication of repeated bacterial infections but more often than not appears to be a disease *de novo* characterized by an as yet undefined abnormality of the sinus mucosa. This predisposes to chronic infections.

Acute otitis media (AOM) is analogous to acute sinusitis in that it is a result of obstruction at the osteum of the eustachian tube. The bacteria responsible for AOM are similar to that responsible for acute sinusitis.

Allergic rhinitis is certainly a predisposing factor for AOM and probably a predisposing factor for sinusitis as well.

Key Words: Sinus ostia; eustachian tube; allergic rhinitis; nasal polyps; *Streptococcus pneumoniae*; *Haemophilus influenzae*; *Moraxella catarrhalis*.

SINUSITIS

Definitions and Epidemiology

Sinusitis is a clinical condition characterized by mucosal inflammation of the paranasal sinuses. Acute bacterial sinusitis is a rapid-onset infection that most commonly develops following a viral upper respiratory infection. It is defined by symptom duration of less than 1 mo and most commonly affects the maxillary sinuses. Recurrent acute siinusitis is defined by episodes of bacterial infection of the paranasal sinuses, each lasting less than 30 d and separated by intervals of at least 10 d, during which the patient is asymptomactic. Subacute sinusitis, with symptoms present between 1 and 3 mo, usually occurs when an acute episode of bacterial sinusitis has not been adequately treated. Sinusitis is diagnosed as chronic when mucosal disease and attendant symptoms have been present for at least 3 mo.

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Sinus disease is one of the most frequently encountered problems evaluated by primary care physicians. It has been estimated that 0.5% of viral upper respiratory infections result in acute bacterial sinusitis. Similarly, chronic sinusitis is also a very common condition and has been estimated to afflict at least 31 million people in the United States.

Pathogenesis

Acute Sinusitis

Four host factors determine the susceptibility to sinusitis, including patency of the ostia, ciliary function, quality of secretions, and local host immunity. Most commonly, a viral upper respiratory infection results in acute obstruction of one or more ostia. This blockage leads to reduced oxygen content and the development of mucosal edema and serum transudation within the sinus cavities. These alterations foster bacterial growth reduce ciliary movement and alter leukocyte function, eventuating in the signs and symptoms of acute bacterial sinusitis. The sinuses will usually return to normal either spontaneously or following antimicrobial therapy. Common conditions that predispose to sinusitis are listed in Table 1.

Cronic Sinusitis

Chronic sinusitis is characterized by persistent mucosal inflammation, with histological evidence of edema and a mixed cellular infiltrate (eosinophils and lymphocytes). The marked thickening of sinus tissue observed microscopically, macroscopically, and radiographically has given rise to the term "hyperplastic sinusitis." Nasal polyps, which are commonly identified in patients with chronic sinusitis, represent evaginations of sinus mucosa and are histologically identical to the tissue from which they originate. Although both aeroblic and anaerobic bacteria as well as fungi may be cultured from the sinus cavities of patients with chronic sinusitis, the true role of these organisms as infectious pathogens is unclear.

Clinical Presentation

Acute Sinusitis

The most consistent feature distinguishing acute bacterial from a viral upper respiratory infection is persistence of symptoms beyond 7–10 d (Table 2). Cough and nasal discharge are the two most common complaints in children, whereas headache and facial pain are unusual in children younger than age 10. Adult patients with acute sinusitis most often complain of discolored nasal discharge, unilateral facial pain, headache, and cough. Although reported in only a minority of patients, upper tooth pain is a complaint very specific for acute sinusitis.

On examination, high temperature and signs of toxicity are unusual and should prompt a search for complications such as meningitis or periorbital abscess. Anterior rhinoscopy frequently reveals erythematous, swollen turbinates and purulent secretions on the floor of the nose. However, the absence of pus does not rule out active infection, because sinus drainage may be intermittent. Facial tenderness elicited by palpation is an unreliable sign in differentiating sinusitis from acute rhinitis. Although transillumination may be useful in evaluating acute maxillary and frontal sinusitis in adults (if interpretation is confined to extremes of light transmission), it is difficult to employ reliably in practice and is rarely used by most clinicians.

Table 1
Conditions Associated With Sinusitis

- Obstruction of the sinus ostia
  - Acute viral rhinitis
  - Chronic rhinitis
  - Nasal polyps
  - Adenoidal enlargement
  - Septal deviation
  - Aerated middle turbinate (concha bullosa)
  - Foreign body (e.g., nasogastric tube)
- Dental infection
- Barotrauma (flying, diving)
- Systemic diseases
  - Antibody deficiency syndrome
  - Down syndrome
  - Cystic fibrosis
  - Wegener's granulomatosis
  - Ciliary dyskinesia syndrome

Chronic Sinusitis

Patients with chronic sinusitis usually have indolent symptoms of nasal congestion, thick mucoid or purulent postnasal drip, and cough (Table 2). Adult patients may also complain of facial fullness and headache. Secondary eustachian tube obstruction or middle ear fluid may result in popping of the ears and muffled hearing. In addition to these chronic complaints, patients may also experience recurrent exacerbations of symptoms resembling acute sinusitis. Importantly, patients with chronic sinusitis, particularly those with nasal polyps, often have concomitant bronchial asthma. A large percentage of patients with chronic sinusitis and asthma are intolerant of nonsteroidal anti-inflammatory drugs and develop flushing, rhinorrhea, nasal congestion, and/or acute bronchospasm after ingesting these medications.

Physical examination often demonstrates swelling and erythema of the inferior and middle turbinates and occasionally mucopurulent secretions on the floor of the nose and middle meatus. Nasal polyps may be present and usually originate from the middle meatus. In children, middle ear effusions are present in half of all cases and serve as a possible clue to the presence of sinusitis. Transillumination is not useful in evaluating chronic sinus disease because mucosal thickening usually yields equivocal results.

Flexible fiberoptic rhinoscopy is a useful and easily learned procedure that can help identify important anatomical lesions not visible by anterior rhinoscopy, including posterior deviation of the nasal septum, nasal polyps, enlargement or inflammation of the adenoid, and tumor.

Diagnostic Tests

In many patients with acute and chronic sinusitis, diagnosis and subsequent therapy can be based on the history and physical findings (Table 3). However, in a significant number of patients, signs and symptoms may be equivocal, and additional testing is required to make a diagnosis.

Table 2
Symptoms Suggestive of Sinusitis

- Acute disease
  Persistence of upper respiratory infection symptoms, usually without fever, beyond 7–10 d
  Children: cough, nasal discharge
  Adults: discolored nasal discharge, unilateral facial pain, headache, cough
- Persistent disease
  Long-standing nasal congestion, thick postnasal drip, cough, facial fullness, sore throat, and hearing problems

Laboratory Tests

Cytological examination of freshly stained nasal secretions (using Hansel's or modified Wright-Giemsa medium) have been used by some physicians to evaluate both acute and chronic nasal complaints. However, although nasal neutrophils are generally prominent in cases of acute viral rhinitis or acute bacterial sinusitis, this is a nonspecific finding. Similarly, although nasal eosinophils are most commonly encountered in patients with allergic rhinitis or eosinophilic nonallergic rhinitis, the presence of eosinophils lacks sensitivity in detecting these conditions and has a poor negative predictive value.

The peripheral white blood count/differential and nasal swab cultures have no utility in determining the presence of infection or in accurately identifying pathogenic bacteria in sinusitis.

Imaging Studies

Although plain radiography has recently fallen out of favor in evaluating sinusitis, we feel that this technique continues to play a helpful role, particularly in children below the age of 5 yr. Although plain X-rays accurately visualize the maxillary and frontal sinuses (particularly the Water's occipitomental view), the ethmoid and sphenoid sinuses are difficult to assess.

Waters' view findings that are diagnostic of sinusitis include a sinus air–fluid level, sinus opacification, or severe mucosal thickening (>50% of antral diameter in children and >8 mm in adults). Plain films, particularly the Waters' view, are helpful in evaluating possible chronic sinusitis in young children, since the maxillary sinuses are usually the principal sinuses involved. In adults with chronic sinusitis, however, plain films may yield false-negative results because infection is limited to the ethmoid sinuses in up to 40% of cases.

Computed tomography (CT) provides a detailed view of all of the paranasal sinuses and the ostiomeatal complex regions. CT is most helpful in patients who have persistent or recurrent symptoms suggestive of sinusitis despite a prolonged trial of medical therapy. CT should be delayed if a viral upper respiratory infection has recently occurred, because 85% of patients have transient abnormalities on CT following a cold. CT of the sinuses should always be used judiciously because even the screening scan remains a relatively expensive test and does require sedation for most children younger than 8 yr of age.

Magnetic resonance imaging (MRI) is extremely sensitive in detecting subtle soft tissue abnormalities of the paranasal sinuses. For this reason it is the technique of choice in imaging suspected sinus neoplasms, fungal infections, and complicated infections that extend intracranially. MRI should not be used for routine diagnosis of sinusitis because

Table 3
Diagnosis of Sinusitis

• Acute
Clinical symptoms usually suffice
Plain films may be helpful in young children (Waters' view)
• Persistent
Computed tomography is gold standard
Plain films of limited utility

it is very costly and does not adequately visualize the bony landmarks required for surgical planning.

Sinus ultrasound is rarely used as a diagnostic test because of its poor sensitivity and specificity in patients with both acute and chronic sinusitis.

Maxillary Aspiration and Culture

Referral should be made to an otolaryngologist for maxillary aspiration when acute sinusitis is associated with signs of severe toxicity (particularly in hospitalized or immunosuppressed patients) or is unresponsive to an adequate trial of appropriate antibiotics.

Microbiology

Acute Sinusitis

The most commonly identified organisms in children with acute sinusitis are *Streptococcus pneumoniae* in 30–40%, *Haemophilus influenzae* in 20–25%, and *Moraxella catarrhalis* in 20%. In adults, *S. pneumoniae* and *H. influenzae* are the two leading causes of sinusitis, whereas *Moraxella* is unusual. Anaerobic organisms are primarily identified in cases of acute sinusitis originating from dental root infections, but are otherwise uncommon. Hospital-acquired sinusitis is most often seen as a complication of nastogastric tube placement and is typically caused by Gram-negative enteric organisms such as *Pseudomonas* and *Klebsiella*.

Chronic Sinusitis

Bacterial isolates in children with chronic sinusitis are usually the same as those seen in acute disease. In children with more severe and protracted symptoms, anaerobic species (such as *Bacteroides*) and staphylococci are cultured more frequently.

Anaerobic organisms and increasingly *Staphylococcus epidermidis* predominate in adults with chronic sinusitis. Among the anaerobes, species of *Bacteroides* and anaerobic cocci account for most of the isolates. However, the role played by these organisms in adults with chronic sinusitis is not entirely clear. Some investigators have suggested that coagulase-negative staphylococcal species may act as antigens that elicit a chronic inflammatory response in the mucosa.

Fungi may cause invasive infection in immunocompromised hosts, including diabetics and patients with defective cell-mediated immunity. These infections may progress rapidly and eventuate in severe complications are even death. Rarely, *Aspergillus*, *Nocardia*, and *Bipolaris* species have also been identified as causes of chronic, indolent, yet invasive sinusitis in patients who are otherwise healthy. Allergic fungal sinusitis is a syndrome that has been attributed to *Aspergillus*, *Bipolaris*, and *Curvularia* species.

Table 4
Antibiotic Treatment of Acute Sinusitis

- Mild symptoms
  - Amoxicillin 45 mg/kg given in two doses
  - For non-type-1 hypersensitivity reactions:
  - Cefdinir 14 mg/kg/d in one or two doses
  - Cefuroxime 30 mg/kg/d in two doses
  - Cefpodoxime 10 mg/kg/d in one dose
  - For type 1 hypersensitivity reactions:
  - Clarithromycin 15 mg/kg/d in two doses
  - Azithromycin 10 mg/kg/d on day 1, with 5 mg/kg/d 4 d in one dose
  - Clindamycin 30–40 mg/kg/d in three doses
- Moderate–severe symptoms[a] (or failure to respond to amoxicillin or recent use of antibiotics or attendance at day care)
  - Amoxicillin-clavulanate 80–90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in two doses
  - Cefdinir, per above
  - Cefuroxime, per above
  - Cefpodoxime, per above

[a]Moderate-severe symptoms defined as a temperature of >102°F (39°C) and purulent nasal discharge present for at least 3 consecutive days in a patient who seems ill.

It is characterized by severe, hyperplastic sinusitis and nasal polyposis and is associated with an elevation of specific immunoglobulin (Ig)E to the fungus in question, total IgE, and eosinophilia of sinus tissue and blood. Although some investigators have suggested that fungi may cause chronic sinusitis via a noninfectious, non-IgE-mediated mechanism, there is at present insufficient evidence to support this theory.

Medical Therapy

Acute Sinusitis

Treatment guidelines have recently been developed by expert panels for both children and adults with acute sinusitis. These consensus statements emphasize that antibiotics are the primary form of treatment for acute sinusitis. For patients with uncomplicated acute bacterial sinusitis that is mild to moderate in severity (Table 4) who have not recently been treated with an antimicrobial, amoxicillin is recommended at a dose of 45 mg/kg/d in two divided doses. If the patient has had a history of a late-onset rash to amoxicillin (non-type-1 hypersensitivity reaction), either cefdinir (14 mg/kg/d in one or two doses), cefuroxime (30 mg/kg/d in two divided doses), or cefpodoxime (10 mg/kg/d once daily) can be used. In cases of type 1 systemic reactions (including immediate-onset urticaria), clarithromycin (15 mg/kg/d in two divided doses) or azithromycin (10 mg/kg/d on day 1, with 5 mg/kg/d 4 d as a single daily dose) can be used. Alternative therapy in the penicillin-allergic patient who is known to be infected with a penicillin-resistant *S. pneumoniae* is clindamycin at 30–40 mg/kg/d in three divided doses.

Most patients with acute bacterial sinusitis who are treated with an appropriate antimicrobial agent respond promptly (within 48–72 h) with a reduction of nasal discharge and cough and an improvement in general well-being. If a patient fails to improve, either the antimicrobial is ineffective or the diagnosis of sinusitis is not correct.

If patients have an illness that is more severe or do not improve while receiving the above dose of amoxicillin, have recently been treated with an antimicrobial, or attend day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80–90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in two divided doses). This dose of amoxicillin will yield sinus fluid levels that exceed the minimum inhibitory concentration of all *S. pneumoniae* that are intermediate in resistance to penicillin and most, but not all, highly resistant *S. pneumoniae*. There is sufficient potassium clavulanate to inhibit all β-lactamase producing *H. influenzae* and *M. catarrhalis*. Alternative therapies include cefdinir, cefuroxime, or cefpodoxime. A single dose of ceftriaxone (at 50 mg/kg/d), given either intravenously or intramuscularly, can be used in patients with vomiting who do not tolerate oral antibiotics. Twenty-four hours later an oral antibiotic is added to complete the therapy. Although trimethoprim–sulfamethoxazole and erythromycin–sulfisoxazole have traditionally been useful in the past as first- and second-line therapy for patients with acute bacterial sinusitis, recent pneumococcal surveillance studies indicate that resistance to these two combination agents is substantial. Therefore, when patients fail to improve while receiving amoxicillin, neither trimethoprim–sulfamethoxazole nor erythromycin–sulfisoxazole is an appropriate choice for antimicrobial therapy. For patients who do not improve with a second course of antibiotics or who are acutely ill, an otolaryngologist should be consulted for consideration of maxillary sinus aspiration.

There are emerging data that shorter courses (e.g., 3 d) of antibiotic treatment may be adequate in treating acute sinusitis. However, we recommend that antibiotics be given for a minimum of 10 d and that the course of treatment should be extended for 7 d beyond the day of significant improvement. There are no data demonstrating that longer courses (e.g., 21 d) are associated with better outcomes. Symptoms recurring soon after a course of antibiotics are usually a reaction to the original organism and should be treated with an alternative β-lactamase-resistant agent for 21 d.

Topical and oral decongestants reduce nasal congestion associated with acute sinusitis and may reduce ostial edema, allowing for improved sinus drainage. Older antihistamines with strong anticholinergic effects such as diphenhydramine and hydroxyzine may cause mucous inspissation and make it more difficult to clear secretions. However, the newer second- and third-generation antihistamines such as loratadine, cetirizine, and fexofenadine have virtually no anticholinergic effects and can be continued in patients who require these agents for concomitant allergic rhinitis.

Chronic Sinusitis

In patients with chronic sinusitis and evidence of purulent discharge, a trial of antibacterial therapy is warranted (Table 5). In patients who have not been previously treated with antibiotics, amoxicillin is a cost-effective choice for first-line therapy. Although there are few published data regarding antimicrobial therapy for chronic sinusitis, anecdotal evidence suggests that patients should be treated for a minimum of 21 d. In patients who are allergic to penicillin, clarithromycin provides good coverage against most relevant pathogens. If the patient has demonstrated no response to these drugs within 10 d, a β-lactamase-resistant antibiotic (per acute sinusitis) should be given for 21 d. For adult patients who do not improve with this treatment, agents with increased anaerobic coverage such as clindamycin or metronidazole may be effective.

In addition to antibiotics, topical nasal corticosteroids should be started to reduce chronic mucosal edema and inflammation. If severe turbinate swelling or nasal polyps are

Table 5
Treatment of Chronic Sinusitis

- Medical therapy
  - Antibiotic for 3–6 wk
  - Nasal corticosteroid
  - Nasal irrigation with saline
  - Allergen avoidance (if indicated)
- Surgery
  - Indicated for moderate-severe, medically refractory cases
  - Long-term variable

present, a 5- to -7 d course of prednisone (0.5 mg/kg/d given in two to three divided doses) may be beneficial. Both topical and oral corticosteroids appear to be safe in chronic sinusitis, and there is no evidence that they increase the risk of intracranial extension or fulminant infection when given to patients with normal immune function. In allergic patients and patients with nasal polyposis, long-term use of nasal corticosteroids may be helpful in preventing recurrences of sinusitis.

Nasal irrigations, performed two to three times a day with a bulb syringe and saline, can be very helpful in removing dried secretions. Other methods to increase nasal humidification (hot showers, room humidifiers, and steam inhalers) are easy to use and may provide symptomatic relief for short periods.

Surgical Therapy

Patients with chronic sinusitis refractory to medical therapy should be referred to an otolaryngologist for consideration of surgery. In children with persistent maxillary sinus disease, antral lavage (with or without adenoidectomy) effectively removes purulent material and often provides long-lasting symptom relief. In adults, however, functional endoscopic surgery has largely supplanted other surgical procedures and is effective in 50–80% of patients. Patients with aspirin-sensitive asthma, nasal polyposis, and pansinusitis are more likely to have recurrent disease and should be discouraged from undergoing multiple repeat surgical procedures.

Patients suspected of having intracranial complications (e.g., periorbital abscess, brain abscess, or meningitis) of acute sinusitis should be referred for immediate surgical consultation. Cardinal signs and symptoms include high fever, severe headache, proptosis, and changes in mental status.

Evaluaton of Patients With Recurrent or Persistent Sinusitis

Fifty percent of children and 30–40% of adults with recurrent or chronic sinusitis are sensitized to common aeroallergens such as plant pollens, house dust mite, and animal danders. Assessment of IgE-mediated hypersensitivities by allergy skin testing or in vitro blood assays should therefore be performed in all patients because they may benefit from a comprehensive program of allergen avoidance, anti-allergic drug therapy, and, in selected cases, immunotherapy. Patients with severe, recurrent episodes of sinusitis associated with other infections (e.g., otitis, bronchitis, and pneumonia) may suffer from one of the antibody deficiency syndromes and should undergo a screening assessment of their immunoglobulin levels. If a deficiency is noted or still suspected after the initial testing, these patients should be referred to an allergist/immunologist for further evaluation.

Table 6
Factors Associated With Otitis Media

Acute viral upper respiratory infection
Chronic rhinitis
Exposure to tobacco smoke
Adenoidal hypertrophy
Variants of eustachian tube anatomy
Cleft palate disease
Down syndrome
Ciliary dyskinesia syndrome
Humoral immunodeficiency

OTITIS MEDIA

Definitions and Epidemiology

Acute otitis media (AOM) refers to an acute suppurative infection of the middle ear space that usually lasts for 3 wk or less. Otitis media with effusion (OME; previously referred to as secretory or serous otitis media) represents persistent middle ear fluid that most often follows an episode of AOM and may last for many months. Recurrent AOM is defined as three or more episodes of AOM during the preceding 6 mo. AOM is the most frequently diagnosed disease of children and is unusual in adult patients. It occurs in roughly 60% of children by the age of 1 yr and in 80% by age 3.

Half of all children have had three or more episodes of AOM by age 3. Otitis media with effusion is similarly common, noted in approx 50% of patients during the first year of life.

Pathogenesis

The two factors that contribute most significantly to otitis media are eustachian tube dysfunction and bacterial proliferation in the nasopharynx. The functions of the eustachian tube include pressure equalization, protection of the middle ear from nasopharyngeal secretions, and mucociliary clearance of the middle ear. Eustachian tube obstruction results in the development of negative pressure that is followed by serum transudation into the middle ear. This sterile effusion may become infected by bacteria refl uxing from the nasopharynx into the middle ear. Incomplete eradication of an initial infection or prolonged underventilation of the middle ear may ultimately result in a chronic, mucoid effusion. Table 6 lists conditions commonly associated with otitis media.

Clinical Presentation

AOM

Children with AOM typically complain of acute unilateral ear pain that occurs several days after a viral upper respiratory infection. The symptoms frequently start early in the morning and are associated with irritability and fever, although nausea, vomiting, and diarrhea are not uncommon. Otoscopy usually reveals a red, thickened, and bulging tympanic membrane. Insufflation (pneumatic otoscopy) generally demonstrates poor mobility of the drum. Importantly, the drum may also appear red in a crying child (because of increased vascularity of the tympanic membrane) and may lead to an incorrect diagnosis of AOM (*see* Table 7).

Table 7
Diagnosis of AOM[a]

1. Recent, abrupt onset of signs and symptoms
2. Presence of middle ear effusion
   - Bulging of the tympanic membranes, AND/OR
   - Limited or absent mobility of the tympanic membrane, AND/OR
   - Air–fluid level behind tympanic membrane, AND/OR
   - Otorrhea
3. Signs or symptoms of middle ear inflammation
   - Erythema of the tympanic membrane, AND/OR
   - Ear pain clearly relatable to the ears

[a]Diagnosis requires that all three of the above features be present.

OME

Children with this chronic condition are usually asymptomatic, but may have subtle loss of hearing. There is usually no recent history of fever, irritability, or other systemic symptoms. The eardrum may appear yellow, orange, or blue and is often retracted. Air–fluid levels or bubbles may be present, and the drum moves poorly with insuffl ation.

Unfortunately, if middle ear fluid is very thin, mobility may appear normal even to highly trained observers. Physical findings suggestive of allergic rhinitis, sinusitis, or tonsillar hypertrophy should be sought because these conditions may play important pathogenic roles in OME.

Diagnostic Tests

Electroacoustic Impedance (Tympanometry)

Tympanometry is easy to perform and is far more sensitive than pneumatic otoscopy in detecting middle ear fluid. If findings are normal, OME can be confidently ruled out.

Audiometry

In children older than 18 mo, audiometry is an important test in determining whether OME has resulted in hearing loss. Fluid may cause up to a 40 dB hearing loss. This test should be employed when middle ear fluid has been present for at least 3 mo before deciding whether ventilation of the middle ear is necessary.

Diagnostic Tympanocentesis

Tympanocentesis with culture of middle ear fluid is indicated in children who are extremely ill with AOM, children who have not responded to an adequate trial of appropriate medical therapy, and children in intensive care nurseries.

Microbiology

The three principal organsims identified in middle ear effusions from both AOM and OME are the same as those isolated from patients with acute sinusitis. *S. pneumoniae*, nontypeable *H. influenzae*, and *M. catarrhalis* are isolated in 35, 23, and 14% of effusions, respectively. Other organisms that are occasionally cultured include *Staphylococcus aureus*, α streptococcus, and group A streptococcus. Special exceptions include very young infants and children in intensive care nurseries in whom group B streptococci and Gram-negative organisms are very common causes of AOM.

Table 8
Criteria for Initial Antibiotic Therapy or Observation in Children With AOM

Age	*Certain diagnosis*	*Uncertain diagnosis*
<6 mo	Antibacterial therapy	Antibacterial therapy
6 mo to 2 yr	Antibacterial therapy	Antibacterial therapy if severe illness; observation option[a] if nonsevere illness
≥2 yr	Antibacterial therapy if severe illness; observation option[a] if nonsevere illness	Observation option[a]

[a]Observation is an appropriate option only when follow-up can be ensured and antibacterial agents started if symptoms persist or worsen. Nonsevere illness is mild otalgia and fever <39°C in the past 24 h. Severe illness is moderate to severe otalgia or fever >39°C. A certain diagnosis of AOM meets all three criteria: (1) rapid onset, (2) signs of middle ear effusion (MEE), and (3) signs and symptoms of middle-ear inflammation. (From American Academy of Pediatrics Subcommittee on Management of AOM, 2004.)

Medical Therapy

AOM

Guidelines very similar to those developed for the treatment of acute sinusitis have been created for treating AOM in children. Although placebo-controlled studies have demonstrated that most children will recover from AOM without treatment, antibiotics do reduce the duration and severity of signs and symptoms. More importantly, antibiotics have reduced the incidence of and death rate from suppurative complications of AOM. If children are older than 2 yr and have nonsevere illness, current guidelines suggest that it is safe to observe a child with AOM for 48–72 h, providing that follow-up care is easily accessible (Table 8). For initial episodes in patients with nonsevere illness, amoxicillin, 90 mg/kg/d given in two doses, remains the drug of choice and should be given for 10 d (Table 9). In most cases symptoms should improve significantly within 2–3 d. If symptoms persist in patients with nonsevere illness or the child presents initially with severe symptoms, amoxicillin-clavulanate, 90 mg/kg/d of amoxicillin with 6.4 mg/kg/d of clavulanate, should be given for an additional 10 d. Children who have either non-type-1 or type 1 allergic reactions to penicillin should be treated with alternative antibiotics, using the same doses described for the treatment of acute sinusitis (*see* Tables 4 and 9). In children with severe illness who do not respond to amoxicillin-clavulanate, intramuscular ceftriaxone should be administered.

Adjunctive measures, including antihistamine–decongestant combinations and topical nasal corticosteroids, have not been proven to be effective in randomly chosen children with AOM. However, these agents may have a beneficial effect in children with concomitant allergic rhinitis.

Recurrent AOM

Prophylactic antibiotics have been shown to be effective in reducing the number of episodes of AOM in children who are prone to recurrence. Amoxicillin (20 mg/kg/d) and sulfisoxazole (50 mg/kg/d) are used most commonly, and treatment should be continued through the high-risk upper respiratory infection seasons (late fall to early spring). Pneu-

Table 9
Recommended Antibacterial Agents for Patients Who Are Being Treated Initially With Antibiotics or Have Failed 48 to 72 Hours of Observation or Initial Management With Antibacterial Agents

Being Treated Initially With Antibacterial Agent	*At Diagnosis for Patients*		*Clinically Defined Treatment Failure at 48-72 h After Initial Management With Observation Option*		*Clinically Defined Treatment Failure at 48-72 h After Initial Management With Antibacterial Agents*	
Severity of AOM[a]	*Recommended*	*Alternative for Penicillin Allergy*	*Recommended*	*Alternative for Penicillin Allergy*	*Recommended*	*Alternative for Penicillin Allergy*
Nonsevere	Amoxicillin, 80-90 mg/kg per day	Non-type I: cefdinir, cefuroxime, cefpodoxime; type I: azithromycin, clarithromycin	Amoxicillin, 80-90 mg/kg per day	Non-type I: cefdinir, cefuroxime, cefpodoxime; type I: azithromycin, clarithromycin	Amoxicillin-clavulanate, 90 mg/kg per day of amoxicillin component, with 6.4 mg/kg per day of clavulanate	Non-type I: ceftriaxone, 3 days; type I: clindamycin
Severe	Amoxicillin-clavulanate, 90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate	Ceftriaxone, 1 or 3 days	Amoxicillin, clavulanate, 90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate	Ceftriaxone, 1 or 3 days	Ceftriaxone, 3 days	Tympanocentesis, clindamycin

[a]Nonsevere illness is mild otalgia and fever <39°C in the past 24 hours. Severe illness is moderate to severe otalgia or fever ≥39°C.

American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004 May;113(5):1451–65

mococcal vaccine should also be encouraged in all children over age 2 who suffer from recurrent otitis.

OME

Whereas at least 80% of effusions resolve spontaneously within 2 mo, effusions that persist for longer than 3 mo will not usually improve without therapy. The most effective medical therapy for OME is probably a 14-d trial of amoxicillin. More potent antimicrobial agents or longer courses of antibiotics have not been shown to be helpful.

Adjunctive measures (antihistamine–decongestants, topical corticosteroids) have also not been shown to be effective. Antibiotic therapy for OME should be considered in children who have associated sinusitis, documented conductive hearing loss, vertigo or tinnitus, or structural changes in the tympanic membrane or middle ear or in infants who are unable to describe symptoms. Following antibiotic therapy, the effusion must be followed carefully to ensure resolution.

Surgical Therapy

If medical therapy for recurrent AOM or OME is ineffective or poorly tolerated, a patient should be referred to an otolaryngologist for evaluation of the condition.

Myringotomy with tube placement is effective in reducing the frequency of acute infections and in decreasing the duration of chronic effusions and their associated hearing loss. If tube placements are not effective or a child has persistent adenoidal infection or enlargement, adenoidectomy with repeat tube placements has been shown to be beneficial in children older than age 4. Tonsillectomy has not been shown to provide any additional benefit over adenoidectomy alone.

Evaluation of Patients With Recurrent AOM or OME

Of children with recurrent AOM and OME, 30–40% have associated nasal allergy. These patients should undergo allergy testing and, if indicated, a complete program of allergen avoidance and antiallergic drug therapy prior to surgical intervention. Children with very severe, recurrent episodes of AOM associated with intracranial complications or bronchial infections should undergo an evaluation of their humoral immunity.

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11 Diagnosis and Treatment of Ocular Allergy

Leonard Bielory, MD

CONTENTS

SUMMARY

Allergic diseases of the eye are allergic conjunctivitis (AC), vernal keratoconjunctivitis, and atopic keratoconjunctivitis (AKC). The key element in the history that unites these three conditions is pruritus. They must be distinguished from other conjunctival abnormalities that mimic atopic disease. These include conjunctivitis sicca, infectious conjunctivitis resulting from both viruses and bacteria, blepharoconjunctivitis, and giant papillary conjunctivitis (GPC). Acute AC is nonthreatening to the site, but both AKC and vernal keratoconjunctivitis, because of corneal involvement, can be threatening to vision. The treatment of allergic eye disease is namely topical, and a number of classes of drugs are available, including antihistamines, nonsteroidal anti-inflammatory drugs, mast cell stabilizers, and corticosteroids.

Key Words: Allergic conjunctivitis; vernal keratoconjunctivitis; atopic keratoconjunctivitis.

INTRODUCTION

The eye is probably the most common site for the development of allergic inflammatory disorders because it has no mechanical barrier to prevent impact of allergens such as pollen on its surface. Primary care providers frequently encounter various forms of allergic diseases of the eye that present as "red eyes" in their general practice. However, the eye is rarely the only target for an immediate allergic-type response. Typically, many patients have other combinations of allergic disorders such as rhinoconjunctivitis,

From: *Current Clinical Practice: Allergic Diseases: Diagnosis and Treatment, Third Edition*
Edited by: P. Lieberman and J. A. Anderson

Table 1
Differential Diagnosis of the Red Eye

Allergic	*Infectious*	*Autoimmune*	*Nonspecific*
Acute	Viral	Episcleritis	Dry Eye Syndromes
Seasonal	Bacterial	Pemphigoid	Foreign Body
Perennial	Inclusion	Uveitis	Acne Rosacea
Chronic	Fungal	Vasculitis	Chemical Induced
Vernal	Parasitic		
Atopic			
Giant Papillary			

rhinosinusitis, asthma, urticaria, and/or eczema; there also exists a systemic allergic component. Even so, ocular signs and symptoms can frequently be the most prominent features of the entire allergic response for which these patients visit their physician.

The primary care physician also needs to be aware of the various other ocular conditions that present as a red eye, some of which can produce profound visual loss if not treated appropriately. The signs and symptoms associated with these various conditions often overlap and can be difficult to differentiate. Therefore, an understanding of ophthalmological examination techniques and diagnostic procedures can further assist the primary care provider to make an accurate diagnosis of ocular allergy (*see* Table 1).

This chapter provides a review of the various forms of allergic inflammation and focuses on the clinical characteristics that help to differentiate one allergic disorder from another as well as from other ocular conditions.

THE OCULAR SURFACE

Allergens and other ocular irritants are easily deposited directly onto the surface of the eye. Many agents that are systemically absorbed can also be concentrated and secreted in tears, causing allergic conjunctivitis (AC) or an irritant form of conjunctivitis. Other causes of the red eye may also include intraocular conditions associated with systemic autoimmune disorders such as uveitis or scleritis. In addition, allergic inflammatory disorders such as those that may affect surrounding skin, mucosa, or even sinuses and release various mediators of inflammation, including histamine, leukotrienes, and neuropeptides, can have effects on the local ocular tissue.

ALLERGIC DISEASES OF THE EYE

Conjunctivitis, in its entirety, is a broad term that describes conjunctival inflammation. There are many causes of conjunctivitis. The clinical presentation of ocular surface allergic disorders is quite varied and depends, in part, on the immunological mechanism involved and the specific ocular tissues that are affected. Based on these differences, the most common forms of allergic ocular disease can be divided into seasonal AC, perennial allergic conjunctivitis (PAC), vernal conjunctivitis, atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC). Of all the possible ocular manifestations of allergic disease, AC is the most common (Table 2).

Table 2
Differential Diagnosis of Conjunctival Inflammatory Disorders

	AC	*VC*	*AKC*	*GPC*	*CONTACT*	*BACTERIAL*	*VIRAL*	*CHLAMYDIAL*	*KCS*
					SIGNS				
Predominant Cell type	Mast cell EOS	Lymph EOS	Lymph EOS	Lymph EOS	Lymph	PMN	PMN Mono Lymph	Mono Lymph	Lymph Mono
Chemosis	+	+/–	+/–	+/–	–	+/–	+/–	+/–	–
Lymph node	–	–	–	–	–	+	++	+/–	–
Cobblestoning	–	++	++	++	–	–	+/–	+	–
Discharge	clear, mucoid	stringy, mucoid	stringy, mucoid	clear, white	+/–	++ mucopurulent	clear, mucoid	++ mucopurulent	+/– mucoid
Lid Involvement	–	+	+	–	++	–	–	–	–
					SYMPTOMS				
Pruritus	+	++	++	++	+	–	–	–	–
Gritty sensation	+/–	+/–	+/–	+	–	+	+	+	+++
Seasonal variation	+	+	+/–	+/–	–	+/–	+/–	+/–	–

AC, allergic conjunctivitis; VC, vernal conjunctivitis; AKC, atopic keratoconjunctivitis; GPC, grant papillary conjunctivitis; KCS, keratoconjunctivitis sicca; BC, blepharoconjunctivitis; PMN, polymorphonuclear cells; Lymph, lymphocyte; Mono, monocyte; EOS, eosinophil

Table 3
Common Clinical Signs and Symptoms of Ocular Infl ammation

Trichiasis: inturned eyelashes
Epiphora: excessive tearing
Blepharospasm: spasm of the orbicularis oculi muscles
Subconjunctival hemorrhages: benign lesions occurring spontaneously, but may follow vigorous rubbing of the eye, vomiting, coughing or Valsalva's maneuvers
Blepharitis: inflammation of the eyelids
Madarosis: loss of eyelashes
Chalazion: inflammation of the meibomian gland
Hordeolum: a sty
Cicatrization: shrinkage and scarring of the conjunctival surface
Episcleritis: benign self-limiting sometimes bilateral inflammatory process of the tunic that surrounds the ocular globe
Scleritis: inflammatory process of the outer tunic surrounding the globe associated with autoimmune disorders, e.g., systemic lupus erythematosus, rheumatoid arthritis

Clinical Examination

The clinical examination of the eyes for signs of ocular allergy begins with the external components that surround the eye and the eye itself. First, one examines the eyelids and eyelashes, focusing on the presence of erythema on the lid margin, as well as telangiectasias, scaling, thickening, swelling (blepharitis, dermatitis), and collarettes of debris at the base of the eyelashes, and evidence of periorbital discoloration, blepharospasm, or ptosis. Next, the conjunctivae are directly examined for chemosis (clear swelling), hyperemia (injection), palpebral and bulbar papillae, and cicatrization (scarring). The discharge from the eye is also noted for increase or discoloration. It is important to differentiate this from the injection associated with inflammation of the sclera (scleritis) that tends to develop over the course of several days. Scleritis is also commonly associated with autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and Wegener's granulomatosis. Another major clinical differential point is that scleritis and/or episcleritis commonly is associated with moderate and severe ocular pain on motion, whereas conjunctivitis is commonly painless. The primary care provider should also be aware of a form of ocular infection described as a ring of erythema around the limbal junction of the cornea (ciliary flush), which is a clinical sign for uveitis, a serious form of intraocular pathology (Table 3).

The presence of follicles or papillae involving the bulbar and tarsal conjunctivae should be noted. Follicles can be distinguished as grayish, clear, or yellow bumps varying in size from pinpoint to 2 mm in diameter with conjunctival vessels on their surface, while papillae contain a centrally located tuft of blood vessels.

Corneal involvement is more commonly seen in the chronic forms of ocular allergy, for example, vernal keratoconjunctivitis and AKC. The slit-lamp biomiocroscope is the optimum device for examination of the cornea, although many important clinical features can be seen with the naked eye or with the use of a hand-held direct ophthalmoscope. The direct ophthalmoscope can provide the desired magnification by "plus" (convex) and "minus" (concave) lenses. The cobalt blue filter on the new hand-held ophthalmoscopic heads assists in highlighting anatomical anomalies affecting the cornea or the conjunctiva that has been stained with fluorescein.

The cornea should be perfectly smooth and transparent. Mucus adhering to the corneal or conjunctival surfaces is considered pathological. Dusting of the cornea may indicate punctate epithelial keratitis. A localized corneal defect may develop into erosion or a larger ulcer. A corneal plaque may be present if the surface appears dry and white or yellow.

The limbus is the zone immediately surrounding the cornea and is normally invisible to the naked eye, but when inflamed this area becomes visible as a pale or pink swelling. Discrete swellings with small white dots (Trantas-Horner's dots) are indicative of degenerating cellular debris that is commonly seen in chronic forms of conjunctivitis.

In addition, because the eye has thin layers of tissue surrounding it, there is an increased tendency to develop secondary infections that can further complicate the clinical presentation.

Acute Allergic Conjunctivitis

Ocular disorders mediated by mast cells are the most common hypersensitivity responses of the eye. AC is a result of direct exposure of the ocular mucosal surfaces to environmental allergens such as pollens from trees, grasses, and weeds interacting with the pollen-specific immunoglobulin (Ig)E found on the mast cells of the eye. Of all the various pollens, ragweed has been identified as the cause in approx 75% of cases of allergic rhinoconjunctivitis in the United States. Common conjunctival symptoms are itching, tearing, and perhaps burning. Involvement of the cornea is rare, with blurring of the vision being the most common corneal symptom. Clinical signs include a milky or pale pink conjunctiva with vascular congestion that may progress to conjunctival swelling (chemosis). A white exudate may form during the acute state, which becomes stringy in the chronic form. Although ocular signs are typically mild, the conjunctiva frequently takes on a pale, boggy appearance that often evolves into diffuse areas of papillae (small vascularized nodules). These papillae tend to be most prominent on the superior palpebral conjunctiva. Occasionally, dark circles beneath the eyes (allergic shiners) are present as a result of localized venous congestion. PAC, like seasonal AC, also exhibits the classic IgE/mast cell-mediated hypersensitivity to airborne allergens. But, instead of being sensitive to grass or weed pollens, patients with PAC are more commonly sensitive to common household allergens such as dust mites, animal dander, and, possibly, cockroach. The ocular reaction seen in both seasonal AC and PAC often resolves quickly once the offending allergen is removed. Obtaining a detailed history from the patient can make the diagnosis of these disorders. Both eyes are typically affected simultaneously, and quite often a family history of hay fever or atopy may be elicited.

Vernal Keratoconjunctivitis

Vernal conjunctivitis is a chronic mast cell/lymphocyte-mediated allergic disorder of the conjunctiva appearing more in males prior to pubescence, after which it is equally distributed among the sexes and "burns out" by the third decade of life (about 4–10 yr after onset). This condition is seasonally recurrent and chronic in nature, occasionally lasting up to 10 yr. Vernal conjunctivitis usually begins in the spring with symptoms that include intense pruritus exacerbated by time, exposure to wind, dust, bright light, hot weather, or physical exertion associated with sweating. Associated symptoms involving the cornea include photophobia, foreign body sensation, and lacrimation. The most remarkable finding of vernal conjunctivitis is intense itching and giant papillae on the

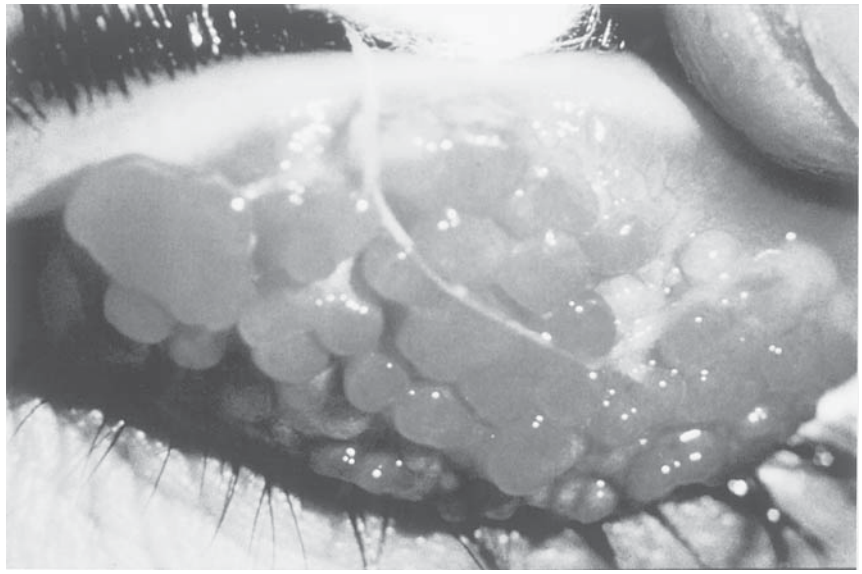

Fig. 1. Giant papillae on the tarsal conjunctiva of a patient with vernal conjunctivitis. Photograph courtesy of Barbara Jennings.

tarsal conjunctiva (Fig. 1). The "giant" papillae reaching 7–8 mm in diameter of the upper tarsal plate can result in large masses of them, leading to the cobblestone effect seen on examination. In addition, patients may develop a thin copious milk-white fibrinous secretion; limbal or conjunctival "yellowish-white points" (Horner's points and Trantas' dots); an extra lower eyelid crease (Dennie's line); corneal ulcers, or pseudomembrane formation of the upper lid when everted and exposed to heat (Maxwell-Lyons' sign). The effects of vernal conjunctivitis can be so severe that blindness may result, affecting one eye more than the other. Diffuse areas of punctate corneal epithelial defects can occur in some cases. These defects are best appreciated with a cobalt blue light after the instillation of topical fluorescein dye. In severe cases, these superficial punctate defects may progress to epithelial "shield ulcers." Conjunctival biopsies reveal increased numbers of eosinophils, basophils and mast cells, as well as plasma cells and lymphocytes.

Atopic Keratoconjunctivitis

AKC is a chronic inflammatory process of the eye associated with a familial history for atopy such as eczema and asthma; primary care physicians should expect to see 25% of their elderly patients with eczema to also have some form of AKC. AKC can be seen in individuals as early as their late teens; it commonly persists until the fourth and fifth decades of life. AKC is an eye disorder with disabling symptoms; when it involves the cornea, it can lead to blindness. Ocular symptoms of AKC are similar to the cutaneous symptoms of eczema and include intense pruritus and edematous, coarse, and thickened eyelids. Severe AKC is associated with complications such as blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex; it is primarily associated in 40% of the older patients, with the peak incidence occurring in the 30- to 50-yr age group. The symptoms of AKC commonly include itching, burning, and tearing, which are much more severe than in AC or PAC and tend to be present throughout the year. Seasonal exacerbations are reported in many patients,

especially in the winter or summer months, as well as exposure to animal dander, dust, and certain foods. Ocular disease activity has been shown to correlate with exacerbations and remissions of the dermatitis. Cataracts associated with AKC occur in 8–12% of patients with the severe forms of atopic dermatitis, but especially in young adults, approx 10 yr after the onset of the atopic dermatitis. A unique feature of AKC cataracts is that they predominantly involve the anterior portion of the lens and may evolve rapidly into complete opacification within 6 mo, whereas AKC patients may develop posterior polar-type cataracts; these are more commonly associated with prolonged use of topical corticosteroid therapy. Keratoconus occurs in a small percentage of patients with atopic dermatitis. Retinal detachment appears to be increased in patients with AKC, although it is also increased in patients with atopic dermatitis in general.

Blepharoconjunctivitis

Blepharitis is inflammation of the eyelid margins that is most often misdiagnosed as an ocular allergy because it commonly causes conjunctivitis as well. Infection or seborrhea are common causes. As in patients with atopic dermatitis, the most important organism isolated from the lid margin is *Staphylococcus aureus*. Antigenic products and not the colonization itself are thought to play the primary role in the induction of chronic eczema of the eyelid margins. The symptoms include persistent burning, itching, tearing, and "a feeling of dryness." Patients commonly complain of more symptoms in the morning than in the evening. This is in contradistinction to patients with dry eye syndromes, who complain of more symptoms in the evening than in the morning because of drying out of the tear film during the day. The crusted exudate that develops in these patients may cause the eye to be "glued shut" when the patient awakens in the morning. The signs of staphylococcal blepharitis include dilated blood vessels, erythema, scales, collarettes of exudative material around the eyelash bases, and foamy exudates in the tear film. Blepharitis can be controlled with improved eyelid hygiene with detergents (e.g., nonstinging baby shampoos) and with steroid ointments applied to the lid margin with a cotton tip applicator that loosens the exudate and scales.

Contact Dermatitis of the Eyelids

In contradistinction to ocular allergy, which is predominantly associated with the activation of mast cells, contact dermatitis is predominantly a lymphocytic delayed type of hypersensitivity reaction involving the eyelids. Because the eyelid skin is soft, pliable, and thin, contact dermatitis of the eyelids frequently causes the patient to seek medical attention for a cutaneous reaction that elsewhere on the skin normally would be of less concern. The eyelid skin is capable of developing significant swelling and redness with minor degrees of inflammation.

Contact dermatitis of the lids and periorbital area more often is caused by cosmetics applied to the hair, face, or fingernails than by cosmetics applied to the eye area. It is important to bear in mind that the sites to which some of these cosmetics are applied may not be affected. This is particularly true for hair dye (Fig. 2) and nail polish. Preservatives such as thimerosal found in contact lens cleaning solutions have been shown by patch tests to be major culprits. Stinging and burning of the eyes and lids are the most common complaints. These subjective symptoms are usually transitory and unaccompanied by objective signs of irritation. Two principal forms of contact dermatitis attributable to eye area cosmetics are recognized: allergic contact dermatitis and irritant (toxic) contact

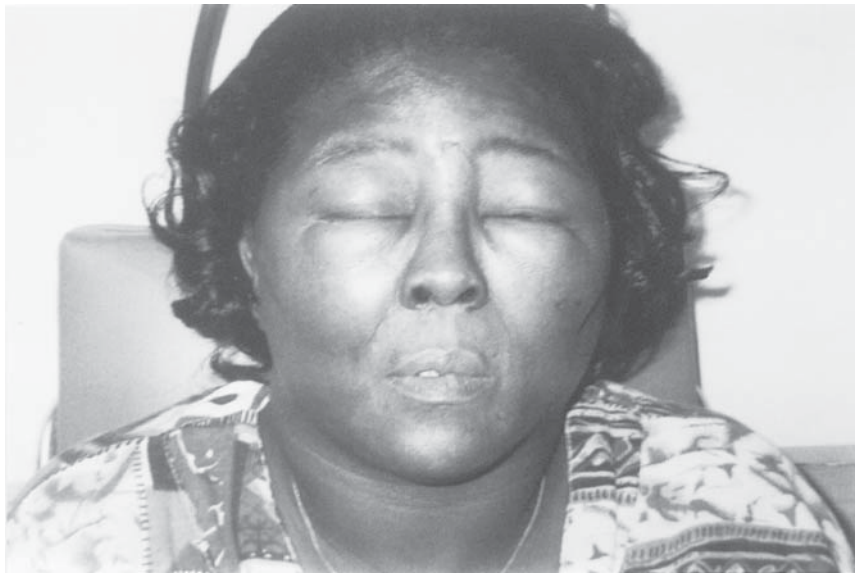

Fig. 2. Angioedema around the eyes 24 h after exposure to hair dye. Patient had a similar reaction to hair dye 2 mo previously.

dermatitis. Most common irritants are found in water-based mascara that usually contains emulsifiers such as sodium borate and ammonium. These "water-based" emulsifiers can be irritating the conjunctival surfaces in certain individuals who may otherwise tolerate an anhydrous, waterproof mascara. The patch test can assist in pinpointing the causative antigen, but interpretation of patch-test results may consequently be difficult, and the likelihood of irritant false-positive reactions must be borne in mind.

Contact allergy is a common cause of eyelid dermatitis in particular, and the allergens may reach the skin in many different ways. Common sources for allergenic sensitizers are topical pharmaceutical products (antibiotics, corticosteroids), cosmetics (fragrance components, preservatives, emulsifiers, hair-care and nail products), metals (nickel), rubber derivatives, resins (e.g., epoxy resin), and plants. Also, latex allergy (immediate-type sensitivity presenting as a contact-urticaria syndrome) was a frequent finding in such patients.

Giant Papillary Conjunctivitis

GPC is increasingly more common with the advent of extended-wear soft contact lenses and other foreign bodies such as suture materials and ocular prosthetics. There is an increase of symptoms during the spring pollen season; symptoms include itching. Signs include a white or clear exudate upon awakening, which chronically becomes thick and stringy, and the patient may develop papillary hypertrophy ("cobblestoning"), especially in the tarsal conjunctiva of the upper lid, which has been described in 5–10% of soft and 3–4% of hard contact lens wearers (Fig. 3). The contact lens polymer, preservatives such as thimerosal, and proteinaceous deposits on the surface of the lens have all been implicated as causing GPC, but this concept remains controversial. Common symptoms include intense itching, decreased tolerance to contact lens wear, blurred vision, conjunctival injection, and increased mucus production. Treatment involves corticosteroids, antihistamines, mast cell stabilizers; frequent enzymatic cleaning of the lenses; or chang-

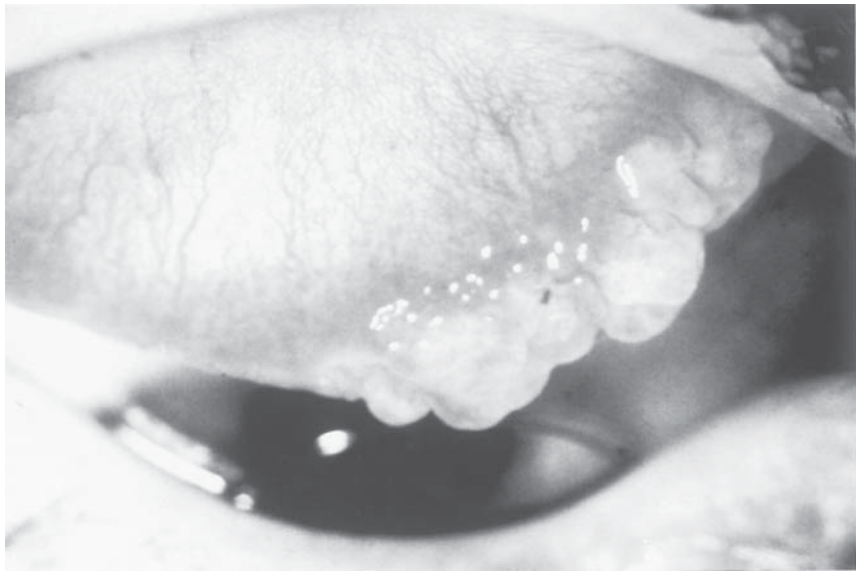

Fig. 3. Giant papillary conjunctivitis in a contact lens patient. Note the giant papillae on inversion of the upper eye lid. Photograph courtesy of Tom Landgraf.

ing the lens polymers. Disposable contact lenses have been proposed as an alternative treatment for GPC. It will usually resolve when the patient stops wearing contact lenses or when the foreign body is removed.

Bacterial Conjunctivitis

Ocular irritation, conjunctival redness, and a mucopurulent discharge that is worse in the morning characterize acute bacterial conjunctivitis. The absence of itching should indicate an infectious cause of conjunctivitis such as bacterial or viral. In bacterial conjunctivitis the eyelids usually become matted to each other; this is primarily noted in the morning when the patient awakens. There is a large accumulation of polymorphonuclear cells on the surface of the eye that causes the discharge to become discolored (yellowish-green) (Fig. 4). Scraping and culturing of the palpebral conjunctiva can assist in the diagnosis and treatment with the appropriate topical antibiotic regimens.

Some forms of bacterial infection, such as inclusion conjunctivitis, that have been associated with chlamydial infections are associated with a preauricular node. Common findings of inclusion conjunctivitis include a mucopurulent discharge and follicular conjunctivitis lasting for more than 2 wk. A Giemsa stain of a conjunctival scraping may reveal intracytoplasmic inclusion bodies and will assist in confirming the diagnosis. In addition, such prolonged ocular infections are commonly associated with a conjunctival response that reveals grayish follicles on the upper palpebra. The condition can be chronic, and treatment consists of lid margin scrubs, warm compresses, and antibiotics. In general, a topical, broad-spectrum antibiotic, such as sulfacetamide, erythromycin, or a combination of polymyxin B, bacitracin, and neosporin, is appropriate. Cultures are necessary only if the conjunctivitis is severe; it would be best if they were carefully examined by an ophthalmologist. The condition should be followed carefully to ensure that the eye improves.

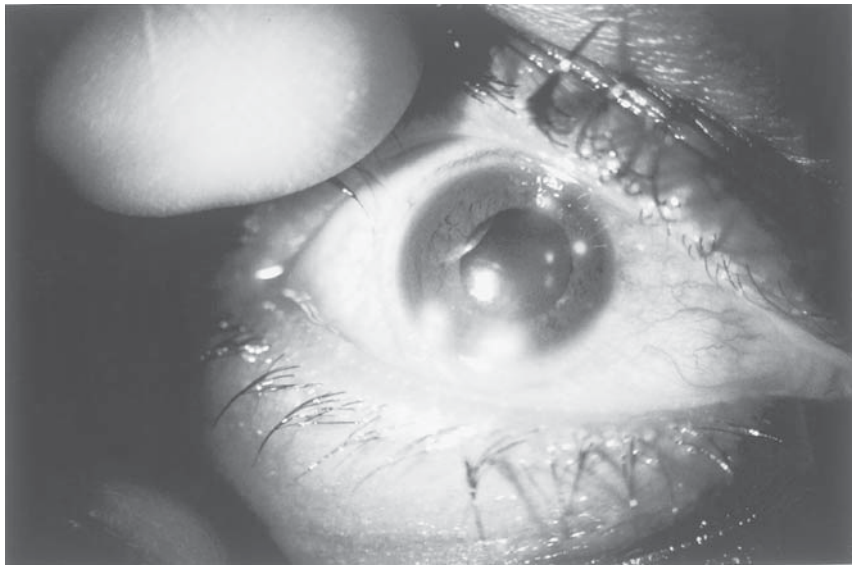

Fig. 4. Bacterial conjunctivitis most likely due to *Staphylococcus*. Note the purulent discharge. Photograph courtesy of Barbara Jennings.

Topical gentamicin and tobramycin are indicated if Gram-negative organisms are suspected or seen on Gram stain. It should be noted that all of these antibiotics have the potential to elicit an allergic reaction. A careful history for drug allergies, a time limit for therapy, and re-evaluation will minimize complications. Topical ciprofloxacin or ofloxacin offers coverage for a wide spectrum of infecting agents, but should be used only when there is the likelihood for therapeutic failure or the conjunctivitis is thought to be the result of multiple infecting organisms or *Pseudomonas* species. Treatment of inclusion conjunctivitis should be aggressive because there is the potential for the cornea to perforate in a short time. Both topical and systemic antibiotics should be used. The patient should be observed for other sexually transmitted diseases.

Viral Conjunctivitis

Viral conjunctivitis usually has an acute onset, is unilateral, and lasts 1 wk, but it frequently becomes bilateral. A major clinical symptom that differentiates this from AC is burning and the absence of itching. Adenoviral infections are among the most common viral ocular infections and are extremely contagious. The viral infection produces an inferior follicular response and a serous discharge. It may also involve the cornea as a punctate keratopathy or superficial ulcerations (herpes simplex or herpes zoster infections).

Common findings of viral conjunctivitis include a watery discharge, conjunctival injection, chemosis, and enlargement of the preauricular (pretragal) lymph nodes. Patient history also assists in the diagnosis. Viral conjunctivitis is usually transmitted between family members or among school children. As in chronic bacterial infections, gray elevated vascular areas known as lymphoid follicles may also be present.

A more serious form of viral conjunctivitis is that caused by herpes simplex, which is one of the leading infectious causes of blindness in Western countries. The viral infection

produces an inferior follicular response and a serous discharge and can occur without any other sign of a herpetic infection. The pain associated with herpetic infections is excruciating. The pain can occur days before the lesions appear. The absence of pruritus should guide the clinician away from a diagnosis of allergic eye disease and toward an infectious complication. It may also involve the cornea in the form of punctate keratopathy or the classic "dendritic" superficial ulcerations. The possibility of herpes keratitis is one of the most compelling reasons for a primary care physician to examine the cornea with fluorescein staining. Treatment of nonspecific viral conjunctivitis is largely supportive and requires no drug therapy. Topical vasoconstrictors may provide symptomatic relief, and they may decrease conjunctival injection. If the corneal epithelium becomes compromised and there is a risk for secondary infection, prophylactic antibiotics may be indicated.

Proptosis

Eyes that protrude past the capacity for the lids to close can become extremely dry. Without proper lubrication and protection, loss of vision can result. One of the most common conditions causing proptosis is Graves' ophthalmopathy with or without hyperthyroidism. This is also commonly associated with conjunctival chemosis that is unresponsive to oral or topical antihistamines. Symptomatic treatment includes ocular lubricants, especially at night. The underlying cause of proptosis should be defined.

Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca is a dry eye syndrome commonly associated with an underlying systemic autoimmune disorder such as Sjögren's syndrome, rheumatoid arthritis, or HIV infection. However, it must be included in the differential of ocular allergy, especially in perimenopausal and postmenopausal women. Tear production decreases with age—60% fewer than at the age of 18. The eye produces approx 400 drops of tears per day. It is characterized by an insidious and progressive lymphocytic infiltration into the main and accessory lacrimal glands. Patients initially complain of a mildly injected eye with excessive mucus production. Symptoms include a gritty, sandy feeling in the eyes compared to the itching and burning feeling many patients complain of with histamine release into the eye. As the cornea becomes involved, a more scratchy and painful sensation as well as photophobia may appear. The corneal epithelial injury can be detected with punctuate staining with fluorescein. The symptoms worsen throughout the day as the limited portion of the aqueous tear film evaporates. Exacerbation of symptoms also occurs in the winter months when heating systems decrease the relative humidity in the household to less than 25%. Schirmer's test demonstrates decreased tearing, generally with 0–1 mm of wetting at 1 min and 2–3 mm at 5 min. Normal values for the Schirmer's test are more than 4 mm at 1 min and 10 mm at 5 min. The most common cause of dry eye syndrome not associated with an autoimmune disorder is long-term use of medications with anticholinergic properties that cause decreased lacrimation. Many drugs with antimuscarinic properties include the first-generation antihistamines, phenothiazines, tricyclic antidepressants, atropine, and scopolamine. Other agents that are associated with a sicca syndrome include the retinoids, β-blockers, and chemotherapeutic agents. Treatment includes addressing the underlying pathology, discontinuing the offending drug if possible, and generous use of artificial tears or ocular lubricants. Recently, the US Food and Drug Administration approved the first topical medication, Restasis™ (cyclosporine), for the treatment of dry eye syndrome, otherwise known as tear film dysfunction. For more severe symptoms, insertion of punctal plugs may be indicated.

OCULAR EXAMINATION

The ocular examination begins with the eyelids and lashes. One should look for evidence of lid margin erythema, telangiectasia, thickening, scaling, and/or lash collars. The sclera and conjunctiva are then examined for the presence of redness (injection). Certain characteristics that can assist in pinpointing the diagnosis are characterized here.

Subconjunctival hemorrhages spontaneously occur after coughing, sneezing, or straining as a result of spontaneous rupture of a conjunctival or episcleral capillary. A painless focal area of solid redness surrounded by normal white sclera on all sides characterizes it. It commonly resolves without any intervention.

Scleritis tends to develop progressively over the course of several days and is associated with several systemic autoimmune disorders, particularly rheumatoid arthritis and Wegener's granulomatosis. Major signs and symptoms of scleritis include moderate to severe ocular pain, tender and inflamed conjunctiva, and thickened and injected sclera.

Uveitis is a significant ocular condition that requires immediate ophthalmological evaluation. One of the signs of this disorder is circumcorneal injection (ciliary flush), which is often described as a ring of redness that completely encircles the edge (limbus) of the cornea. Pupil size is also extremely helpful in formulation of the diagnosis of a red eye. In iritis, the affected pupil is usually smaller and sluggish. In acute-angle closure glaucoma attacks, the pupil is usually mid-dilated and sluggish or fixed.

The cornea is examined next. A corneal opacity, seen as a whitish infiltrate, is often a sign of a bacterial corneal ulcer. Corneal ulcer is an ophthalmological emergency. Fluorescein stains help to differentiate among punctate epithelial defects (diffuse punctate staining), herpes simplex keratitis (dendrite-like shaped staining), and abrasion (large solid area of staining seen after trauma).

OPHTHALMIC PROCEDURES AND TESTING

Primary health care providers should also be familiar with some ophthalmic procedures and test to assist in completing detailed and thorough history and physical examination in order to assist them in confirming a diagnosis of ocular allergy. More importantly, these various tests help to differentiate between the many disorders that mimic allergic disorders of the eye.

The Schirmer's tear test is the most commonly used and easily performed test for the evaluation of dry eye. Tear production is assessed by the amount of wetting seen on a folded strip of sterile filter paper after it is placed into the conjunctival sac. The patient is seated with the room lights dimmed and is then asked to "look up" as the lower eyelid is gently pulled downward. Excess moisture and tears are dried along the eyelid margin and conjunctiva with a sterile cotton-tipped applicator. The rounded end of the test strip is bent at the notch approx 90–120 degrees and is hooked into the conjunctival sac at the junction of the middle and lateral one-third of the lower eyelid margin. The patient's eyes remain closed throughout the examination. The test strips are removed after 5 min. The length of the moistened area from the notch to the flat end of the sterile strip is measured using a millimeter ruler or the scale imprinted on the test-strip package. Some of the test strips have a leading edge of tear film that changes color, thus improving the reading of the results. The Schirmer's I test (without anesthesia) measures both basal and reflex tearing, whereas the Schirmer's II test (with anesthesia) measures only the basal secretion of tearing and is performed as outlined previously, but with topical anesthesia instilled.

Fluorescein is a water-soluble dye used to examine the cornea and conjunctival surfaces. It stains the denuded epithelium. It is placed into the eye either with a sterile fluorescein sodium ophthalmic strip (Fluor-l-Strip) or with a dropper in liquid form. A cobalt blue filter is needed to best appreciate the fluorescein-staining pattern of the conjunctiva and cornea. This filter produces a blue hue against the intense green color of the fluorescein dye. The patient is asked to blink several times to spread the fluorescein uniformly and evenly over the entire corneal and conjunctival surface. Soft contact lenses must be removed prior to fluorescein instillation to prevent their permanent staining. At least 1 h must pass after completion of the examination before the soft contact lenses can be replaced in the eyes.

Conjunctival scraping can also assist in differentiating various forms of red eye. After the administration of a topical local anesthetic, the palpebral conjunctiva (under the upper lid) is gently scraped several times with a spatula for cytological examination. The sample is spread on a slide and stained with May-Grunwald, Giemsa, or another orthochromatic stain to identify eosinophils or neutrophils. The absence of inflammatory cells does not rule out the diagnosis of AC, but the presence of eosinophils strongly suggests it.

Conjunctival and eyelid cultures are obtained using a sterile cotton-tipped applicator moistened in thioglycolate broth. The lower palpebral conjunctiva is lightly wiped with the applicator stick for 5 s as the patient is asked to look up. Moistened swabs are preferred because they pick up and release bacteria better than do dry swabs. The sample is then placed into the transport medium.

Ocular provocation testing can be likened to "skin testing" of the eye. Known quantities of specific allergen are instilled onto the ocular surface, and the resulting allergic response is measured. This technique is commonly performed by allergists in a research study, especially in the assessment of new drugs against ocular allergies.

OCULAR DRUG FORMULATIONS

Solutions and suspensions are the most common formulation of ocular medications. Like other medications, ocular drugs contain inactive ingredients, including preservatives, agents to increase viscosity, antioxidants, wetting agents, buffers, and agents to adjust tonicity. Preservatives control growth of microorganisms that may be introduced into the solution accidentally. Some of these agents can stain contact lenses or have a high incidence of hypersensitivity reactions. Ocular ointments are ideal for prolonged contact of the drug with the eye. Ointments can cause blurry vision; the patient should be informed of the possibility of a temporary decrease or blurring of vision. Drugs formulated into ocular gels also serve as vehicles for prolonged contact of the drug with the eye. Sometimes the use of multiple ocular medications is necessary, in which instance drops should be administered no less than 5 min apart to allow for adequate drug–tissue contact time and to prevent one drug from diluting the other. When using an ointment and solution, apply the solution before the ointment, since it can retard the entry of subsequent ocular drops.

DRUGS USED IN THE TREATMENT OF OCULAR ALLERGIC DISORDERS

There has been an increase in research and development in the area of ocular allergy. The majority of available information is buried in the category "allergic rhinoconjunctivitis," but we need to focus on the importance of the quality of life and thus consider the treatment of "conjunctivorhinitis."

The primary stage of treatment focuses on avoidance, which provides modest symptom improvement. This form of intervention can be implemented with the use of over-the-counter forms of artificial tears. These are safe for all ages. Refrigeration of all ocular products further improves their soothing qualities. The use of cold compresses is extremely soothing by decreasing nerve C fiber stimulation for mild to moderate symptoms. Many patients are concerned about the extensive superficial vasodilation; this is easily treated with ocular decongestants. Topical vasoconstrictor agents do provide rapid relief, especially for conjunctival injection, but the relief is often short-lived, and overuse of vasoconstrictors may lead to rebound hyperemia and irritation (conjunctivitis medicamentosa). Concern is often expressed about a rebound effect with vasoconstrictors; although this adverse effect is difficult to measure, it does not seem to be a major problem.

In the conjunctiva, H_1 stimulation principally mediates the symptom of pruritus, whereas the H_2 receptor appears to be clinically involved in the vasodilation. Although topical antihistamines can be used alone to treat AC, combined use of an antihistamine and a vasoconstricting agent is more effective than either agent alone. There are three H_1 antihistamines for ocular use, including an alkylamine (pheniramine maleate) and two ethylenediamines (pyrilamine maleate and antazoline phosphate) that are available in combination with a vasoconstrictor, either phenylephrine or naphazoline.

As monotherapy, oral antihistamines are an excellent choice when attempting to control multiple early-phase and some late-phase allergic symptoms in the eyes, nose, and pharynx. Despite their efficacy in relief of allergic symptoms, systemic antihistamines unfortunately may result in unwanted side effects, especially on conjunctiva as it relates to its anticholinergic drying effects. The newer second-generation antihistamines (cetirizine, fexofenadine, loratadine, and desloratadine) are preferred over older first-generation antihistamines in order to avoid the commonly associated sedative effects, but may retain some of the anticholinergic effects. Focused therapy with topical (ophthalmic) antihistaminic agents is often efficacious and clearly superior when the allergic symptom or complaint is isolated, such as ocular pruritus. Topical antihistaminic agents not only provide faster and superior relief compared to systemic antihistamines, they also possess a longer duration of action on the conjunctiva than other classes. Antihistamines have started to develop a claim of mild anti-inflammatory properties as well. Some of this anti-inflammatory effect seen in pure antihistamines (levocabastine and emedastine) may be attributed directly to the blocking of the histamine receptor that has been shown to downregulate intercellular adhesion molecule-1 expression and in turn limit chemotaxis of inflammatory cells. Some topical multiple-action H_1 antagonists (olopatadine, ketotifen, azelastine, and epinastine) have been shown to prevent activation of basophils, neutrophils, eosinophils, and macrophages or inhibit release of leukotrienes, superoxide anions, oxygen free radicals, platelet-activating factors, and other inflammatory mediators.

Levocabastine was identified from a series of cyclohexylpiperidine derivatives as a potent antihistamine agent having rapid and long-lasting activity. Levocabastine has pronounced selective H_1 receptor activity, 6.5 times more potent than astemizole with minimal to nonexistent binding to dopamine, adrenergic serotonin, or opiate receptors. Interestingly, recent focusing by industry on isomers to improve potency of pharmacotherapeutic agents has also shown that the levo isomer of this compound has greater binding affinity and specificity than the dextro isomer; therefore, only the levo isomer is used in the preparation, which is a suspension, in the treatment of AC.

Azelastine is a second-generation H_1 receptor antagonist that was first shown to be clinically effective in relieving the symptoms of allergic rhinitis following oral or intranasal administration and is presently approved for allergic conjunctivitis.

Emedastine is a relatively selective histamine H_1 antagonist, with no apparent effect on adrenergic, dopaminergic, or serotonin receptors. Relief of the signs and symptoms of AC have been demonstrated in patients treated for 6 wk with emebastine in an environmental study.

After many years of clinical use, the possible mechanisms of action of cromolyn sodium are still unknown, although there are many hypotheses. At first it was thought that the material had an effect on phosphodiesterase or cyclic AMP, but most recently it appears that cromolyn may act on B-lymphocytes switching from μ (IgM) to ε (IgE) heavy chains. This is a novel potential mechanism for the prevention of mast cell-mediated disorders. Sodium cromoglycate was originally approved for more severe forms of conjunctivitis (GPC, AKC, and vernal conjunctivitis). Many physicians have used it for the treatment of AC with an excellent safety record, although the original studies reflecting its clinical efficacy were marginal for AC when compared with placebo. The efficacy of the medication appears to be dependent on the concentration of the solution used: a 1% solution, no effect; a 2% solution, a possible effect; a 4% solution, a probable effect. Lodoxamide is a mast cell stabilizer that has recently been approved for the treatment of all forms of vernal conjunctivitis in a concentration of 0.1% four times a day.

Olopatadine is both an inhibitor of mast cell mediator release and an H_1 receptor antagonist. Many consider this to be both a topical antihistamine and mild anti-inflammatory agent, and it is presently the largest prescribed ocular allergy agent in the United States. It has been approved for the treatment of the signs and symptoms of AC.

Pemirolast potassium, a pyridopirimidine compound, is approved in Japan for use in the treatment of bronchial asthma, allergic rhinitis, and allergic/vernal conjunctivitis. Although its mechanism is not entirely understood, it appears from available data that pemirolast prevents mast cell degranulation and subsequent release of histamine (and 5-hydroxytryptamine in some species), perhaps through inhibition of phospholipid by-products involved in intracellular signal transduction.

Epinastine is a potent histamine H_1- and H_2-receptor antagonist with mast-cell-stabilizing and anti-inflammatory activities that was recently approved in the United States for the prevention of itching associated with AC. It does not significantly penetrate the blood–brain barrier and its safety and tolerability appears to be equal to that of most other topical antihistamines.

When topically administered medications such as antihistamines, vasoconstrictors, or cromolyn sodium are ineffective, milder topical steroids are a consideration. Topical corticosteroids are highly effective in the treatment of acute and chronic forms of AC; regretfully, they are required for control of some of the more severe variants of conjunctivitis, including AKC, vernal conjunctivitis, and GPC. The local administration of these medications is not without possible localized ocular complications, however, including increased intraocular pressure (glaucoma), viral infections, and cataract formation. Fluorometholone, 0.1%, eye drops are often selected as useful in the treatment of external ocular inflammation. Two modified steroids have been investigated recently for their efficacy in AC. Rimexolone and another modified corticosteroid, loteprednol etabonate, are highly effective in the treatment of AC and are only rarely associated with a significant rise in intraocular pressure.

More data are being released on immunotherapy. The efficacy of allergen immunotherapy is well established; patients given immunotherapy require 10- to 100-fold greater exposure toallergen to develop a breakthrough of allergic symptoms.

Future developments in the treatment of ocular allergy include research into the use of immunophilins such as cyclosporine. Cyclosporin A is a fungal antimetabolite that can be used as an anti-inflammatory agent. Topical cyclosporine has been approved for topical treatment of patients with dry eye syndromes (tear film dysfunction), but its potential may also be in the treatment of ocular allergy as well. Cyclosporine has been shown to inhibit mast cell mediators such as histamine and mast cell–leukocyte cytokine-induced cascades. It reduced the number of neutrophils, eosinophils, and lymphocytes infiltrating the conjunctiva 24 h after challenge with compound 48/80, a well-known mast cell-degranulating agent. In addition, FK-506, a hydrophobic macrolide lactone, is of special interest in ophthalmology because it may be effective in the treatment of a variety of immune-mediated diseases such as corneal graft rejection, keratitis, scleritis, and ocular pemphigoid (Table 4).

In some cases, the primary health care provider must consider patients with contact lenses. Because 25% of the general US population have allergies and more than 20 million patients wear contact lenses, the overlap of these two issues is large. Individuals who suffer from the more chronic forms of ocular allergy—AKC, viral conjunctivitis, and GPC—should refrain from using contact lenses. In some cases of GPC a "lens-free holiday" will help in the resolution of symptoms. The application of topical medications in contact lens wearers poses many issues, including permanent staining of the contact lens by the preservative and alteration of drug distribution while wearing the contact lens. Individuals should not wear their contact lenses while placing topical medications into their eyes. They should place the medication into the eyes first, wait 10 min, and then insert their contact lenses.

SUGGESTED READING

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Table 4
Treatment Options for the Various Forms of Allergic Conjunctivitis and for Occasional/Intermittent (Acute) Symptoms of Ocular Allergy

Primary

1. Avoidance of allergens: Effective and simple in theory, but typically difficult to practice. There is commonly more than 30% symptom improvement.
2. Cold compresses: Decrease nerve C fi ber stimulation; effective for mild to moderate symptoms; reduce superfi cial vasodilation.
3. Preservative-free tears: Effective inexpensive OTC treatment that is extremely soothing; even more soothing if products are refrigerated; safe for all ages and can be used as needed without concern

Secondary

1. Topical antihistamine: Topical application of antihistamine more effective than systemic in relief of itching; have a quick onset.
   - Levocabastine: Approved for children 3 yr and older
   - Emedastine: Approved for children 12 yr and older
2. Decongestants: Have limited duration of action; no effect on itching
3. Topical antihistamine/decongestant combination: Limited agents that are OTC that relieve redness and minimally affect itching (pheniramine-naphazoline, antazoline-naphazoline)
4. Oral antihistamines: Systemic antihistamine treatment should be accompanied by eyedrops, as systemic agents may cause drying, and thus further irritation, of the eyes.
   - Sedating antihistamines (e.g., diphenhydramine, chlorpheniramine): Oral agents mildly effective for itching; common anticholinergic effects may cause dry eyes, nose, mouth and throat; sedation; excitability; dizziness; disturbed coordination
   - Nonsedating antihistamines (e.g., loratadine, fexofenadine): Oral agents mildly effective for itching may not effectively resolve ocular symptoms; may be associated with dry eyes, which can potentially worsen signs and symptoms of allergy
5. Topical mast cell stabilizers
   - Cromolyn: Used prophylactically
   - Lodoxamide: Relatively potent; relatively rapid onset of action; provides effective relief of symptoms; has additional eosinophilic effect; approved for use for diseases with corneal changes
6. Topical nonsteroidal anti-inflammatory agents
   - Ketorolac: Approved for treatment of ocular itching; stinging/burning on instillation experienced by up to 40% of patients
7. Topical antihistamine/mast cell stabilizer
   - Olopatadine: more effective at relieving symptoms; twice-a-day dosing because of long duration of action
8. New topical agents under development
   - Azelastine (topical antihistamine/mast cell stabilizer)
   - Ketotifen* (topical antihistamine/mast cell stabilizer)
   - Pemirolast* (Mast cell stabilizer)
   - Cyclosporine (anti-inflammatory immunomodulator)
9. Topical corticosteroids: Relieve inflammatory symptoms of itching, redness, and edema; appropriate for short-term use in severe conditions (atopic keratoconjunctivitis, ‡ giant papillary conjunctivitis, vernal keratoconjunctivitis) and in recalcitrant cases of perennial allergic conjunctivitis; contraindicated in herpes simplex or ocular viral, fungal or mycobacterium infection; may permit secondary infection or cause intraocular hypertension, glaucoma, or cataracts; intermediate therapy (more than 1 wk) should be monitored by an eye-care professional
   - Loteprednol: Low-potency steroid approved for allergic conjunctivitis
   - Rimexolone: Low-potency steroid approved for allergic conjunctivitis
10. Allergy skin testing: To identify and possibly improve environmental measures
11. Immunotherapy: If avoidance and pharmacotherapeutic measures fail

* Recently approved.

12 Urticaria and Angioedema

Albert F. Finn, Jr., MD

CONTENTS

SUMMARY

One in five individuals will suffer from hives at some point during his or her lifetime. These individuals usually look to their family doctor for help. As such, patients presenting with hives will be a common occurrence in the primary care setting. Clinicians will need to develop an approach that determines treatment needs based on triggers, duration, and underlying cause. If medications are recommended, these need to provide symptom relief; however, not intolerable side effects. Short-lived episodes are generally amenable to antihistamines, though chronic urticaria requires a skilled approach. Recognition of underlying causes requires diligence, but may suggest a need for modifiers of systemic autoimmune diseases. Research efforts continue to yield information on mechanisms of pathophysiology.

Key Words: Angioedema; anti-IgE receptor antibody; autoimmune thyroid disease; chronic idiopathic urticaria; histamine-releasing factors; hives; mast cell; physical urticaria.

INTRODUCTION

Patients exhibiting hives and associated soft tissue swelling are common in the outpatient setting. These complaints brought to the primary care physician generally will result in a diagnosis of urticaria and angioedema. The patients refer to the urticaria and angioedema by various descriptive terms, such as hives, welts, or an itchy rash. Indeed, the lesions that are described by patients with a variety of terms can have a diverse appearance. Categorically, urticarial lesions are pruritic and have a center portion that is elevated. The elevated center is often surrounded by an erythematous halo. This prototypical lesion morphologically has a central wheal with a surrounding flare. However, the configuration of the lesions can be quite different, with some lesions typically being

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Fig. 1. Chronic urticaria, which can affect quality of life on a daily basis.

round and circumscribed, whereas others can be serpiginous or diffuse. Characteristically, the lesions should blanch with pressure, and they generally resolve within 24 h, leaving no residual change to the skin. Lesions that do not blanch, do not result in pigmentation or scarring of the skin, or are not pruritic should be assessed for other dermatological processes or vasculitis.

Swelling of the subcutaneous tissue, or angioedema, commonly accompanies urticaria. This swelling generally results from the same pathophysiology. However, the actual process is occurring deeper in the tissue. As a result, the erythema that is seen surrounding superficial lesions is not observed, although the swelling can be visualized. Angioedema generally occurs on the extremities and digits as well as areas of the head, neck, face, and, in males, genitalia. Patients often describe it as being painful in comparison to urticaria, which is described as itchy.

A primary care physician will see many patients with urticaria and angioedema, which affect up to 15–20% of the general population, more commonly women. The majority of outbreaks are acute and self-limiting. Less than 10% of urticarial eruptions will become a chronic process. When urticarial lesions develop, they are associated with angioedema in as many as 50% of cases. Approximately 10% of the cases have only angioedema in the absence of urticaria, and the remaining 40% have solely urticaria.

Acute urticaria is a daily problem that primary care physicians handle frequently and effectively. The etiology is often elusive. However, its acute and self-limited character limits morbidity. Chronic urticaria and angioedema tend to be a much more vexing problem, often disabling and interfering with the patient's quality of life (Fig. 1). Recently, research suggests an autoimmune etiology for a subpopulation of those with chronic urticaria and angioedema, which could result in different approaches to the treatment of these patients.

CLASSIFICATION AND ETIOLOGICAL CONSIDERATIONS

Urticaria and angioedema are classified by several characteristics. The most common classification scheme is based on duration. Urticaria that lasts less than 6 wk is deemed acute, and episodes that persist beyond 6 wk are classified as chronic. Designation of acute or chronic urticaria by duration is important, as it portends underlying pathophysiology and should guide both the prognosis and the therapeutic interventions.

Acute urticaria is very common in both children and adults. The acute type is a self-limited process that occurs when mast cells in the skin degranulate. This process is an isolated event and often occurs following exposure to an allergen. It is mediated by immunoglobulin (Ig)E, which is affixed to the surface of mast cells in the skin. When the allergen advances via the bloodstream to the mast cells in the skin, IgE is crosslinked, and the mast cells degranulate. This degranulation results in the release of a host of mediators of inflammation, including histamine, products of arachidonic acid metabolism, and cytokines. This acute event will result in increased vascular permeability and local edema, which is visible as the wheal. The patient will experience itching of the skin and swelling of the dermal tissue. Allergens that can result in acute urticaria include foods, antibiotics such as penicillin, and venoms from bee or fire ant stings. Virtually any antigen that can be disseminated systemically, and for which there is an IgE response, has the potential to cause diffuse hives. If an allergen can penetrate the skin locally, hives will develop at the site of exposure. This might happen, for example, following exposure to latex from latex gloves. These individuals develop acute "contact" urticaria in the geographic distribution of the glove. If sufficient latex is absorbed through the skin and reaches the circulation, generalized urticaria can occur.

Acute urticaria can result from nonspecific stimulation of mast cells as well. This occurs when a physiochemical process degranulates mast cells in the absence of an allergen. Thus, IgE on the surface of mast cells is not directly involved. An example in which mast cells can be degranulated directly is exposure to certain radiocontrast media (RCM). This type of exposure to RCM during a radiographic procedure will change the osmolality of the environment in which the mast cell resides and can result in degranulation. Complement may also be directly activated by these agents, and C5a anaphylatoxin can contribute to mast cell degranulation. These patients will develop acute urticarial eruptions that can progress to anaphylaxis with hypotension and bronchospasm. The use of low-ionic radiocontrast media has lessened the occurrence of this acute urticarial event. Other etiological factors that should be considered in individuals with acute urticaria include coincident viral illnesses. Acute viral prodromes in children are associated commonly with nonspecific urticarial eruptions. However, often these patients are also taking penicillin, which can confound the issue. Noteworthy, although many medications can result in a specific IgE-mediated degranulation of mast cells, codeine and other opioid-derived medications can cause nonspecific degranulation of mast cells via opioid receptors. This acute urticarial eruption does not require IgE and is not a specific allergic process, although it does result in an urticarial eruption and is treated similarly.

In certain individuals, urticaria and angioedema are the result of agents that alter the metabolism of arachidonic acid. The occurrence of hives and angioedema is of an acute nature and is often self-limiting. Once again, this interaction occurs in the absence of a specific response with the involvement of IgE. Therapeutic agents included in this category are aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Rarely, these responses to NSAIDs can be fulminant and life-threatening.

Thus, when a child or an adult has an isolated event of a short duration of urticaria, the clinician must attempt to identify a specific cause or exposure. In the child, typical allergens causing acute urticaria include medications such as antibiotics. A common inciting group is penicillin or other β-lactams regularly used for respiratory tract infections. Food is another common cause of acute urticaria in children, with the leading allergens being derived from egg, milk, soy, peanut, or wheat. In adults, foods more commonly encountered that result in allergic urticaria include shellfish and tree nuts (walnuts, hazelnuts, pecans, etc.). Virtually any food can result in an allergic reaction. However, historical evidence will usually reveal that a particular food resulted in the outbreak of hives shortly after ingestion. In addition, repeated ingestion of that food will result in repeat episodes of acute urticaria. One should be very suspicious of an individual who believes that he or she is allergic to a certain food even though the individual has ingested it on other occasions without typical urticarial or allergic symptoms.

In children, the possibility should always be considered that an acute viral illness is responsible for the urticarial eruption. If the child is also taking an antibiotic for a presumed bacterial infection, it should be determined whether the eruption is from an underlying viral etiology or exposure to the antibiotics. In making this determination, skin testing for penicillin allergy, for example, might be indicated, in contrast to the unsubstantiated conclusion that the child is "penicillin allergic."

The widespread acceptance of NSAIDs for musculoskeletal symptoms and their availability as an over-the-counter (OTC) medication have resulted in many episodes of urticaria and angioedema following their use (Fig. 2). Careful review of all recently used medications could help assess this etiological consideration. Note that adults are not the only individuals who use NSAIDs; this group of medications is commonly used by the public in the treatment of febrile illnesses for children. Furthermore, aspirin enjoys popularity because of its benefit in preventing heart disease and can be the cause of an acute urticarial eruption. Thus, careful questioning regarding OTC preparations must be pursued in adults and children alike.

Chronic urticaria and angioedema, by definition, result in a skin process of greater than 6 wk in duration. Patients with this classification of urticarial disease tend to be a far more troublesome group with severe, protracted and often disabling disease. Typically, they make multiple visits to their primary care physicians because of lack of efficacy from therapeutic regimens. This group of patients does require a more intense effort on behalf of the clinician to rule out (at least initially) the possibility of recurrent episodes of acute urticaria. Once it has been determined that this protracted episode of urticaria is not a result of repetitive exposures to an allergen or agent that results in recurrent acute urticaria, the diagnosis of chronic urticaria and angioedema may be established.

Acute Urticaria and Angioderma

- Less than 6 wk in duration
- Short-lived and self-limiting
- More common in children
- Associated with isolated exposure to allergens (foods, drugs, bee sting, latex)
- Associated with exposure to agents resulting in nonspecific reactions (radiocontrast dye, NSAIDs, codeine)

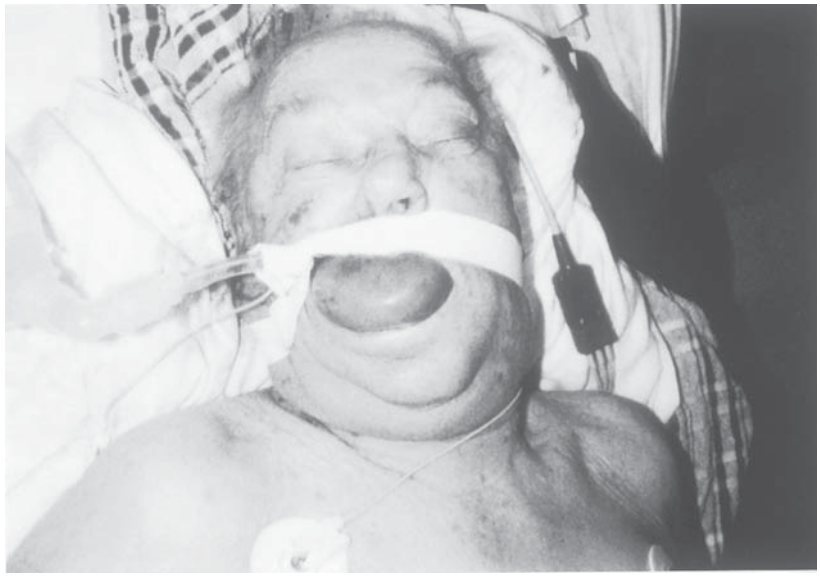

Fig. 2. Glossal angioedema from use of NSAIDs.

Patients with chronic urticaria and angioedema typically are observed for IgE-mediated causes (allergies) that result in their recurring hives. However, this is generally unrewarding, as true allergy(i.e., IgE-mediated hypersensitivity) is rarely the etiological factor responsible for chronic urticaria. Food-elimination diets and skin testing for foods, although generally negative, often help to convince the patient and the clinician alike that foods are not contributing to this process. When positive, eliminating the suspected offender should quickly reveal whether it is relevant to the patient's symptoms. Only strongly positive reactions should be seriously considered. In addition, a thorough review of the patient's medications will disclose whether any agents might be causing a chronic urticarial eruption, although this is uncommon. The use of angiotensin-converting enzyme (ACE) inhibitors can result in recurrent episodes of angioedema. However, urticarial skin lesions are not observed. The swelling is thought to be a result of increased bradykinin levels because kininase normally inactivates bradykinin and ACE inhibitors interfere with the normal activity of kininase. This is an example of a metabolic or pharmacological cause of swelling that is not immune.

Once the diagnosis of chronic urticaria and angioedema has been established and they are believed not to be secondary to allergens such as foods or drugs or recurrent exposure to nonspecific agents such as codeine or NSAIDs, the possibility of underlying systemic disease must be entertained. Atypical aspects of the gross appearance of the hives should heighten concern that a systemic process could be involved. Lesions that do not blanch or are associated with petechiae or purpura suggest vasculitis. Lesions that result in pigment changes, scarring, or blistering or in which individual lesions persist longer than 36 h suggest systemic diseases that could be resulting in lesions that resemble hives.

Once the evaluation has been completed and the chronic hives do not appear to be associated with any other systemic disease, the lesions are, by exclusion, deemed idiopathic. In the past, more than 95% of all chronic urticaria was suspected to be of idiopathic

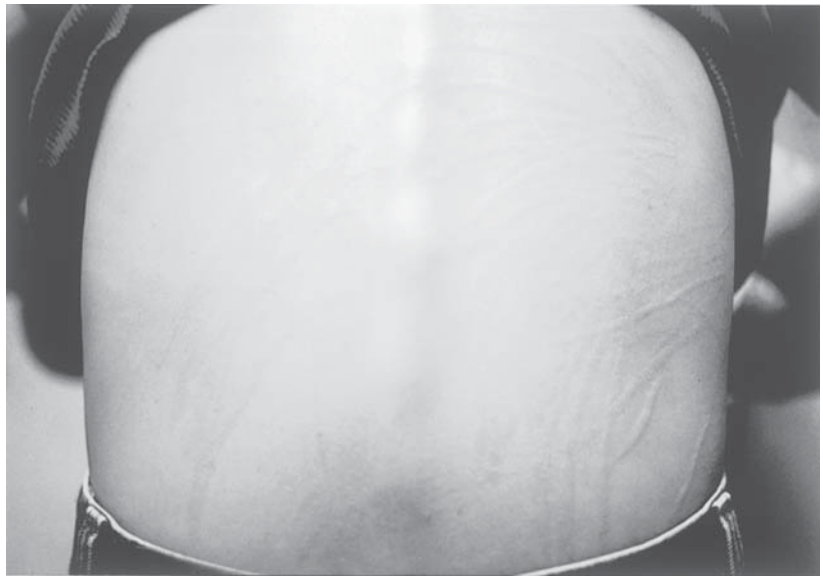

Fig. 3. Dermatographism resulting in linear hives on back after scratching.

classification, assuming that physical causes of hives such as dermatographism had been excluded. Recently, information has resulted in an improved understanding of the cause of chronic idiopathic urticaria. Evidence from research suggests an autoimmune etiology in a large number of the cases that have been previously deemed idiopathic urticaria. Recent data suggest that perhaps 35–45% of individuals with chronic idiopathic urticaria actually do have an underlying autoimmune disease.

Physical urticaria includes a group of urticarial eruptions and angioedema that occur secondary to a physical stimulus. They can be of the acute or chronic type with respect to their duration, but typically are present for many months and in that sense are chronic. They result from a specific thermomechanical or physical stimulus. These stimuli include exposure to cold or hot temperatures, tensile movement of the skin, application of pressure to the skin, exposure to light of various wavelengths, and the induction of a cholinergic response with sweating. Practitioners often encounter physical urticaria that is described as dermatographism. This results when scratching of otherwise normal-appearing skin produces a linear hive that lasts less than 2 h (Fig. 3). This is true of all physically induced hives, with the exception of pressure-induced urticaria, and distinguishes this group of patients from the aforementioned groups with chronic urticaria in which individual lesions last more than 4 h and often 8–24 h. Dermatographism can follow or coexist with acute or chronic urticaria. Mast cell degranulation occurs when the skin is disturbed by the physical stimulus of tensile force. Other mechanical stimuli that can result in urticaria or angioedema include pressure and vibration. Pressure applied to the skin and subcutaneous tissue often can cause the development of hives at the point of pressure or the development of swelling several hours later. The specific stimulus of vibration also can result in angioedema. Individuals who use mechanical devices that result in vibrations, such as jackhammers and vortexes in laboratories, describe soft tissue swelling. Individuals who ride motorcycles report development of swelling and/or hives on their inner thighs.

Table 1
Physical and Physiological Stimuli That Can Result in Urticaria and Angioedema (Physical Urticaria)

Thermal stimuli	Cold: idiopathic cold urticaria Heat: cholinergic urticaria, local heat urticaria
Mechanical stimuli	Dermatographism Delayed pressure urticaria/angioedema Vibratory urticaria/angioedema
Light-induced urticaria	Solar urticaria, types I–VI
Exercise stimuli	Cholinergic urticaria Exercise-induced anaphylaxis (with urticaria)

Thermal stimuli can result in urticaria and angioedema. Exposure to cold is a common stimulus for the development of hives on the face and hands. Patients will describe hives on the parts of their bodies that are exposed to cold water or cool air. If they have significant exposure to cold water over a sufficient portion of their bodies, they can develop hypotension, which may lead to a life-threatening episode. Swimming is a classic example. Heat applied to the skin can also result in urticaria. This is a rare disorder termed local heat urticaria. More commonly, systemic overheating or exercise results in a cholinergic response of sweating with the development of urticaria. Cholinergic urticarial lesions have a characteristic appearance in that they are punctate (1–5 mm) and intensely pruritic. They resolve within 1 h following removal of the stimulus or cessation from exercise. Note, however, that an entity deemed exercise-induced anaphylaxis occurs when an individual develops multiple manifestations of mast cell degranulation, including urticaria, bronchospasm, and cardiovascular collapse, in association with exercise. The distinguishing feature that separates cholinergic urticaria from exercise-induced anaphylaxis is that individuals with cholinergic urticaria develop their hives reproducibly following an increase in core body temperature from exposure to a warm climate, exercise or hot showers. They react within 5–10 min. Individuals with exercise-induced anaphylaxis must undergo a major physiological challenge of exercise such as jogging to develop symptoms, and do not develop hives solely when exposed to a warmer environment (i.e., hot showers or passive sweating). Furthermore, it does not occur reproducibly with every challenge; the exercise often has to occur for a protracted period, and the hives are large. On the other hand, respiratory symptoms or hypotension are rarely, if ever, seen with cholinergic urticaria (Table 1).

Other physical stimuli have been noted to result in urticarial eruptions. Cases in which individuals develop urticaria when the skin is exposed to water are deemed aquagenic. Furthermore, several cases have been described in which a combination of physical stimuli can result in urticarial eruptions. For example, hives that develop following exercise in a cold environment are classified as cold-induced, cholinergic urticaria. Pressure-induced urticaria is an exception: the lesions develop 4–6 h after the stimulus, and the appearance of the hives resembles those of chronic urticaria visually and histologically. The term chronic idiopathic urticaria presumes seemingly spontaneously occurring hives or swelling in the absence of a physical stimulus or identifiable allergen.

EVALUATION

First and foremost, in establishing a diagnosis the primary care clinician knows the importance of a complete history and physical examination of the patient. The patient with urticaria or angioedema typically is assigned the correct diagnostic classification following the history and physical examination. This information establishes whether the disease process is acute or chronic. Hives or swelling persisting beyond 6 wk will be assigned to the chronic designation. Questioning will reveal whether those cases with a duration of more than 6 wk represent recurrent episodes of acute urticaria following inadvertent ingestion or exposure to allergens. A history will reveal whether a child has had an acute viral prodrome and/or is taking antibiotics for a presumed bacterial infection. Furthermore, a careful history will reveal medications or OTC preparations that can result in urticaria. Review of the patient's dietary history is paramount in determining whether foods in the diet or food additives are the culprit. Finally, a discussion with the patient regarding activities and any relationship of hives or swelling with exposure to physical stimuli or exercise might reveal physical urticaria as the diagnosis. Mild dermatographism or pressure-induced urticaria can be present in patients with chronic urticaria; other physically induced hives are always separate. If the urticaria has persisted beyond 6 wk and does not appear to be recurrent episodes of acute urticaria, the primary care clinician must pursue other issues in the patient's history. The patient needs to be questioned about traveling to areas that could have endemic parasitic disease (eosinophilia is a clue to this). The review of systems also must pursue complaints that reflect the possibility of underlying systemic disease. Symptoms of importance include fevers, night sweats, unintentional weight loss, changes in vision, mouth sores, swollen lymph nodes, nausea, vomiting, abdominal pain, genitourinary discomfort, or joint discomfort. A careful and complete physical examination should be performed. Specific attention should be focused on mucosal lesions, adenopathy, thyromegaly, abnormal chest findings on auscultation, hepatosplenomegaly, synovitis, and joint effusions.

Commonly, an episode of acute urticaria in a child or an adult is secondary to the ingestion of a specific food or medication. The history will reveal this connection, and treatment will be empiric for symptom relief. The evaluation should be expanded to confirm or refute any food and medication allergy. Skin tests often confirm the suspicion that a dietary component is responsible for the allergic reaction. In equivocal cases, the gold standard for establishing a food allergy is a double-blind, placebo-controlled food challenge. However, this should be recommended and performed only by an individual who is trained in this procedure. Life-threatening allergic reactions can be induced on challenging individuals with foods or medications to which they have an IgE-mediated process. Penicillin and other β-lactams frequently are responsible for acute IgE-mediated eruptions. This diagnosis can be confirmed through skin testing to investigate IgE-mediated processes to both the major and minor determinants of penicillin. Skin testing to cephalosporins can be done as well. Skin testing is especially helpful for the patient in whom it is unclear whether the infectious process or the antibiotic is responsible for the urticarial eruption. Again, this procedure does carry significant risk for side effects and should be performed only in a controlled setting by individuals who are trained and experienced in the diagnosis and treatment of allergic reactions. Further laboratory workup might not be indicated in the patient in whom a diagnosis of urticaria has been established following the history and physical examination.

Evaluation and Workup of Urticaria and Angioedema

Acute Urticaria/Angioedema

- History and physical
- Consider skin testing or double-blind, placebo-controlled food challenge for possible food allergy.
- Consider penicillin skin testing with major and minor determinants for possible β-lactam allergy.
- Skin biopsy not recommended (will show only dermal edema)

Chronic Urticaria/Angioedema

- History and physical examination
- Laboratory studies to be considered (CBC, UA, ESR, thyroid function tests, ANA, serum chemistries, antiperoxidase antibody, antithyroglobulin anti body)
- Skin biopsy if lesion is atypical or if there is suspicion of underlying systemic disease

The evaluation of chronic urticaria and angioedema is fundamentally different from that of acute urticarial disease. Other coincident disease must be considered in the patient who discloses a history of more than 6 wk of urticaria and angioedema. Generally, the history and physical will have excluded the possibility of a clear relationship between a specific food or medication and the development of hives or swelling. The history should reveal whether the individual has hypertension or heart disease and is presently taking an ACE inhibitor that might be resulting in chronic angioedema. Historical evidence of musculoskeletal disease and the possible need for NSAIDs might suggest a nonspecific mast cell degranulation following the alteration of arachidonic acid metabolism in mast cells. Travel to underdeveloped countries and gastrointestinal complaints might provide evidence of an underlying parasitic infection. Similarly, a history of blood transfusion, intravenous drug abuse, or jaundice might establish the possibility of viral hepatitis causing an urticarial eruption. Any atypical aspects to the gross appearance of the lesions described by the patient might indicate other systemic disease. Following a careful history and physical examination, laboratory studies might be helpful in the patient with protracted disease. Laboratory studies that can be considered include a complete blood count with differential, urine analysis, and determination of the erythrocyte sedimentation rate. Underlying hepatic or renal disease might be reflected in abnormalities found in serum chemistries. If petechiae or purpura are present, antinuclear antibody and cryoglobulin determinations might be helpful. Thyroid function tests, including serum thyroxine (T_4) and thyroid-stimulating hormone (TSH), as well as antiperoxidase and antithyroglobulin antibody, should be performed. Approximately 25% of individuals with chronic idiopathic urticaria have abnormal thyroid laboratory results. Other autoimmune serological findings might be useful for the individual in whom there is suspicion of an underlying autoimmune disease. Finally, IgG anti-IgE receptor antibodies have been described in approx 35–45% of patients with chronic idiopathic urticaria. This antibody crosslinks the IgE receptor and activates complement, which together lead to mast cell degranulation. However, at this time anti-IgE receptor antibodies are exclusively used in research efforts and are not clinically available.

Skin biopsy can be a helpful tool in patients with atypical skin lesions that have a questionable appearance and are suggestive of vasculitis. Histopathological study of an acute urticarial lesion reveals dermal edema with a minimal cellular infiltrate. Physically induced hives (except delayed-pressure urticaria) have no infiltrate at all. This results primarily from the release of histamine, which causes vasodilatation and increased vascular permeability. However, chronic urticaria does reveal a prominent perivascular mononuclear cell infiltrate ($CD4^+$ lymphocytes and monocytes) with increased numbers of mast cells and variable numbers of neutrophils and eosinophils. Although this is similarly nonspecific as compared with the dermal edema seen with acute urticaria, the cellular infiltrate does reflect chronicity of the process and release of chemotactic substances in sufficient concentration and of sufficient duration to attract blood cells. The vessel wall is, however, intact. There is no necrosis of cells or deposition of immune complexes. Thus, it is clearly distinguishable from true vasculitis.

The most important reason for performing a skin biopsy is to eliminate the possibility of any coincident systemic disease that would have a different prognosis or require a different therapeutic approach. Invasion of the dermal blood vessels with neutrophils in combination with leukocytoclasis, nuclear debris, and deposition of either complement or immunoglobulins suggests vasculitis. This finding should prompt further investigation to differentiate the possibility of cutaneous vasculitis from a systemic disorder in which there is a cutaneous vasculitis component.

PATHOPHYSIOLOGY OF URTICARIA AND ANGIOEDEMA

Mast cells and basophils have high-affinity receptors for IgE on their surfaces. If an individual develops a specific IgE response to an antigen, re-exposure to that antigen has the potential of crosslinking IgE on the mast cell or basophil, causing cellular degranulation. Degranulation of mast cells and basophils results in histamine release as well as prostaglandin D_2 and leukotriene C_4 from mast cells, plus other mediators of inflammation. If the mast cells are located in the skin, the patient will develop urticaria. However, if there is more generalized degranulation of mast cells and basophils, the patient can develop bronchospasm and cardiovascular collapse. Thus, the crosslinking of IgE by an allergen, such as penicillin, or a food allergen, such as peanut, results in the degranulation of mast cells or basophils and causes acute urticaria. In patients with chronic urticaria, there is no specific allergen that can be identified that crosslinks specific IgE on the surface of mast cells or basophils. In this light, research efforts have been focused on discovering a factor or factors that could cause histamine release from dermal mast cells. Over the past two decades, a number of substances have been identified that have been termed histamine-releasing factors (HRFs). These HRF-type substances have been proven to release histamine and other mediators from basophils in the absence of any specific allergen. Sources for the HRF substances have included platelets and white blood cells. The finding that white blood cells, specifically lymphocytes, elaborate substances with the potential to release histamine became relevant when considering the biopsy finding of a perivascular mononuclear infiltrate in chronic urticaria. In fact, immunohistochemistry does reveal a predominance of T-lymphocytes in and around blood vessels of the skin from patients with chronic urticaria. Therefore, the mononuclear cells found in proximity to dermal blood vessels might be elaborating HRF substances that, in turn, could cause mast cell histamine release from resident mast cells or infiltrating basophils. Once these cells

Table 2
Cytokines Reported to Activate or Prime Basophils for Histamine Release

Interleukin-1
Interleukin-3
Granulocyte-macrophage colony-stimulating factor
Connective tissue-activating protein III
Neutrophil activating peptide-2
Macrophage infl ammatory protein-1α and -1β (MIP-1α, MIP-1β)
Monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 (MCAF or MCP-1)
Regulated upon activation, normally T-cell expressed and secreted (RANTES)
Monocyte chemotactic and activating factors-3 and -4 (MCP-3, MCP-4)

degranulate, the histamine and other mediators found within their granules can result in urticaria and angioedema. Note, however, that most of the HRF substances identified to date cause basophil degranulation but not mast cell degranulation.

Histamine-releasing ability was first established as a property of interleukin (IL)-1; however, it is not very potent. Continued efforts by various investigators next revealed HRF properties associated with IL-3, granulocyte-macrophage colony-stimulating factor, connective tissue-activating protein III, and neutrophil-activating peptide 2. (These cytokines are outlined in Table 2.)

In most cases, these agents have been shown to effectively cause histamine release from basophils with mixed results in mast cell preparations. Whether these agents cause significant histamine release from cells seen in biopsies of patients with chronic urticaria has not been established. However, these HRFs have been demonstrated in iatrogenically induced blisters formed over urticarial lesions in patients with chronic idiopathic urticaria. The most potent of these factors are contained within a group of chemotactic cytokines known as β-chemokines. These include the following (Table 2): MCP-1, RANTES, MCP-3, MCP-4, and MIP-1α and -1β.

Previously, the association of thyroid disease (specifically Hashimoto's thyroiditis) with chronic idiopathic urticaria had been demonstrated in approx 12% of patients. These individuals were found to have elevated titers of either antimicrosomal or antithyroglobulin antibodies. This finding was further studied at our clinical facility, The National Urticaria Research and Treatment Center, Inc., Charleston, South Carolina, and the presence of antithyroid antibodies has been shown to be higher in patients with severe chronic idiopathic urticaria. As many as 20–25% of patients with recalcitrant hives have been found to have increased antimicrosomal (peroxidase) and antithyroglobulin antibodies even if they are euthyroid. This higher incidence of elevated autoimmune thyroid serological findings could reflect an association more common in severe disease or a difference in current methods for measuring thyroid autoantibodies. Regardless, this association of autoimmune thyroid disease serves to heighten interest in the possibility of an autoimmune mechanism in chronic urticaria and angioedema. To date, a causal relationship between autoimmune thyroid disease and chronic idiopathic urticaria has not been established. Recent efforts pursuing HRFs have identified an immunoglobulin of the IgG isotype that causes mast cell secretion. This immunoglobulin has been identified as an autoantibody against the high-affinity IgE receptor found on mast cells and basophils. It

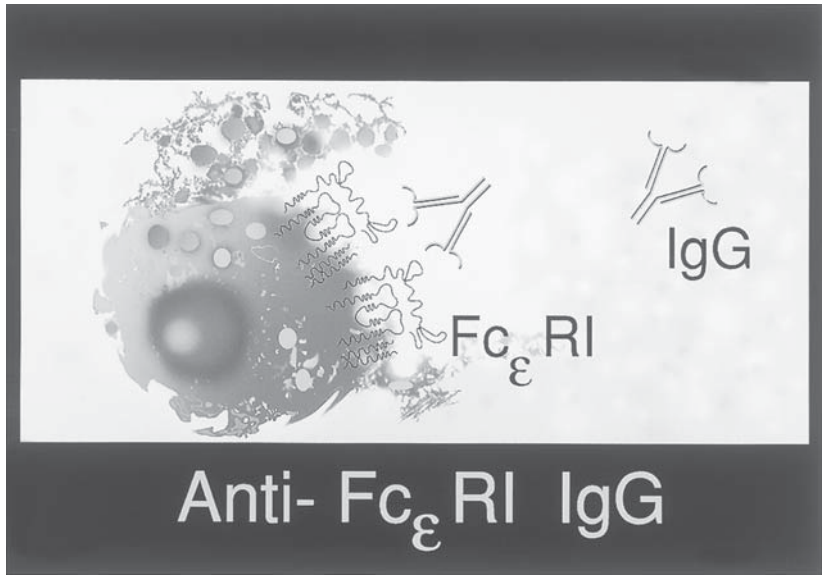

Fig. 4. High-affinity IgE receptor found on mast cells and basophils.

is capable of causing degranulation from dermal mast cells. Various methods used in several laboratories have confirmed the capability of this IgG autoantibody to elicit histamine release from mast cells and basophils. These methods have included the induction of degranulation from rat basophil leukemic cells transfected with the α subunit of the IgE receptor, degranulation of human basophils, and degranulation of cutaneous mast cells. Further, the specific target of this IgG autoantibody is the α subunit of the high-affinity IgE receptor found on basophils and mast cells (Fig. 4). Studies have demonstrated this anti-IgE receptor autoantibody (Fig. 5) in approx 35–45% of patients with the diagnosis of chronic idiopathic urticaria.

With this evolving insight into the autoimmune activity present in patients with chronic idiopathic urticaria, a growing consensus supports the idea that the histopathological lesions are secondary to autoantibody-dependent activation of cutaneous mast cells. Most recent data suggest complement activation and liberation of C5a, which itself is chemotactic and can degranulate cutaneous mast cells. This would result in the release of histamine, prostaglandin D_2, leukotriene C_4, enzymes, cytokines, and chemokines from mast cells, followed by release of cytokines and chemokines from vascular endothelial cells. These products, particularly C5a and chemokines, would encourage the influx of cells as seen on biopsy. Furthermore, cells that accumulate in the dermis around blood vessels do have the potential to elaborate and secrete other histamine-releasing factors that might, to some degree, contribute to ongoing mast cell degranulation. Recent studies have revealed that certain subclasses (i.e., IgG_1, IgG_3) of the IgG autoantibody may have greater importance related to complement activation and mast cell degranulation. However, the extent to which this IgG autoantibody, complement, and other HRFs contribute to the histological appearance of the urticarial lesions seen in chronic idiopathic urticaria has not been determined to date.

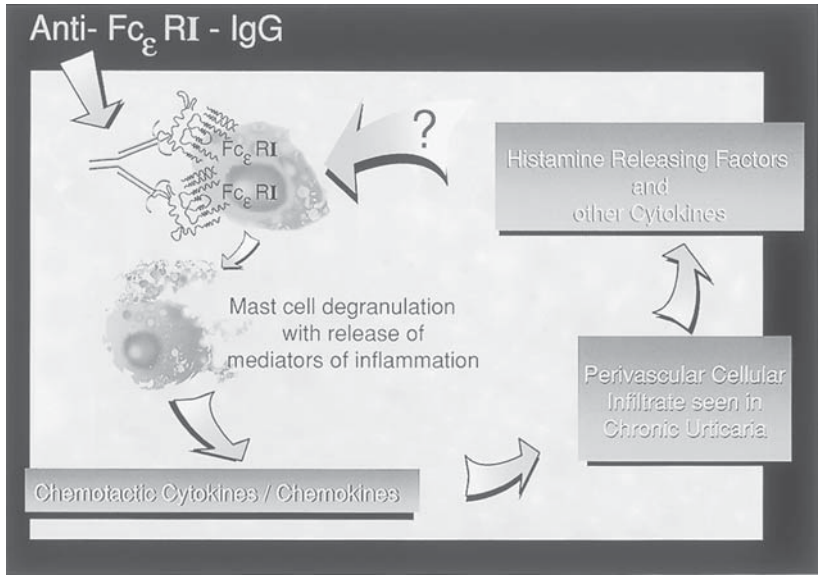

Fig. 5. Autoantibody (IgG) specifi c for the α-subunit of the high-affinity IgE receptor on mast cells and basophils.

TREATMENT OF URTICARIA AND ANGIOEDEMA

In the primary care setting, the common encounter is with that patient who develops acute urticaria following the ingestion of a food or medicine to which he or she is allergic. The patient with an acute allergic reaction often develops urticaria with or without angioedema. If the allergic response extends beyond the skin, bronchospasm, laryngeal edema, or hypotension from cardiovascular collapse might occur. However, in the case of urticaria and angioedema, the patient is treated first by avoidance of that agent. If the patient is hemodynamically stable, the acute urticaria will resolve over the next 12–24 h if there is no further allergen exposure.

Treatment of Acute Urticaria and Angioedema

- Avoidance of food, drug, or other allergen
- Symptomatic relief (H_1 antihistamines, oatmeal baths)
- Short course (no more than several days) of corticosteroid for severe or protracted episodes and to prevent late-phase response
- Epinephrine to be considered only for acute intervention of severe attacks. *Use carefully in the older patient.*

Some degree of relief can be immediately provided with the use of oatmeal baths. Alcohol-containing beverages should be avoided, as they will cause vasodilation, which can worsen the pruritus. An extensive battery of antihistamines is available for symptomatic relief. First-generation H_1 histamine blockers do have the significant side effects of

sedation and mucosal drying. Recently developed second-generation antihistamines (e.g., cetirizine [Zyrtec™]; fexofenadine [Allegra™]; loratadine [Claritin™]; desloratadine [Clarinex™]) are less soporific and have been demonstrated to be safe and effective in the treatment of urticaria. If the acute urticarial eruption is persistent or especially pronounced, a short course of systemic corticosteroids could lessen the intensity or duration of the episode.

Systemic corticosteroids must be used judiciously, as they are associated with significant side effects. However, a course of systemic steroids for acute urticaria need not be longer than several days. Exceedingly high doses of systemic steroids or protracted courses are not justified, as this is a short-lived allergic reaction, and the steroids are primarily aimed at preventing any late-phase response. Subcutaneous epinephrine may be employed when acute urticaria and angioedema progress toward frank anaphylaxis. Adrenergic agents should be employed carefully in older patients who might have cardiovascular or cerebrovascular disease predisposing them to myocardial or cerebral ischemia.

Physical urticaria can be similarly treated with antihistamines. However, physical urticaria can be of protracted duration. The first approach to physical urticaria should be avoidance or lessening of the stimulus causing the urticaria or angioedema. In the individual in whom a thermal stimulus is causing the urticaria or angioedema, exposure to extremes of temperatures should be avoided. In those patients with cold-induced urticaria, appropriate clothing should be used to minimize exposure to cold climates. Individuals should avoid holding cold objects, such as soft-drink cans, and should wear cotton inserts under vinyl gloves when preparing cold food. They must avoid swimming or bathing in cold water, as profound hypotension can develop, which could be potentially life threatening. Individuals with urticaria and angioedema secondary to pressure should wear loosely fitting clothing. They should avoid the use of tight shoes or sitting for long periods, which can result in angioedema of the buttocks. Women with pressure-induced urticaria and angioedema should not carry pocketbooks or luggage with a strap that might apply pressure to the shoulder. The use of tools that require the application of pressure, such as drills or sanders, should be avoided. Mechanical tools that induce vibration, such as orbital sanders or jackhammers, should be avoided in individuals with vibratory urticaria and angioedema. Those patients with cholinergic urticaria that is induced by warm environments or exercise causing sweating must limit activities leading to this cholinergic response. Finally, individuals with dermatographism should try to minimize any scratching of their skin, for it will result in linear urticaria. Antihistamines are very helpful, and nonsedating ones should be tried first. If insufficient relief is obtained, the older sedating ones can be utilized. The drugs of choice are: for cold urticaria, cyproheptadine (Periactin™) 16–32 mg/d in divided doses (four times a day); for cholinergic urticaria, hydroxyzine (Atarax™) 100–200 mg/d in divided doses (four times a day); and for dermatographism, any of these or diphenhydramine (Benadryl™) 100–200 mg/d in divided doses (four times a day). These are adult doses for severe disease and should be adjusted downward for milder disease and for children.

Long-term care for chronic urticaria and angioedema can be challenging. Antihistamines are the initial mainstay of treatment. H_1 antihistamines will result in symptomatic relief, although they are often less than optimal. Because chronic urticaria/angioedema is a chronic disorder, the long-term use of sedating antihistamines can be problematic. Often, H_1 antihistamines can be combined with H_2 antihistamines in the more severe cases. Approximately 15% of histamine receptors found on endothelial cells are of the

H_2 subtype, and studies have suggested that the combination of H_1 and H_2 antihistamines in treating chronic urticaria is beneficial. The antidepressive agent doxepin has been found to be effective in the attenuation of symptoms found in chronic idiopathic urticaria. It does have significant antimuscarinic and antiserotoninergic properties in combination with its antihistaminic activity. However, it is very sedating, and its use generally is limited to nighttime hours. The use of sedating antihistamines must be accompanied by warnings to the patient that these agents do cause sedation, and appropriate precautions must be taken. Nevertheless, high doses spread out four times a day (e.g., 25–50 mg hydroxyzine) lead to tolerance of the soporific effects if taken regularly in the vast majority of patients.

Because up to 25% of patients with chronic idiopathic urticaria have coincident thyroid abnormalities, an interest has developed regarding thyroid replacement. In patients with chemical or clinical hypothyroidism, replacement therapy is the standard of care. However, in individuals in whom there is no evidence of clinical or chemical hypothyroidism, thyroid replacement has not been demonstrated uniformly to be beneficial to the chronic urticarial disease. The use of thyroid supplementation does have significant side effects, including development of clinical hyperthyroidism, osteopenia, and cardiac arrhythmias. In this light, present recommendations are that individuals with the presence of elevated autoimmune thyroid antibodies should be monitored for the development of chemical or clinical hypothyroidism. This monitoring should include measurement of T_4 and TSH approx every 6–12 mo. A small percentage of individuals who do have autoimmune thyroiditis will become hypothyroid over time. If this percentage is higher in individuals with chronic idiopathic urticaria and autoimmune thyroiditis has not been determined.

Corticosteroids by the systemic route will attenuate the symptoms of chronic urticaria and angioedema. These effects are generally short lived, and the patient's symptoms generally recur following discontinuation of the steroid. Because this is a chronic disorder, there is little rationale to the ongoing use of systemic steroids if they will result in significant side effects. Systemic steroids will result in a cushingoid appearance, weight gain, glucose intolerance, hypertension, hyperlipidemia, osteopenia, and easy bruising. With this in mind, the regular or protracted use of systemic corticosteroids is routinely avoided. However, the histopathology of lesions seen in chronic urticaria does reflect an inflammatory aspect with a significant cellular component.

Chronic Urticaria/Angioedema

- H1 antihistamines (e.g., nonsedating—cetirizine, fexofenadine, loratadine, desloratidine, or sedating diphenhydramine, hydroxyzine)
- H_2 antihistamines (e.g., cimetidine, ranitidine, famotidine)
- Short course of systemic corticosteroid (no longer than 1–2 wk)
- Consideration of alternate-day, low-dose steroid and other immunomodulators in severe, refractory disease

Short bursts of systemic steroids will attenuate the cellular influx. However, the degree to which they affect any autoimmune process that is associated with an anti-IgE receptor antibody is not clear. Although systemic corticosteroids have not been demonstrated to affect pathogenic titers of autoantibodies in other disease states or inhibit mast cell

degranulation, they do have the potential to modulate secretion of cytokines and/or histamine-releasing factors that could contribute to the local inflammatory response seen in the skin, including the migration of lymphocytes, monocytes, eosinophils, and basophils. However, to reiterate, no studies have been performed to establish steroid regimens as preferred in the long-term treatment of chronic urticaria, and as such, the prolonged use of systemic corticosteroids should be avoided. Thus, alternative therapies are being pursued on a case-by-case basis in the most severe forms of chronic urticaria and angioedema. For example, corticosteroids are advocated on an alternate-day basis (e.g., 20 mg prednisone every other day with a slow, gradual decrease in dosage). Regimens of this sort are well tolerated for weeks or even months, but with care being taken to avoid inordinate weight gain or other steroid side effects. Conceptually, the use of plasmapheresis could be considered if an IgG autoantibody is believed to be responsible for the mast cell degranulation. However, plasmapheresis has been demonstrated to have variable success in disease states associated with autoimmune processes. In addition, if significant amounts of the inciting IgG autoantibody were removed, the effect would be short lived, as IgG levels in plasma would be reconstituted from other extravascular sites and the plasma cells would continue synthesis. Controlled studies will be helpful to ascertain the utility of systemic steroid regimens, immunomodulators, immunosuppressives (e.g., cyclosporine), and plasmapheresis in the long term for management of chronic urticaria and angioedema that is secondary to an autoimmune abnormality.

CONCLUSION

The primary care physician will encounter many cases of urticaria and angioedema. The most common presentation will be of an acute episode following ingestion of a food to which the individual is allergic or use of a medication to which the individual has developed an allergy. The primary treatment will be empiric with avoidance of the allergen and the use of H_1 antihistamines. A short course of systemic steroids should be reserved for the most severe cases. Generally, the patient will be warned of the predisposition to further allergic reactions, which can be more severe in intensity. An evaluation can include skin testing for foods, penicillin, or cephalosporins if deemed necessary. A Medic-Alert bracelet is often useful to emergency health care providers, should the patient be at risk for life-threatening attacks in the future. A self-injectable epinephrine syringe (EpiPen™, Twinject™) is appropriate if future life-threatening episodes are possible.

Physically induced hives are suspected based on the history and can be confirmed by challenge (e.g., exercise to the point of sweating for cholinergic urticaria, scratching the skin for dermatographism, or a 5-min application of ice on the forearm for cold urticaria). The treatment employs antihistamines in dosages differing with the severity.

The more troublesome cases of urticaria and angioedema are those of the chronic classification. These patients often have persistent or severe disease that is refractory to antihistamine therapy. They might require maximum doses of both H_1 and H_2 antihistamines. An evaluation can be extended to ensure that underlying systemic disease is not responsible for the mast cell degranulation. With information recently developed regarding the autoimmune aspects of chronic idiopathic urticaria, the use of immunomodulators might be appropriate in select cases. The most commonly utilized is alternate-day low-dose prednisone. The possibility of coincident thyroid disease should be investigated in all individuals with chronic idiopathic urticaria, because up to 25% of these individuals

will have the presence of thyroid autoantibodies. In addition, many of these individuals will develop overt clinical or chemical hypothyroidism. Studies presently focused on the relevance of the anti-IgE receptor antibody are expected to be illuminating. The contribution of this autoantibody to the fundamental pathogenesis could reveal future therapeutic directions that will be helpful in the long-term management of these patients. Until such time that the relevance of the anti-IgE receptor antibody as well as other HRFs to the pathogenesis has been determined, the use of immunomodulators, immunosuppressives, or plasmapheresis cannot be recommended routinely. Finally, no consensus suggests the uniform benefit of thyroid supplementation in individuals who have elevated thyroid autoantibodies but are chemically and clinically euthyroid. Further study of populations of patients with chronic idiopathic urticaria and coincident autoimmune thyroid disease will need to be performed to evaluate their progression to overt hypothyroidism. It should be emphasized that if an autoimmune origin proves to be correct for 35–45% of patients with chronic urticaria, the remaining 55–65% are still "idiopathic." But the cause appears most likely to be an endogenous abnormality affecting the skin rather than a response to an exogenous substance not yet identified.

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13 Atopic Dermatitis

Stacie M. Jones, MD, Ariana Buchanan, MD, and A. Wesley Burks, MD

CONTENTS

SUMMARY

Atopic dermatitis is a complex, multifactorial disorder that first develops in most patients before the age of five. The diagnosis relies on information compiled from all aspects of clinical history, physical examination, and laboratory data. Strong correlations exist between atopic dermatitis and other atopic conditions such as asthma and allergic rhinitis. Underlying IgE-mediated sensitivitiy to both aeroallergens and foods have been shown to be strong triggering factors in atopic dermatitis. In addition, *Staphylococcus aureus* can exacerbate atopic dermatitis both by causing secondary infection of compromised skin and by secreting exotoxins that function as "superantigens" directly stimulating T-cell proliferation. Successfut treatment of atopic dermatitis involves a multifaceted approach that addresses avoidance of underlying triggering factors, proper care of dry skin, and pharmacologic management, including oral antipruritic agents, topical corticosteroids, and oral antibiotics when necessary.

Key Words: Atopic dermatitis; aeroallergens; food allergy; *Staphylococcus aureus*; allergy skin tests; corticosteroids.

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INTRODUCTION

Atopic dermatitis (AD) is a complex, multifactorial disorder that was first described in the medical literature more than 100 yr ago. Although clinicians and researchers agree that this disorder is caused by many factors, the role of allergic disease has remained at the forefront of clinical research. In the late 19th century, Besnier provided a detailed description of a chronic, pruritic dermatitis beginning in infancy and showing associations with asthma and rhinitis. The term *prurigo Besnier* was subsequently used to describe these patients. In 1902, Brocq coined the term *neurodermatitis* to refer to a chronic, pruritic skin condition seen in patients with apparent nervous disorders. Coca (1933) was the first to denote the familial occurrence of hay fever, asthma and eczema and introduced the term *atopy* to describe the inherited nature of human hypersensitivity disorders. In 1933, Wise and Sulzberger condensed the past terminology into the descriptive term we use today—*atopic dermatitis*.

Key Clinical Features of Atopic Dermatitis

- A chronic eczematoid dermatitis with 90% of cases beginning before age 5
- Characteristic distribution pattern that varies with age
- Intensely pruritic
- 50–80% of patients will suffer from allergic respiratory disorders later in life

NATURAL HISTORY

Prevalence

Although AD is known to be a common skin disorder, its true prevalence has been difficult to define. With wide variation in the severity and time course of disease as well as differing diagnostic criteria used, the prevalence of AD has been the subject of much debate among physicians and clinical investigators. However, within the last decade, the development of unifying diagnostic criteria and methodology for epidemiological studies has allowed a better understanding of how much of the population is affected by this disease. Estimates place the lifetime prevalence of AD in industrialized nations in children between 10 and 20% and the 1-yr prevalence in adults at 1 to 3%. It is well recognized that AD is more prevalent in industrialized countries compared with non-industrialized countries or tropical regions. Over the past three decades, the prevalence has increased two- to three-fold, following the trend for increasing prevalence in other atopic disease, especially asthma.

Disease Course

AD is a chronic disease of infants, children, and young adults. Onset of disease is typically during early infancy. Sixty percent of affected individuals manifest characteristic lesions during the first year of life. Ninety percent of individuals will be affected by age 5 yr. The remaining individuals will typically manifest disease during late childhood or adolescence. It is rare for symptoms to begin during adulthood and should be a clue to question the accuracy of diagnosis.

The clinical course is variable and unpredictable. Some infants and children will have a mild course with spontaneous remission by 2–3 yr of age. Others will have more

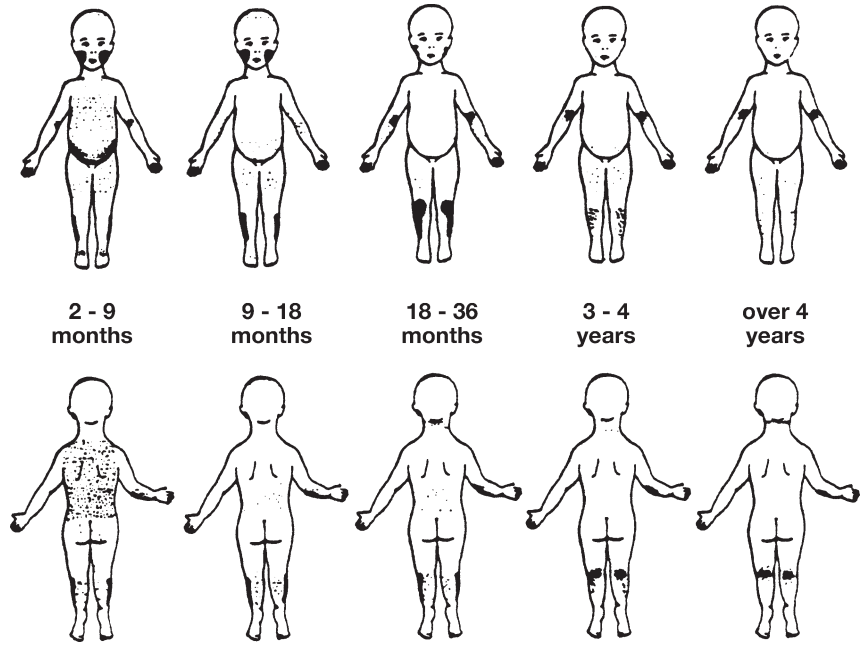

Fig. 1. Distribution of atopic dermatitis in relation to age. (Adapted from Sedlis. J Pediatr 1965; 66(2):235.)

persistent disease with a chronic unremitting course throughout childhood and even into adulthood. Still others will have a waxing and waning course highlighted by unexplained remissions of varying degrees followed by equally unexplained exacerbations.

Characteristic Distribution

AD is typically divided into three clinical phases based on age of onset. The infantile phase is from birth to 2 yr of age. The onset in this group is typically after 2 mo of age, but onset during the first few weeks of life may be seen. The childhood phase is between 2 and 11 yr. The adolescent and adult phase begins at age 12 yr and proceeds through adulthood. Each of these phases has a typical distribution of skin lesions that can prove useful in diagnosis (Fig. 1).

The infantile phase is characterized by erythematous, pruritic, exudative, maculopapular lesions that contrast to the more dry, lichenified lesions seen later in childhood and adult life. In infancy these lesions first appear on the cheeks, forehead, and scalp. Progression then occurs to involve the trunk and extensor surfaces of the extremities. As the infant grows older the distribution of lesions may change to involve the entire extremity surface or the more typical flexural distribution of childhood.

During the childhood phase, lesions of atopic dermatitis are typically dry and involve a more flexural distribution of the extremities. The face, with the exception of the lips and perioral region, is less commonly affected by the age of 4–5 yr. The hands can be especially difficult areas to control in this age group. Intense pruritus and secondary scratching can produce a very anxious, hyperactive child.

The adolescent and adult phase is most commonly manifested as lichenified, pruritic macular lesions involving the face, neck, upper trunk and flexural regions of the extremi-

Table 1
Common Allergens in Atopic Dermatitis

Aeroallergens	*Food allergens*	*Microorganisms*
Pollens	Milk	Bacteria
Molds	Egg	*Staphylococcus aureus*
Dust mite	Peanuts	Streptococci
Animal dander	Soy	Fungi/Yeasts
Cockroach	Wheat	*Pityrosporum ovale/orbiculare*
	Shellfish	*Trichophyton* species
	Fish	Other yeast species (*Candida*, *Malassezia*)

ties. Many young women in their 20s experience hand involvement (i.e., hand eczema) as the first or only manifestation of AD. As previously noted, the onset of disease later in life is very uncommon and should be a clue to search for other etiological factors or diseases.

PATHOGENESIS

Role of Allergens

There is a strong correlation of atopic dermatitis with other atopic conditions such as asthma and allergic rhinitis. The term "atopic march" has been coined to define the natural history of atopic diseaases characterized by a sequence of progression in the clinical signs of atopic disease with some manifestations becoming more prominent while others subside. Typically, the cutaneous manifestations represented by AD represent the beginning of the "atopic march," with approx 50% of patients with AD (especially severe AD) developing asthma and approx 66% developing allergic rhinitis. Because of earlier historical observations of AD associated with other atopic diseases, investigators have explored the role of various allergens as causal factors in these diseases (Table 1).

Aeroallergens

Pollens were the first aeroallergens reported in association with AD. Ragweed pollinosis has been of particular interest, with clinicians citing case reports of patients with seasonal exacerbation of AD and of clearing in a pollen-free environment. In the 1950s Tuft performed intranasal challenges with ragweed pollen and noted rhinorrhea and itching of affected skin areas in AD patients. More recently, investigators have shown positive prick skin tests and patch tests to common pollens in patients with seasonal distribution of their AD. In a study of children, 90% of AD children tested with epicutaneous patch testing developed eczematous lesions in one or more AD predilection sites when tested with dust mite, cockroach, mold and grass mix. Others have shown positive immediate skin tests to birch pollen in AD patients who had worsening of their disease during the birch pollen season.

Mold allergens have also been implicated as causal factors in patients with AD. Tuft induced symptoms of dermatitis in his patients following inhalation challenge with Alternaria when compared with talc powder or pine pollen. Rajka has also demonstrated eczematous lesions in two of five atopic individuals with AD following inhalation of mold extract.

Key Features of the Pathogenesis of Atopic Dermatitis

- Immediate hypersensitivity may be key to pathogenesis in the majority of patients.
- Exacerbations clearly related to contact with aeroallergens or the ingestion of foods to which a patient is allergic.
- Many patients have IgE-mediated allergic responses to microorganisms growing on the skin.
- Nonimmunological factors, such as climate and nonspecific irritants, may play a role.

The largest body of scientific and clinical data regarding aeroallergens and atopic diseases exists in reference to dust mite allergy. Sensitivity to dust mite was first examined in patients with asthma. Reports soon followed of improvement in AD when patients were placed in a dust-free environment and subsequent aggravation of symptoms after exposure to dust. Extensive studies of dust mite antigen and atopic disease association have been performed. They and others have shown positive prick skin testing and patch testing to dust mite antigen in patients with AD. In a recent epidemiological survey, the homes of patients with moderate to severe AD showed a higher dust mite concentration than homes of controls. Elevated serum levels of dust mite–specific antibody and increased basophil sensitivity have also been shown in AD patients when compared with controls. Several groups of investigators have also demonstrated an increased lymphocyte response and specific cytokine profile (e.g., TH_2-type profile with IL-4, IL-5) production in patients with AD and evidence of dust mite allergy. Perhaps the best clinical evidence for dust mite allergen playing a role in the AD condition of some patients comes from reports of patients showing improvement when living in a dust-free environment and having flares of disease upon return to an environment of exposure to dust mite.

Two other types of aeroallergens are felt to play a role in the pathogenesis of AD—animal dander and cockroach allergens. Both of these allergen groups have been studied in association with asthma and allergic rhinitis and are felt to be important factors in certain susceptible individuals. Less scientific information is available with regard to AD; however, anedoctal clinical experience would support their causative roles. Of the animal danders, cat and dog dander are implicated most commonly in atopic disease states. Cat dander allergy, in particular, can manifest as severe in some atopic individuals, especially those with asthma. Cockroach allergens have been recognized more recently in atopic disease, especially in endemic areas and climates. In a study of atopic children, many of them had positive prick and intradermal skin tests to animal dander and cockroach, indicating the possible relevance of these allergens in atopic disease. More study is needed to define further the role of animal dander and cockroach allergens in AD.

Foods

Adverse reactions to foods have been reported in the medical literature since the early 1900s when Smith reported the case of a man with "buckwheat poisoning." In 1918 Talbot was one of the first physicians to observe an improvement in a patient's eczema while on a milk and egg restriction diet. Tuft (1950s) considered food allergy to be the

most important pathogenic factor in infants and young children with AD, yielding to inhalant allergies in older children and adults. Since that time many investigators have studied children with AD and food hypersensitivity. In general, they have shown that dietary manipulation has resulted in dramatic improvement in many patients with AD, especially young children.

Bock and colleagues were the first to establish the use of double-blind, placebo-controlled food challenges (DBPCFC) to assess patients with suspected food hypersensitivity. Because there is poor correlation between allergen-specific IgE antibodies (skin tests or radioallergosorbent tests [RAST]) and clinical symptoms related to food hypersensitivity, oral food challenges (both open and blinded) have been crucial in assisting many investigative groups in the study of food hypersensitivity and AD. Sampson first reported findings of food hypersensitivity in 26 children with AD. These findings were confirmed during a study in our institution in which 46 children with AD were studied with DBPCFC. Positive challenges were detected in 33% of patients, with 91% reacting to only one or two foods. These groups have shown a direct correlation between hypersensitivity to foods (Table 1) and the development of AD. In addition, these groups have consistently reported improvement in AD in food protein-sensitive patients while on food elimination diets.

Perhaps the largest body of information regarding AD and food hypersensitivity has been provided by Sampson and coworkers. They have evaluated hundreds of children with AD for food hypersensitivity with more than 1000 DBPCFC. The most commonly implicated foods in causing a reaction were egg, milk, peanut, fish, and tree nuts. Cutaneous symptoms were seen in 75% of positive challenges. The most common cutaneous manifestation consisted of a pruritic, erythematous morbilliform rash involving the AD predilection sites. Other symptoms noted during positive challenge included respiratory (stridor, wheezing, nasal congestion, rhinorrhea, and sneezing) and gastrointestinal (nausea, vomiting, abdominal cramping, and/or diarrhea). All patients found to be allergic to particular foods were placed on an appropriate avoidance diet of that food. Virtually all patients reported improvement in symptoms, either noted as complete resolution or marked clearing.

In a more recent study in our institution we sought to further delineate the role of food hypersensitivity in AD and to determine if patients with AD who had food hypersensitivity could be identified by screening prick skin tests using a limited number of food allergens. Patients with AD attending the Arkansas Children's Hospital Pediatric Allergy Clinic were enrolled. After a detailed medical history and physical examination, the patients underwent allergy prick skin testing to a battery of food antigens. Patients with positive prick skin tests underwent DBPCFC; 165 patients were enrolled and completed the study; patients ranged in age from 4 mo to 21.9 yr (mean 48.9 mo); 98 (60%) patients had at least one positive prick DBPCFC. A total of 266 DBPCFC were performed. Sixty-four patients (38.7% of total) were interpreted as having a positive challenge; seven foods (milk, egg, peanut, soy, wheat, cod/catfish, cashew) accounted for 89% of the positive challenges. Utilizing screening prick skin tests for these seven foods we could identify 99% of the food allergic patients correctly. This study confirms that the majority of children with AD have food allergy that can be diagnosed by a prick skin test for the seven foods.

Sampson and colleagues have presented studies of mediator release that provide further evidence that food-specific IgE-mediated mechanisms play a role in the pathogenesis of AD. They have demonstrated increased plasma histamine levels in AD patients following a positive food challenge, increased spontaneous histamine release from basophils in patients with AD and food hypersensitivity, spontaneous release of a cytokine (histamine-releasing factor) from mononuclear cells in these patients and increased cutaneous hyperirritability to a variety of minor stimuli. These mediators and the associated cutaneous hyperirritability were all noted to be diminished to normal levels after 6–9 mo of food allergen avoidance.

In an earlier study examining the natural history of patients with AD and food hypersensitivity, Sampson reported that 26% of patients lost their clinical hypersensitivity during the first year of allergen avoidance, and 11% lost reactivity during the second year. Therefore, Sampson and others have shown that most children tend to "outgrow" their food hypersensitivity to most foods early in life. Some of these children also show subsequent resolution of their AD, whereas others manifest aeroallergen sensitivity that seems to perpetuate the AD cycle.

Through the years, much attention has been focused on the role of maternal dietary restriction during pregnancy and lactation in the prevention of AD and food hypersensitivity. The most current and comprehensive information to date comes from a study that followed 288 American children from birth through age 4 yr and 125 of these children through age 7 yr. Some mothers and infants were randomized to a prophylactic group consisting of maternal avoidance of cow's milk, eggs, and peanuts during the third trimester of pregnancy and during lactation; use of a casein hydrolysate formula for supplementation or weaning; avoidance of all solid foods for 6 mo; and avoidance of defined allergenic foods for up to 24 mo. Others provided a control or "untreated" group in which no prophylaxis was implemented. After 7 years the only atopic parameters affected between groups were the prevalence of food allergy and milk sensitization prior to age 2 yr. No difference was seen in the prevalence of AD, asthma, allergic rhinitis, food sensitization, or positive skin tests to inhalant allergens. Other studies in children have shown a direct correlation between the number of solid foods introduced before age 6 mo and the prevalence of AD at age 2 yr. These and other studies indicate the potential role of food allergens in the development of AD and the potential benefits of early allergen avoidance in some high-risk infants.

Microorganisms

The role of microorganisms in the pathogenesis of AD has received much attention in recent years. Their potential role as complicating skin pathogens has long been recognized as important, but more recently their role as "allergens" perpetuating the allergic response has been of particular interest. It is postulated that the altered skin barrier seen in patients with AD provides a portal of entry for various pathogens to gain access to the immune system, thus activating mast cells, basophils, Langerhans' cells and other immune cells (Fig. 2). Recently, Ong and coworkers demonstrated that atopic dermatitis skin is deficient in antimicrobial peptides that are needed for host defense against bacteria, fungi, and viruses, thus enhancing the susceptibility of patients with atopic dermatitis to secondary skin infections. The primary classes of microorganisms involved include bacteria and yeasts.

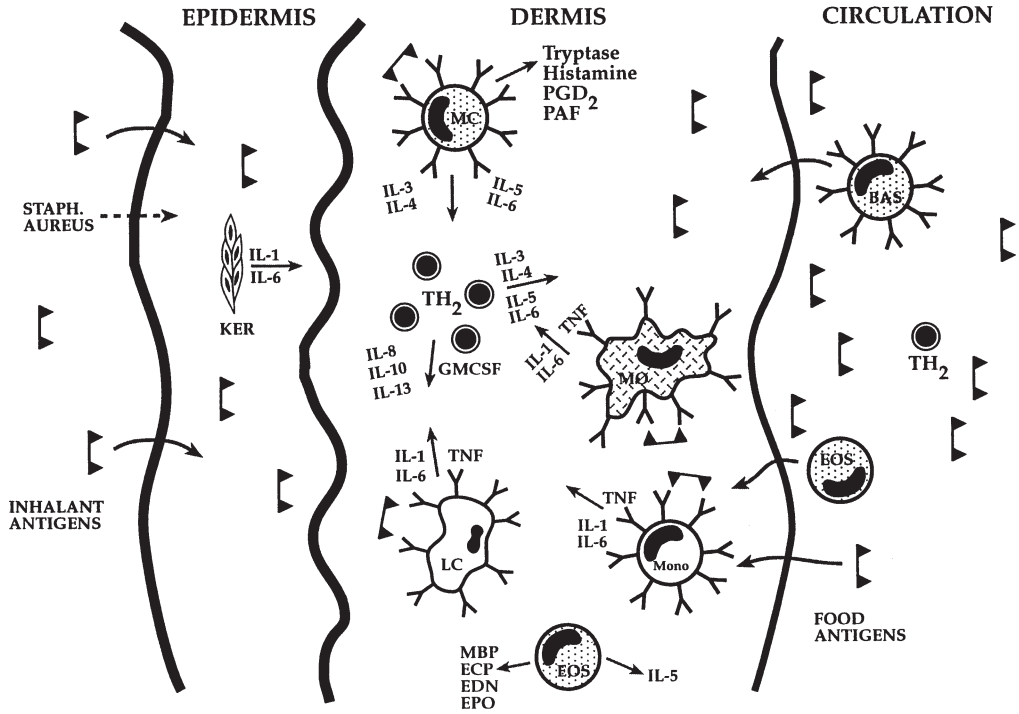

Fig. 2. Schematic representation of the immunopathological events in atopic dermatitis. Allergens transported via circulation or through fi ssures in the skin enter the epidermis and dermis and activate local infl ammatory cells. These cells secrete a variety of mediators and cytokines that perpetuate the cutaneous infl ammatory response. TH_2 = T-lymphocytes capable of secreting interleukin (IL)-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, GMCSF; KER = keratinocytes; MC = mast cells; LC, Langerhans cells; EOS, eosinophils; Mono, monocytes; BAS, basophils, MΦX, macrophages. (Adapted from Sampson HA. Acta Derm Venereol 1992;176:34–37.)

The most extensively studied and widely recognized microorganism of importance in the disease process of AD is *Staphylococcus aureus* (*S. aureus*). *S. aureus* skin colonization of both affected and normal skin has been shown to be increased in patients with AD compared to controls. Some investigators have demonstrated colonization in more than 90% of lesions in some individuals with AD. In addition increased IgE-specific antistaphylococcal antibodies have been demonstrated in sera of patients with AD. More recently investigators have focused on the role of staphylococcal exotoxins in the disease cycle of AD. These studies have focused on the role of stimulating T-cell-dependent IgE production and subsequent enhancement of the allergic response. Evidence for an IgE-mediated mechanism has been supported by Neuber's reports of increased CD23 (low-affinity receptor for IgE) expression in cells from AD individuals following stimulation with *S. aureus*. Leung and coworkers have reported specific IgE antibodies to staphylococcal exotoxins produced from staphylococcal organisms grown from the skin of 32 of 56 AD patients. Basophils from 10 AD patients with IgE antibodies to these exotoxins released histamine in response to specific staphylococcal exotoxins. Basophils from normal individuals or from patients with AD but without IgE anti-exotoxin antibodies

failed to release histamine after exotoxin stimulation. Other data show that low concentrations of toxic shock syndrome toxin-1 (TSST-1) are able to stimulate mononuclear cells from AD patients to produce IgE in a T-cell-dependent fashion. These groups and others have also suggested that these exotoxins may function as "superantigens," thereby perpetuating the immune response by stimulating T-cell proliferation independent of the usual allergic mechanisms. To further emphasize the role of *S. aureus* in the AD process, it has been clearly demonstrated that patients with AD show a better clinical response when treated with combinations of antistaphylococcal antibiotics and topical steroids than with steroids alone. Other bacteria, such as streptococcal species, may also be important, but little clinical or investigative information exists to document their role.

Various species of yeast organisms have been implicated as causal factors in the pathogenesis of AD. *Malassezia furfur* is now the unifying name for a fungus with both yeast forms (Previously classified as *Pityrosporum orbiculare* and *P. ovale*) and a mycelial form (previously classified as *M. furfur*) that commonly inhabits the seborrheic regions of the skin and the scalp in normal individuals. Colonization is more commonly seen in older children and adults than in infants and younger children. Many investigators have shown a strong correlation between active AD lesions and specific antibodies to *P. ovale*. The antibodies have been demonstrated via prick skin testing and serum analysis via RAST. Wessels showed the presence of *P. ovale*-specific IgE antibodies in 49% of AD patients. In addition, patients with head, neck, and upper trunk distribution of AD lesions and evidence of specific antibodies to *P. ovale*, have been reported to show clinical improvement following ketoconazole therapy. Mononuclear cells from AD patients have been shown to demonstrate a higher proliferative response and atopic cytokine pattern to *P. orbiculare* stimulation than nonatopic controls. Although not conclusive, these data suggest the pathogenic role of *Malassezia* species in some patients with AD and emphasize the need for consideration when refractory AD is seen in the typical head and neck distribution, especially in older children and adults. A possible role of other yeasts, such as *Candida albicans*, *Trichophyton*, has been implicated in the pathogenesis of AD. Specific IgE antibodies to *M. furfur* have been detected in 70% of sera from *Malassezia furfur*-sensitized patients with AD. More extensive study is needed to draw firm conclusions regarding the role of these yeasts in the pathogenesis of AD.

Role of Environmental Factors

AD is a complex, multifactorial disease. The course of the disease is influenced by many primary and secondary factors that are often difficult to tease apart. Environmental factors frequently act as "triggers," causing exacerbations of disease, yet they are not primary causes of the underlying disease.

Climate

Several environmental factors can influence the course of disease in AD. One of the most important, yet often obscure, factors is climate. Individuals will respond differently to various climatic influences. Most authors report disease intensification during the winter months and patients having the most comfort during the months of summer. Rajka has reported that improvement during the summer may be due to better sebum and sweat secretion, ultraviolet (UV) rays from sun exposure, exposure to water during swim activities, reduced exposure to indoor allergens (i.e., dust mite and molds), less exposure

to infection and less psychosocial stressors during summer vacations. He also mentions that some of these same influences may in fact aggravate the skin condition of other patients. Clinical researchers have noted the impaired sweating mechanism in patients with AD, making excess sweating and strong heat-adverse factors in those individuals. UV light exposure without appropriate skin protection can also be harmful. Although indoor allergen exposure may be minimized during summer months, outdoor allergen exposure (i.e., grass pollens) may be exacerbating in some regions. As a general rule, cold dry weather is more aggravating to patients with AD secondary to the drying effect. Hot humid weather may also be aggravating as a result of increased perspiration and the increased potential for secondary skin infection. Extremes or sudden changes of any climatic condition (i.e., temperature and humidity) can be aggravating to patients with AD, most likely secondary to an impaired ability for immediate skin adaptation. Several reports have emphasized the beneficial effect of sunny climates such as California or Florida or dry, warm climates as found in Arizona. As previously stated, these factors are only secondary in the large majority of patients and are vary individually.

Irritants

Factors other than primary irritants (i.e., allergens and infection) may complicate the course of AD. Clothing fabrics can influence the comfort level and the amount of pruritus experienced by AD patients. Wool fabrics clearly provide the most irritation and should be avoided in patients with AD. Synthetic fibers such as nylon and polyester may also be poorly tolerated by some individuals. Cotton is generally the fabric that provides the most comfort and least pruritic potential, and its use should be emphasized to patients.

Certain laundry detergents, bleaches, soaps and household cleaning chemicals act as irritants for patients with AD. Mild laundry detergents without bleach are generally better tolerated. Washing clothing through a rinse cycle twice usually ensures removal of the detergent and may be beneficial in some sensitive patients. Mild skin soaps should also be used for bathing by AD patients. They are generally less drying, less irritating and less likely to induce pruritus. Skin should be protected from household cleaners by wearing protective gloves or clothing. The skin barrier is frequently altered in AD and will not withstand the general intrusions that normal skin can endure.

Some foods can also act as triggers of irritation and pruritus. Certain fruits and vegetables, such as tomatoes and citrus fruits, are especially irritating in some individuals. These foods are not primary allergens, but rather irritants causing pruritus secondary to their acidic composition.

Psychosocial Factors

Most clinicians agree that psychosocial factors influence the disease process of AD and further agree that these factors remain secondary and not primary in disease etiology. Emotional upset, stress, job or school tension and unstable or unsupportive home environments all can contribute as exacerbating factors. Some investigators have stated that these psychological influences may lead to autonomic dysregulation, abnormal vascular responses and mediator release, all of which act to trigger an adverse response. In addition, the chronic pruritus seen in all patients with AD, especially those with severe disease, will cause sleep disturbance, hyperirritability and emotional distress, which contribute to the vicious cycle. Although not primary causes of disease, these issues must be addressed in caring for patients with AD to provide maximal symptomatic relief

during periods of disease exacerbation. These issues are especially important in children and adolescents and may occasionally require psychological as well as medical intervention.

Occupation

Choice of career or occupation may strongly influence the disease state for some adult patients with AD. Surveys have reported AD more frequently in occupations in which exposure to dust, wool, textiles, or chemicals is common. The dry, hyperirritable skin of AD is prone to cracking, scaling, and infection following exposure to irritants. For this reason, patients in a workplace of high exposure have frequent or persistent flares of disease. Studies have reported that 65–75% of AD patients report hand eczema, often related to nonspecific irritants in the workplace. The consequences of hand dermatitis and exacerbation of AD may be quite serious in some individuals, requiring a change of duties or occupation to minimize exposure to irritants.

Key Features of Diagnosis

- There is no single diagnostic marker; therefore, the diagnosis is dependent on a global evaluation.
- Morphology, distribution, pruritus, and associated atopic diseases are note worthy features of history and physical examination.
- Laboratory findings of peripheral eosinophilia, increased serum IgE, positive allergy skin tests, and positive food challenge can be markers of disease.

GENETIC ASSOCIATIONS

Like other atopic conditions, AD has a strong genetic predisposition. As many as 60–80% of patients with AD have a family history of a first-degree relative with AD, asthma or allergic rhinitis. In studies of twins, Rajka reported a much higher concordance for atopy in monozygotic twins, whereas AD alone revealed only a 50% concordance in both monozygotic and dizygotic twins. Rajka's data cast doubt on the strictly hereditary influence, yet underscore the importance of the combination of hereditary and environmental factors in the disease process. Numerous reports have suggested HLA associations among families with atopic disease in general and AD specifically. Based on genomic studies assessing for susceptibility loci for atopic dermatitis, multiple pathophysiologically relevant candidate genes have been identified including areas on chromosome 3q21, 1q21, 17q25, and 20p. An area on chromosome 5q31-33 that contains a clustered family of Th_2 cytokine genes has been of particular interest. Other genetic variations reported in AD include a mutation in the promoter region of RANTES, a gain-of-function polymorphism in the α-subunit of the IL-4 receptor and IL-13 coding variants. These data are not definitive at present and suggest that a single set of genes is not responsible for atopic disease inheritance. Multiple patterns of disease inheritance such as autosomal dominance, autosomal-recessive and multifactorial inheritance have been found, emphasizing the obvious complexity of genetic influence on the disease process. Throughout all these studies, however, it is maintained that individuals from atopic families are at greater risk for development of atopic disease in some form.

CLINICAL MANIFESTATIONS

History

AD typically begins early in life, most commonly with skin lesions developing within the first 6 mo. Although this pattern is typical, alterations in presentation frequently occur. A careful history can therefore be useful in making the diagnosis of AD. As noted previously, a family history of atopic disease may provide a clue to the etiology of a patient's skin disease. As many as 80% of patients with AD have a positive family history of atopy. A comprehensive history with regard to possible exacerbating triggers can also be helpful. These triggers may include foods, seasonal allergens, environmental conditions, irritants, emotional distress, and occupational exposures. A careful history will often uncover an exacerbating factor that is unapparent to the patient or the physician. The most prominent and persistent feature detected by historical evaluation is intense pruritus associated with a chronically relapsing course of skin disease.

Physical Findings

Although typical distribution of lesions can be detected during various stages of development (Fig. 1), no firm diagnostic pattern is seen among all patients. The diagnosis of AD therefore relies on information compiled from all aspects of the clinical history, physical examination and laboratory data. Hanafin and Rajka have provided useful guidelines to assist in diagnosing AD (Table 2).

The rash of AD typically begins as an erythematous, papulovescicular eruption that, with time, progresses to a scaly, lichenified maculopapular dermatitis. Weeping, crusting lesions of the head, neck and extensor surfaces of the extremities are common in infancy (*see* Fig. 1). These lesions may involve the entire body surface, yet the diaper area may be spared. The scalp is often affected in infants with some having features of concomitant scalp seborrhea. Because of intense pruritus and scratching, traumatic injury occurs over time, providing a portal of entry for secondary bacterial infection. The early erythematous lesions will frequently discolor after a while and become dry, hyperpigmented lesions as seen in chronic dermatitis of the older child. Older children and adults have a more flexural distribution of lesions (*see* Fig. 1). Lesions are typically dry, lichenfied maculopapular lesions. These lesions commonly remain intensely pruritic with resultant scratching, traumatic skin injury and secondary infection. Hyperpigmentation of chronic lesions is seen with areas of hypopigmentation from older, healed AD lesions. Dry skin, ichthyosis, hand eczema, and chronic chelitis may also be prominent features of the disease. Skin lichenification may be persistent long after "active" dermatitis lesions resolve.

Clinicians have long recognized that patients with AD have a generalized "pallor" to their skin. This has been attributed to an abnormal vascular response that can be demonstrated by the abnormal "blanching" response seen in these patients. This delayed blanching response can be seen in both affected and normal skin of AD patients, as demonstrated by application of pressure or cold on the skin. In addition, these patients will frequently demonstrate "white dermographism." When the skin of an AD patient is stroked with a blunt object, a red line will form and then will be rapidly replaced by a white line without an associated wheal. Under the same conditions, normal skin will develop a red line owing to capillary dilatation, an erythematous flare caused by arteriolar dilatation, fol-

Table 2
Guidelines for the Diagnosis of Atopic Dermatitis

Must have three or more basic features

- Pruritus
- Typical morphology and distribution:
  - a. Flexural lichenification or linearity in adults
  - b. Facial and extensor involvement in infants and children
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, AD)

Plus three or more minor features

- Xerosis
- Ichthyosis/palmar hyperlinearity/keratosis pilaris
- Immediate (type I) skin test reactivity
- Elevated serum IgE level
- Early age of onset
- Tendency toward cutaneous infections (especially *Staphylococcus aureus* and herpes simplex)/impaired cell-mediated immunity
- Tendency toward nonspecific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course infl uenced by environmental/emotional factors
- White dermographism/delayed blanch

Data from Hanafin and Rajka. *Acta Derm Venereol* 1980;(suppl 92):44.

lowed by a wheal secondary to the leaky, dilated capillaries. These abnormal vascular responses of AD have also been implicated in the temperature instability and poor regulatory responses seen in some patients.

Another prominent physical finding in patients with AD is an impaired sweating mechanism. Several investigators have documented this phenomenon, with patients demonstrating less sweating under periods of stimulation. In addition, patients frequently complain of increased pruritus during periods of sweating. Increased transepidermal water loss has also been noted in patients with AD. This has been attributed to fewer sebaceous glands and less total lipid content of AD skin. All of these findings contribute to the clinical manifestations of dry skin and increased pruritus.

LABORATORY FINDINGS

Laboratory tests provide few clues to the diagnosis of AD. Several parameters can be helpful in eliciting triggering agents and underlying causes of disease, but none is diagnostic.

Hematological Findings

Peripheral blood eosinophilia is commonly seen in patients with AD. Eosinophils usually comprise 5–10% of the total white blood cell count in AD patients. The degree of eosinophilia typically does not correlate with the degree of disease severity and is generally not a useful parameter to follow disease activity. Eosinophil mediators, such as major basic protein (MBP) and eosinophil cationic protein (ECP), have been found in the circulation and biopsy specimens of patients with AD. Eosinophil cationic protein has been found in increased amounts in the circulation of AD patients with disease activation compared to AD patients with inactive disease or with normal controls. Additionally, soluble IL-2 receptor (IL-2R) and the eosinophil-specific vascular adhesion molecule, E-selectin, have both been seen in higher circulating levels in patients with AD than in controls and appear to correlate with disease severity in preliminary study. These parameters (ECP, IL-2R, E-selectin) have therefore been proposed as useful markers for disease activity. More information in larger, controlled trials is needed to determine if these parameters are actually valid means of following the disease status in AD.

Serum IgE Antibody

Many investigators have found a correlation between elevated serum IgE concentrations and the presence of AD. Juhlin reported that 82% of AD patients observed had elevated serum IgE levels. In two subsequent surveys, Johnson and O'Loughlin reported the incidence of elevated IgE in AD to be 43% and 76%, respectively. Both noted that increased levels were seen more commonly in patients suffering from more severe disease and in those with concomitant atopic respiratory disease. In addition, these investigators reported a significant number of patients with typical AD and normal IgE concentrations. Other groups have also found elevated IgE levels in nonatopic individuals. At present, most investigators agree that the finding of an elevated serum IgE concentration is a secondary, not a primary, phenomenon. Serum IgE determinations in patients with AD provide little practical benefit in the diagnosis or management of AD.

Skin Test Reactions

Prick and intradermal skin tests to various aeroallergens and food allergens are commonly used in the assessment of AD and provide the most sensitive test for allergen detection. Controversy exists among allergists and dermatologists with regard to the clinical relevance of positive tests. Some investigators have reported that as many as 80% of individuals with AD will have positive specific IgE to a variety of allergens. This finding has been explained by some groups to be nonspecific and only an indicator of a generalized atopic state. Others report the clinical significance of specific IgE antibody and skin test reactivity in some patients with AD and report the observation of clinical improvement while instituting specific allergen avoidance. Knowledge of the allergens eliciting positive skin test reactions can be used as a clinical guide for the management of disease and detection of exacerbating conditions. These tests must be interpreted with caution. The presence of a positive skin test to an aeroallergen or a food allergen may not

have strict clinical relevance and must be analyzed in light of the clinical history. For aeroallergen sensitivity, findings of seasonal distribution of other associated disease, such as allergic rhinitis and asthma, may provide additional clues for interpreting positive skin tests and instituting appropriate avoidance procedures. In the case of food allergen sensitivity, Sampson found prick skin tests to have an excellent negative predictive accuracy of 82–100%, but a poor, highly variable, positive predictive accuracy of 25–75% when compared to blinded food challenge. Positive results must be correlated with the clinical history and dietary assessment and then confirmed with a trial of an allergen-elimination diet and subsequent food challenge.

RAST

Radioallergosorbent tests (RAST) provide another method of evaluating a patient for the presence of IgE antibody to specific allergens in the serum. RAST can be performed on patients with AD in whom the extent of body surface involvement and severity of the dermatitis prohibits skin testing. Care must be taken when ordering such testing because there is a distinction between a standard RAST that provides a more qualitative measure and a newer form of RAST, Pharmacia ImmunoCAP® fluorescence enzyme-linked immunosorbent assay (CAP-FEIA), which is a quantitative measure of specific IgE. Standard RAST is less reliable than skin testing, especially when assessing for food-allergen sensitivity. However, Sampson has reported the correlation of specific IgE, as measured using CAP-FEIA, with improved clinical predictabilty for food allergy diagnosis for at least some of the major food allergens. Using CAP-FEIA results, Sampson has established decision points for several major food allergens that represented a 95% likelihood of reaction on challenge.

HISTOPATHOLOGY

The appearance of AD lesions on routine histological specimens is not pathognomonic and can frequently be seen in a variety of inflammatory skin disorders, such as contact dermatitis, acute photoallergic dermatitis and inflammatory pityriasis rosea. The histopathological changes detected depend on the stage of the lesion (Fig. 3). These stages are typically divided into acute and chronic.

The acute AD lesion (Fig. 3B) is characterized by hyperkeratosis, parakeratosis, and hyperplasia of the epidermis, with absence or diminution of the granular cell layer. In addition, spongiosis, secondary to intercellular and intracellular edema of keratinocytes, is prominent. A marked mononuclear cell infiltrate, composed primarily of lymphocytes and occasional monocytes, is seen around the dermal venous plexes. Normal numbers of mast cells, basophils, eosinophils and Langerhans' cells are found in the acute lesions.

Chronic lesions of AD (Fig. 3C) are characterized by marked hyperkeratosis of the epidermis with elongation of the rete ridges, prominent parakeratosis and papillomatosis of the dermis. Only minimal amounts of spongiosis are detected. There is a marked inflammatory infiltrate in both the perivenular and intervascular areas that consists of monocytes, macrophages and lymphocytes. Increased numbers of mast cells and Langerhans' cells can also be detected, but eosinophils are rarely found. Demyelination and fibrosis of the cutaneous nerves can be seen at all levels of the dermis.

Immunohistochemical staining using monoclonal antibodies in specimens from acute and chronic skin lesions, reveals that the predominant lymphocytic infiltrate consists of

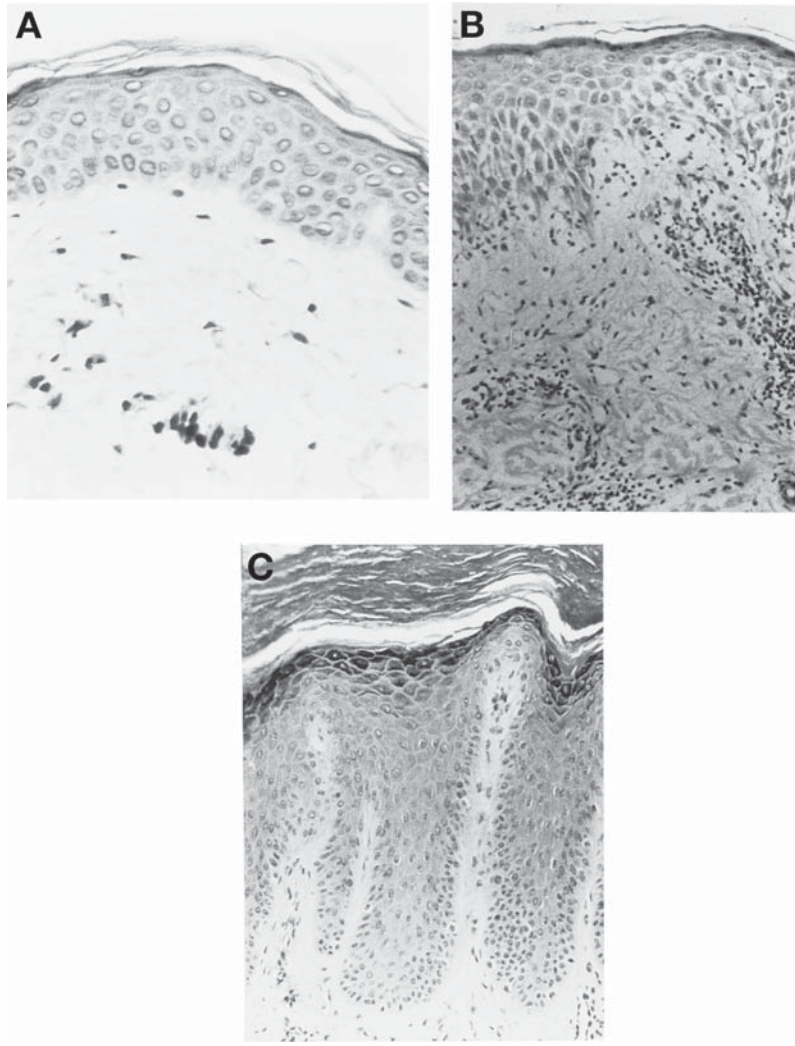

Fig. 3. Skin biopsy specimens of normal skin **(A)**, acute lesions of AD **(B)**, and chronic lesions of AD **(C)**.

T-cells bearing the CD3, CD4 surface antigens (i.e., helper/inducer T-cell phenotype) and only occasional CD8 positive surface antigens (i.e., cytotoxic/suppressor T-cell phenotype). There are no natural killer cells or B cells in the lymphocytic infiltrate. In addition, most cells express major histocompatibility complex (MHC) class II surface antigens, indicating an "activated" state. Increased numbers of Langerhans' cells (i.e., CD1a and HLA-DR antigen-positive cells) are detected in lesional biopsies, especially chronic lesions. These Langerhans' cells and associated infiltrating macrophages display IgE molecules bound to their surface. Epidermal keratinocytes located in the dermis of lesional skin also show evidence of activation with increased surface expression of MHC class II antigens and expression of the adhesion molecule, intracellular adhesion molecule-1 (ICAM-1). These cells are felt to be of importance with regard to antigen presentation and processing and subsequent lymphocyte activation and trafficking.

Although biopsy specimens from lesional skin of AD show few eosinophils, large amounts of major basic protein (MBP) are deposited in the chronic skin lesions. MBP is a cationic protein released by activated eosinophils and has been found to have cytolytic activity in lesional skin of patients with AD, as well as in respiratory biopsies from asthmatics. In addition, MBP has been shown capable of stimulating mast cell and basophil degranulation. Other investigators have found increases of other eosinophil mediators (i.e., eosinophil cationic protein and eosinophil-derived neurotoxin) in the biopsy specimens and skin blister fluid of patients with AD following allergen challenge. These findings support the important role of eosinophils and their mediators in the pathogenesis of AD.

IMMUNOPATHOLOGY

Although the full understanding of the immunopathology of AD remains to be elucidated, various immune abnormalities can be routinely detected in these patients. Findings include increased serum IgE, abnormal delayed-type skin reactivity to common antigens (i.e., tetanus antigen), decreased incidence of contact dermatitis (i.e., poison ivy dermatitis) and increased susceptibility to cutaneous viral infections such as herpes simplex, verruca vulgaris, molluscum contagiosum, and vaccinia. In vitro experiments also show a decreased lymphocyte response to mitogens (i.e., phytohemagglutinin) and recall antigens (i.e., tetanus) and a defective cytotoxic T-cell response. Reduced chemotaxis of monocytes and polymorphonuclear leukocytes has also been reported in AD. These data indicate that a combination of mechanisms may be important in the immunopathogenesis of AD (Fig. 2).

Immunological Abnormalities

- Uncontrolled synthesis of IgE with T-cell profile of immediate hypersensitivity (TH2 cells predominate)
- Decreased delayed hypersensitivity with increased susceptibility to cutaneous viral infections
- High spontaneous basophil histamine release

Role of IgE in AD

Support for an IgE-mediated mechanism in AD is suggested by the following findings typical of AD: elevated serum IgE concentration, positive immediate skin tests and RAST to a variety of food and aeroallergens, association with other atopic diseases (i.e., asthma and allergic rhinitis) and a positive family history for atopy in 80–90% of patients. In addition, bone marrow transplant data have documented the ability to transfer IgE antibody, specific allergen sensitivity, and AD to previously nonatopic bone marrow recipients. Although the histological appearance of AD lesions suggests a type IV, cell-mediated hypersensitivity reaction caused by the cellular infiltrative pattern, recent information on the allergic late-phase reaction (LPR) has shown a distinctive cellular infiltrate that is consistent with that seen in AD. Following allergen challenge, IgE-bearing mast cells bind allergen and become activated, releasing cytokines and mediators that perpetuate the allergic response. This immediate or early reaction occurs within 15–

60 min of allergen challenge and is characterized by erythema, pruritus, and increased capillary permeability. Approximately 4–8 h after the initial allergen challenge, the LPR begins with infiltration of eosinophils, neutrophils, lymphocytes, and monocytes into the site of inflammation. At 24–48 h, lymphocytes and monocytes predominate the cellular infiltrate. This infiltrate seen during the LPR following antigen challenge is similar to the infiltrate noted in the lesions of AD.

Clinical and laboratory correlates have been made in numerous studies in patients with food hypersensitivity and AD. Following positive food challenge, Sampson and colleagues have shown a rise in plasma histamine, without a change in complement activity, basophil number or total basophil histamine content. Skin biopsy specimens obtained 4 and 14 h after challenge revealed eosinophil infiltrate and deposition of major basic protein. They concluded that food allergen-induced mast cell activation was shown to trigger both an early and a late-phase reaction in the skin of patients with AD.

IgE molecules have also been found to participate in the inflammatory response via mechanisms other than direct mast cell activation. Sampson has shown that children with AD and food hypersensitivity have high spontaneous basophil histamine release in vitro when compared with normal controls or AD patients without food hypersensitivity. Mononuclear cells from these patients also secreted high levels of histamine-releasing factor (HRF). These levels were associated with cutaneous hyperreactivity to a variety of minor stimuli. After an appropriate food elimination diet was implemented for approx 1 yr, spontaneous basophil histamine releasibility and production of HRF fell to baseline levels and correlated clinically to less cutaneous hyperreactivity. In addition, passive transfer of this releasing factor could be demonstrated in nonatopic controls. Basophils from nonatopic individuals were stripped of all IgE molecules and sensitized with IgE from food-allergic patients. This rendered the "normal" basophils capable of secreting histamine in response to HRF.

The observation that Langerhans' cells and macrophages infiltrating into the dermis of AD skin lesions bear IgE surface molecules provides an important link to understanding the immunopathology of AD. These IgE-bearing cells also express the low-affinity receptor for IgE (CD23) and presumably function in antigen processing and presentation. Mudde and coworkers demonstrated that in vitro, IgE-bearing Langerhans' cells from dust mite allergic patients were capable of capturing house dust mite allergen for antigen presentation, whereas IgE-negative cells from normal controls or atopic controls who were not dust mite allergic were unable to capture the allergen. Once activated, these cells have been shown to produce cytokines, such as IL-1 and tumor necrosis factor (TNF), that are important in lymphocyte attraction and activation at the inflammatory site. In Mudde's study, IgE-positive cells were shown to activate lymphocytes after specific allergen challenge, whereas IgE-negative cells did not result in lymphocyte activation. In addition to mast cells, these cells likely function as a bridge between initial allergen contact and processing and subsequent lymphocyte activation and perpetuation of the immune response.

Role of T Cells in AD

The role of T-lymphocytes in the pathogenesis of AD has been the subject of many investigative studies during the last 15–20 yr. The concept that T-cells play a critical role in IgE regulation has been elegantly demonstrated in the murine model. Recently, evidence for this same type of interaction has been found in human studies. Cytokines produced by activated lymphocyte clones regulate the immune response. In the murine

model, T-helper (TH) cells are divided into two distinct subpopulations based on the cytokine profile secreted. T-helper type 1 (TH_1) cells produce IL-2, IL-3, IL-10 and IFN-γ and function in cell-mediated immunity responses (i.e., infection and delayed-type hypersensitivity). TH_2 cells produce IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13 and GM-CSF and function in hypersensitivity responses. These same profiles have been seen in human studies, but with some degree of overlap.

It has been demonstrated that IL-4 acts as an isotype switch factor that commits B-cells to produce IgE. Furthermore, B-cells from patients with AD have been shown to spontaneously produce higher levels of IgE than normal controls. These B-cells also have increased expression of the low-affinity IgE receptor (CD23) on their surface. In vitro data have also shown that IL-4 not only increases IgE production but also up-regulates the expression of CD23. Numerous investigators have shown an imbalance in cytokine profiles in patients with AD. These patients typically have a TH_2-like cytokine profile with increased secretion of IL-4 and IL-5, in particular. Human T-cell clones from such patients demonstrate decreased production of IFN-γ and increased production of IL-4, resulting in an ability to induce IgE synthesis. This reciprocal relationship between IFN-γ and IL-4 and subsequent induction of IgE synthesis has been documented by several groups. Many have shown that production of IFN-γ or its addition to cell culture will inhibit IgE production and will downregulate the expression of CD23. Van der Heijden and coworkers have also demonstrated a high frequency of IL-4-producing allergen-specific T cells in lesional skin from AD patients. Van Reijsen noted the same allergen-specific clones from lesional skin with 70% demonstrating a TH_2 phenotype. Both groups suggested that percutaneous sensitization to aeroallergens (e.g., dust mite) may occur and that activation of TH_2-type allergen-specific T cells may be responsible for the high levels of specific IgE found in 80% of AD patients. These data suggest that atopic patients, and those with AD in particular, have an inability to produce IFN-γ and therefore have a predominance of TH_2-type cells, resulting in increased IL-4 production, increased IgE synthesis and continuation of the allergic immune response. Recent data have also suggested that this TH_2-like cytokine profile can be demonstrated from CD8+ (T suppressor) T-cells, in addition to CD4+ (T-helper) T-cells in AD patients when compared to nonatopic controls.

Some groups have suggested a model of sequential T helper cell activation in AD involving both TH_2- and TH_1-type T-cells. These investigators have noted more abundant expression of IFN-γ in some chronic AD lesions, suggesting the possible role of TH_1-type cytokines in maintaining the inflammatory response of AD. Of further interest is the apparent differential expression of certain cytokines in acute versus chronic AD skin lesions. Increased expression of IL-16 has been noted in acute AD skin lesions only. IL-16 has chemotactic activity specific for CD4+ (T helper) cells; therefore, it may play a role in the initiation of skin inflammation in AD via enhanced recruitment of CD4+ T-cells. Differential expression of IL-13 and IL-12 has also been demonstrated in acute vs chronic AD skin lesions, respectively. These data provide further evidence for a TH_2 phenotype (i.e., IL-13) in acute lesions leading to inflammation. In contrast, the increase in IL-12 in chronic lesions suggests a possible role for IL-12 producing cells in modulating chronic inflammation, possibly via preferred activation of TH_1-type cells instead of TH_2-type cells. Of additional interest is the role of memory T-cells in recognizing skin-related allergens. Memory T-cells display the cutaneous lymphocyte-associated antigen (CLA) that acts as a skin homing receptor for T-cells recognizing skin-related allergens. In vivo studies have demonstrated activation and increased expression of CLA+ T-cells

Table 3
Differential Diagnosis for Atopic Dermatitis

Skin diseases
Seborrheic dermatitis
Nummular eczema
Contact dermatitis
Psoriasis
Metabolic disorders
Phenylketonuria
Acrodermatitis enteropathica
Celiac disease/dermatitis herpetiformis
Immunological diseases
Wiskott-Aldrich syndrome
Nezelof syndrome
DiGeorge anomaly
Severe combined immune deficiency
Selective IgA defi ciency
Hyper-IgE syndrome
Other disorders
Leiner's disease
Langerhans cell histiocytosis disease

in patients with AD compared to controls. These CLA+ T-cells demonstrate an increased production of the TH_2-type cytokine, IL-13, and induction of IgE antibodies, indicating their potential pivotal role in the allergic inflammation of AD. Obviously, the immunological aspects of AD are very complex, but provide an intriguing look at interactions between the skin and the immune system that are being continually updated by experts in both fields.

DIFFERENTIAL DIAGNOSIS

Many types of primary skin disorders, metabolic disorders and immunological diseases have associated skin conditions that resemble AD (Table 3). Certain characteristics of these conditions help to distinguish them from AD.

Skin Diseases

Seborrheic dermatitis is is the most common skin disorder confused with AD. It is characterized by a greasy yellow or salmon-colored scaly dermatitis that begins within the first few weeks of life, usually before the typical age of onset of AD. Lesions are primarily distributed on the scalp, cheeks and postauricular areas, but may also occur on the trunk, perineum and intertriginous regions of the hands and feet. In contrast to AD, significant pruritus is generally not a feature of seborrhea.

Nummular eczema is a disorder characterized by well-circumscribed, circular lesions occurring primarily on the extensor surfaces of the extremities in areas of dry skin. Lesions begin as vesicles and papules that coalesce to form the discrete nonexudative, coin-shaped lesions. Lesions are only mildly pruritic. This disorder is not typically associated with atopy or increased serum IgE.

Contact dermatitis, both irritant and allergic, can be seen in infants and young children. The skin eruption of irritant dermatitis varies with etiological agent, but is commonly seen on the cheeks, chin, extensor surfaces of the extremities, and the diaper area. Irritant dermatitis is typically less pruritic than AD and improves with removal of the irritant (i.e., soaps, detergents, abrasive bedding). Allergic contact dermatitis is characterized by a pruritic, erythematous papulovescicular eruption that involves exposed areas of contact. This dermatitis is uncommon during the first few months of life and can frequently be delineated by a careful history.

Psoriasis is a primary skin disorder that is most commonly seen in older children and adults, but may be seen on occasion in younger children. Fully developed lesions are distinctively different in appearance from those of AD. Lesions are usually erythematous and covered by a silvery scale. Distribution is primarily on the scalp, extensor surfaces of the extremities and the genital region. Nail involvement is commonly seen with pitting or punctate deformities of the nail surface.

Metabolic Disorders

Phenylketonuria is an inherited disorder caused by inability to metabolize phenylalanine secondary to a defect in the enzyme phenylalanine hydroxylase. Affected individuals have fair complexion and blond hair. If untreated, seizures and mental retardation result. Approximately 25% of these individuals have an eczematous-like rash associated with their disease.

Acrodermatits enteropathica is a lethal autosomal recessive disorder with clinical symptoms resulting from profound zinc deficiency secondary to an undefined defect in zinc absorption. The condition is characterized by dermatitis, failure to thrive, diarrhea, alopecia, nail dystrophy, severe gastrointestinal disturbances and frequent infections. Dermatitis lesions are vesciculobullous and are distributed in a symmetrical pattern in the acral and perioral regions. Treatment of choice is elemental zinc replacement.

Celiac disease is a malabsorption disorder secondary to sensitivity to gliadin, the alcohol-soluble portion of gluten found in cereal grains. An eczematous dermatitis, dermatitis herpetiformis, has been reported to occur in some patients. Dermatitis herpetiformis is a highly pruritic skin rash that is characterized by a chronic papulovescicular eruption on the extensor surfaces and buttocks. This disorder is associated with celiac disease in up to 85% of patients. Treatment for celiac disease is life-long dietary avoidance of gluten-containing foods.

Immunological Diseases

Wiskott-Aldrich syndrome is an X-linked disorder characterized by the triad of thrombocytopenia, recurrent infections and eczema. Patients have impairment of both humoral and cellular immune function. Increased serum IgE is frequently found. The distribution of the eczematous rash is different from that typically seen in AD and is less responsive to usual medical management.

Nezelof and DiGeorge syndromes are disorders of T-cell immunity. Both have been associated with eczematous rashes and elevated serum IgE concentrations in some patients. The cause of the rash is unknown, but it is likely associated with the underlying immune dysfunction.

Severe combined immune deficiency (SCID) is a disorder of profound humoral and cellular immune deficiency. In the first 6 months of life, infants frequently have failure

to thrive, recurrent infections, diarrhea and dermatitis. Like other immune deficiency syndromes, the eczematous-appearing rash is in an atypical distribution and less responsive to conventional therapy.

Selective IgA deficiency is the most common immune deficiency disorder, affecting approx 1 in 400 individuals. It is characterized by decreased mucosal immunity, resulting in recurrent sinopulmonary, gastrointestinal and genitoureteral infections. Some patients remain asymptomatic while others manifest evidence of disease. IgA deficiency may be seen in association with atopic disease in some patients. These patients may develop asthma, allergic rhinitis or atopic dermatitis. The dermatitis is more typical of AD, both in character and distribution.

Hyper-IgE syndrome is an immune deficiency disorder characterized by markedly elevated serum IgE concentrations primarily in association with recurrent, severe staphylococcal abscesses of the skin and lungs. A chronic, pruritic dermatitis is commonly seen, but does not occur in the same distribution or have the same course as AD. Immunological abnormalities have been found in both humoral and cellular function.

Other Disorders

Leiner's disease (erythroderma desquamativum) is a disorder that usually begins during the first few months of life and is characterized by severe generalized seborrheic dermatitis, intractable diarrhea, recurrent infections (usually Gram-negative organisms), and marked wasting and dystrophy. The dermatitis involves an intense erythema of the entire body and extensive large, yellow, greasy scales affecting large portions of the body surface. These scales are desquamative, and large skin areas may slough. IgE levels are typically normal and eosinophils are not present. The exact etiology of this disease is unknown but a familial form exists and has been associated with dysfunction of the fifth component of complement (C5).

Langerhans' cell histiocytosis disease is a lethal disorder that is a spectrum of diseases affecting the reticuloendothelial system. A subset of that spectrum, previously known as Letterer-Siwe disease, involves a dermatitis that displays features of both seborrhea and AD. The eruption usually begins on the scalp and postauricular areas as a scaly, erythematous rash resembling seborrhea. The rash progresses to involve the trunk with dark, crusted papules that may be associated with petechiae or purpuric papules.

COMPLICATIONS

Infection

Secondary infection of the skin is the most common complication of AD. Infection can be caused by a variety of bacterial, viral and fungal organisms. The most frequent infections occur with bacterial organisms, most commonly Staphylococcus aureus. As previously stated, some investigators have demonstrated an increased colonization of the skin of patients with AD, with more than 90% of lesions showing colonization in some patients. These organisms gain access to the deeper skin layers because a loss of skin integrity in AD permits secondary infection. Although *S. aureus* is the most common culprit causing impetiginous lesions, β-hemolytic streptococci are also common. Infected skin lesions may be difficult to detect because of the similarity of appearance of chronic AD and secondary infection. Infected lesions may appear more erythematous, pruritic and crusting with areas of open excoriations. Deep pyogenic infections such as furuncles,

abscesses and cellulitis are unusual in AD. Systemic antibiotics are the treatment of choice and frequently provide significant relief of symptoms and aid in clearance of skin lesions.

Viral infections are a particularly troublesome complicating factor in some patients with AD. Patients have an unusual susceptibility to certain types of viral infections. The most common organisms found are those of herpes simplex (eczema herpeticum), verruca vulgaris (common warts), molluscum contagiosum and vaccinia (eczema vaccinatum). Kaposi's varicelliform eruption is a particularly severe, explosive infection caused by herpes simplex or vaccinia infection. Viral lesions are typically vesiculopustular in appearance and occur in clusters on both affected and unaffected skin, but with a predilection toward affected skin. The lesions of molluscum contagiosum are papular, centrally umbilicated lesions surrounded by a pale halo. All viral lesions can be seen on any portion of the body. Infection may be localized or result in systemic toxicity (i.e., herpes and vaccinia). Appropriate antiviral therapy may be indicated on a long-term basis to combat these infections, some of which can become latent and recur later (i.e., herpes simplex). In addition to the mentioned viral infections, patients with AD may be at increased risk for developing severe infection following exposure to varicella.

Fungal infections can also complicate the course of AD. *Trichophyton rubra* and *M. furfur* or *orbiculare* are the most commonly implicated organisms. *Candida albicans* have also been implicated in some reports, but strong evidence for those yeasts being a source of infection does not exist at present. Infection with *M. furfur* is typically seen in the adolescent or adult patient with AD in whom a typical head and neck distribution of lesions is noted. Topical and systemic antifungal agents may be necessary to control infection.

Ocular Conditions

Ocular abnormalities may be seen in patients of all ages with AD. The most common and potentially severe complication is the development of anterior subcapsular cataracts in some patients with AD. The incidence has been reported to be between 5 and 16%, with most cataracts occurring between 10 and 30 yr. Rarely, posterior subcapsular cataracts may occur, but this is more commonly seen in the patient treated with systemic corticosteriods.

Other ocular conditions seen in association with AD include conjunctivitis, keratitis and keratoconus (elongation of the corneal surface). Conjunctivitis is frequently a year-round complication of AD, but may also be seen in a seasonal distribution in association with allergic rhinitis in patients with aeroallergen hypersensitivity. Vernal conjunctivitis, characterized by a "cobblestone" pattern of papules on the inner eyelid, may be especially troublesome, requiring prompt treatment to prevent corneal abrasion. The association of AD and keratoconus is unexplained, yet of concern in approx 1% of patients with AD. Corneal erosions may also be seen in patients with secondary herpetic infections that go undiagnosed and untreated.

Skin Conditions

Pityriasis alba and keratosis pilaris are two benign skin conditions that are commonly seen in patients with AD. Pityriasis alba is characterized by patchy areas of depigmentation of the skin, primarily occurring on the face and extensor surfaces of the extremities. Keratosis pilaris is a follicular hyperkeratosis characterized by fine papular lesions sur-

Table 4
Treatment for Atopic Dermatitis

- Environmental control
  - Climatic control
  - Nonabrasive clothing and bedding (cotton)
  - Minimization of emotional stress
  - Avoidance of irritants
  - Avoidance of aeroallergens
- Dietary control
  - Specific food allergen restriction
- Skin care
  - Minimize trauma
  - Avoidance of harsh soaps/detergents
  - Hydration
  - Lubrication
- Antipruritics
  - Hydroxyzine
  - Diphenhydramine
  - Other nonsedating antihistamines
- Corticosteroids
  - Topical
    - 1% Hydrocortisone ointment to facial lesions
    - Medium-potency ointment to body lesions
  - Systemic (rare use only)
- Tar preparations
- Antibiotics
  - Antistaphylococcal/antistreptococcal
  - Antifungal (rare use only)
  - Phototherapy
- Immunomodulatory therapy
  - Pimecrolimus
  - Tacrolimus

rounded by dry skin that primarily occur on the buttocks and extensor surfaces of the upper arms and thighs. Both conditions may be seen in other skin disorders and in patients with otherwise normal skin. Their causes are unknown, but both remain only as benign nuisances.

TREATMENT

At present there are no known cures for AD, and current therapy is largely symptomatic. Certain therapeutic measures can be instituted that will dramatically reduce symptoms and control the overall skin condition (Table 4).

Environmental Control

Environmental control measures, in the form of minimizing both allergen exposure and pruritic stimuli, should be instituted in all patients with AD. Minimization of extreme fluctuations of temperature and humidity results in less pruritus. Sweating will induce pruritus in many patients with AD; therefore, a moderate temperature environment should be main-

tained. Clothing should be loose and free of wool. Cotton fabrics are generally the best tolerated. Coarse fabrics in clothing and bedding should be avoided. Complete rinsing of detergents, soaps and bleach from clothing and bedding will also minimize their irritant potential. Occupational aggravating agents such as chemicals, irritants and solvents should be avoided by older patients with AD. Minimization of emotional stress will also lessen the potential for pruritus.

Avoidance of known aeroallergens should be instituted when possible. The most easily avoided allergens are dust mites and animal danders. Dust mite-sensitive patients should institute full dust mite-avoidance procedures consisting of the following: plastic or hypoallergenic covers encasing mattresses and pillows, removal of all feather pillows and stuffed animals from the patient's room, frequent high-temperature washing of the bedding and removal of carpeting and draperies from the patient's room when practical. Animals (especially cats and dogs) should be removed from the home, and contact should be minimized. Practical avoidance of other aeroallergens (e.g., avoidance of cut grass) should be attempted.

Dietary Restriction

In patients with food hypersensitivity, food-allergen avoidance results in improvement of AD. Sampson and coworkers have shown that following a strict avoidance diet of relevant food allergens patients experience symptomatic relief of pruritus and clearing of skin rash. Because of the high false-positive rate of prick skin testing and standard RAST for food allergens, an elimination diet followed by a blinded (single- or double-blind) or open food challenge should be performed to confirm clinical reactivity to a particular food, unless a convincing history of anaphylaxis is obtained. An exception to this rule is when an elevated CAP-FEIA is obtained that demonstrates a greater then 90–95% likelihood that a patient will have a positive food challenge. Several investigators have shown the utility of this test for the diagnosis of food allergy without the need for food challenge. Improvements have been made regarding assessment for the development of tolerance among food-allergic patients. Perry and collegues have recently suggested new decision point guidelines for food re-introduction and challenge dependent on CAP-RAST level in previously known food-allergic patients. Extensive elimination diets should not be prescribed on the basis of skin test positivity alone because of the obvious nutritional complications. The period of dietary restriction is allergen dependent, but generally should last for 1–2 yr before reintroduction or rechallenge with the implicated food. For some allergens, such as peanuts, a much longer elimination period may be necessary. In fact, new data suggests that approx 20% of children less than 5 yr with peanut allergy will outgrow the peanut allergy.

Skin Care

General measures to reduce skin trauma resulting from scratching should be instituted. Appropriate bedding and clothing can help minimize itching. In infants and children, gloves and socks can be used to reduce scratching, especially during sleep. Fingernails should be trimmed to minimize skin trauma from scratching.

Skin hydration is an extremely important measure in controlling the rash and pruritus associated with AD. Although some clinicians feel that frequent or routine bathing is contraindicated in AD, many others institute frequent bathing as part of the treatment protocol. Bathing hydrates the chronically dry skin of AD and may reduce the likelihood

of bacterial superinfection, which will reduce pruritus and activation of lesions. In addition, swimming has long been recognized by patients with AD as soothing therapy. Patients should bathe in lukewarm water for 30 min once or twice a day (depending on the severity of disease). Burow's solution, oatmeal or oils (i.e., Alpha-Keri) may be added to the bath water to further reduce pruritus. Hydrating body wraps with water-soaked towels may be used in addition to bathing to maximize hydration of severely affected areas. Showers are inadequate in the management of AD because of the lack of hydration obtained. Mild soaps (i.e., Dove or Basis) should be used for cleansing. Harsh soaps may be drying and serve to increase pruritus.

Lubricants should be applied to the skin immediately following bathing and other times during the day with a minimal application of twice daily. Lubricants will counteract dryness and "seal in" the hydration obtained from the prolonged bathing experience. Lubricants should be free of alcohols and perfumes, both of which can be irritating and drying. Effective lubricants include Vaseline, Unibase (oil-in-water preparation), Eucerin or Aquaphor (water-in-oil preparations) plus others.

Antipruritics

Of major importance in the successful treatment of AD is interruption of the itch–scratch cycle. In addition to the methods mentioned previously, antihistamines and occasionally sedatives provide valuable relief of symptoms. Hydroxyzine (2 mg/kg/d divided every 6 h or given at bedtime; maximum adult dose 600 mg/d) and diphenhydramine (5 mg/kg/d divided every 6 h or given at bedtime; maximum adult dose 400 mg/d) have been shown to dramatically reduce itching and reduce sleep disturbance in patients with AD. Other nonsedating antihistamines (e.g., loratidine and cetirizine) may also be useful for daytime use to relieve pruritus when a sedating medication is prohibitive. In young children with severe disease, short-term sedation with chloral hydrate (50 mg/kg/d given at bedtime) may be needed until control of symptoms can be obtained. Topical application of doxepin cream also provides relief of pruritus, but poses a greater risk for side effects because of its systemic absorption. Doxepin should be used with close observation in all patients, especially children and patients with large skin surface areas affected.

Corticosteroids

Corticosteroids are used in AD to control inflammation. These preparations are very effective in controlling skin lesions of AD, but should be used wisely. There is little role for systemic corticosteroids in the management of AD except in the most severe cases. When used, oral corticosteroids should be prescribed for only a limited time and should be tapered judiciously. The skin disease will typically clear quickly with the use of oral corticosteroids, but frequently relapse once their use is discontinued. In addition, the side effects associated with use of systemic corticosteroids are well known and generally preclude their use.

Topical corticosteroid use in AD is the mainstay of therapy. The potency of topical steroids used is dependent on the severity of the skin disease and the location of skin lesions. In general, topical steroid potency is related to the vehicle and the chemical preparation. Gel preparations penetrate more effectively, but are drying and therefore not of great benefit in AD. Ointments penetrate well and enhance hydration, but feel occlusive and may be poorly tolerated during periods of high temperature (i.e., summer). Creams and lotions are less potent and penetrate less effectively than gels or ointments,

but are more comfortable to some patients. Except in mild cases, ointments should be used because of their higher penetrance and potency. The lowest strength that gives adequate results should be used. Halogenated corticosteroid preparations, such as 0.1% betamethasone (Valisone), 0.025% fluocinolone (Synalar), and 0.1% or 0.025% triamcinolone (Aristocort, Kenalog), have potent anti-inflammatory properties and can be used sparingly on affected body lesions. These preparations should not be used on the face and neck. Hydrocortisone cream or ointment, 1%, can be used sparingly on the face and neck, but stronger preparations should be avoided. Topical steroids should be applied twice daily after application of lubricating creams or ointments as discussed. These preparations will penetrate the lubricant and reach the affected skin. Although generally safe from systemic absorption, diffuse application of topical steroids over long periods can have the adverse effects of striae, atrophic thinning of skin, ulcerations, hirsutism, acne, and telangectasia. In addition, cases of adrenal suppression secondary to use of topical steroids have been reported. Although these complications are rare with prolonged use of low-potency topical steroids, their use in children and adults with severe disease should be monitored.

Tar Preparations

Coal tar preparations have been used for many years in the management of AD. Although topical corticosteroids have generally replaced the routine use of these keratolytic agents, they are still effective in the management of chronic, lichenified skin lesions that respond poorly to corticosteroids. The mechanism by which coal tar preparations work is unknown, but clinical evidence has shown that they have both anti-inflammatory and antipruritic effects. These preparations are will tolerated, but prolonged use may lead to folliculitis and photosensitivity. Shampoos containing tars are especially useful in the patient with scalp involvement (i.e., as in both AD and seborrhea).

Antibiotics

As previously stressed, patients with AD have a high degree of bacterial colonization of both affected and unaffected skin. The risk and occurrence of bacterial superinfection of the AD skin is therefore high, most commonly with *Staphylococcus aureus* and streptococcal organisms. In addition, Leung and others have shown that some patients with AD produce specific IgE antibodies to various exotoxins produced from *S. aureus*. Because of these factors, antistaphylococcal and antistreptococcal antibiotics should be used liberally in the AD patient with documented or suspected bacterial superinfection. Skin cultures can be helpful in documenting the type of organism present and the antibiotic sensitivities of the organism. From a clinical standpoint, exudative, crusted or excoriated lesions should raise the clinical index of suspicion for secondary bacterial infection. Appropriate antibiotic therapy should be instituted for 10–14 d. In cases of limited distribution of infected skin lesions, topical antibiotic therapy with preparations such as Bactroban ointment may be adequate. For most cases, systemic antibiotics will be required to eradicate the infection. An increased skin care regimen with more frequent bathing may also help to reduce the bacterial load.

A few reports have addressed the issue of secondary infection caused by fungal infections, such as Pityrosporum ovale, in which investigators have advocated the use of topical agents such as Sebulex or Selsun shampoo, to fight fungal growth. Others have recommended the use of oral antifungal agents when fungal organisms are documented or highly suspected. Experience to date is relatively empiric and not well established.

Phototherapy

UV light therapy with UVA rays has been offered to some AD patients for control of lesions. Rajka has reported favorable results in a small series of AD patients when phototherapy was provided to eczematous skin lesions and maintenance therapy was sustained. This method of therapy has been proposed for the patient who is poorly responsive to conventional therapy or in whom severe AD is present. Rajka also notes that phototherapy may be beneficial in children with severe disease requiring systemic steroids to reduce the potential side effects of long-term corticosteroids. Most commonly, UV therapy must be given at least weekly and sustained over long periods to prevent relapse. This regimen raises the issue of adverse effects of long-term UV light exposure, such as induction of malignant disease and chronic skin changes. Most clinicians feel that the risk–benefit ratio is too high to encourage this form of therapy for the average AD patient. Phototherapy should therefore be reserved for the complicated case that is poorly responsive to other forms of therapy.

Recently, omalizumab, a humanized IgG1 monoclonal antibody against IgE has been shown to be effective in treatment of allergic asthma and allergic rhinitis. As such, this therapy could potentially decrease the effects of IgE in AD, but the high serum IgE levels seen in AD may limit its utility. However, omalizumab may have a role in treatment of food-induced AD. In a population of peanut-allergic patients, the threshold of sensitivity to peanuts on oral food challenge was significantly increased after treatment wiht anti-IgE, suggesting protection against unintented ingestion of the food allergen.

Immunotherapy

Although allergen immunotherapy has been useful in some atopic conditions (i.e., allergic rhinitis), its role in the treatment of AD has been limited. In clinical practice, immunotherapy will frequently exacerbate the condition of AD rather than provide relief. Some clinicians advocate the use of immunotherapy, especially in older patients with significant aeroallergen hypersensitivity, but recommend initiating therapy with a much smaller dilution of allergen extract than in standard therapy for allergic rhinitis. The dose of extract needed to induce tolerance is often greater than the dose tolerated by the patient with AD, thereby precluding its use in most patients.

Immunomodulatory Therapy

As previously discussed, AD is associated with abnormalities of the immune system, especially with regard to cytokine production and IgE regulation. In particular, many investigators have shown a predominance of TH_2-type lymphocytes, which produce excess amounts of IL-4 and therefore upregulate IgE production. These patients are noted to have little IFN-γ production in comparison. Some of these same investigators have also shown that IFN-γ suppresses IgE production in vitro and has effects on immune effector cell function. Several immunomodulatory agents, including recombinant IFN-γ, cyclosporin A, and tacrolimus (FK506), have been used in clinical trials of AD.

A recent, double-blind, placebo-controlled, multicenter trial was conducted to examine the effects of recombinant IFN-γ (rIFN-γg) administration to patients with chronic AD. Patients treated with IFN-γ had a significant reduction in symptoms and a mean reduction in circulating eosinophils when compared to the placebo-treated group. A previous trial of 23 patients also showed a significant fall in IgE synthesis in rIFN-γ

treated patients. In another trial of 15 patients (adult and pediatric) treated for a minimum of 22 mo, patients had a significant reduction in mean body surface involvement of AD from 61.6% at baseline to 18.5% at 24 mo.

Two topical calcineutin inhibitors, tacrolimus (FK506) and pimecrolimus, have recently been approved for the tratment of AD. Both of these medications inhibit the activation of a number of key effector cells involved in AD, including T-cells, dendritic cells, keratinocytes, and mast cells. The distinciton between pimecrolimus and tacrolimus is that pimecrolimus is a cream that is somewhat weaker than tacrolimus but less irritating. Short-term, multicenter blinded, vehical-controlled trials in both adults and children have shown both topical tacrolimus and pimecrolimus to be effective. The most common reported side effects for both drugs are stinging and local irritation. Long-term studies with both drugs have shown sustained efficacy and no significant side effects. Because topical calcineurin inhibitors are not atrophogenic, they can be advantageous over topical corticosteroids in some circumstances, including in patients who are poorly responsive to topical steroids or have steroid phobia and treatment of face and neck dermatitis. Although systemic absorption of these compounds is low, these drugs need ot be carefully monitored in any child with extensive skin disease because of their high ratio of body surface area to weight.

Cyclosporine A, a potent T-cell suppressant, has been evaluated extensively in two recent clinical trials. In the first, 42 patients were treated for one or two 6-wk treatment periods and observed for 2 yr. A 58% reduction was noted in symptoms and AD scoring with 95% of follow-up cases still in remission after 2 yr. In the second study, 100 adults with AD were treated for a maximum of 48 wk in an open trial. Most (65%) patients showed complete resolution or significant reduction in their symptoms and lesions, yet most reported relapse after cessation of therapy. Tolerability of cyclosporine therapy was rated good or very good in 85% of patients.

These studies provide examples of potential immunomodulatory therapy that will likely become of more importance as our understanding of the immunopathogenesis of AD expands. Further long-term evaluation of therapeutic efficacy and safety is needed, especially in pediatric populations. Other newer medications, such as phosphodiesterase inhibitors and leukotriene modifiers, may have clinical relevance for the treatment of AD in the future. Currently, information on these medications is limited to in vitro analysis and anecdotal reports.

Alternative Medical Therapy

As alternative therapeutic approaches to medical care have become more popular in the United States and other Western countries, interest has developed regarding the application of some of these therapies for patients with AD. Chinese herbal therapy (CHT) has been evaluated in several trials, most of which are not population- or placebo-controlled. Xu and colleagues reported a reduction of inflammatory cells and markers (e.g., low-affinity IgE receptor [CD23], plus others) in 10 patients treated for 2 mo. These authors concluded that CHT is efficacious for patients with AD. Other case reports and small series using different CHT have drawn the same conclusions. Obviously, this form of therapy for AD needs to be evaluated by blinded, controlled trials in larger studies before it can be recommended for use. In addition, in some reports, CHT has been associated with significant adverse symptoms, such as cardiomyopathy, highlighting the fact that at this time CHT should not be used without caution and close observation.

Another alternative therapy, known as bioresonance or biophysical information therapy (BIT), has been reported as beneficial for AD in case reports and uncontrolled trials. To more rigorously test the efficacy of BIT for AD, Schoni observed 32 children with AD in a double-blind trial. Results showed no benefit of BIT in patients with AD compared to controls, leading the authors to dismiss the role of BIT as alternative therapy for AD.

The use of probiotics has been growing in popularity in recent years. Probiotics are live microorganisms that when ingested confer a health benefit on the host. Of the various organisms used as probiotics, *Lactobacillus* has been of particular interest in AD. The use of combination lactobacilli in infants and children with AD has been associated with reduction in disease, especially in younger children with allergen sensitization. In a double-blind, placebo-controlled crossover study, Rosenfeldt and coworkers found that the administration of two probiotic *Lactobacillus* strains to children with AD caused a significant reduction in clinical severity as measured by patient reprot with the effect being more pronounced in allergic patients (high IgE and at least one positive skin prick test). The combination of a low side-effect profile and our emerging understanding of the role of gut flora in the development of atopic disease and its relationship to the "hygiene hypothesis" make therapy with probiotics attractive. Larger scale studies are needed to advance our understanding of the role of these therapies in clinical practice.

Psychotherapy

AD is a very aggravating chronic disease that can be emotionally challenging for patients and families alike. Emotional distress and problems can trigger episodes of pruritus and worsen the AD. In addition, young patients and their families may have difficulty understanding and coping with this chronic condition and may need help to establish parameters for discipline without adding to the emotional tension of an already aggravated child. Older children and adolescents may also experience body image problems related to the obvious skin abnormalities. For all of these reasons, some patients and their families will benefit from social service support and/or psychological counseling to address these issues. This is particularly important in the patient with severe chronic disease.

PROGNOSIS

Currently there are no prospective, longitudinal studies evaluating the prognosis and disease remission of AD. Vickers retrospectively evaluated 2000 children with AD after 20 yr and noted an overall clearance rate of 84%. Vowles likewise evaluated 84 patients after 13 yr and found only 45% resolution of disease. These and other studies reflect the difficulty in assessing prognosis with reports of disease resolution ranging from 37 to 84% in various retrospective surveys. In addition, no specific disease factors are predictive of the disease severity or course. Some patients are noted to have spontaneous resolution of their disease during infancy and early childhood. Improvement may also be seen during puberty in some patients, but exacerbations noted in others. Cases in adults will often resolve or significantly improve after the second decade of life. As is common with atopic diseases, some cases of AD resolve, but patients develop other forms of atopy such as allergic rhinitis and asthma. Until a well-designed, prospective, longitudinal

survey of AD is conducted, predictions of disease outcome will remain purely speculative and based on clinical experience. These factors reiterate the need for consistent long-term follow-up and management to best serve the needs of patients with AD.

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14 Contact Dermatitis and Other Contact Reactions

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Contents

SUMMARY

Contact dermatitis is probably the most common form of eczematoid dermatitis. It can be either irritant or a result of a delayed hypersensitivity response. It is characteristically diagnosed by location and the pattern of appearance of the rash. Eczema that fails to heal without treatment should make one suspect contact dermatitis. Removal of the offending agent is the important therapy followed by topical corticosteroids. The responsible agent can be diagnosed by patch testing.

Key Words: Eczematoid dermatitis; contact dermatitis; delayed hypersensitivity; patch tests; eczema.

WHAT IS CONTACT DERMATITIS?

Contact dermatitis typically is an eczematous reaction, usually to a substance applied to the skin surface. It may have an allergic cause, or it may be irritant (nonallergic). The archetype of the allergic form is poison ivy dermatitis, whereas soap dermatitis is a typical

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example of irritant contact dermatitis. Of course, there are many forms of allergic contact dermatitis that differ prominently from poison ivy reactions, and irritant dermatitis is extremely diverse in cause and often in presentation. Both irritant and allergic contact dermatitis are very common. They often complicate other forms of eczema, which can be confusing to the inexperienced. Recognition, critical to success in managing such patients, is greatly facilitated by a high index of suspicion.

Irritant reactions are caused by (nonimmune) damage to cells in the epidermis from a variety of stimuli ranging from physical agents, such as friction, cold, and sunburn, to chemical reagents, such as acids, bases, organic solvents, and so on. The subject is quite complex, as the specific injury varies and individuals may be exposed to multiple irritants in many occupations as well as at home. Fundamentally, agents that cause contact dermatitis on a basis other than allergy are by definition irritants. In occupationally induced contact dermatitis, irritant reactions account for about 70% of the total.

Allergic contact dermatitis is a delayed hypersensitivity response mediated by T-cells, with Langerhans cells as the characteristic presenting cells. The number of cytokines and cell types involved in regulation of the response is beyond the scope of this chapter. For a more detailed explanation, *see* Chapter 1.

Other "contact" reactions include allergic and nonimmunological contact urticaria, photoallergic and phototoxic dermatitis, protein contact dermatitis, and systemic contact dermatitis, including some id reactions and some cases of dyshidrotic eczema There are also noneczematous presentations of allergic contact dermatitis.

Photoallergic dermatitis is essentially an allergic contact dermatitis in which the antigen must be activated by light, whereas phototoxic reactions are equivalent to light-induced irritant dermatitis. The former tends to be eczematous, whereas the latter frequently resembles a severe sunburn. Both are located in sun-exposed sites.

Contact urticaria may be either allergic (IgE-mediated) or nonimmunological, in which a wheal occurs through inflammation without allergy. An example of the former is hives appearing on the hands of a chef allergic to shrimp following the peeling of shrimp. An example of the latter is the erythema and swelling seen after local exposure to dimethyl sulfoxide or Trafuril.

HOW DOES ONE RECOGNIZE CONTACT DERMATITIS?

1. The first step in recognizing contact dermatitis is to suspect it. One should always consider the possibility of a contact reaction in anyone with an eczema. Even noneczematous conditions may have a contact reaction superimposed upon the pre-existing condition.
2. The eruption is typically eczematous, and as such it will normally show spongiosis histologically. Acute lesions demonstrate weeping, oozing, crusting, and scaling, and chronic lesions tend to show thickening, hyperkeratosis, lichenification and scratch papules.
3. The pattern is manmade. A good example is glove dermatitis (Fig. 1). Here one usually sees an eczema involving the palms and dorsum of the hands with a sharp cutoff above the level where the gloves are worn. Another suggestive picture is earlobe dermatitis (Fig. 2), in which the ears have been pierced and a weeping, oozing, crusting, and itching eruption surrounds the puncture site.
4. A recognizable pattern may be present. This is often learned by experience, but almost all physicians in the United States recognize poison ivy dermatitis (Figs. 3–5) with its characteristic streaks caused by finger strokes and hand prints. Insole dermatitis to shoes

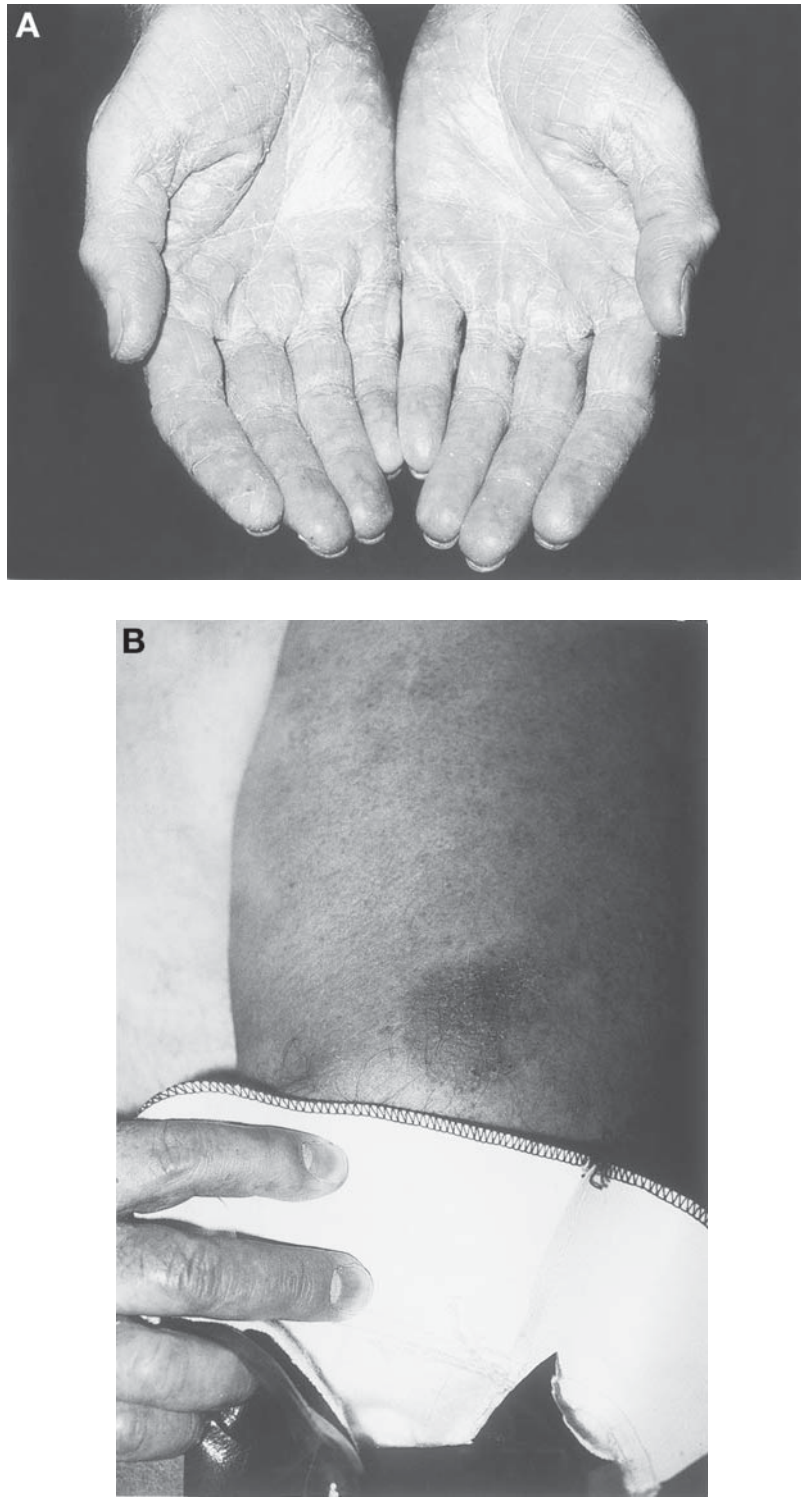

Fig. 1. (A) Glove dermatitis from rubberized work gloves. **(B)** Positive patch test to a piece of the glove.

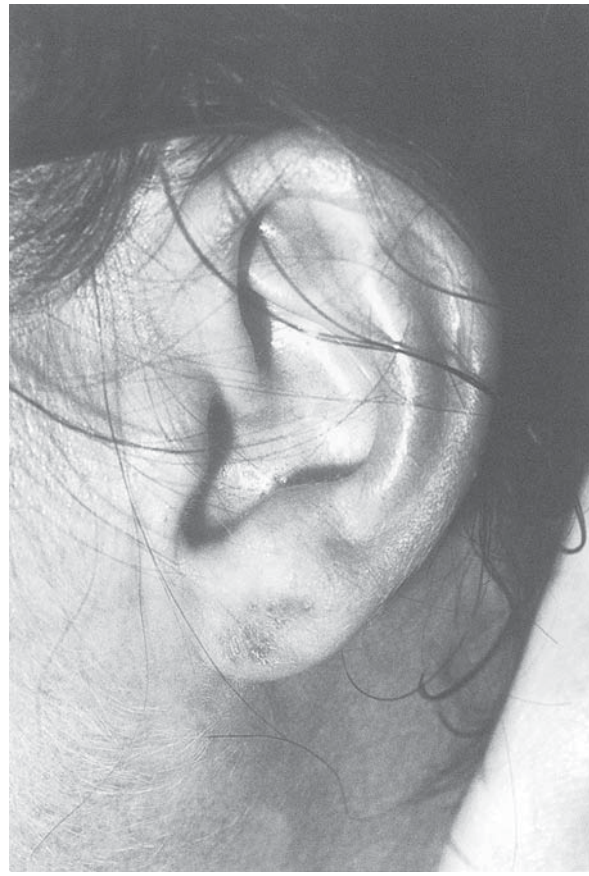

Fig. 2. Earlobe dermatitis in a nickel-sensitive individual. The nickel spot test is helpful here as it allows the patient to test jewelry for free nickel before it is worn.

(Fig. 6) characteristically involves contact sites on the plantar surface with sparing of the longitudinal arch and proximal toes and accentuation of pressure sites, such as over the metatarsal heads and the tips of the toes. In one case the allergen is transferred from the hands, and in the other the eruption is seen where the causative object touches the skin (Fig. 7). One must be careful, however, in trying to identify a cause by pattern alone, as experts are often fooled. Therefore, patch testing is used for confirmation.

5. Eczema that fails to heal with treatment should make one suspect contact dermatitis. Those subspecializing in contact dermatitis see this regularly. Sometimes the original problem is no longer present, and the patient proves to be allergic to a cosmetic lotion or topical medication that he or she applied to soothe the original dermatitis (Figs. 8 and 9). Sometimes a typical medication pattern is seen, with eczema spreading around lesions from the applied substance and fewer lesions at the periphery where less has been applied. In some cases of milder sensitivity, and especially corticosteroid allergy, one may see the original condition unchanged, but refusing to heal.
6. There is often a previous history of contact allergy or irritation. For example, one might look for contact dermatitis to an aminoglycoside in a nurse with previous allergy to neomycin.

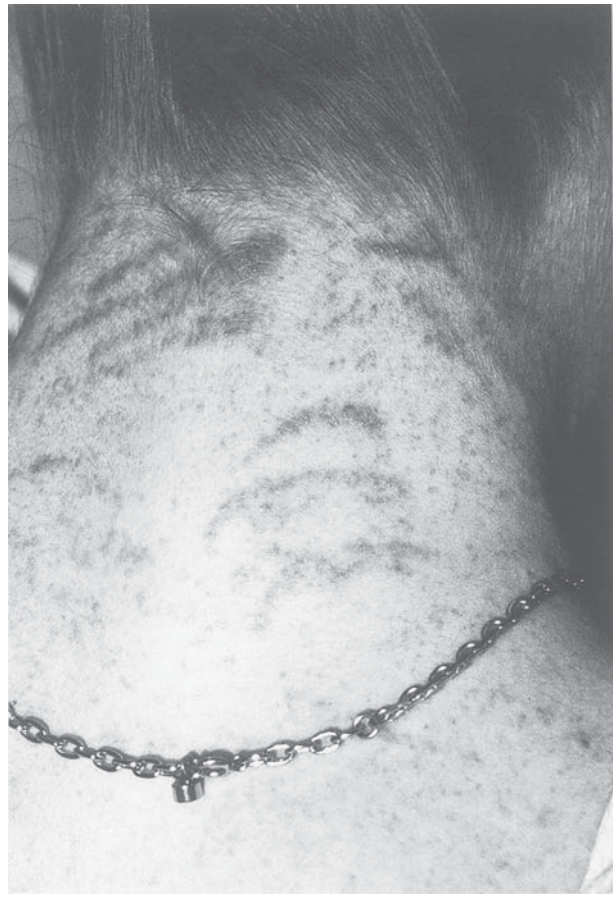

Fig. 3. Classic streaks of poison ivy dermatitis. This pattern is caused by hand transfer of a strong antigen.

7. A known allergy, irritation, or predisposing condition is present. Atopics of all types typically are susceptible to certain irritants (e.g., soaps or propylene glycol). Persons with stasis dermatitis and chronic allergic contact dermatitis often develop sensitivity to agents used on the eruption.
8. There is often a history of the use of multiple agents, either prescribed or over the counter (OTC). This is especially true in stasis dermatitis.
9. There may be a history of high-risk exposure, which is often associated with occupation or avocation. Hospital aides commonly develop irritant dermatitis from bathing patients, from shampooing patients' hair, from scrubbing rooms, and so on. Dishwashers commonly develop irritant hand eczema. Construction workers are more likely to develop chromate allergy from exposure to cement and mortar. In some occupations exposure is a complex mixture of irritation and allergy, not only to substances found on the job, but also to materials used for treatment and putative protection. For example, beauticians develop irritant dermatitis from shampoo and allergic contact dermatitis from glyceryl monothioglycolate in acid perms and *p*-phenlyenediamine in hair dye. They then commonly become allergic to the gloves used to try to protect their hands so they can continue to work!

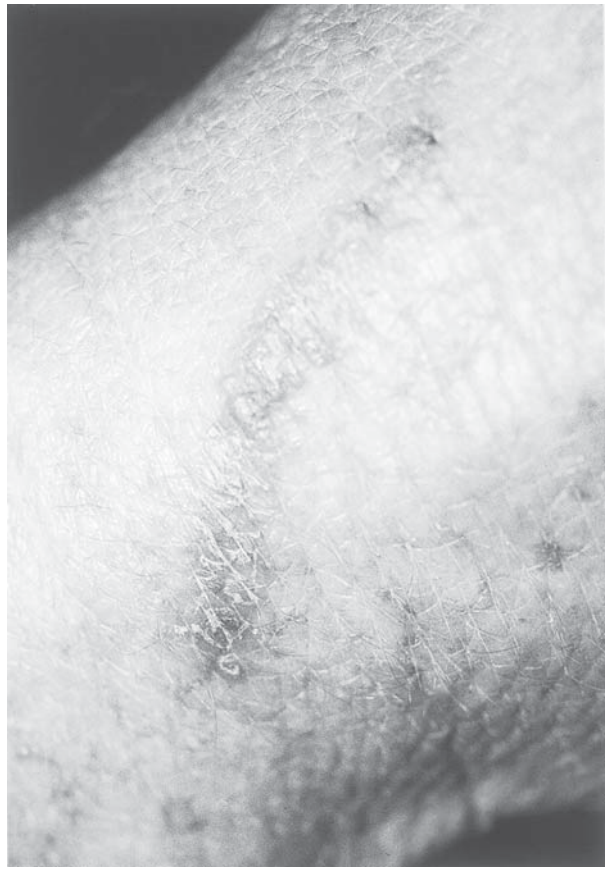

Fig. 4. Streak of poison ivy dermatitis.

HOW DOES ONE SEPARATE IRRITANT FROM ALLERGIC CONTACT DERMATITIS?

This can be a very sticky, yet practical problem. There are no absolute rules, so one must use the weight of the evidence. Some helpful criteria are found in Table 1.

Irritant reactions tend to occur often within minutes, burn rather than itch, and heal rapidly on avoidance. Irritant patch test responses typically are evident within a few minutes, although they may be cumulative or even delayed. They are often somewhat dose-related, disappearing on dilution. They are often sharply marginated, and they occur on first exposure so that prior sensitization is unnecessary. Irritant reactions from soap, detergents, and solvents are often shiny, dry, and fissured.

Allergic contact dermatitis tends to itch more reliably than irritant dermatitis (but there are exceptions); the reaction may spread for days after the allergen has been removed; it is also less dose related; it occurs in susceptible persons (not everyone breaks out to even poison ivy); and it requires prior sensitization. Allergic contact dermatitis typically appears after 36–48 h, but can be seen earlier with strong allergy or in sites where absorption is rapid (e.g., the face).

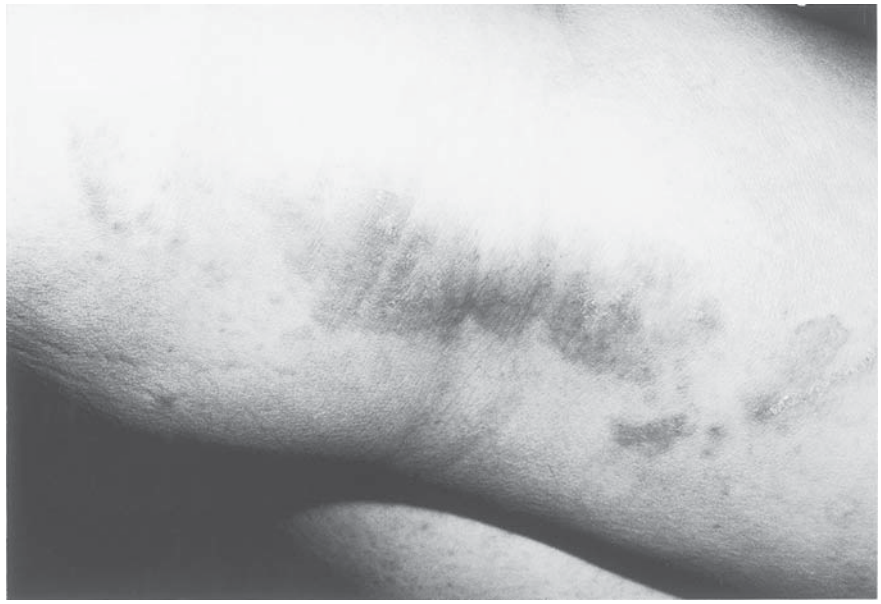

Fig. 5. Poison ivy dermatitis.

Putative histological differences, and even sophisticated cytokine studies, have recently been questioned, so it may be difficult to separate irritant and allergic contact responses histologically. Patch testing may uncover unsuspected allergy in someone who seems to have an irritant dermatitis. Negative patch test results (sometimes wrongly) suggest an irritant cause. Reactions suggesting an irritant cause can be confirmed by serial dilution, since irritation more often disappears sharply with decreased concentration. Some persons have both irritant and allergic contact dermatitis at the same time. Sensitization commonly occurs from irritants, and many allergens (e.g., poison ivy) are both irritant and allergic. Furthermore, the already tender skin from either cause is more susceptible to the other as a secondary event. *It is wise to have persons with irritant dermatitis avoid known allergens and those with allergic contact dermatitis avoid irritants.*

HOW CAN ONE SEPARATE CONTACT DERMATITIS FROM OTHER DERMATOSES IN DIFFERENT ANATOMICAL SITES?

Contact dermatitis can mimic many other skin conditions. A reasonable listing that can be used in differentiation is given in Table 2. The differential diagnosis in certain regions, especially the hands, deserves a bit more explanation.

The Hands

Hand eczema is a very special problem because there is commonly more than one cause for the eruption. Contact dermatitis of the hands is often irritant with dry scaly patches, which in some atopics are converted to a discoid eczema. Dermatitis under a ring is usually an irritation from soap. Occupational factors are important because persons handling raw meat (e.g., slaughterhouse, chicken processing and fishery workers, butchers and chefs), those engaged in wet work, and mothers with small children are particu-

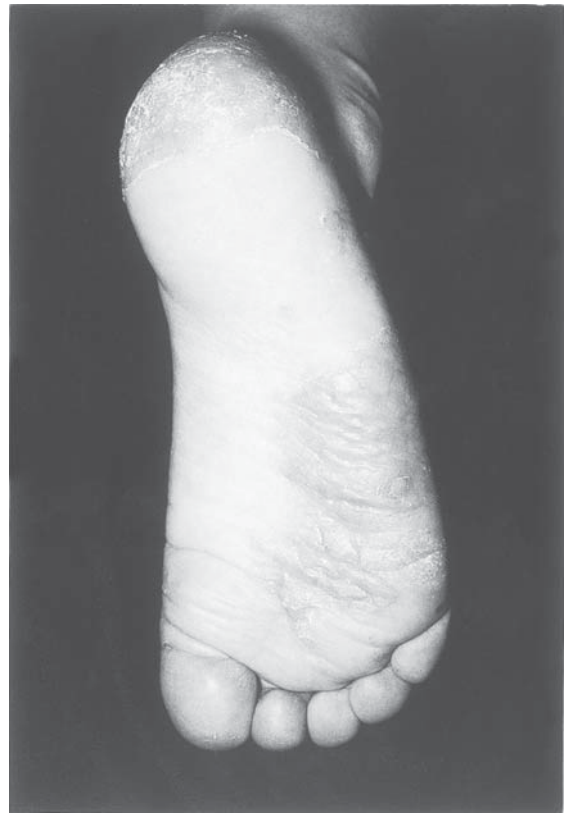

Fig. 6. Six-year-old girl with contact dermatitis to shoes. She reacted to potassium dichromate on patch testing, suggesting leather as a source.

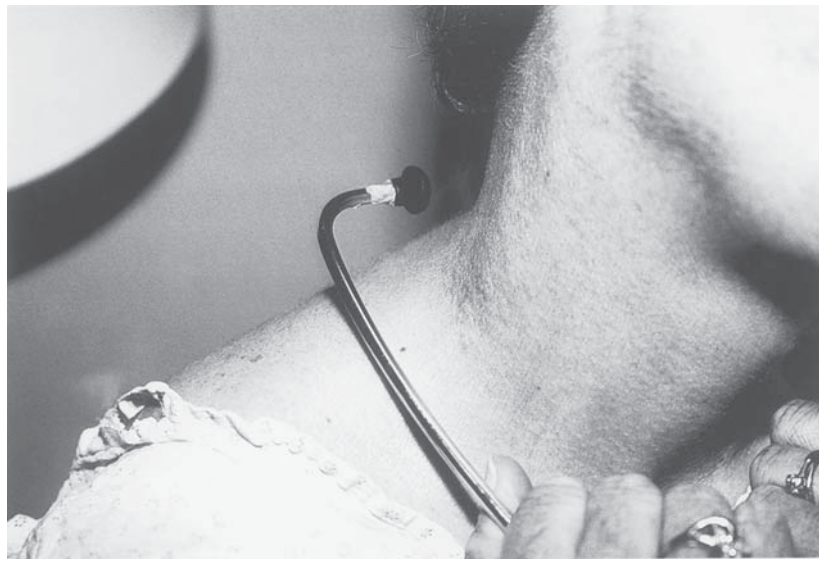

Fig. 7. Nickel sensitivity to metal tubing of a stethoscope.

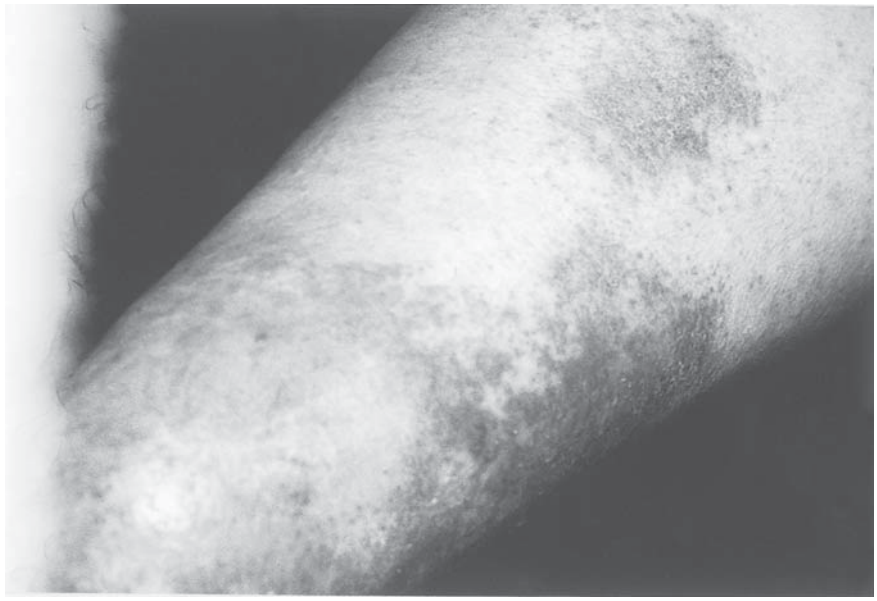

Fig. 8. Eczema that seems to spread where an ointment or lotion is applied suggests sensitivity to a medication. Patch testing was positive to neomycin, which was a component of the cream the patient had applied.

larly vulnerable. Another often unsuspected cause is in mechanics, machine repairmen, and so forth, who try to remove insoluble metal dust, carbon, and rubber dust with soap and abrasives, irritating the skin in the process. Often a nonsensitizing cream will remove such materials without irritation. Allergic contact dermatitis is covered in the section on regional contact dermatitis.

Persons with a nummular or discoid pattern (Fig. 10) are often atopic individuals. Sometimes women who had atopic eczema as children but who have enjoyed a prolonged remission break out anew from the stress of wet work and irritant exposure with the rearing of children.

Dyshidrotic eczema, or pompholyx (Fig. 11), is identified morphologically by its deep-seated single vesicles (at least initially) and the tendency for the vesicular eruption to form an apron pattern. It is commonly a dermatophytid, but systemic contact dermatitis, stasis eczema with id, infectious eczematoid dermatitis, nummular eczema, and other causes can often be found if one looks carefully. Some cases are, however, idiopathic.

Hyperkeratotic hand eczema may occur from contact dermatitis. When it does, it is often difficult to know whether one is faced with one or more than one condition. Perhaps the main things to rule out are certain skin diseases that characteristically occur in areas of trauma. This is often called the Koebner phenomenon in psoriasis, lichen planus, and the like. On the fingers and palms, psoriasis is often misdiagnosed as eczema because it is located in areas of contact such as the thumb and index and middle fingers, along with frictional areas of the palms. Psoriasis in this location usually does not itch, it fissures in winter, and it is usually associated with other findings characteristic of psoriasis, such as pitting of the fingernails, onycholysis, and lesions of the elbows, knees, and scalp (espe-

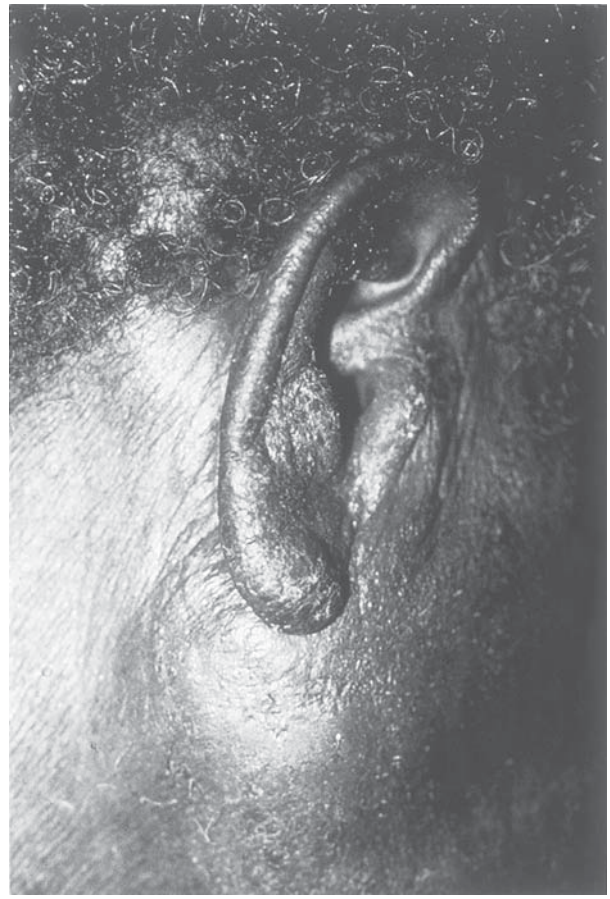

Fig. 9. Depigmentation following a reaction to ear drops containing neomycin. This patient was allergic to multiple aminoglycosides but not to streptomycin, which lacks the 2-deoxystreptamine ring.

cially in the nuchal area) and in the intergluteal fold. A positive family history should make one suspicious, but it is often negative. Lichen planus can also be located on the hands. Lesions of that disease elsewhere are usually more typical in morphology, and, unlike most cases of psoriasis, a biopsy can be helpful. Certain drugs are often aggravating factors in psoriasis and lichen planus and may be the cause of the latter.

Lesions on the hands (and feet) can also be caused by infectious and parasitic conditions, including dermatophytosis, scabies, and herpes simplex, which can all on occasion mimic contact reactions. The morphology and distribution help, and a potassium hydroxide (KOH), Tzanck test, and/or culture will confirm the diagnosis.

On the hands, allergic contact dermatitis is suspected especially when the grip and frictional areas of the palms are involved, but patch testing can be justified in most patients with hand eczema, as it helps establish the cause. A glove-like pattern is a giveaway for glove dermatitis. This is usually a reaction to rubber, but it can also be caused by leather and other materials. Occupational patterns (Fig. 12) are often seen in the grip areas of the fingertips in florists and are a result of *Alstroemeria*—in chefs from

Table 1
Differentiating Allergic and Irritant Contact Dermatitis[a]

	Allergic	*Irritant*
Appearance	Redness, vesicles, papules, oozing, crusting, lichenification	Redness, chapping, scaling, fissures, pustules
Population involved	Sensitive individuals (only one person at this job)	Anyone with adequate dosage (many doing the same job)
Onset following exposure	Varies with location (usually days)	Minutes to hours, but may be cumulative
Require for previous exposure	Yes	No
Dose dependency	Less	More Dilution tends to abolish the reaction
Typical symptoms	Itching	Burning, pain
Localization of patch test response	May spread beyond application site after removal of chamber	Often sharply marginated, limited to occluded area
Patch test, relevance	Positive and relevant	Negative or positive and not relevant

[a]Irritant and allergic reactions often coexist and can be difficult to reliably separate clinically or histologically. The criteria given are commonly used in evaluating patch test responses, but they are not absolute.

garlic, in hairdressers from glyceryl monothioglycolate in acid perms, and in industrial workers due to epoxy and other adhesives, for example. Sometimes a pattern can suggest a source, as with liquid soaps, which cause an eczema of the finger webs extending onto the palm at the base of the middle and adjacent fingers. Sometimes the contact dermatitis alters the appearance of the original condition, such as the fingertip eruption one sees from shampoo (which may be irritant or allergic) or the spreading eczema that occurs from reactions to medications. A diffuse dermatitis of the dorsum sparing protected areas may be light induced. Remember, however, even typical presentations require patch-test confirmation.

Flexural Areas

In intertriginous areas, contact reactions are often from topically applied agents. Inframammary eruptions can be from the bra, especially from metals or rubber chemicals. In the hairy part of the axilla, deodorant ingredients must be ruled out, whereas in the periaxillary area clothing dermatitis may be present. In the differential diagnosis, various causes of intertrigo may be confusing, including candidiasis, seborrheic dermatitis, seborrheic psoriasis, tinea, and gram-negative superinfections. Hailey-Hailey disease is a familial condition inherited as an autosomal-dominant, located usually on the neck, axillae, or groin. Here a biopsy will make the diagnosis; the family history is often positive.

Table 2
Differential Diagnosis of Contact Dermatitis

Other eczemas	*Other dermatoses*
Atopic eczema	Cutaneous T-cell lymphoma
Nummular eczema	Psoriasis
Stasis eczema	Seborrheic dermatitis
Dyshidrotic eczema (pompholyx)	Zinc nutritional and vitamin deficiency
Asteatoic eczema	Glucagonoma syndrome
Infectious eczematoid dermatitis	Tinea
Lichen simplex chronicus	Candidiasis
ID reactions	Scabies
Juvenile plantar dermatosis	Herpes simplex
Frictional lichenoid eruption	Lichen planus
	Dermatitis herpetiformis
	Some bullous dermatoses, (Hailey-Hailey, pemphigus, etc.)
	Disorders of cornifi cation, etc.
	Graft vs host reactions
	Immunodefi ciency disease (Wiskott-Aldrich syndrome, etc.)
	Phenylketonuria
	Drug reactions
	Syphilis
	Actinic prurigo, polymorphic light eruption, noncontact phototoxicity
	Papular urticaria
	L.E., dermatomyositis, etc.
	AIDS-related dermatosis

Elbows and Knees

Over the elbows, rubber dermatitis, topically applied lotions, OTC and prescribed medications, and clothing should be suspected. One must, of course, consider anything on which the patient might lean. I have seen nickel-induced eczema in this location from metal contact. Even poison ivy-like dermatitis has occurred from furniture lacquered with varnish from the Japanese lacquer tree, a relative of poison ivy. In the differential diagnosis, psoriasis, dermatitis herpetiformis, frictional lichenoid eruption (in children), Gianotti-Crosti syndrome, and papulovesicular acrodermatitis syndrome should come to mind, among other things. Systemic contact dermatitis and id reactions may also appear here. In children with atopic eczema, elbow and knee eczema often is caused by allergy to dust mite.

Scalp

The scalp usually is not prominently involved even when hair-care products cause allergic contact dermatitis, because the hair is protective. What one usually sees is scalp involvement together with other areas. Shampoos commonly cause involvement in a rinse-off distribution anterior to and behind the ears, sometimes on the adjacent neck and forehead, and in persons who shampoo their own hair, the fingertips may be involved.

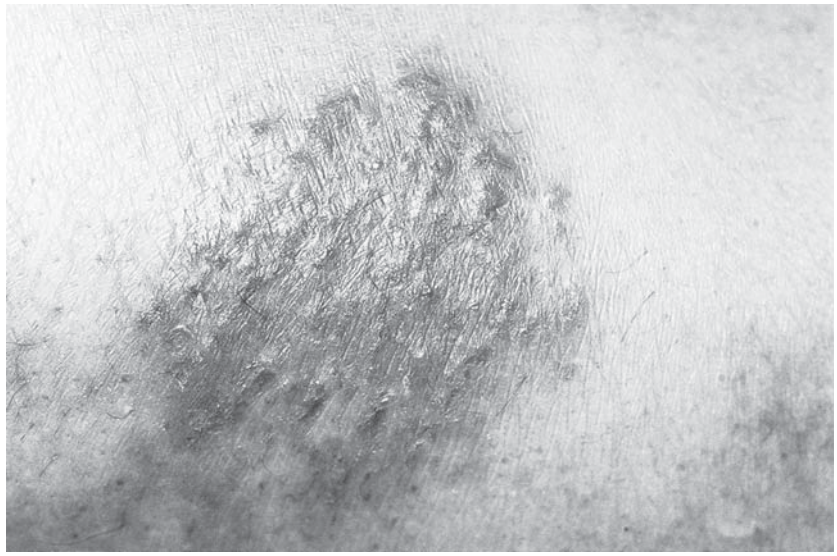

Fig. 10. Coin-shaped plaque of nummular eczema.

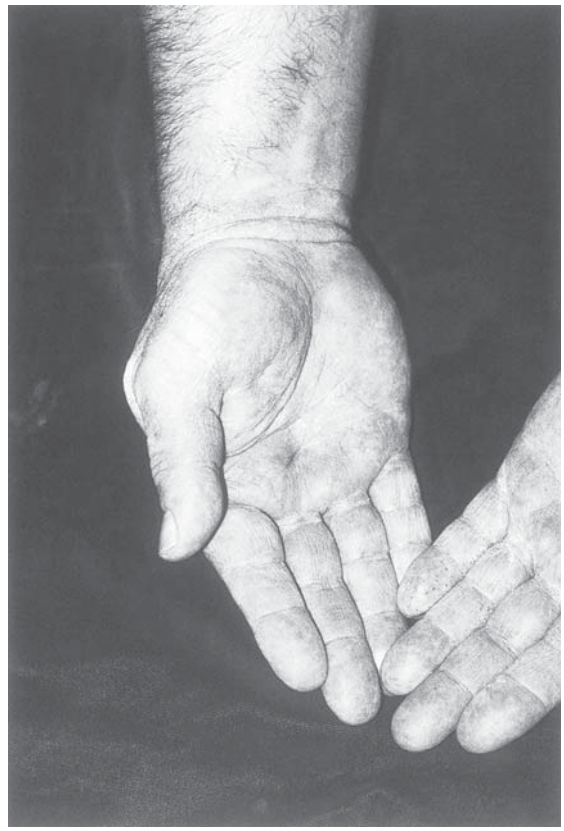

Fig. 11. Dyshidrotic eczema or pompholyx of the palm. Note the deep-seated individual vesicles suggesting an endogenous eczema.

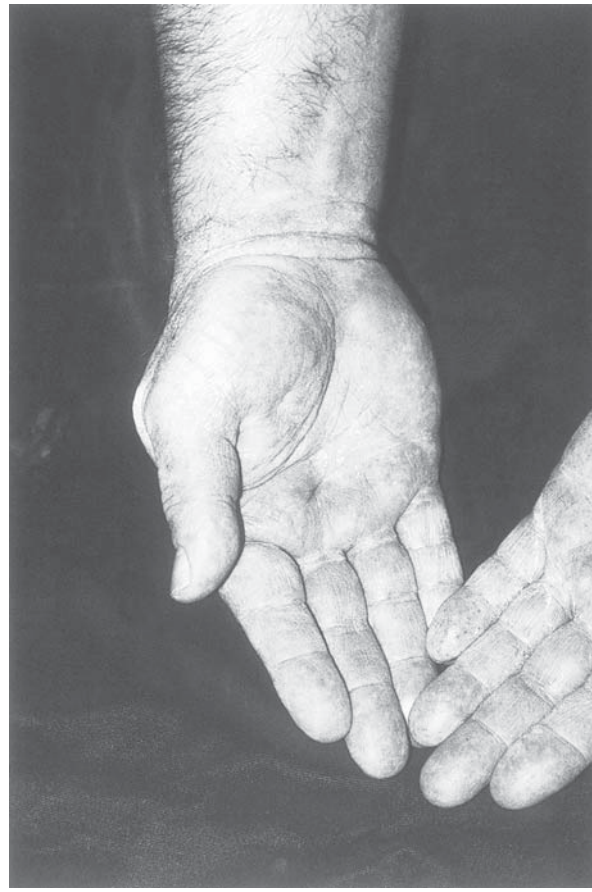

Fig. 12. Hand eczema in a factory worker handling carpet. Reactions on patch testing were from rubber chemicals. The source proved to be rubber backing on the carpet.

Hair dye reactions cause severe involvement of the adjacent neck posteriorly, the ears superiorly, and especially the forehead. Beauticians break out on the hands. Allergy to acid perms may cause a similar eruption in the near term and a chronic pattern where the hair touches, as the allergen is retained in the hair. One also should think of dermatitis herpetiformis in the scalp as well as follicular lichen planus, seborrheic dermatitis, seborrheic psoriasis, some types of folliculitis, and pityriasis rubra pilaris. Eruptions limited to the hairy scalp are seldom allergic contact dermatitis.

Eyelids

Eyelid dermatitis is a complex problem, often with multiple causes. More than 80% of patients have allergic contact dermatitis, protein contact dermatitis, or both. In some 8% of cases, seborrheic dermatitis or psoriasis is present, and atopic eczema is common. Many such patients fall into multiple categories. Sources of allergic contact dermatitis include metals, medications, personal-care products, and nail products (e.g., artificial nails and nail lacquer).

Treatment comprises omitting cosmetics and previous medications and avoidance of hand transfer. Wearing glasses during the daytime and a sleep mask or blindfold at night helps prevent inadvertent contact. Symptomatic treatment is usually begun with 1% hydrocortisone in petrolatum, applied with a vinyl glove, provided there is no allergy to either. Testing to hydrocortisone is done intradermally with 1 mg hydrocortisone sodium succinate in 0.05 mL. One can patch test to a finger of the vinyl glove. Cosmetics are restarted one by one well after the patient is clear, in a use test, with daily application of one new product per week.

Lips and Perioral Skin

Contact dermatitis of the lips includes lipstick dermatitis, caused by any of several ingredients, topical and dental medications, objects habitually chewed (e.g., metal or plastic in pens and pencils or rubber in pencil erasers) musical instruments (e.g., reeds or wooden instruments, such as recorders or flutes) flavors, or dental braces (which can also be a source of irritation directly or from drooling). Other conditions to be considered include candidal cheilitis, cheilitis glandularis, cheilitis granulomatosia, lichen planus, lupus erythemtosus, and actinic cheilitis, to name a few.

In the periorificial locations, contact dermatitis can occur from flavors and other ingredients of orally administered agents (e.g., toothpaste dermatitis at the commisure), hand transfer of black rubber chemicals and metal allergens (e.g., nickel and cobalt), medications used on self and others, and following a visit to the doctor or dentist, rubber dermatitis from the gloves or rubber dam used. One should also think of zinc and vitamin deficiencies as well as glucagonoma. Around the mouth one can also see an irritant reaction to chronic licking, and lichen planus can localize here.

Face

On the face, one sees cosmetic sensitivity typically, and this may be irritant as well as allergic. However, there are many other causes. Hand transfer occurs from poison ivy and Compositae (weed) allergens as well as nail polish. Other materials contacted include sources of phototoxic and photoallergic dermatitis, sunscreens, contact with a pillow or a child's favorite doll, and, of course, the ubiquitous therapeutic agents, including not only those prescribed, but also the long list of lotions and home remedies so often applied. The list is actually too long to include everything, so one should be circumspect.

Trunk

On the trunk, clothing dermatitis is often the first thing considered, especially when the eruption is located around the axillae, the lower rib cage, and pressure areas of the back Causes of clothing dermatitis include not only formaldehyde-releasing fabric finishes, but disperse and other dyes, detergents left in clothing (both irritant and allergic), medications used that contaminate clothing, metal snaps and supports, elastic fibers, and even epoxy used to cement pads or to mark labels. Waistband eruptions may be from detergents or from latex allergens or an antigen in bleached underwear, dibenzyl carbamyl chloride. Other dermatoses found on the trunk include most papulosquamous diseases and cutaneous T-cell lymphoma. Drug eruptions and systemic contact dermatitis can also be a problem here.

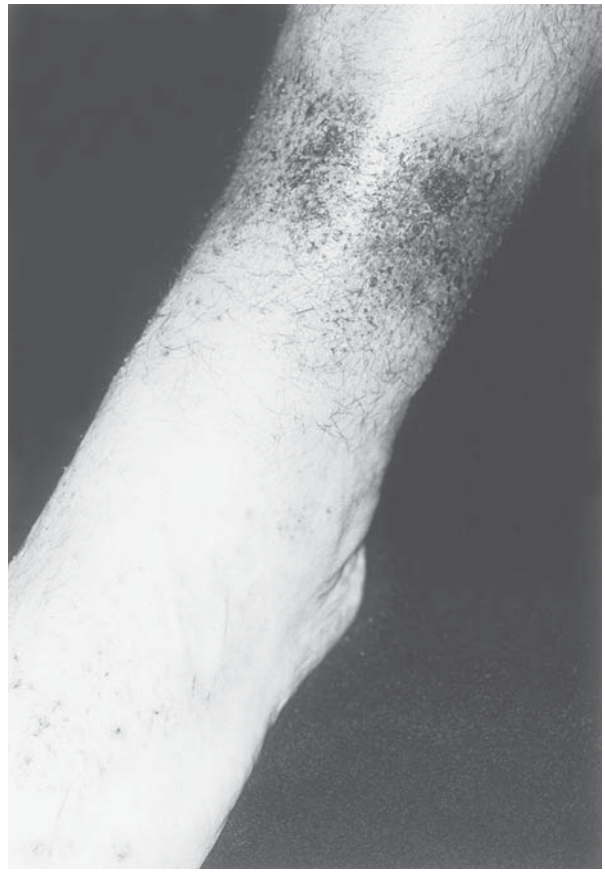

Fig. 13. Allergic reaction to diethylthiourea in a wet suit.

Feet

The feet typically break out in reaction to shoes and topically applied materials. The most common pattern of shoe dermatitis is insole dermatitis from either rubber chemicals or adhesive allergens in sponge rubber insoles of athletic shoes. This characteristically involves the plantar surface except for the proximal toes and the longitudinal arch. The pattern in shoe dermatitis depends on the cause and the points of contact, so one sees a different pattern with leather (chromate) sensitivity and rubber allergy other than the insoles. Differentiation includes dyshidrotic eczema, atopic dermatitis, id reactions, tinea, psoriasis, lichen planus, cutaneous T-cell lymphoma, and palmoplantar pustulosis, among other things.

Lower Extremities

On the legs and thighs, contact dermatitis may be from nickel or phosphorus sesquisulfide in matches, rubber or dyes in stockings, detergents, fabric finishes, and clothing (Fig. 13); even reactions from epoxy in knee pads have been reported. The differential diagnosis includes nummular, atopic, and stasis eczema (Fig. 14), poison ivy dermatitis (Figs. 3–5), contact from medications (Figs. 8 and 9), other eczemas, and many other dermatological diseases.

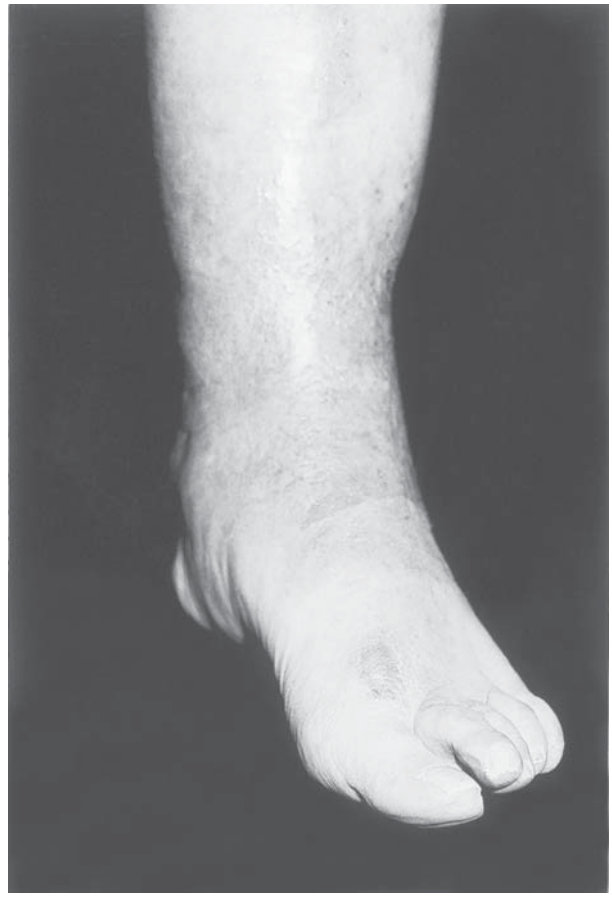

Fig. 14. Stasis dermatitis is often complicated by allergic contact dermatitis to substances applied for treatment or symptomatic relief. This patient was allergic to an OTC lotion.

EXFOLIATIVE DERMATITIS

Exfoliative erythroderma may be caused by contact and other eczemas (especially atopic dermatitis). However, it may also be caused by malignant disease (especially cutaneous T-cell lymphoma), psoriasis, seborrheic dermatitis (especially in infants), pityriasis rubra pilaris, several different congenital ichthyoses, drug eruptions, pemphigus foliaceous, pemphigoid, scabies, and other things. Here, a wise generalist will seek consultation early.

SPECIAL FORMS OF ECZEMA AND CONTACT REACTIONS: PROTEIN CONTACT DERMATITIS

In 1976, a group of Danish investigators described eczematous reactions to foods in food service workers, with irregular results on patch testing but positive immediate sensitivity. Not all of these individuals were atopic according to the report. These reactions appear as early as 30 min, which is much earlier than ordinary contact dermatitis. The first report found that most reactions to food were to meats, but a few were to

vegetables. The published antigens causing protein contact dermatitis have been divided into the following categories: (1) fruits, vegetables, spices, plants (including natural rubber latex); (2) animal proteins; (3) grains; and (4) enzymes. Atopic eczema patients commonly are sensitive to house dust, and some health care workers presenting with hand eczema (or contact urticaria) are sensitive to latex or glove powder. Such sensitivity is picked up with testing for immediate sensitivity. Several methods have been reported, including prick testing, ImmunoCAP or radioallergosorbent (RAST) testing, rub testing, scratch testing, and scratch chamber testing. Patch testing may or may not be positive. Persons with protein contact dermatitis may or may not have contact urticaria.

Patch Testing

The most important confirmatory test in allergic contact dermatitis (and in establishing a diagnosis of irritant dermatitis) is the patch test. Here one attempts to prove the presence of allergy by reproducing the disease in a controlled situation. Usually standard commercial allergens (Table 3) are used for screening examinations. There are two commercially available sources of patch test materials in Canada or the United States. One set, available from Chemotechnique or Trolab as the European Standard Series, contains 24 allergens (Table 3). The other series, marketed as the TRUE test, contains 24 ready-to-use allergens (Table 3). Both series contain single allergens as well as mixtures. The TRUE test can be applied by removing the cover on each set of 12. These are marked by number with the antigens loaded.

Patch testing is done on clear skin on the upper back. Otherwise aluminum (Finn) or polyethylene chambers on Scanpor tape are usually used to hold the antigens. These are packaged 10 per strip with two rows of five. One should mark the first of these with numbers 1–5 and 6–10 along the left and right rows, and the second set of 10 chambers is marked 11–15 and 16–20, prior to removing the cover to load the chambers. The reason for this is that when the cover is removed and the strip is placed on the table for loading, the chambers can easily be turned around. If chambers are not marked, one could easily load the strips backward or even apply them upside down.

The chambers in the TRUE test are already loaded. The European standard tests are loaded from syringes into the aluminum or polyethylene chambers. Chambers are filled about half to two-thirds full, with liquids loaded last. To hold liquids, one must use a cellulose pad inside the chamber. A dab of petrolatum applied to the chamber prior to adding the cellulose pad will prevent the pad's falling out. Strips are applied with a rolling motion, from below upward, to the upper back while the patient is in a slightly flexed position. The external (upper) arm is an acceptable alternate site, but the forearm is not. The site is marked with a fluorescent highlighter by outlining the paper tape strip and marking each chamber's position on both sides as well as top and bottom. Then the second strip is applied. Remember, the liquids are not loaded until everything else is ready. Chambers are left on for 48 h and read at 72 h, and once more 1–4 d later. Accurate records, including a diagram, are kept detailing the substances applied, the location of each, the date of application, and the vehicle and concentration used. Because much of this is routine, printed forms can be made up in advance. It helps to include a drawing of the back or the site of application to help identify responses when marks are difficult to locate. It does little good to find a reaction without knowing what caused it.

An important step for those new to the procedure is learning the discipline of reading the tests. This often requires experience. Standard criteria for scoring reactions are as

Table 3
Sources of Standard Contact Allergens

Compound	*Tests available*	*Description*
Benzocaine, (caine mix)	E, T	Local anesthetic, OTC preparations, crossreacts with procaine, PABA sunscreen, sulfa, etc.
2-MBT	E, T	Rubber accelerator
Colophony	E, T	Rosin in pine and other conifers. Solder fl ux, tape, mascara, topical and dental medications, varnishes, putty, paint, pine products, etc. May indicate allergy to fragrance, fl avor, chrysanthemum
p-Phenylenediamine	T	Permanent hair dyes, may crossreact with black rubber (some), color film developer, sulfa, PABA sunscreens, the benzocaine group and some epoxy hardeners
Imidazolidinyl urea		Preservative found in a variety of cosmetic products
Cinnamic aldehyde		Fragrance and fl avor ingredient. Cinnamon
Wool alcohols	T	Sensitizing component in lanolin. Found in many cosmetic products and lotions. Found in other materials from veterinary products to furniture polish. Will not detect all lanolin reactors, so some add Amerchol 101
Carba mix	T	Accelerator in rubber products. Also found in agricultural chemicals, slimicides, etc.
Neomycin sulfate	E, T	Topical antibiotic. Often crossreacts with other aminoglycosides. Coreacts with bacitracin
Thiuram mix	E, T	Rubber accelerator, especially in latex gloves. Closely related to carba mix chemicals. Rubber products, agricultural chemicals, animal repellents
Formaldehyde	E, T	In wrinkle-free fabric fi nishes, cosmetics, shampoo, biocides, paper, plywood and many other products. Released by many preservatives.
Ethylenediamine	T	In one topical steroid-nystatin generic. May crossreact with Merthiolate, aminophylline, hydroxyzine
Epoxy	E, T	Resin used in many epoxy adhesives, paints, electrical dielectrics (insulation)
Quaternium-15	E, T	Cosmetic preservative. Releases formaldehyde. In many liquid soaps, shampoos and other wet products.
p-tert-Butylphenol formaldehyde resin	E, T	Adhesive in shoes, fi berglass, wood, etc.
Mercapto mix	E, T	Rubber accelerator related to 2-MBT
(IPPD) Black rubber mix	E, T	Antioxidant in (esp. outdoor) rubber
Potassium dichromate	E, T	Cement, mortar, leather, inks, paints
Balsam of Peru	E, T	Used in United States to detect fragrance allergy. Crossreacts with citrus peel, vanilla, eugenol, colas, fl avored beverages
Nickel sulfate	E, T	In steel, jewelry, many metal objects. Said not to be available from stainless
Methyl(chloro) isothiazolinone	E, T	Preservative in wet products, coolant, shampoo, creams, lotions, air conditioners, etc.
Fragrance mix	E, T	Mixture of eight perfume chemicals used as screen for fragrance and flavor sensitivity. Found as fl avors in foods and medications, as perfumes in personal care products from cosmetics, shampoo and soap to toilet tissue, laundry and household products
Cobalt	E, T	Ingredient in metal products, jewelry. Commonly coreacts with nickel.
Clioquinol	E	Less frequent reactor. Contains iodo chlorhydroxyquin or clioquinol (in Vioform) and chlorquinaldol. May also be in veterinary products
Paraben mix	E, T	Preservatives in cosmetics, medications, foods and industrial products
Primin	E	Active ingredient in *Primula obconica,* German primrose
Sesquiterpene lactone mix	E	Screen for Compositae dermatitis
Thimerosal	T	Preservative in contact lens solutions, eye drops, allergy injections, immunization reagents, tincture of Merthiolate; may predict piroxicam photoreaction. Many true positives not relevant
Control	T	Negative control

E, European series; T, TRUE.

Table 4
Potential Causes of False-Positive and False-Negative Reactions to Patch Testing for Contact Dermatitis

False-positive reactions	*False-negative reactions*
Nonspecifi c (irritant) responses	Technical failure
Inappropriate solvents, acids, alkalis, etc.	Separation of patch from skin (inadequate occlusion time)
Irritant interaction of aluminum chamber with metal antigens	Loss of occlusion
Nonspecifi c pustular responses to metals	Time of reading (too early or too late)
Concentration, evaporation of liquid, edge effect Improper marking	Material not fresh
Unknown materials	Only one reading done (*see* text)
Contamination	Failure to employ light in photodermatitis reactions
Concentration errors	Patient taking systemic corticosteroids or applying topical corticosteroids at site of application
An "angry" back (skin responds nonspecifi cally to multiple stimuli)	Inadequate penetration
Mislabeling	Wrong site used to apply patch
Misreading	Test applied to hairy skin
Allergy to test apparatus (tape, chambers, etc.)	Inadequate dose of allergen
Color left by colored allergens	Time of application too brief
Phototoxic reactions	

follows: +/- reactions show erythema only; 1+ reactions are erythematous, and sometimes raised slightly or with a few papules but not vesicular; 2+ reactions are vesicular; 3+ reactions are bullous and often irritant.

Potential causes of false-positive and false-negative readings are given in Table 4. Once significant (2+ or nonirritant 3+) reactions are found, the relevance must be assessed by comparing the reaction with the probabilities of exposure. The patient should be provided detailed instruction on how to identify sources of that antigen or those antigens. Printed handouts in the patient's language can be found in Guin (1995).

HOW DOES ONE MANAGE A PATIENT WITH SUSPECTED CONTACT DERMATITIS?

The principal rules for complex cases of suspected contact dermatitis involve the following procedures:

1. Remove the patient from all possible contact sources in the involved area. Of course, in some situations (e.g., clothing dermatitis), this is not possible. However, all white polyester textiles are seldom a problem, and such materials are a good substitute. Many women are reluctant to omit wearing makeup, but they are much more receptive when shown the potential for developing additional allergy (meaning they will have difficulty eventually finding products they will tolerate) if not removed from a source of allergic contact dermatitis.
2. Patch test the patient to lotions he or she has applied and to cosmetic materials used on the site, provided they are known to be nonirritant. One can usually test a moisturizer lotion by placing it in an aluminum patch-test chamber using the cellulose pad. One

should not test mascara, cleansing cream, soap, shampoo, and so on, as these are irritant. A cavalier willingness to apply unknown and often irritant materials, especially from work, can result in deep ulcers and scarring and can even sensitize the patient.

3. Avoid all products giving a positive test and all products possibly containing a chemical giving a positive test.
4. Reinstitute products giving a negative test, one at a time.
5. Treat with a steroid in petrolatum (only) and test this to be sure it is tolerated. Hydrocortisone has to be tested as an intradermal (Solu-Cortef 1 mg/0.05–0.1 mL) and read at 72 h. Any erythema at that time is suspect; most can be confirmed with a usage test to one area.

   Application to the face should be done without touching the area with the hands. A vinyl glove or a finger wrapped in plastic wrap can be used to apply the steroid ointment. This avoids hand transfer.
6. Finally, the solution to managing allergic contact dermatitis is to avoid contact with all offending agents. In addition, and especially for hand eczema, the patient must be taught how to perform normal daily functions without irritation, as the inflamed skin is very easily irritated, which will prolong the time to recovery.

Making It Work

The most important aspect of the management of chronic contact dermatitis is the identification of the causative agent. Subsequent to the identification, of course, the treatment is avoidance. Patients with chronic contact dermatitis obviously should not be treated with long-term systemic corticosteroids, and continuous use of potent topical glucocorticoids also can be followed by complications. Topical tacrolimus or pimecrolimus are often useful. Avoidance, however, makes treatment unnecessary, unless another cause is present.

For acute contact dermatitis, such as poison ivy dermatitis, where the cause is known, patients who do not have a contraindication can be treated with short courses of oral corticosteroids. For example, prednisone given in an initial dose of 60 mg daily and tapered over a 10 to 14-d period is sufficient to suppress symptoms in most cases. One should avoid potential sensitizers to prevent developing new allergies (the extended allergen syndrome). Calamine lotion (not Caladryl) and tap water compresses are relatively safe. Midpotency (or at least less than category 1) topical steroids are sometimes used under occlusion for a 24-h wrap, and this can be combined with systemic treatment in severe cases.

HAND ERUPTIONS IN HEALTH CARE WORKERS

Health care workers with hand eruptions may have irritant dermatitis, atopic hand eczema, dyshidrotic eczema, psoriasis, allergic contact dermatitis, contact urticaria (usually to natural rubber latex), contact urticaria or protein contact dermatitis to glove powder, or many other conditions. Glove reactions have become so common, however, and the consequences so serious on occasion, that protocols for health care workers are appearing in many hospitals.

When health care workers develop hand eczema, the reactions may or may not be related to gloves. Similar to any other hand eczema, management requires avoidance of irritants, and it requires a search for possible allergy to rubber chemicals in latex gloves (especially thiuram and carbamates), contact urticaria to latex proteins, and occasionally to rubber chemicals or cornstarch in glove powder and rarely to other gloves. We gen-

erally test persons to the rubber chemicals with a patch test to rubber chemicals for both 20–30 min (for contact urticaria to rubber chemicals) and the standard 48-h application for contact dermatitis. We also test to gloves other than latex, as well as formaldehyde, glutaraldehyde, and contents of soaps to which they are exposed, for example, chlorhexidine, cocamidopropyl betaine, the standard patch test series, and other preservatives used in soaps and shampoos, including parachlorometaxylenol, quaternium-15, and other preservatives. A RAST test can be ordered to latex, and, if negative, prick testing can be done by an experienced allergist or by a dermatologist set up to do these tests. One should understand the dangers of anaphylaxis and other severe reactions and be prepared for them if one does prick testing to latex in the office. Prick testing to sterile cornstarch helps find allergy to glove powder.

Nitrile gloves contain carbamates or 2-MBT. Neither vinyl (polyvinyl chloride) gloves nor nitrile gloves normally contain natural rubber latex protein (although one should read the label on the box carefully). Powder-free gloves are free of cornstarch. However, highly allergic persons may come into contact by handling objects (such as charts) that were also handled by physicians and nurses wearing powdered natural-rubber latex gloves, and glove powder in the air may transfer latex protein causing asthmatic symptoms in highly allergic persons. Persons with urticarial reactions to natural rubber latex proteins may also be allergic to certain foods, especially banana, avocado, chestnut, and kiwi, but the list of reported foods is long.

HOSPITAL PROTOCOLS FOR SUSPECTED NATURAL RUBBER LATEX SENSITIVITY

Many hospitals are now beginning to incorporate into their routine management of hospital employees with hand eruptions suspected of possibly being from natural rubber latex or other glove reactions. Such protocols often contain one or more of the following components:

1. New employees are questioned about latex allergy when hired and, if positive, are instructed to use latex-free gloves and to so inform their supervisor to assure availability in the workplace.
2. Work areas where latex materials are used are to develop protocols to allow avoidance by the employee.
3. The hospital employee health service will usually evaluate each ostensibly sensitive employee on a case-by-case basis. The employee's chart is commonly marked, and some hospitals require a special identification bracelet.
4. Appropriate referrals for workup by a dermatologist or allergist are usually done by the employee health section.
5. Appropriate substitute materials should be available in the workplace. Therapeutic protocols usually include latex-free resuscitation equipment.

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15 Food Allergy and Intolerance

John A. Anderson, MD

Contents

SUMMARY

Adverse reactions to foods can be divided into those that are allergic and those resulting from food intolerance. Allergic food reactions are IgE-mediated and are usually limited to individuals with other atopic diseases such as allergic rhinitis, atopic dermatitis, and allergic asthma. The serious form of IgE-mediated reactions to food is anaphylaxis. The most common foods to cause this are peanuts, shellfish, and tree nuts. Acute urticaria from foods is also most commonly caused by these three agents. Atopic dermatitis can be related to food allergy as well.

Food allergy also appears in infancy, and in many instances the problem will subside as the child matures. In general, the more severe the original reaction, the longer this takes. Reactions to peanuts, tree nuts, fish, and shellfish are more likely to be associated with lifelong sensitivity.

Sensitivity to foods can be determined by allergy testing. Both skin and in vitro tests can be useful in this regard, but the gold standard for the diagnosis of food allergy is the double-blind, placebo-controlled food challenge.

Key Words: Anaphylaxis, acute urticaria, double blind placebo controlled food challenge, atopic dermatitis, food intolerance

INTRODUCTION

Definitions and Classifications

Adverse reactions to foods can be divided into two major groups: food allergy, which depicts an immunological, usually involving IgE, reaction to a food; and food intolerance, which involves all other adverse reactions, some of which are the result of unknown mechanisms, but none of which involves immune reactions (Table 1). Recently, revision of these commonly accepted definitions has been suggested in Europe, as follows: adverse reactions to food would be termed food hypersensitivities, food intolerances would be

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Edited by: P. Lieberman and J. A. Anderson

Table 1
Classification of Adverse Reactions to Food

Food allergy (immunological reaction)	IgE-mediated reactions, e.g., food anaphylaxis, urticaria/angioedema and immediate gastrointestinal hypersensitivity
	Cell-mediated inflammation, e.g., dietary protein-induced proctitis/proctocolitis, enterocolitis, enteropathy, celiac disease
	IgE- and cell-mediated reactions, e.g., atopic dermatitis, eosinophilic gastroenteropathies
	IgG- and cell-mediated reactions, Heiner's syndrome
Food intolerance (nonimmunological reaction)	Anaphylactoid reactions to foods or additives
	Food toxicity or poisoning (usually from contamination)
	Idiosyncratic reaction to a food, e.g., enzyme deficiency)
	Pharmacological reaction to a food (drug-like effect)

called nonallergic food hypersensitivities, and either food hypersensitivities or food allergy would be simply known as food allergy. This chapter is based on the previously accepted terms generally used in the United States.

Food anaphylaxis is an IgE-mediated, generalized clinical reaction to a food because of mast cell/basophil chemical mediator release after first sensitization and then re-exposure to the same food. Anaphylactoid reactions to a food or food additive clinically resemble food anaphylaxis but do not involve IgE sensitization and are the result of direct chemical mediator release from the mast cell/basophil.

Other terms that are occasionally used to describe types of food intolerance include food toxicity or food poisoning, idiosyncratic reaction, and pharmacological reactions to foods. Food toxicity may be the result of natural or acquired toxins in some foods or the result of micro organisms or parasitic contamination of natural or processed foods. Some of these clinical reactions are allergic-like and must be differentiated from food allergy. An idiosyncratic reaction to a food also resembles allergy, but does not involve immune mechanisms. Primary and secondary lactose sugar intolerance because of the lack of bowel wall enzyme lactase to digest the sugar is an example of such a reaction. Finally, a pharmacological reaction occurs to some foods containing chemicals (e.g., caffeine), and some food additives (e.g., food colors) have drug-like effects.

Incidence and Prevalence

The incidence of food intolerance reactions greatly exceed food allergies in all age groups. Only some food intolerance reactions resemble allergic reactions. One well-documented study of 480 consecutively born infants found that the incidence of adverse reactions to foods confirmed by double-blind, placebo-controlled food challenge (DBPCFC) during the first 3 yr of life was 8%. In three well-done studies involving infants (United States, Sweden, Denmark), the incidence of allergic and intolerance reactions to cow's milk protein was found to be 2%. The prevalence of peanut allergy in the United States and United Kingdom is estimated to be between 0.5 and 1% of the general population. Recent evidence from studies on the Isle of Wright would indicate that the prevalence of peanut sensitivity is increasing, as much as three times (1989–1996), perhaps as a result of more exposure there of susceptible individuals to peanuts

at an earlier age. The prevalence of documented food additive reactions among 4274 Danish schoolchildren found the incidence of such reactions in children in general to be 1–2%.

Recent telephone surveys in the US have indicated that the incidence of food allergy in adults has risen from an estimated 1–2% to 3–4% of the general population. Food exposure is the most common identifiable cause of an allergic or allergic-like reaction in persons presenting to emergency departments in the US, United Kingdom, France, and Italy. In a study involving the prevalence of serious anaphylaxis and anaphylactoid reactions seen in 73 emergency departments in the state of Colorado over a 2-yr period (ages 2–71), it was estimated that the overall incidence of such reactions that occur yearly in the United States is 0.004% or 1:250,000 population.

Based on a review of the countrywide health records of a northern midwestern state from 1983 to 1987, the annual incidence of food induced anaphylaxis was 7.6 cases per 100,000 persons per year. This data has been extrapolated to indicate that currently, bases on the total US population, there are approximately 30,000 episodes of food individual anaphylactic episodes per year in the US. In a well-controlled study involving adults, the incidence of food allergy and food intolerance (allergic-like reactions) in the Netherlands was estimated to be 1.5% of the total population.

Natural History of Clinical Reactions to Food Allergy

Among children in whom allergic and allergic-like reactions have been documented by DBPCFC during infancy, 80–87% were able to tolerate that food upon rechallenge by 3 yr of age. The usual foods to which these children originally were clinically sensitive were cow's milk, eggs, soy, or wheat proteins.

In studies of infants with adverse reactions to cow's milk based formula, some of which were IgE-mediated and some not, 56% became milk tolerant by the age 1 yr, and 87% by the age of 3 yr. All the children with non-IgE reactions were clinically tolerant by age 3 compared with 75% with IgE-mediated milk allergy.

In general, the more severe the original reaction to the food, the longer it takes for clinical tolerance to be achieved. For example, in studies following more serious egg allergic children over 14 yr, 36% had developed complete clinical tolerance, 44% had reduced sensitivity and could tolerate some processed foods, but 20% were still at risk of a reaction with ingestion of even small amounts of egg protein.

Individuals who develop an allergic reaction at any age to peanuts, tree nuts, seeds, fish, or seafood are most likely to have a life-long risk to re-exposure to the specific food protein. Until recently, peanut sensitivity was felt to last at least 14 yr. Current studies have now shown that 20–25% of children originally allergic to peanut were able to tolerate this protein when orally challenged at a later time.

Little is known about the true natural history of food allergy to tree nuts, seeds, fish, or seafood. However, these allergies have been assumed to represent a life-long risk, especially if the sensitivity is acquired as an adult. There are case reports of individuals who became clinically tolerant overtime (e.g., fish).

Some patients with allergic rhinitis who are allergic to tree or grass pollens also react upon contact of the mouth with fresh fruits or vegetables. This is called the oral allergy syndrome (OAS) and is frequently a result of cross-reactions between the proteins in the foods and pollen (e.g., melons or bananas and ragweed pollen) (Tables 2 and 3). The natural history of such a food reaction is not entirely clear, but it may correlate with the degree of clinical reactivity to pollens.

Table 2
Clinical Reactions to Food and Food Additives

Anaphylaxis	General reactions Isolated reactions to the skin (e.g., urticaria with and without angioedema) Systemic reactions (laryngeal edema, rhinitis/conjunctivitis, asthma, shock, death) Oral allergy syndrome Food-dependent exercise-induced anaphylaxis
Atopic dermatitis exacerbated by food allergy	
Gastrointestinal reaction (involving food)	Infant formula allergy or intolerance Dietary-protein-induced proctitis/proctocolitis, enteropathy or enterocolitis Immediate gastrointestinal hypersensitivity Gastroesophageal reflux Eosinophilic gastroenteritis Celiac disease
Pulmonary reaction (involving food)	Heiner's syndrome Rhinitis and asthma
Other food-intolerance reactions that may be confused with allergy	Food poisoning and toxicity (including anaphylactoid reactions to histamine-containing foods) Primary and secondary lactose intolerance Migraine and other headaches Vasoactive amines Specific food-induced mediator release. Reactions to specific food additives Chinese restaurant syndrome from MSG Asthma from SO_2/sulfites Urticaria from colors and possibly other agents (sodium benzoates BHA, BHT, nitrates) Behavior effects Sugar Color in attention deficit disorder Pseudo-food allergy

MECHANISMS OF ALLERGIC AND ALLERGIC-LIKE INTOLERANCE REACTIONS TO FOODS AND FOOD ADDITIVES

Food Allergy

Most cases of allergic reactions to foods are a result of type I immune reaction involving IgE antibody directed to that food. As with other allergic reactions, the susceptible person must be first exposed to the food protein, usually intermittently over time, before sensitization occurs. This process involves the development of IgE antibody to that specific food protein.

Once the IgE antibodies are formed, they tend to stick to tissue mast cells on the surface of the body and, in some cases, circulating basophils. The mast cells and the basophils

Table 3
Usual Foods and Food Additives Associated With Adverse Reactions

Condition	*Likely causative food or additive*
Anaphylaxis (generalized systemic and urticaria/angioedema)	Egg and cow's milk (children); peanuts; tree nuts (almond, Brazil nut, cashew, fi lbert, pecan, walnut), crustacean seafood (shrimp, lobster, crab, crayfi sh), fi sh, seeds
Oral allergy syndrome	Pollen sensitivity — Raw food Ragweed — Melons (watermelon, cantaloupe), bananas Birch tree — Apple, pear, hazel nut, carrot, potato, celery, kiwi Grass — Peaches, celery Mugwort — Celery
Food-dependent exercise induced anaphylaxis (F-EIA) wheat	(Within 2 h) any meal, or celery, shrimp, oyster, chicken, peach,
Infantile atopic dermatitis	Egg, cow's milk, peanut, wheat, soy
Infantile formula intolerance	Conventional cow's milk- or soy protein-based infant formula
Celiac disease	Gluten: wheat, oat, rye, barley
Heiner's syndrome	Cow's milk protein
Scromboid fi sh poisoning	Tuna, mackerel, bonita, mahi mahi, bluefish
Urticaria from histamine-containing or -releasing foods	Histamine-containing foods Parmesan and Roquefort cheese, spinach, eggplant, wines Histamine-releasing foods Chinese restaurant foods, alcoholic beverages (especially red wine), strawberries, seafood
Lactose intolerance	Lactose sugar in cow's milk, cheese, yogurt
Headaches (especially migraine)	Vasoactive amine — Food Caffeine — Coffee, cola Phenylethylamine — Cheeses (especially Gouda and Stilton) Serotonin — Banana, pineapple, plantain, avocado, plum, tomato Theobromine — Chocolate Tyramine — Camembert and Cheddar cheese, yeast, red wine, pickled herring, chicken livers
Chinese restaurant syndrome	MSG
Asthma due to a preservative	SO_2, sulfites, yellow color (uncommon), MSG (rare, if any)
Urticaria due to a food additive	Colors, especially yellow, red, blue (BHA, BHT, sodium benzoate, nitrites—rare, if any)
Attention deficit syndrome	Colors, especially yellow

are the effector cells of allergy and contain either preformed chemical mediators or are able to facilitate formation of other mediators in the immediate tissue around the cell once stimulated. Re-exposure to the same food protein results in chemical mediator release or formation in the tissue, which causes the clinical allergy signs and symptoms.

As shown in Table 2, the most common type of IgE-mediated food reaction is cutaneous (pruritus, urticaria, or angioedema) followed by systemic anaphylaxis. In OAS, also an IgE-mediated event, itching and swelling of the mouth parts occur with direct contact

Proven Food Allergy in Infants

The most likely foods involved in allergic reactions in children below the age of 2 in the United States are

- Cow's milk
- Eggs
- Peanuts
- Wheat
- Soy

with raw fruits or vegetables. Occasionally (1–2%) these patients also react with systemic symptoms. In food-dependent exercise-induced anaphylaxis (F-EIA) (*see* Table 2), increased histamine release is induced by exercise. IgE reactions to foods only become clinically evident within 2 h of a meal, following vigorous activity.

Gastrointestinal reactions in infants primarily due to cow's-milk-based formula, including dietary protein-induced proctitis/proctocolitis, enteropathy, enterocolitis, and perhaps gastroesophageal reflux, do not have IgE antibodies to food protein.

These clinical syndromes are felt to be a result of the products of cell-mediated inflammation (*see* Table 1). Celiac disease represents an immune response to gluten (wheat or other cereal grains). It is caused by a gliadin-specific T-cell response in genetically susceptible individuals.

Atopic dermatis and the eosinophilic gastroenteropathies are felt to represent, at least in part, an overlap between IgE- and cell-mediated immunological inflammation. Atopic dermatitis is a skin condition, primarily in children, whose pathogenesis involves both nonimmune and immune factors. IgE antibody formation in general is usually enhanced in this condition. However, in only one-third of children with atopic dermatitis is food allergy clinically important.

It has been shown in studies with atopic dermatitis individuals who are proven to be allergic to a food by DBPCFC that, while eating that food, in vitro histamine release is increased nonspecifically owing to the presence of "IgE-dependent histamine-releasing factors" in the serum. This tendency has a definite connection with the broad-based chronic inflammation found in the skin of the atopic dermatitis patient who is allergic to specific food proteins.

Food Protein Allergens and Antigens

Purified major antigens have been identified for cow's milk (e.g., casein, β-lacto globulin, α-lactalbumin), chicken egg, peanut, soy, fish, and shrimp. These major food allergens are heat stable. Thus, individuals who are allergic to foods such as milk, peanut, or fish can develop symptoms once sensitized to re-exposure to very small amounts of these specific foods in a natural, cooked or processed form. For example, most peanut-allergic individuals react to 100–1000 mg, of peanut, but a few have reacted to much less. One kernel of peanut contains about 800 mg of crude allergen protein. It has also been estimated that a meal of peanut containing food usually contains the equivalent of at least two peanuts. Although cooking does not effect most foods with major antigens, in the case of peanut, dry-roasting (the usual way they are processed in the US) actually enhances the allergic nature of the protein.

There are also minor food allergens, such as those found in fresh fruits and vegetables, that cross-react with pollens, as is seen in the oral allergy syndrome. In this condition, reactions are the result of homology between food and pollen to common plant proteins such as proflin. These latter allergens are heat labile. Individuals allergic to a fresh fruit, such as apple, can usually eat an apple pie. A recent study would seem to indicate that short microwave exposure to a fresh fruit is enough to denature the allergen to allow it to be tolerated to some degree by individuals who develop symptoms to these fresh fruits.

Although there is some immunological cross-reactivity between different foods, especially those in the same family, characteristically, individuals react clinically more often only to a few foods in a given food family. For example, in the legume family, most individuals are clinically sensitive only to peanut and can tolerate peas, beans, and soy protein, even though IgE antibodies to these foods can be detected either in IgE immediate-reacting skin tests or in vitro IgE food-protein-specific antibody assays. The major fish antigen is found in all fresh and saltwater fish, but, almost all fish-allergic individuals can tolerate canned tuna fish (the only exception is a single recent case report).

There are reports that food-allergic individuals are more likely to become allergic to other foods even though they are in different families. Examples include: (1) tree-nut allergy in peanut (legume family)-allergic individuals and (2) clam/oyster (mollusk family) in shrimp (crustacean family)-allergic patients. When these relationships have been investigated relating to nuts and peanut, "dual-food sensitivities" were most likely a result of the highly atopic nature of the individuals eating both types of food, rather than any cross-family immunological relationships.

Exposure to food protein usually occurs orally. Occasionally, individuals can become sensitized or, after developing a food allergy, have a reaction to re-exposure of food through either the aerosol or contact route. Examples include bakery workers who develop IgE-mediated wheat protein sensitivity (and subsequent asthma called baker's asthma) from exposure and then re-exposure to wheat flour dust. Another example is the fish-allergic individual who may develop urticaria or systemic anaphylaxis when exposed to the odor/steam of cooked fish. Inhalation reactions have also been reported with crab, egg, milk, peanuts, beans, rice, and potatoes. Contact reactions have occurred with eggs, milk, peanut, fish, and crab.

Recently, attention has been called to the risk of lactose exposure in a severe-milk allergic individual using a dry powder asthma inhaler (DPI). Sufficient milk proteins to cause anaphylaxis was found in lactose USP and in the DPI containing lactose as an inactive ingredient.

Serious allergic reactions occur occasionally in people who are allergic to substances in foods other than food proteins. Examples including reports of individuals who have reacted to house dust mites in beignet flour, psyllium (cholesterol control) in breakfast cereal, fish parasite (*Anisakis simplex*) in raw or undercooked fish or seafood, α-amylase (from *Bacillus subtiliis*) in bread flour, and latex (natural rubber) protein from gloves used by food preparers.

Allergic-Like Food Intolerance Reactions

The mechanisms for most food intolerance reactions are not known. Most infants who develop isolated gastrointestinal symptoms (vomiting, diarrhea, blood in stool) resulting from formula intolerance do not demonstrate IgE antibody reactions. This condition can occur while the child is ingesting cow's-milk-based conventional formula, breast milk from mothers eating a normal diet, or soy protein-based infant formulas. Approximately

one-half of the individuals with documented eosinophilic gastroenteritis are allergic. The rest are not, yet the disease pathology between the allergic and nonallergic group is similar.

An example of an anaphylactoid reaction to food is a scromboid fish poisoning (*see* Tables 2 and 3). In this situation, certain fish that are spoiled or contaminated with either *Proteus* or *Klebsiella* species such as tuna, mackerel, bonito (scroboid varieties), or mahi and bluefish. The bacteria decarboxylate histadine in fish tissue to create histamine. When the fish is cooked and eaten, the diner experiences a sharp peppery taste, burning of the mouth parts, followed by nausea, vomiting, diarrhea, facial flush, and headache—all resulting from the high levels of histamine in the tissue. This is the same major chemical mediator released from the mast cell or basophil as the result of an allergic reaction.

Other common foods that may contain a significant amount of histamine include Parmesan and Roquefort cheeses, spinach, eggplant, red wines, and some Chinese restaurant foods (Table 3). Other pharmacoactive agents in foods that produce symptoms that could be confused with allergy include caffeine (in coffee and cola), tyramine (in cheese), phenylethylene (in cheese, red wine, and chocolate), serotonin (in banana, pineapple, avocado, tomato), and theobromine (in chocolate) (Table 3).

The possible effects of these various natural vasoactive amines is variable, but there are reports of these chemicals aggravating migraine headache. Patients taking monoamine oxidase (MAO) inhibitor drugs for the treatment of conditions such as depression need to be very careful about eating these types of foods, because MAO is important for the metabolism of vasoactive amines. Thus, eating these foods and taking these inhibitor drugs may result in increased blood levels of the vaso-active amines. Both severe blood pressure elevation and headache have been reported.

Lactose intolerance is an idiosyncratic reaction caused by the lack of bowel wall lactase, which is necessary to metabolize lactose sugar found in cow's milk. Individuals with lactose intolerance who ingest milk cannot digest it, and the sugar ferments in the bowel, causing gas, discomfort, and perhaps diarrhea. Primary lactose intolerance is a common inborn error of metabolism in certain population groups (e.g., approx 80% of North American African American, Arab, and Asian populations). This condition is a less common problem in other ethnic groups (10% incidence in north European Caucasian populations).

The symptoms begin about age 7, but may occur earlier if the patient develops a severe viral or bacterial gastrointestinal infection. Lactose intolerance may occur after any gastrointestinal infection and is usually a temporary condition lasting about 2 wk. Secondary lactose intolerance of a more permanent nature, however, can occur with chronic gastrointestinal conditions, such as sprue or cow's milk allergy. Each patient with lactose intolerance is different, and many may tolerate some degree of lactose sugar in their diet.

Food Additive Intolerance Reactions

Allergic reactions have been reported to occur to the preservative sulfites (and SO_2), sodium benzoate, butylated hydroxyzole (BHA), butylated hydroxytylene (BHT), the sugar substitute aspartame, artificial colors (especially yellow, red, and blue), and the flavor enhancer monosodium glutamate (MSG). The symptoms of principal concern are urticaria and asthma. In most cases, even if it is proven that the food additive is involved in the clinical symptoms, the exact mechanism of the reaction is unknown.

Food Additive Reactions

- In general, proven adverse reactions to food preservatives, colors or flavor enhancers are uncommon.
- Chewing foods containing sulfites may release SO_2, which, when inhaled, may exacerbate asthma.
- Very few patients have been proven to develop urticaria after ingesting food coloring agents.
- Behavioral abnormalities in children usually cannot be attributed to diet content (e.g., amount of sugar, presence of allergic protein, or type of food additive).

In sulfite-induced asthma, the principal mechanism is believed to be the inhalation of SO_2 as sulfite-containing foods are chewed in the mouth. In addition, a small number of individuals have been identified who have a sulfite oxidase enzyme deficiency, which prevents metabolism of this preservative and could result in high blood levels. In a few cases of documented urticarial reactions to color, histamine and prostaglandin increase has been found in the urine after specific food allergy additive challenge.

In the attention deficit disorder syndrome with hyperactivity (ADD), food colors, especially yellow, have been implicated in 3% or less of the cases in inducing a drug-like effect on the patient's ability to learn.

The evidence for IgE-mediated food immune reactions as being involved in the pathogenesis of migraine headaches is very poor. However, a small number of documented cases of migraine patients, on DBPCFC, demonstrate increases in plasma histamine PGFa and PGD_2 that correlate with specific food protein challenge and headache.

CLINICAL REACTIONS TO FOODS AND FOOD ADDITIVES

Food Anaphylaxis

The signs and symptoms of anaphylaxis resulting from food allergy are no different from those of anaphylaxis as the result of allergy to β-lactam antibiotics, stinging insects, or natural rubber latex. The symptoms and signs may be mild or severe. Milder symptoms/signs include contact urticaria, generalized pruritus, erythema, and urticaria with or without angioedema. More severe symptom/signs occur with generalized systemic anaphylaxis from a food and may be multiple or single in nature. These symptoms include laryngeal edema, rhinitis with or without conjunctivitis, asthma, blood pressure decrease, or shock and possible cardiovascular collapse and death. Occasionally, additional symptoms include nausea, vomiting, abdominal cramps, diarrhea, and uterine or bladder cramps.

Most generalized anaphylactic reactions to foods of any significance are biphasic in nature with an early and late phase separated by about 1–8 h. Some very serious reactions are protracted and last continuously for 5–32 h without remission.

Individuals tend to develop serious anaphylactic reactions to a relatively small group of foods, including cow's milk and eggs (usually infants and children), peanuts, tree nuts (walnut, pecan, almond, cashew, Brazil, filbert), crustacean seafood (shrimp, lobster, crayfish), fish, and seeds (Table 3).

Food Anaphylaxis

Lifelong sensitivity may occur at any age to these commonly eaten foods:

- Peanuts
- Seafoods (especially shrimp, lobster, and crab)
- Tree nuts (e.g., almonds, Brazil nuts, cashews, filberts, walnuts, and pecans)
- Fish
- Seeds

Most individuals who die or nearly die with food anaphylaxis are very allergic in general and reactive to many things in their environment, including pollen, animals, house dust, and mold allergens. Most of these patients have allergic rhinitis and asthma. Many of the children with food allergies have, or have had, atopic dermatitis. Individuals who have been reported either to have died from or nearly died from a systemic reaction from food are usually aware of their specific food allergy. Most deaths occur when the individual is away from home. The specific food to which the individual is allergic is usually eaten in a disguised form (e.g., in a pastry, candy, salad, sandwich, or hors d'oeuvre). Often the difference between life and death is whether or not adrenaline was given quickly (e.g., within 1 h after the start of a reaction) when the dangerous food is ingested or the exposure occurs.

There are two special anaphylaxis syndromes that are specific for food allergy. The first is OAS or the fruit and vegetable syndrome (Table 2). In this syndrome, individuals with pollen sensitivity, usually manifested by allergic rhinitis/conjunctivitis or hay fever, develop specific food sensitivities to fresh fruits and vegetables upon contact of these raw foods with the mouth. The mechanism is a result of partly cross-reactivity between the pollen protein and the food protein (*see* Mechanisms). The food cross-reactivity includes melons and bananas among US ragweed-allergic individuals, apples, pears, potatoes, hazelnuts, carrots, celery, and kiwi among birch-pollen-allergic individuals, peach, tomato, and celery among grass-allergic individuals, and celery allergy among European mugwort-weed-sensitive individuals (Table 3). These crossreactivities between foods and pollens may be further complicated by the fact that individuals with anaphylaxis to natural rubber latex may also be sensitive to certain foods, including bananas, chestnut, avocado, and kiwi, and that these sensitivities may be a result of cross-reactivity between pollens, such as ragweed and grass.

The symptoms of OAS are usually confined to exposure to raw foods to either the mouth or hand, and the type of symptoms includes pruritus, swelling, tingling, or fullness. In some cases, full-blown systemic anaphylaxis may result. In the majority of cases, however, symptoms begin within 5 min of raw food contact and may be ameliorated by discontinuing contact and washing the hands or rinsing the mouth, so that symptoms resolve within 30 min.

A second food-specific anaphylactic syndrome is F-EIA. EIA is a relatively newly described physical urticaria in which vigorous exercise is associated with urticaria or shock. In half the cases, this syndrome requires a cofactor, such as eating a meal (in general) or ingestion of a specific food, including celery, shrimp, oysters, chicken,

peaches, or wheat (Table 3). All symptoms begin within 2 h of a meal, and usually the individual can eat the specific food in spite of the presence of IgE antibodies to that food, as long as he or she does not exercise in this 2-h period.

Atopic Dermatitis

Atopic dermatitis (AD) is an inherited genetic skin disorder that involves both IgE- and cell-mediated immune mechanisms. After allergen-induced mast cell activation, the skin is infiltrated by monocytes, lymphocytes, and finally eosinophils and their by-products. Severe purities precedes the eczema, which has a characteristic distribution in infancy, childhood, and adult life. In allergic families, this condition begins in early infancy, often as breast-feeding is discontinued, and usually begins to clear by 3–5 yr of age. By this time the child often has additional symptoms of allergic rhinitis, asthma or both leading to the use of the term "dermo-respiratory syndrome."

Most children with AD have high total IgE and many positive skin test reactions or evidence of in vitro antiallergic antibodies. Many of these reactivities are directed to foods. It has been proven, using DBPCFC, that about one-third of children with atopic dermatitis react with an exacerbation of their rash to specific food challenge, such as egg, cow's milk, peanut, wheat, and soy (Table 3). Other clinical reactions to foods in this group of patients are less common.

Children with AD and food allergy have been found to have increased "spontaneous" (nonspecific) histamine release from their blood basophils (in vitro) when they were regularly eating the specific foods to which they were allergic to (*see* Mechanisms).

It has been found in studies using DBPCFC involving food-allergic atopic-dermatitis children that the allergy skin test or in vitro test is usually positive to the offending food, but that in food skin-test-positive situations, the likelihood of that food being clinically significant in the rash is no more than 50%.

In these studies, if the food skin test was negative, the DBPCFC was almost always also negative. It was found in these studies that the skin test and in vitro IgE food-antibody tests results were more reliable as an index of possible food involvement than was the mother's history of such reactions. Individuals who were confirmed to be allergic by food challenge were usually sensitive only to a few foods, not multiple foods. A negative food skin test or in vitro IgE food-antibody test practically ruled out the possibility that the DBPCFC would be positive to that food.

It has also been shown that if the food to which the patient was found to be allergic on DBPCFC was strictly eliminated from the diet for a time, the dermatitis would improve. The clearing of the skin rash has been correlated in these children with a decrease in in vitro basophil histamine release.

Gastrointestinal Reactions Involving Food

A wide variety of signs and symptoms involving the gastrointestinal tract could be attributed to a food allergy. However, most are not specific, and the possible causes for most of these signs and symptoms are multiple. Itching and swelling of the mouth, however, are certainly suggestive of an allergic reaction as in the OAS. Infants who have formula intolerance can develop vomiting, have diarrhea, or simply have blood loss in the stool. Some individuals simply fail to thrive.

Gastrointestinal allergic disorders that primarily affect infants include dietary protein-induced proctitis/proctocolitis, enteropathy, and enterocolitis. Infants with proctitis/proc-

Allergy and Gastrointestinal (GI) Food Reactions

- Most GI reactions to diet are *not* a result of food allergy.
- Milk protein allergy/intolerance usually occurs in infants.
- Lactose (milk sugar) intolerance usually is a problem in older children or adults and runs in families.
- Food protein anaphylaxis (allergy) occurs within minutes to 2 h after food ingestion and almost always includes urticaria—with or without GI symptoms.
- The fi ndings of eosinophils on GI biopsy is suggestive but not diagnostic of food allergy.

tocolitis seem generally healthy, but have specks or streaks of blood and mucus in the stool. The mean age is 2 mo. Most infants are being breast-fed and are reacting to maternally ingested proteins excreted in the breast milk. Cow's milk (or egg/soy) restriction from the mother's diet usually solves the problem. No IgE food antibodies can be found on skin tests or in vitro tests.

The symptoms of dietary protein enteropathy include diarrhea and vomiting, which can lead to malabsorption and failure to thrive. Enterocolitis is more severe, since both the small and large bowl are inflamed. Intestinal biopsies show friable mucosal surfaces, eosinophilic infiltrates, and either occult or gross blood loss.

In these infants, often the elimination of conventional cow's-milk-based infant formula feeding and replacement with a casein hydrolysate infant formula plus rechallenge to conventional formula is the only way to prove the etiology, since IgE antibodies to food protein may not be found on in vitro studies.

In studies, 30–42% of infants with gastroesophageal reflux were found to have eosinophilic infiltrates in the esophagus wall and milk allergy/intolerance. In all these dietary protein-induced gastroenteropaties, cell-mediated inflammation is suspected (*see* Mechanisms).

Immediate gastrointestinal hypersensitivity is an acute IgE-mediated disorder of children who react with in minutes or up to 2 h with nausea, vomiting, and abdominal pain following food injections. The usual causes are cow's milk, egg, peanut, soy, wheat, and seafood.

Eosinophilic gastroenteritis is a chronic problem of older children and adults that involves the entire gastrointestinal tract (especially stomach and small intestine). These tissues are infiltrated with eosinophils. The symptoms include cramping, abdominal pain, nausea, vomiting, diarrhea, and blood loss in the stool. Only one-half of the reported cases of eosinophilic gastroenteritis are highly allergic, including reactions to many foods. When these specific foods are eaten, the condition is exacerbated. When the patient switches to a diet devoid of offending foods, however, the condition does not completely clear.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (wheat, rye, and barley) in a genetically susceptible person. The disease is associated with HLA-DQ2 in 90–95% of cases. The typical syndrome of malabsorption associated with chronic diarrhea, weight loss, and abdominal distention is now uncom-

mon. The onset now is often atypical (or even silent) and may include single symptom of diabetes, anemia, fatigue, behavior changes, and irritable bowl. Once diagnosed, the treatment is life-long gluten elimination.

Infant colic is not due to food allergy. It occurs in 20% of children regardless of the diet, including maternal breast milk. Recurrent abdominal pain in older children usually has nothing to do with food allergy. Intermittent bouts of diarrhea, along with abdominal cramping, are again not likely to be due to food allergy. Probably the most common problem diagnosed under these circumstances is irritable bowel syndrome. However, other conditions, such as ulcerative colitis and regional ileitis, polypoid disease, and cancer must be ruled out.

Pulmonary Reactions Involving Food

In 1956, Heiner and Sears identified a group of infants with recurrent anemia and pneumonia associate with in vitro cow's milk precipitins in the serum. Some of these children later developed pulmonary hemosiderosis. This syndrome is believed to be the result of pulmonary aspiration of milk formula just after birth and the development of IgG cow's milk antibody titers as a result of sequestration of milk in the lung (*see* Mechanisms). Later, upon repeated exposure to cow's milk in the diet, both a type III immune complex and a type IV cell-mediated reaction occur. Today, such reactions in infants are rare, but should be considered in infants with recurrent pneumonia and anemia of undetermined etiology.

Rhinitis and/or asthma-like symptoms (wheezing, respiratory distress) occur as part of systemic anaphylaxis to foods. It has been shown in studies of children with atopic dermatitis who are allergic to foods that after specific food avoidance, followed by DBPCFC 2 wk later, one-third are likely, upon challenge, to develop respiratory symptoms, such as rhinitis or asthma, along with exacerbation of their skin rash. Other than these two situations, isolated rhinitis after food ingestion as a result of allergy is rare.

The estimated prevalence of food allergy induce asthmatic reactions is also low (2–6%) except in those with documented food anaphylaxis or concurrent atopic dermatitis (up to 24%).

From studies in the United Kingdom, there appears to be an increase risk (5- to 10-fold) of future respiratory allergy (rhinitis or asthma or both) in infants who have an allergy to eggs or egg and milk, especially if they have eczema.

Other Food Intolerance Reactions That May Be Confused With Allergy

Reactions, such as anaphylactoid events following ingestion of scromboid fish protein, are described under Mechanisms. Urticaria may occasionally occur following ingestion of certain foods containing histamine or as histamine reactors as listed in Table 3. Examples include cheese, alcohol, red wine, or strawberries.

One of the most common gastrointestinal problems that is confused with milk allergy is primary (and secondary) lactose intolerance. The pathogenesis of this reaction is described under Mechanisms. As pointed out, the problem with milk usually begins around age 7, but may start earlier in childhood if the child has had significant gastroenteritis. Then, for the rest of his or her life, ingestion of cow's milk is a problem. This sequence of events is different from that of the individual who is milk protein allergic in that the milk-allergic individual has trouble during early childhood and later is usually able to tolerate milk clinically.

In the lactose-intolerant patient, the degree of exposure to milk sugar is important. Certain foods are better tolerated than others: cheese is better tolerated than whole milk, and naturally fermented yogurt is better tolerated than cheese. Since the problem is common in certain ethnic groups, older family members may report the same problem with milk ingestion, and lactose intolerance is usually simple to diagnose. If it is important to document this syndrome, this can be done by a gastroenterologist using a breath hydrogen test after lactose ingestion.

The triggering of headaches by vasoactive amines naturally or by food additives may occur with the foods listed in Table 3 and described under Mechanisms. Although the issue of allergy being involved in migraine headache pathogenesis has been long debated, it is rarely proven. In a few cases of patients with migraine headaches, chemical mediator release while eating a specific food may be involved in the headache. Migraines are very common in the general population (e.g., 25% of all adult women and 15% of all adult men). In addition, allergies are also common; therefore, it would be easy to find both conditions (migraine headache and atopic disease) present in the same individual.

Adverse reactions to food additives are not nearly as common as is generally believed. Reactions to BHA, BHT, benzonates, and nitrates are very rarely substantiated by objective measurements. The most common FDA-reported food additive reactions are those to aspartame, and the usual type of symptom is headache. Fifteen percent of reports of adverse effects from aspartame, however, are "allergic-like," usually urticaria. Although there are two documented cases of aspartame-induced urticaria/angioedema reported in the world literature, a recent large nationwide, multicenter study using DBPCFC was unable to confirm a significant association between aspartame and urticaria. The types of adverse reactions to food additives that have been confirmed over the years include the Chinese restaurant syndrome resulting from MSG, asthma resulting from SO_2 or sulfites in food, and occasional episodes of urticaria/angioedema resulting from food coloring (*see* Table 3).

The first report of the Chinese restaurant syndrome was a 1968 self-report of a Chinese physician who ate at a Chinese restaurant and experienced symptoms of nausea, headache, sweating, thirst, facial flushing, tightness and burning of the face and chest, abdominal pain, tearing of the eyes, and a sensation of "crawling" in the skin. Typically, the symptoms begin 15–30 min after eating a meal containing a large amount of MSG, which is a salt of a glutamic acid. These symptoms usually subside without specific medical treatment once the individual discontinues ingestion of the MSG-containing food.

The second most likely food additives (after aspartame) to be reported to FDA as being responsible for an adverse reaction are sulfites and SO_2. Although a few cases of anaphylactoid-type reactions, usually involving urticaria/angioedema, have been reported, most reactions are the result of asthma exacerbation in a known asthmatic. Some of the early cases were serious, and a few led to death. Although SO_2 and sulfites have been used for many years as food and beverage preservatives, it was not until the 1970s and 1980s that reports emerged about serious asthma attacks being precipitated directly upon opening a package containing SO_2-preserved foods or eating (and inhaling SO_2 indirectly) sulfite-containing foods ($_{see}$ Mechanisms). Of particular importance were fresh vegetables and fruits in salad bars in restaurants (especially lettuce) to which a sulfite solution had been applied to preserve that food. FDA has estimated that approx 5% of all asthmatics are at risk for a reaction to SO_2 or sulfite, and studies have shown that the more serious asthmatic is at greater risk of an exacerbation of the asthma than a mild asthmatic.

In the late 1980s, FDA made significant changes in the regulations concerning the maximum level of sulfites that could be in foods in the United States, as well as restrictions on the use of sulfites in restaurants, especially in salad bars. Since that time, the number of reports of sulfite-induced asthma has dropped dramatically. Although there have been reports of MSG-induced asthma exacerbations in Chinese restaurants in Australia that were confirmed by challenge studies in the 1980s, there has not been a similar problem with MSG in the United States.

Although in Europe food additives of all types have been implicated as primary causes of chronic urticaria in about 15% of the cases, most studies in the United States have failed to confirm a significant relationship with any additive except for a few isolated cases of color (particularly yellow)-induced urticaria and angioedema (Table 3).

Tartrazine (FD&C yellow #5) was originally felt to "cross-react" in some way with aspirin and to be a factor in asthma exacerbation in aspirin-sensitive asthmatics. Careful DBPCFC with tartrazine in proven aspirin-sensitive asthmatics has failed to confirm this association with yellow #5. Independent of aspirin sensitivity, there are a few isolated asthmatic patients who are sensitive to yellow #5.

Food additives (particularly colors, especially yellows) have been implicated in causing or exacerbating behavioral problems in children. Probably the most widely known theory regarding this relationship was the Feingold theory about colors (and other food additives) causing hyperactivity in patients with ADD (*see* Tables 2 and 3). Most subsequent studies have shown that colors do have a drug-like effect, but that this effect occurs in no more that 5% of children with ADD, and the effect has to do with learning abilities. There are no studies that show that colors in the market today are not safe for the general population.

In the mid- to late 1980s, diets high in sugar were believed to cause abnormal behavior, especially hyperactivity in normal children, those with ADD, and juvenile delinquents. The misnomer sugar allergy was coined. DBPCFC studies have documented the fact that sugar in the diet does not have an adverse effect on behavior and, in some cases, may have a calming effect. In the 1960s, Pearson coined the term pseudo-food allergy to describe a syndrome that usually occurs in adults who believe that they have food allergy and restrict their diet to such a degree that they develop signs of malnutrition (*see* Table 2). Almost all the patients who have been reported with this condition have been found to have psychological problems, especially depression. The symptoms they complain about include fatigue, headaches, "mental fuzziness," malaise, arthralgia, and myalgias. When DBPCFC studies were done, none of the patients studied reacted to the foods to which they were supposedly sensitive; with psychological counseling all resumed a normal diet without adverse effect.

DIAGNOSIS OF FOOD ALLERGY OR INTOLERANCE

History

As outlined in Table 4, a good history is the most important factor in diagnosing a food allergy or intolerance. The history should include:

1. The description of the problem
2. The timing of the onset in relationship to the specific food or additive in the diet and the duration of the event
3. The quantity of the suspected food ingested

Table 4
Diagnosis of Food Allergy and Intolerance

History	Description of problem
	Timing of onset and duration of event related to diet
	Frequency of symptoms
	Other important circumstances
IgE-reacting skin testing and in vitro IgE antibody testing	
Food diary and diets	
Confirmatory food challenges	Open
	Double-blind, placebo-controlled
Other tests	Mast cell tryptase
	Analysis of potential food allergen ingredient content in processed foods
	Breath hydrogen and lactose tolerance

4. Whether similar symptoms to this same food (or other foods) have occurred before
5. The frequency of symptoms (continuous or intermittent in nature)
6. Additional circumstances

Most individuals who develop food allergies have other manifestations of allergy or have family members with allergic disease. This includes atopic dermatitis, urticaria, asthma, and allergic rhinitis/conjunctivitis. A history of asthma in a food-allergic individual should be considered a risk factor for possible serious life-threatening reactions of an anaphylactic nature to that food.

Certain foods are associated with different types of allergic and intolerance reactions (Table 3). This should be kept in mind when taking a history of the presenting complaint. Most food anaphylactic reactions (e.g., urticaria or systemic anaphylaxis) occur within minutes (and almost always within 2 h) after exposure to the food. In these types of cases, it is often easier to pin down a likely food candidate because of the close association in time. More difficult are cases in which the problem is chronic (e.g., atopic dermatitis) and in which many nonallergic factors play a role. In studies involving children who were allergic to food and had atopic dermatitis, the patient's history of the likelihood of a specific food being involved was often not helpful. Food-allergy skin testing or in vitro IgE specific food-antibody testing were more helpful in narrowing the field of likely foods responsible for the allergic reaction. Finally, being a "good detective" may take a great deal of time, especially when the culprit food responsible for the adverse reaction is not obvious and/or a part of a prepared food.

IgE Food Allergy Skin Testing or In Vitro Food Allergen-Specific Antibody Testing

Only the epicutaneous prick type of immediate-reacting IgE (allergy) skin testing is used to diagnose food allergy. Tests are done with a drop of food allergen concentrate (usually 1:10 weight by volume) on the forearm or back and read in 15 min. Either commercial allergy extract or fresh material (e.g., juice from a fresh apple in the oral allergy syndrome) can be used. Reactions in which the wheal is measured at 3 mm or more than the negative saline control are considered to be positive.

Confirming the Diagnosis of an Adverse Food Reaction

- DBPCFC is the "gold standard" for the diagnosis of an adverse reaction to food.
- A positive DBPCFC does not identify the mechanism of reaction.
- In most cases of systemic (life-threatening) anaphylaxis, a DBPCFC is not clinically necessary since it is risky; the presence of IgE allergen-specific antibody can help establish a "presumptive" diagnosis.
- Food diaries and short-term elimination diets at home may be helpful tools, but in themselves do not confi rm the diagnosis.
- IgE food prick tests or in vitro assays may assist the clinician in narrowing down the field of likely foods in suspected food allergy.

In vitro IgE food allergens-specific antibody testing, especially using the quantitative CAP fluorescent enzyme immunoassay (FEIA), is the diagnostic method of choice in cases of systemic anaphylaxis, since it is safer than skin testing. It usually follows that if the allergy skin test is negative, then the in vitro test will also be negative. However, in the case of a convincing history of a serious allergic reaction, it is advisable to do an in vitro test, after a negative skin test to verify the lack of presence of IgE food-specific antibodies.

The food allergy skin test (or in vitro test) is helpful to screen for food allergies. If one of these two tests is positive in infants, there is up to a 50% chance (for commonly eaten food) that the individual, if challenged, would be actually found to be clinically sensitive to that food. If the skin test or the in vitro allergy food tests are negative, however, almost 100% of the time if one would challenge with that food the challenge would be negative.

If either the immediate food allergy skin test or the IgE food allergy-specific in vitro test is positive in adults (in whom the frequency of true food allergies is less than in infants and children), with any food there is only a 3% chance that if the adult were challenged with the food, it would be clinically relevant. Again, if either the food skin test or the in vitro test is negative in adults, there is close to 100% chance that a food challenge would be negative.

In the case of systemic anaphylactic reactions to food, usually the in vitro allergy skin test is positive. In this case, a presumptive diagnosis of food anaphylaxis is made without the necessity for challenge studies.

With the use of the CAP-FEIA in vitro test, the actual numerical value is expressed in kilo-units of IgE food antibody per liter (KUa/L). This has been shown to predict the likelihood of a positive subsequent food challenge. Older children or adults with high levels of allergen specific antibody in KUa/L (eggs: 7; milk: 15; peanut: 14; tree nuts: 15; fish: 20; soy: 30; wheat: 26) or infants (egg: 2; milk: 5) can be considered to be allergic without the necessity of a confirmatory challenge.

In addition, when the patient's history is taken into account, in vitro food IgE antibody approaching 60% of these diagnostic cut-off levels may also be considered to be food allergic (*see* Sampson 2004, Suggested Reading).

Any individual can have IgG food-specific antibodies. These antibodies represent a natural reaction to exposure to foods eaten. Studies have not shown a correlation between the amount of IgG food antibodies and any allergic or other medical problem. Unfortunately, some patients or families have been misinformed about the potential value of such tests.

Table 5
Major Food Allergen-Free Diet Foods and Beverages Allowed[a]

Apricots	Chicken	Pineapple	Sugar (cane or beet)
Arrowroot	Gingerale	Plums	Sweet potatoes
Artichokes	Ham (boiled)	Poi	Tapioca (whole or pearl, not minute)
Asparagus	Kidney beans	Potatoes	
Bacon	Lamb	Potato chips	Turkey
Beef, all-beef wieners	Lentils	Prunes	Vanilla extract
	Lettuce	Rice	Water
Beets	Maple syrup or maple-flavored cane syrup	Salt	White soda
Blueberries		Soybeans	White vinegar
Carrots		Soybean sprouts	Yams
Celery	Navy beans	Soy milk	
Cherries	Olive oil	Spinach	
Any vegetable shortening or oleomargarine that contains no milk			

[a]All fruits and vegetables, except lettuce, must be cooked.

In Europe, the delayed-reacting patch test has been adopted in an attempt to increase the probability of predicting food allergy. In this test, food allergens are placed on a patch and left on the skin for 24 h before reading. A positive test is an eczematoid-type of reaction. Some investigators have claimed that the results of patch tests, coupled with results of prick skin tests and/or in vitro tests, more accurately predict food allergy in patients with AD. This type of food testing has not been accepted in the United States for routine use in clinical situations.

Food Diary and Diets

Food diaries may be helpful in the patient with a history of several, but intermittent, episodes of acute urticaria or other symptoms suspected of being related to diet. If there is no obvious cause, a diary of events, including a diet for subsequent episodes, may be helpful in pinning down the ultimate diagnosis.

Temporary use of diets composed of foods to which most individuals have no allergy or intolerance is sometimes helpful when the patient has a chronic problem suspected of being related to diet, but not involving anaphylaxis. Examples of these allergen-free diets and foods can be found in numerous textbooks and in Table 5. Usually the patient is kept on such a diet for 2 wk, and then one new food is added to the diet every 3 d (and the previously added food is kept in the diet, providing no adverse symptoms occurred). This is continued until a normal diet has been resumed.

Food Challenges

It is usually advisable to refer patients potentially requiring food challenge to an allergist/immunologist for evaluation of the problem. The gold standard in substantiating an adverse reaction to food regardless of the etiology is the DBPCFC. Usually if a food challenge confirmation is necessary, an open sequential food challenge, beginning with a small dose first, is done first under controlled conditions, followed by at least a 2-h wait. In most clinical situations, no challenge is indicated if the situation involves systemic anaphylaxis. A good history backed up by the finding of IgE antibody to that food in in vitro

Table 6
DBPCFC Guidelines

The challenge should be performed by personnel knowledgeable in the management of anaphylaxis.
The procedure should be done under controlled conditions, in the hospital, clinic, or office.
The suspected food should be eliminated from the diet 10–14 d prior to challenge.
Antihistamines should be discontinued 12 h prior to challenge.
The individual to be challenged should be in a stable cardiovascular, pulmonary, and metabolic condition prior to challenge.
The individual to be challenged should be in a fasting state (6–12 h) when challenged.
The challenge should start with a low dose (e.g., 10 µg for most foods) so as not to provoke symptoms.
Gradual increases in dose (suspected food or placebo) going to 10 µg, 1 mg, and gradually to 100 µg by doubling the amount every 30 min depending on the judgment of the testing physician.
The maximum dose of food used in challenge should approx 10 g of lyophilized food.
The minimum recommended observation period following completion of the DBPCFC procedure for:
- suspected anaphylaxis is 2 h
- isolated GI signs/symptoms is 4–8 h
- food intolerance reactions is 4–8 h

In follow-up of negative specific food challenge, open feeding with this food is recommended for the subsequent 24–48 h.

Modified from Sampson HA, Metcalfe DD. Food allergies. JAMA 1992;268:2840–2844 and from Clin Exp Allergy 2004;34:689–695.

testing is enough for presumptive diagnosis (*see* IgE Testing). If open challenge is positive, to make absolutely sure of the cause of the reaction, the DBPCFC technique is advised (*see* Table 6 for this procedure). Details on the use of this type of challenge can be found in standardized text books.

Other Tests

Serum mast cell tryptase is helpful tool in diagnosing serious systemic anaphylaxis and anaphylactoid reactions (*see* Chapters 5 and 16). Usually this enzyme is present in the blood for up to 2 h after the event, about the time the patient is seen by a physician in an emergency situation. Unfortunately, in many cases of anaphylaxis in reaction to food, blood mast cell tryptase increase cannot be detected. Therefore, if the enzyme is detected (i.e., test is positive), it is helpful information. If the test is negative, however, it does not rule out a systemic food reaction.

In some situations it is necessary to do a detailed analysis of a meal or processed foods, using immunological techniques to pin down a particular type of food protein suspected of being responsible for an allergy or an intolerance. Even trace amounts of food protein may be important in precipitating anaphylaxis in very sensitive individuals. The label on processed foods may not indicate a contaminant or an offensive food protein that ended up in the final product through some misadventure during the food processing.

The idiosyncratic reaction of lactose intolerance (commonly mistaken for cow's milk allergy) can be confirmed by means of a breath-hydrogen analysis after lactose ingestion.

MANAGEMENT OF FOOD ALLERGY OR INTOLERANCE

The management of proven or suspected food allergy usually consists of strict avoidance of that food. In some food-intolerance reactions, such as lactose intolerance, the reaction is quantitative, since small amounts of lactose sugar-containing foods can be tolerated. This is in contrast to the case of systemic anaphylaxis, in which food allergens in trace amounts can trigger a serious life-threatening event once the patient is sensitized and preformed IgE antibodies exist to that food.

Long-term specific food avoidance may be a problem for patients, especially when they are away from home, while at school eating in the cafeteria, at a restaurant, or at a party. Some foods, like nuts and peanuts, are easily disguised in candies, bakery products, hors d'oeuvres, or salads or salad dressings. The cooking steam from food (e.g., fish or seafood) may precipitate a reaction for specifically sensitive individuals. Processed foods may not have detailed labeling to identify a dangerous food. Occasionally, a food company makes an error in the process of manufacturing a processed food and inadvertently includes an undeclared allergen. Particular ingredients in a restaurant meal may be difficult to identify (it is usually not advisable to take the waiter's viewpoint—only the cook knows!). In a study of "hidden foods" producing allergic reactions in restaurants, 50% were found in the dressing, egg rolls, or sauces. The reactions caused, by eating other foods were: desserts (43%), entrees (35%), appetizers (13%), or other exposures (9%).

Reactions to foods in the schools is a special problem. It is estimated that 2 million school-aged children have food allergy. Allergy to cow's milk is the most common problem in preschools and peanut reactions in elementary school students. Often, it is the food brought in for a party, school project, or shared by a classmate that is the offending food that caused the reaction.

Fortunately, recent published studies on peanut allergy found that this allergen can be easily eliminated from the skin with hand washing and from countertops and tables with the use of common household cleaners (*see* Perry et al. 2004, Selected Reading).

In a situation in which a definite food allergy is known or a presumptive diagnosis has been made, it is best for the individual to carry an EpiPen (0.3 mg) or an EpiPen Jr. (015 mg) and to wear Medic Alert jewelry about that sensitivity or intolerance (Table 7). Patient information concerning food allergies and food intolerance can be obtained through the Food Allergy and Anaphylaxis Network (FAAN) and other organizations (Table 7).

Key to successful avoiding another exposure to an offending food, and if it does occur, minimizing the reaction involves careful planning. An example is the FAAN's school food allergy program. Treatment protocols (to be filled out by the physician) for inadvertent exposure can also be obtained from FAAN (*see* Table 7).

Emergency Treatment

For first aid management, it is advised to use epinephrine (0.2–0.5 mg in adults; 0.1 mg per kg to a maximum of 0.3 mg in children) im as soon as possible after the symptoms begin, even though these early signs of anaphylaxis may be mild. Although the reaction to food may remain mild (e.g., symptoms confined to the skin) and an antihistamine would relieve symptoms, rapid progression to a life-threatening situation can also occur. Therefore epinephrine is advised (with or without antihistamines). After the first aid treatment, the patient should be transferred to the nearest hospital emergency department for monitoring and additional treatment as required (*see* Simons 2004, Suggested Reading).

Table 7
Management of Food Allergy or Intolerance

Strict avoidance of the offending food (anaphylaxis) or in small amounts (some food intolerance).
Food substitution (e.g., infant formula)
Future role of allergen immunotherapy

In case of systemic allergen immuno-therapy:
EpiPen auto-injector (0.3 mg aqueous epinephrine) or EpiPen Jr. (0.15 mg epinephrine) use in <6 yr of age) (Dey Lab; Napa, CA 94556)

Systemic anaphylaxis: Medic Alert jewelry (Medic Alert Foundation, Turlock, CA, 800-642-0045)

Patient support:
Food allergy and anaphylaxis network (FAAN)
10400 Eaton Pl Ste 107, Fairfax VA 22030-3179
(800) 929-4040, (703) 691-3179; Fax (703) 691-2713
E-mail: Faan@foodallergy.org , website: www.foodallergy.org.

Asthma and Allergy Foundation of America (AAFA)
1125 Fifteen Street NW, Washington D.C. 20005
(800) 727-8462; (202) 466-7643, Fax: (202) 466-8940
E-mail: info@aaafa.org
www.aaafa.org.

Allergy and Asthma Network Mothers of Asthmatics.(AANMA)
2751 Prosperity Ave, Suite 150 Fairfax, VA, 22031
(800) 878-4403 Fax (703) 573-7794.
E-mail: aanma@aol.com
www.aanma.org

American Academy of Allergy Asthma & Immunology (AAAAI)
611, E. Wells St. Milwaukee, WI 53202.
(414) 272-6071, fax: (414) 272-6070
E-mail: info@aaaai.org

American College of Allergy, Asthma & Immunology (ACAAI)
85 W. Algonquin Rd, Suite 550 Arlington Heights, IL 6005-4425
(847) 427 1200
E-mail: mail@acaai.org

Unfortunately, often the food-allergic individual does not have an EpiPen/EpiPen Jr readily available when it is needed or is reluctant to use it (or, if a child, the caretaker is reluctant). To often a "wait and see how bad it gets" attitude prevails. Don't count on the emergency medical service (EMS) to supply the epinephrine. A recent statewide review of epinephrine laws in the United States, by FAAN, demonstrated that in the majority of states, EMS technicians with only basic training (usually the first to arrive on the scene) are not allowed to carry and administer epinephrine.

Currently, there are only two fixed doses of epinephrine available in auto-injectors, thus making it difficult to precisely administer the appropriate dose of epinephrine to treat anaphylaxis in each age group. Hopefully, this situation will be corrected in time, or alternative routes of administration will be shown to be effective. Oral administration of activated charcoal at this time should not be considered to be a practical first aid treatment for food anaphylaxis.

Immunotherapy

Allergen-specific immunotherapy is routinely used by allergists to help in the long-term management of inhalant and insect sting allergies. When this type of conventional treatment was tried using peanut extract, the adverse reaction rate was found to be unacceptable. Recently, successful immunotherapy with an experimental recombinant peanut protein in a mouse model of peanut allergy has been shown. This gives hope for use of this type of treatment in humans for the future.

Serial injections of humanized monoclonal anti-IgE (to disrupt the crosslinking of IgE molecules on the surface of mast cells by binding to the principal IgE-binding site) is the most promising of possible new therapies in food allergy. In a recent study involving individuals with prior peanut anaphylaxis, treatment with anti-IgE (TNX-901) increased the average patient's tolerance on oral challenge from 1/2 peanut to almost 9 peanuts.

Food Rechallenge

Although most children out grow their food allergy (*see* Natural History) to foods such as cow's milk, egg, wheat, and soy by age 3, others have a prolonged or lifelong problem and persistent avoidance is necessary. In children who are peanut allergic, it has been shown that approx 1/4 of the individuals may later be able to tolerate peanut protein on rechallenge.

Individuals who have not had a clinical reaction upon inadvertent exposure for 1–2 yr, are over 4 yr of age and have an in vitro peanut-specific IgE level (CAP-FEIA) less than 2–5 KUa/L have a 50% chance of passing a peanut rechallenge under controlled conditions. Unfortunately, there have been reports involving a total of five children who had peanut allergy, who became tolerant, and then, with eating peanuts, redeveloped clinical sensitivity and an elevation in IgE peanut-specific antibodies.

Dietary follow-up of individuals who had had peanut allergy and then were shown to become tolerant has shown that many did not eat peanuts regularly (or the parents were reluctant to give them peanut or peanut products). Subsequent occasional exposure may increase the risk to re-occurrence of peanut allergy.

There are no guidelines for rechallenge involving other food allergies. In one small series of patients allergic to fish, 16% appeared to become tolerant over time based upon rechallenge. Again, though, there is a case report of a child who was originally allergic to fish, then able to eat fish, who redeveloped sensitivity within a short period of time.

Infant Formula Substitution

A particular problem exists for infants who are allergic or intolerant to conventional cow's-milk-based formula. Although some individuals who are allergic and have urticaria can use a soy-based formula substitute, any child with a gastrointestinal problem should be given a casein protein hydrolysate infant formula. Table 8 lists the substitute infant formulas available commercially in the United States for milk allergy. Nutramigen™ or Alimentum™ is usually preferable to Pregestimil™ in the United States. An elemental amino acid formula should be tried in the few infants who are very sensitive to cow's milk protein and cannot tolerate casein hydrolysate formula. And the two amino-acid-based infant formulas available in the United States are Neocate™ and Ele Care™.

Prevention of allergy has been attempted in infants born to allergic parents by the use of special diets. Studies have compared the use of:

1. Dietary restriction in the mother in the last trimester (of a diet devoid of allergy-type foods)

Table 8
Commercial Substitute Infant Formulas for Milk-Allergic and Intolerant Children

Cow's-milk-based
Casein protein hydrolysate
Nutramigen[a]
Pregestimil[a]
Alimentum[b]
Whey hydrolysate
Carnation Good Start[c]
Soy-protein-based
Numerous, such as Isomil[a], ProSoyBee[b]
Elemental amino acid-based
Neocate[d], Ele Care[b]

[a]Mead Johnson, Evansville, IN 47721.
[b]Ross Product Div., Abbott Lab, Columbus OH 43216.
[c]Clintec Nutrition Co., Deerfield, IL 60015.
[d]Scientific Hospital Supplies, Inc., Gaithersburg, MD 20877.

2. Breast-feeding for 6–12 mo
3. Casein hydrolysate formula feeding in the infant
4. Avoidance of allergic-type solid food in the infant for 1 yr to conventional formula feeding (peanuts, tree nuts, eggs, and fish)

The results of these investigations demonstrate that the specially fed infants had fewer food-related allergy symptoms for the first 2 yr of life than infants who were fed conventional diets. However, at 2 yr and later in children, there were no differences in the respiratory allergic symptoms between the two groups.

The whey hydrolysate formula Carnation Good Start™, instead of conventional cow's milk formula, is not a good substitute for individuals proven to be allergic to cow's milk, since serious reactions may occur. The use of this formula, however, has been shown to be less likely to result in clinical allergy than the use of conventional cow's milk infant formula. Therefore, this type of feeding as an alternative to prolonged breast-feeding is a suitable preventive measure in an infant born to allergic parents to reduce possible food allergy symptoms in the first 2 yr of life. Amino-acid-derived formulas have not been used for primary allergy prevention.

Probiotics (e.g., feeding of lactobacillus) have been used experimentally to try to prevent the onset of food allergy in susceptible infants. For example, in a Finnish placebo-controlled trial, some reduction in atopic dermatitis rates occurred, but no change was found in total or food-allergen-specific IgE.

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16 Allergic and Allergic-Like Reactions to Drugs and Other Therapeutic Agents

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CONTENTS

SUMMARY

Drug reactions can be produced by a number of different mechanisms, including true allergic, IgE-mediated events, events due to other immunological reactions, intolerance, idiosyncrasies, overdoses, and a particular sensitivity to well-recognized side effects of a drug. Predictable reactions include, for example, an overdose, and unpredictable reactions include allergic reactions and idiosyncratic responses. Probably the most common class of drugs to produce reactions is antibiotics, and β-lactams are possibly the most frequent offenders in this regard. An immunological reaction such as those resulting from β-lactams diagnosis can be assisted by allergy testing, but in nonimmunological events such testing is not helpful. When a drug or diagnostic agent to which a patient has previously experienced a reaction is required, measures such as desensitization and pretreatment can be used according to the nature of the previous reaction and the drug or diagnostic agent in question.

Key Words: Anaphylaxis; urticaria; erythema multiforme; desensitization; pretreatment; skin testing; β-lactam antibiotics; nonsteroidal antiinflammatory drugs; sulfonamides; radiocontrast media

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Table 1
Definition of Terms Used to Describe Adverse Reactions to Drugs and Therapeutics

Drug allergy: drug reactions resulting from an immunological mechanism
Drug intolerance: adverse reaction to drugs resulting from nonimmunological or unknown mechanisms
Drug overdose: toxic reaction owing to excess drug dose or impaired excretion
Side effect to a drug: unavoidable secondary pharmacological action of a drug
Drug interactions: actions of two or more drugs on the toxicity or effects of each individual agent
Idiosyncratic drug reaction: a measurable, abnormal response to a drug that differs from its pharmaceutical effect
Other terms used to describe allergic/intolerant reactions
Allergic-like or pseudo-allergic reactions to drugs: drug reactions that clinically resemble those of drug allergy; the mechanism usually involves clinical mediators or activators, enzyme inhibition, or may be unknown
Anaphylaxis and anaphylactoid reactions to drugs: generalized drug reactions owing to chemical mediator release/activation either involving IgE (anaphylaxis) or direct action of the drug on the mast cell (anaphylactoid)

INTRODUCTION

Definitions

Drug allergy is a common term often used to depict any unexpected and unwanted event or effect that occurs when an individual is taking a specific drug or therapeutic agent. A better, overall term to describe these circumstances would be an adverse reaction to a drug (Table 1).

These reactions can be further classified into either drug allergy (reactions resulting from an immunological mechanism) or drug intolerance (reactions resulting from nonimmunological or unknown mechanisms). Some reactions closely resemble allergic reactions and are termed allergic-like or pseudo-allergic. This includes anaphylactoid reactions that clinically resemble anaphylaxis, since in both situations chemical mediator release or activation is responsible for these symptoms. Some idiosyncratic reactions to drugs can be confused with drug allergy.

Classifications

Because of the different mechanisms involved in adverse reactions, it is impossible to classify all reactions to drugs and therapeutic agents under one heading. Table 2 classifies adverse reactions to these agents under four categories: generalized, immunological, organ specific, and allergic-like reactions. A specific drug reaction may be classified under more than one category, as outlined in Tables 1 and 2.

In addition to the different definitions and classifications involving adverse reactions to drug, some experts, have simply referred to these events under two categories: predictable reactions (including drug overdose, side effects and interactions) or unpredictable reactions (including drug intolerance, idiosyncratic reactions, and allergic-like/pseudoallergic reactions. Important in this general division is that unpredictable adverse drug reactions (those that allergy specialists usually are concerned with) are (1) unrelated

Table 2
Classifi cation of Different Manifestations of Adverse Reactions to Drugs or Therapeutics[a]

Generalized reactions
Mast cell–derived mediator reactions
Systemic anaphylaxis and anaphylactoid reactions
Generalized urticaria and angioedema
Serum sickness-like reactions
Drug fever
Drug-induced vasculitis
Drug related lupus
Stevens-Johnson/toxic epidermal necrolyis
Anticonvulsant drug hypersensitivity syndrome
Immunological reactions
Type I: IgE-antibody–mediated (e.g., β-lactam antibiotics, insulin urticaria or anaphylaxis)
Type II: antitissue cytotoxic antibodies (e.g., drug-induced hemolytic anemia or thromocytopenia)
Type III: antigen-antibody immune complex involving complement reactions (e.g., serum sickness-like drug reactions)
Type IV: cell-mediated hypersensitivity (e.g., neomycin contact dermatitis)
Organ-specifi c drug reactions
Skin (e.g., pruritus, maculopapular, morbilliform and erythemic rashes, urticaria/angioedema, erthema multiforme, fi xed drug eruptions, phototoxic and photoallergic reactions)
Blood (e.g., drug-induced hemolytic anemia, thrombocytopenia)
Liver (e.g., hepatitis)
Lung (e.g., fibrosis)
Kidney (e.g., nephritis)
Pseudo-allergic (allergic-like) reactions
Ampicillin/amoxicillin rash
RCM reactions
Reactions to aspirin and nonsteroidal anti-inflammatory agents
Reactions to enzyme inhibitors (e.g., ACE inhibitor-induced angioedema)
Reactions involving histamine release (e.g., vancomycin red man syndrome)

[a]A specifi c drug reaction may be classifi ed under more than one category.

to the drug's pharmacological action, (2) are generally independent of drug dose, and (3) often related to either an immune response in the patient or the patient's genetic susceptibility.

Incidence

It has been estimated that more than 80% of all drug reactions are predictable, and the rest are unpredictable with allergic or allergic-like reactions accounting for less than 5–10% of all adverse events.

The exact incidence of all types of adverse reactions to drugs and therapeutic agents is unknown. However, it is estimated that 1–2 million individuals in the United States experience a drug reaction each year. The most frequent manifestation of a drug reaction is a skin rash. Reports indicate that 2% of adult medical admissions each year to a

community hospital are the result of drug reactions. Most of these cutaneous reactions were morbilliform eruptions (94%), but 5% were urticarial.

Studies involving adults admitted to either medical or surgical wards in tertiary care hospitals demonstrate a yearly serious adverse reaction rate of 6.7%. The overall proportion of both serious and nonserious adverse reactions was 23.8%. Most drug reactions involve nonimmune or unknown mechanism and are thus defined as drug intolerances, not drug allergies (*see* Table 1).

In the case of two types of drug reactions, penicillin and other β-lactams as well as conventional radiocontrast media (RCM), the incidence of allergic and allergic-like reactions has been calculated. The risk of developing an allergic reactions, usually a rash, to a single course of penicillin has been estimated to be 2%, and to cephalosporin it is 2–3%. The risk of developing anaphylaxis to penicillin is no more than 0.04% (1/2500 courses of the drug), but it is rare to have such a reaction with a third-generation cephalosporin. Fatalities to penicillin are unusual. The risk ranges between 0.0015 and 0.002% (1 death/50,000–75,000 courses of the drug). These previous estimates were based on small series of inpatients. Recently, studies of a very large outpatients population in England who received a prescription for penicillin (usually amoxicillin) demonstrated an allergic reaction rate of 0.18%. this increased to 1.89% with the second prescription of antibiotics.

The overall reaction rate to conventional RCM (hypermolarity) has been reported in a review of 10,000 consecutive intravenous pyelogram (IVP) procedures to be 2–3%. The frequency of fatalities has been reported to be 1/50,000 IVP procedures. Overall reaction rated to lower-molarity RCM have been less than conventional high-molarity material and have been reported to be approx 0.5%. Serious reactions to RCM that require subsequent hospitalizations are estimated to be 1/2900 conventional RCM infusions and 1/8400 infusions with the low-molarity RCM. Death from conventional RCM is reported to be 1/10,900 but is rare with low-molarity RCM use (1/165,000–500,000 procedures).

In 2001 it was estimated that 75% of previous reported fatal drug-induced anaphylactic reactions in the United States were due to β-lactam antibiotics. It was reported in Denmark that between 1968 and 1990, the most common cause of drug-induced anaphylaxis or anaphylactoid reactions was RCM, antibiotics, or allergenic extract. In the United Kingdom, these same types of fatal drug reactions between 1992 and 1998 were most likely to occur to anesthetics (53%), antibiotics (31%), or RCM (16%).

Factors That Influence Incidence

Table 3 lists important factors that may influence the likelihood of an adverse reaction during the use of a drug or therapeutic agent. Some drugs are more likely to be involved in reactions than others. Antibiotics, especially β-lactams and sulfonamides, followed by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) and central nervous system (CNS) depressants, are most commonly involved in these serious reactions. The β-lactam antibiotics, trimethoprim sulfamethoxazole (TMP-SMX), and whole blood are most likely to be involved in skin rashes, the most common manifestation of adverse reactions. Minor drug reactions (e.g., nausea) are more often involve with narcotic use, antibiotics, and cardiovascular drugs.

Allergic sensitization to drugs is more likely to occur after multiple, intermittent courses of a drug than with continuous administration of that drug. All types of reactions to medicine occur more often when patients are treated with multiple agents than with

Table 3
Factors Influencing the Frequency of Adverse Reactions to Drugs and Therapeutic Agents

Drug type	Familial history of reactions
Degree of drug exposure	Atopy
Routes of administration	Viral infections
Age and sex	Concomitant drug use

single agents. Allergic drug sensitization is least likely to occur with oral administration. Topical application of drugs/chemicals favors contact sensitization. Once sensitization has occurred, however, elicitation of a drug reaction upon re-exposure to that drug may occur by any route, but the oral route is the safest, and the intramuscular (im) route is more risky than the intravenous (iv) route.

There are probably less adverse drug reactions in children and the elderly. Drug-induced skin rashes are reported to be one-third higher in females. Individuals who have a severe reaction to one drug (e.g., β-lactam antibiotics) may be at increased risk for reactions to other antibiotics. Children of parents with a confirmed reaction to a β-lactam antibiotic have more risk that the general population to develop reaction to β-lactam antibiotics. Although being "allergic" or atopic does not increase the risk of development of an allergy to β-lactam antibiotics, it may increase the risk of having an anaphylactoid reaction to RCM exposure.

A maculopapular (toxic) rash due to amoxicillin/ampicillin is more likely to occur when the patient treated with this drug has an Epstein-Barr virus infection (acute infectious mononucleosis). Both drug allergies (e.g., to β-lactam antibiotics) and drug intolerance reactions (e.g., systemic or skin reactions to may types of therapeutic agents) are more likely to occur in patients afflicted with HIV than HIV-seronegative individuals. The risk of drug reactions increases with the degree of immunosuppression. The presence of other viral infections and altered drug metabolism because of chronic disease may also be an important factor effect in risk. Concurrent administration of β-adrenergic blocking agents with other drugs increases the risk of anaphylaxis, in the case of β-lactam antibiotic use, and of serious anaphylactoid reactions in the case of RCM use. Concurrent use of angiotensin-converting enzyme inhibiting agents with other drugs may also increase the risk of a serious anaphylactic or anaphylactoid reaction.

MECHANISMS OF ALLERGIC AND ALLERGIC-LIKE REACTIONS TO DRUGS AND THERAPEUTICS

The exact mechanism involved in most reactions to drugs and therapeutic agents is unknown. Fully 90% of adverse reactions fall into the drug intolerance group. Of those reactions that are classified as a drug allergy, the best-studied reactions are those to β-lactam antibiotics, particularly penicillin and insulin.

Drug Reactions Usually Involving IgE or Other Immunological Mechanisms

β-Lactam Antibiotics

β-lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monabactams. Penicillin and cephalosporin each have a β-lactam ring (Fig. 1). Carbapenems and monabactams also share this ring structure.

Overview of Adverse Drug Reactions

- Most reactions do not involve immune events.
- A skin rash is the most common type of drug reaction.
- Most drug reactions occur in adult females and those individuals who are frequently intermittently exposed to multiple medications.
- More allergic drug reactions occur to β-lactam antibiotics than to other antibiotics.
- Reactions to RCM and aspirin/nonsteroidal anti-infl ammatory agents are frequent causes of allergic-like or nonimmunological reactions.

In the human body, penicillin is metabolized to form various products (Fig. 2). Most of the parent drug is broken down into penicolloyl, which readily combines with a carrier protein to become a complete antigen. This is called the major determinant (most common metabolic by-product). The remainder of penicillin stays either in its native state or is metabolized to other chemical structures, such as penicilloate. These agents, coupled with a protein, are referred to as minor determinants (less common metabolic by-products). The ease with which these penicillin metabolites and the parent penicillin couple to tissue proteins is believed to be important in why these drugs are so often involved in allergic reactions and other drugs are not.

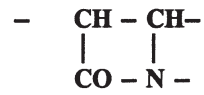
Of individuals who have become allergic to penicillin, most develop type I (*see* Table 2) IgE-specific reactions to the major determinant, and an urticarial (or maculopapular/morbilliform) rash is the usual manifestation. In individuals sensitized to the minor determinant, specific systemic anaphylaxis is more of a risk.

In addition to allergies that develop the β-lactam ring side-chain chemical structures (R-, in Fig. 1) of either the penicillins or cephalosporins may elicit the production of IgE-allergen specific antibodies, which are clinically significant. Individuals, particularly in Europe, have been identified with allergic reactions to ampicillin, amoxicillin or individual cephalosporin, but not to penicillin. These reactions have been referred to as β-lactam antibiotic side-chain hypersensitivities. In the case of the monabactams, if IgE antibodies do develop, they are likely a result of side-chain specifics. Recent surveys have shown that side-chain hypersensitivities are relatively uncommon among β-lactam-allergic individuals living in North America.

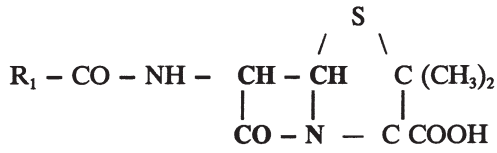
Penicillin and other β-lactam antibiotics may also be responsible for a type II or type III immune reaction (Table 2). Immune hemolytic anemia can result from the binding of the drug or its metabolites to the surface of a red cell, followed by a specific antibody-mediated cytotoxic reaction that is directed against the drug antigen or at the cell membrane component altered by the drug. This reaction and immune throbocytopenia may occur with other drugs as well.

In type III immune reactions, soluble immune complexes are responsible for the syndrome of serum sickness. Although originally this term depicted reactions to "horse serum," penicillin and other β-lactams as well as other drugs can react in a serum sickness-like fashion. Clinically, events are characterized by fever and a rash that includes a papular urticarial and/or urticarial, lymphadenopathy, and arthralgia, which occur 2–4 wk after the beginning of the drug therapy. At this point, drug and drug antibody

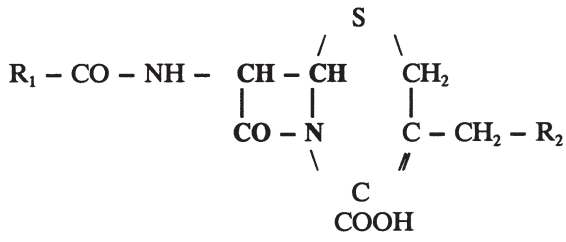
BETA LACTAM CHEMICAL STRUCTURES



Beta Lactam Ring



Basic Penicillin



Basic Cephalosporin

Fig. 1. β-Lactam chemical structures.

immune complexes are in slight antigen excess, and the complement system is activated. Clinical symptoms of serum sickness begin to subside when the drug/metabolites are eliminated from the body by the reticuloendothelial system.

INSULIN

Human insulin has a molecular weight of approx 6000, and its amino acid sequence differs from pork insulin by only one amino acid. Insulin is a potent antigen. Approximately 40% of patients receiving porcine insulin therapy develop IgE antibodies. These antibodies are almost always directed against the insulin molecule itself, even though animal-derived insulin contains other proteins that may stimulate an immune reaction. Thus individuals can have allergic reactions to human recombinant DNA insulin (alone) and patients with systemic allergy to animal source insulin have positive skin tests to human insulin.

Local reactions to insulin injections are not uncommon but these allergic reaction usually disappear in 3–4 wk of continued administration. Systemic insulin reactions are rare and usually occur when insulin is discontinued and then restarted. Insulin resistance is very rare and related to the development of high titer of IgG insulin antibodies.

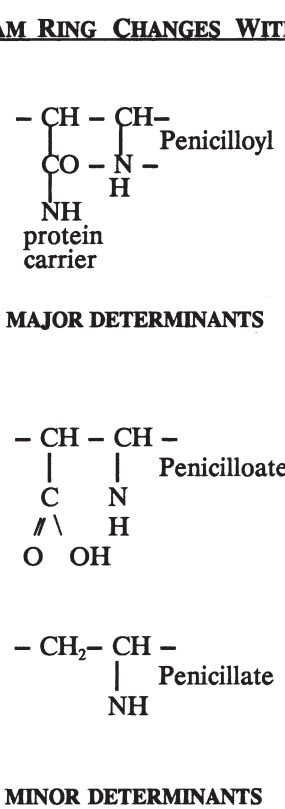


Fig. 2. β-Lactam ring changes with metabolism.

Heterologous Serum, Protamine and Vaccines

Animal serum exposure (e.g., horse serum in snake bite antivenom) may be responsible for IgE-mediated anaphylaxis in individuals presensitized to these animals. Horse serum may also cause serum sickness.

Protamine is a low molecular weight protein derived from the sperm of salmon. IgE sensitizations and subsequent reactions occur in 0.05-10% of individuals where protamine used frequently (e.g., diabetics using NPN insulin).

Although infrequent, systemic allergic reactions, do occur to vaccines. Most of these reactions are now felt to be a result of IgE antibodies directed against porcine gelatin used as a stabilizer in these vaccines. Gelatin is found in various amounts in measles, mumps and rubella (MMR), varicella, rabies, Japanese encephalitis, influenza, and DTP vaccines.

Previously, chicken egg allergy was thought to be a risk in individuals who required MMR vaccine immunization. However, measles and mump vaccines are grown on chicken embryo fibroblasts, which contain little or no egg protein. MMR has been shown to be safe for administration in egg-allergic individuals. Influenza and yellow fever vaccines are grown on egg products, and therefore the final product contains enough egg protein to potentially induce and IgE allergic reaction in chicken-egg-allergic individuals.

Blood or Blood Products

Reactions to blood transfusions may be a result of hemolysis secondary to the use of ABO-incompatible blood products. Patients with this type of reaction develop fever, chills, low blood pressure or shock, back pain, and hemoglobinuria within 1–2 h after a transfusion. Isolated transfusion fever can occur from the presence of interleukin (IL)-1,6, and 8 and tumor necrosis factor (TNF)-α in the blood products. Urticaria (1–3 per 100) wheezing (1–2 per 1000), or anaphylaxis (1–20 per 50,000) reactions have been reported with the transfusion of blood products, usually as a result of complement activation and release of C3a and C5a. Individuals with IgA deficiency (as common as 1:700) may develop IgE antibodies to IgA and therefore are at risk for an allergic reaction when given blood products.

Monoclonal Antibodies

New biological agents are now available and more are being developed to treat many disease conditions. In some cases, allergic-like reactions have occurred (including anaphylaxis or anaphylactoid reactions and serum sickness-like reactions). Although the exact mechanism of these events is often not clear, the potential for IgE antibodies development exists.

Sulfonamides and Other Antimicrobial Agents

In their native state, sulfonamides are not immunologically reactive. However, with metabolism, the breakdown products of these drugs have the potential to react with carrier proteins and become complete antigens and induce IgE antibodies. In general, however, most drug reactions (usually a rash) induced by sulfonamides are not felt to be a result of IgE or other immune events. Recent studies indicate that individuals with a history of sulfonamide antibiotic rash are not at risk for reactions to sulfa-containing nonantibiotic drugs because of cross-sensitivity.

Vancomycin antibiotic iv infusion has been responsible for generalized flushing, the so-called red-man syndrome. The mechanism of reaction in this case thought to be related to direct toxic release of histamine from mast cells/basophiles. Rare cases of vancomycin–IgE-antibody-induced anaphylaxis have been reported.

Urticaria and other anaphylactoid reactions have been reported to occur in 1.2/100,00 prescriptions of ciprofloxin (a quinolone). Most of these reactions occur with the first administration of the antibiotic and are not a result of IgE antibodies.

In the case of rash due to either macrolide or tetracycline antibiotics, they tend to be mild and not IgE mediated. A photosensitivity may occur with the use of some tetracyclines.

Aspirin NSAIDs, and Selective Cyclooxygenase-2 Inhibitors

Aspirin (ASA) and NSAIDs may both cause or exacerbate urticaria/angioedema and anaphylactoid reactions. They are one of the most common reasons for drug-induced urticaria in adults. These drugs are responsible for a syndrome consisting of perennial rhinitis, sinusitis, nasal polyps, and severe asthma. Current studies indicate an important role for increased leukotriene production (especially LTC_4, LTD_4, and LTE_4), kininogen, and histamine release in these allergic-like reactions. IgE antibodies against aspirin or NSAIDs have not been identified. Most, if not all these reactions resulting in asthma are felt to be related to inhibition of the cyclooxygenase (COX)-1 products (ASA is both a

COX-1 and COX-2 inhibitor). Recently, COX-2 inhibitor drugs have been developed mainly to reduce the possible undesirable side effect of G.I bleeding produced by ASA use. Studies have shown that COX-2 inhibitor agents are generally safe in asthmatics reactive to ASA or NSAIDs. However, there are reports of patients who have had urticaria or anaphylactoid reactions to ASA or NSAIDs who have reacted to one or more COX-2 inhibitor drugs for unknown reasons.

RCM

The imaging efficacy of RCM depends upon the iodine concentration that can be delivered to a space within the body. Since RCM was first discovered in 1923, the character of the iodinated compound has progressed from a monoiodinated to a tri-iodinated benzoic acid compound. The conventional RCM is hypertonic, having osmolarity up to six times that of plasma. A newer, nonionic RCM has been developed that has an osmolarity less than 50% of the conventional material and retains the same iodine concentration. This change in osmolarity of the newer RCM material has reduced the vascular wall toxicity and allergic-like reactions with the use of these agents, presumably by reducing the capacity of the newer agent to form bonds with body proteins.

The exact mechanism by which RCM elicits an anaphylactoid reaction is unknown. However, in vitro histamine release does occur, probably through direct interaction between RCM and a cell membrane receptor. Unfortunately, there is no consistent documented relationship between histamine release by these agents and clinical adverse events.

RCM can activate the complement system. Conventional RCM has been shown to have a direct effect on C3 and C4 to produce C3b and C4b anaphylatoxins (which in turn can cause histamine release). The newer low-osmolarity RCM has been shown to activate complement through the alternate pathway by inhibition of factors H and I. The exact role activation of complement by either conventional or the newer RCM agents plays in the production of an anaphylactoid reaction is still speculative.

Angiotensin-Converting Enzyme Inhibitor Drugs and Angiotensin II Receptor Antagonist Drugs

ACE inhibitor (ACE-IN) drugs may produce cough or angioedema (anaphylactoid reactions) in different groups of patients. Cough occurs as frequently as in 10–25% of patients, usually starting within the first 8 wk of use, but occasionally as late as 1 yr. It usually disappears within 1–2 wk after discontinuing the medication.

Severe angioedema of the face, mouth or throat may occur in 1–2/1000 patients and can be life threatening. This may occur within the first week or as late as several years of therapy. The risk of angioedema is greater with the use of these agents in African Americans and in patients with hereditary angioedema, idiopathic urticaria/angioedema, or idiopathic anaphylaxis.

Although the mechanism of these reactions is not entirely clear, increased histamine release, inhibition of bradykinin degradation, and abnormal prostaglandin and substance P metabolism are suspected.

There appears to be less cough associated with the use of angiotensin II receptor antagonist (A-II RAS) drugs. However, in patients who have had angioedema with a specific ACE-IN drug, switching to another ACE-IN agent or use of an A-II RAS does not decrease the risk of reaction and is not advised.

General and Local Anesthetics

Systemic allergic-like reactions during general surgery are usually secondary to anaphylaxis to muscle relaxants such as succinylcholine or isoquinolones. The incidence of anaphylaxis is 1 in 5000–15,000 procedures with a mortality rate of approx 5%. Half of these reactions are felt to be owing to IgE antibodies, but one-third occur without previous exposure to muscle relaxants and may be a result of direct histamine release.

Fairly frequently, the allergist is called upon to evaluate an individual who has a reaction to local anesthetics. Rarely are these a result of an IgE mechanism, and they are either toxic, psychologic, or neurologic in nature. Often reactions are the result of concomitant administration of epinephrine in the drug preparation added to reduce the absorption of the local anesthetic.

Chemotherapeutic Agents

Allergic-like adverse reactions to many agents used in cancer therapy have been reported. The risk is greatest with repeated use of L-aspariginase (up to one-third of cases). Urticaria or asthma may occur within 1 h of administration. Similar reactions have been reported with the use of taxanes. Although an IgE mechanism has been suspected, none has been proven.

Carboplatin has been shown to be associated with anaphylaxis in 30% of patients after multiple cycles of iv therapy, typically on the eighth cycle. These reactions are believed to be IgE mediated based upon a negative IgE id skin test of undiluted drug in nonreactive patients and positive skin test in reactive individuals.

Opiate Drugs

Urticaria or anaphylactoid reactions can occur in otherwise normal individuals upon exposure to morphine, codeine, or synthetic opiates. These reactions are usually caused by direct action of the drug on the mast cell to release mediators, rather than an IgE mechanism.

SIGNS AND SYMPTOMS

Generalized Reaction

Anaphylaxis and anaphylactoid reactions to drugs and other therapeutic agents have the same signs and symptoms of reactions as other agents that frequently cause allergic reactions (e.g., insect stings, foods, natural rubber latex). Reactions range in severity from mild pruritus, skin erythema and urticaria/angioedema to more generalized and systemic reactions of laryngeal edema, rhinitis/conjunctivitis, asthma, shock, and possibly death. IgE sensitization is involved with the following drug reactions: β-lactam antibiotics, insulins, protamine, blood products, chymopapain, monoclonal antibodies, vaccines, natural rubber latex used in drug-delivery systems, ethylene oxide used to clean dialysis agents, or neuromuscular agents used in anesthesia induction. Anaphylactoid reactions may occur to sulfa RCM, ASA, NSAIDs, local/general anesthetics, ACE-IN, vancomycin, chemotherapeutic agents, protamine, and monoclonal antibodies and blood products.

Other generalized allergic-like drug reactions (Table 2) include serum sickness, in which the symptoms begin 7–21 d into drug therapy. These drug-induced serum sickness-like reactions are characterized by fever, malaise, urticaria, arthralgia, and lymphadenopathy. Reactions occur not only to blood products, but to β-lactam antibiotics,

Urticaria and Drug Reactions

- Severe urticaria may be a manifestation of cutaneous (mild) anaphylaxis/or anaphylactoid reactions.
- Urticaria is suggestive, but not diagnostic, of an allergic etiology.
- Urticaria may be caused by other factors, such as viral infections.
- A drug-induced skin rash that does not include urticaria does not rule out immunological involvement.

sulfonamides, thiouracil, cholecystographic dyes, hydantoin, aspirin, and streptomycin as well as to other agents.

Isolated drug fever typically occurs between day 7 and 10 of therapy and may occur with many drugs, especially antibiotics and blood products. Drug-induced lupus erythematosus (DLE) is usually characterized by mild fever, malaise, and arthralgias. Butterfly rashes on the face, renal and CNS involvement, and Raynaud's phenomenon are less common in the drug form than in the idiopathic systemic form of the disease (SLE). The drugs usually involved with this condition include procainamide, hydralazine, isoniazid, chlorpromazine, and hydantoin. The signs and symptoms usually improve or decrease with discontinuation of the specific drug involved. Drug-induced vasculitis may occur with hydralazine, antithyroid medications, or penicillamine. The anticonvulsant drug hypersensitivity syndrome is characterized by fever, facial edema, maculopapular rash, and generalized lymphadenopathy. This syndrome may be induced by phenytoin, carbamazepine, and phenobarbitol.

Skin Reactions

Isolated skin lesions in reaction to drugs are the most common adverse symptoms of drug reactions. Almost any type of manifestation can occur (*see* Table 2). However, a maculopapular/morbilliform rash is the most frequent, followed by urticaria in allergic or allergic-like reactions. Usually, drug reactions are symmetrical and begin in the extremities in the ambulatory patient or on the back in bedridden patients. The ampicillin/amoxicillin rash typically occurs on the knees and elbows first before spreading over the body. Urticaria/angioedema occurs with all types of reactions, including drug allergy, drug intolerance, and infections. A fixed drug eruption is a rare localized patch of eczema that reappears at the same site with repetitive drug treatment. Many drugs can be involved, but the reaction is more commonly associated with phenobarbital or antibiotic treatments.

Phototoxic (sunburn) rash may occur with short-term sun exposure while patient are taking drugs such as doxycycline or chlorpromazine. Prolonged sun exposure may produce a photoallergic (urticarial or eczema) rash in individuals taking drugs such as griseofulvin, psoralens, and sulfonamides.

Erythema multiform (EM minor) consists of target-like rashes, usually without associated oral mucosal involvement are frequently caused by viral infections and are self-limited. When EM (plus other rash types) includes involvement of two or more mucosal surfaces, a diagnosis of EM major or Stevens-Johnson syndrome (SJS) is made. Toxic epidermal necrolysis (TEN), also known as Lyell's disease, is a severe extension of SJS

Febrile Mucocutaneous Reactions

- Includes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- Syndrome consists of fever, erythema multiforme rash and ulceration of two or more mucous membranes, plus with TEN, skin sloughing
- SJS and TEN are frequently drug associated; however, these reactions may be precipitated by viral infections and other unknown events
- If drug-associated, repeat exposure to the same drug is contraindicated

and is characterized by systemic symptoms and extensive denudation. Drugs are the usual cause of SJS and TEN and include antibiotics (e.g., sulfanomides and β-lactums) and antiseizure medications. Infections, including mycoplasm and viral, have been implemented in SJS. Although an exact mechanism for SJS and TEN is not known, it has been proposed that those reactions resemble a graft-vs-host reaction and may involve production of CD95 (FAS) apoptotic ligand, which leads to cell death.

Any drugs that have been implicated in EM major (SJS and TEN) should be strictly avoided, since re-exposure may be associated with a more serious reaction.

Severe skin and systemic reactions to antiseizure medications can occur. These are termed either drug hypersensitivity syndromes (DHS) or drug reactions associated with eosinophyillia and systemic symptoms (DRESS). These reactions can be differentiated from TEN by having less (or no) mucous membrane involvement, no skin loss, and the presence of eosinophils (and atypical lymphocytes) in the complete blood count plus systemic organ involvement (e.g., heart, lung, liver, kidney).

Signs and Symptoms of Other Organ-Specific Reactions

Type II immune reactions (*see* Table 2) to drugs such as β-lactam antibiotics may result in a hemolytic anemia, usually 7 d after beginning therapy. Quinine, quinidine, and heparin have been involved in immune thrombocytopenic-type reactions. Hepatitis has been shown to occur with several drugs, including sulfonamides, phenytoin, and halothane. Methicillin as well as sulfonamides have been involved in producing interstitial nephritis in rare patients. Phenytoin and gold have been involved in reactions characterized by systemic eosinophilia and pneumonitis. The Churg-Strauss syndrome, a systemic eosinophilic granulomatosis and vasculitic process involving asthmatics, has been reported in increasing numbers of patients receiving leukotriene antagonists, glucocorticosteroids, and macrolide antibiotics, although there may be no causal relationship.

GENERAL APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF ALLERGIC AND ALLERGIC-LIKE REACTIONS TO DRUGS AND THERAPEUTICS

Initial Measures

Initially, when an adverse drug reaction is suspected, especially when associated with significant symptoms, the drug should be discontinued (Table 4). Any treatable signs and symptoms should then be promptly attended to. Simple pruritus and urticaria with or

Table 4
General Approach to Diagnosis and Management of Allergic Drug Reactions

Initial measures

1. Discontinue suspected medication
2. Treat reaction
3. Draw blood for possible confi rmation of etiology in select situations (e.g., tryptase in anaphylaxis/anaphylactoid reactions; complement assay (C3, CH50 levels in serum sickness, Coomb's test in hemolytic anemia).
4. Substitute appropriate medication whenever possible

Follow-up measures

1. Skin test in case of drug allergy (e.g., β-lactam antibiotics,[a] insulin, vaccines, and latex[a])
2. Skin test/subcutaneous drug challenge (local anesthetics)
3. Oral sequential challenge under controlled conditions (nonanaphylactic conditions)
4. Strict avoidance based on presumptive diagnosis
5. In very select cases and when appropriate, desensitize with original medication if no substitute is available (e.g., β-lactam, insulin, TMP-SMX,ASA).
6. Preventive measures for inadvertent exposure in serious situations (e.g., Medic Alert, EpiPen auto-injector)

[a]In vitro tests available to some degree.

without angioedema will usually improve with a H_1 antihistamine such as over-the-counter (OTC) diphehhydramine (Benadryl) 25–50 mg, two to four times daily or loratadine (Claritin) 10 mg 1–2 times daily. Prescribed nonsedating antihistamines such as cetririzine (Zyrtex) 10 mg, fexofenadine 60–180 mg, desloratadine (clarinex) 5 mg, or sedating hyroxyzine (atarax) 10–25 mg are also effective. These latter drugs are usually recommended one time daily, but may be used two times daily if the symptoms are more severe and the drugs are tolerated.

In addition, an H_2 antihistamine, such as OTC ranitidine (Zantac) 75–150 mg, or cimetidine (Tagamet) 100–200 mg, one to two times daily and/or a prescribed leukotriene antagonist such as motelukast (Singular) 10 mg once daily can be used to enhance the control of itching, rash or swelling. Adrenalin 1:1000, 0.1–0.3 mL sc will help the pruritus and the acute rash, or swelling in an office or emergency room situation.

Usually, systemic corticosteroids are prescribed for short periods until out patient follow-up. The type of specific medication, route and dosage will depend upon the situation. Since use of ASA or NSAIDs can intensify pruritus, urticaria, or angioedema regardless of cause, these drugs should be avoided. More complete advice on the management of systemic anaphylaxis/anaphylactoid reactions and urticaria/angioedema can be found in the following chapters

There are few (if any) absolute confirmatory tests available initially when an adverse reaction to a drug is suspected. Diagnosis is usually, therefore, presumptive. Management is important in spite of this fact (e.g., drug discontinuation, treatment of signs and symptoms of the reactions, substitution of another drug if necessary).

One test (if positive) that can help confirm the fact that the reaction involves mediator release is an in vitro mast cell tryptase blood test. In severe cases of systemic anaphylaxis/anaphylactoid reactions, tryptase is released along with other mast cell chemical media-

tors. This enzyme remains increased in the bloodstream for several hours after the event, allowing the possibility of confirming a mast cell degranulation (and histamine and other mediator involvement) in the reaction at the time that the patient is seen in the office or emergency room for the acute symptoms.

When serum sickness is suspected, the complement system is usually activated, and low serum levels of C3, C4, and possible CH50 (total hemolytic complement assay at 50%) may in retrospect help confirm the suspicion of this condition. In cases of hemolytic anemia, a positive Coombs test will help confirm the immune nature of this condition.

In almost all cases, the drug or therapeutic agent presumed to be responsible for the adverse reaction can be avoided, and a substitute medication should be available to treat the primary condition. Occasionally, this is not possible if the primary condition is serious and the offending drug is important to therapy. In some of these cases, medication pretreatment (RCM) graded oral drug challenge or drug desensitization may be necessary.

Drug Allergy Testing

Elective immediate reacting allergy skin testing is usually available only in the case of β-lactam antibiotic sensitivity, insulin sensitivity and with reactions to components of vaccines (e.g., egg, gelatin). It is available experimentally for papain sensitivity and suspected sensitivity to neuromuscular blocking agents. In vitro blood/serum assays are available only to latex, β-lactam antibiotics (penicillin major determinant only) and papain (experimental). These in vitro assays are helpful, if positive. A negative test does not rule out sensitivity. At one time, in vitro cell-mediated drug lymphocyte transformation testing was available in some experimental laboratories. There is little or no current evidence regarding the value of this type of drug reaction testing.

Drug allergy testing (skin testing in vitro studies) usually should be done by allergy–immunology specialists who are knowledgeable about the use and interpretation of such tests. Often investigation and management of drug suspected allergy is restricted to large clinics or hospitals and other academic centers that not only have referrals of complicated cases of this type but also have necessary diagnostic agents and experience in drug challenges or desensitization.

Graded Drug Challenge (Test Dosing)

If it is necessary to verify that an individual can safely take a medication that previously was associated with an allergic or allergic-like reaction, a graded drug challenge or test dosing may be considered. This usually is a situation where there is no test available, symptoms are minor (e.g., maculopapular rash to an antibiotic not associated with systemic symptoms) which usually is not associated with severe, life-threatening types of reactions. In case of suspected local anesthetic reactions, a well-studied protocol consisting of skin testing followed by a graded sc injection challenge helps confirm the safety of local anesthetics for subsequent use (*see* Table 5).

In the case of antibiotics, the recommended initial dose of oral challenge is 1:100 (1%) of a single daily therapeutic dose (e.g., 250 mg). Following a suitable interval, further increase (e.g.10%, 20%, 30%, 40%) of the total challenge dose can be given at 15- to 20-min intervals. Often, this can be done in an office setting, following informal consent, if the allergist–immunologist is prepared for possible systemic allergic-like reaction. Following completion of the challenge, a wait of at least 2 h in the office is recommended and further antibiotic exposure is not advisable for 24 h.

Table 5
Local Anesthetic Skin Testing and Challenge

Route	*Dilution*	*Dose*
Prick test[a]	Undiluted	1.0 drop
Intradermal test[a]	1:100	0.02 mL
SC challenge[b]	1:100	0.1 mL
SC	1:10	0. 1mL
SC	FS	0.1 mL
SC	FS	0.5 mL
SC	FS	1.0 mL
SC (optional)[c]	FS	2.0 mL

[a]Skin test with a battery of local anesthetic types (free of epinephrine) and if indicated, with and without methylparabens.

[b]Challenge with a single type of local anesthetic (negative result on skin test) sequentially at 15- to 20-min intervals, as recommend by Anderson, and [c]Grammer/Greenberger (see Suggested Reading).

Follow-Up Measures

In most cases, after a presumptive diagnosis of drug allergy or intolerance has been made the individual is advised to avoid these medications. In some cases of reactions to drugs, drug desensitization is possible and necessary. Example of the use of this procedure will be discussed under the management of B-lactam and sulfonamide sensitivities. In the case of anaphylaxis/anaphylactoid reactions and other serious systemic events (e.g., SJS, TEN, or DHS) re-exposure to the medication is not advised.

In situations in which there are documented life-threatening drug reactions (e.g., systemic anaphylaxis) and inadvertent re-exposure is a risk, the patient should be advised to carry an EpiPen (0.3 mg epinephrine) auto-injector. If the patient is below 6 yr of age, an EpiPen Jr (0.15 mg epinephrine) auto-injector is advised.

DIAGNOSIS AND MANAGEMENT OF SELECTED ALLERGIC AND ALLERGIC-LIKE DRUG REACTIONS

β-*Lactam Antibiotics*

In patients with a history of an allergic reaction to penicillin or other β-lactam antibiotics, penicillin skin testing should be done electively. Only 20% of adults and 10% of children with this diagnosis turn out to be actually allergic based on allergy skin testing (the positive penicillin allergy skin test rate is higher in the first year after labeled allergic to penicillin).

1. In many cases, the original reaction, usually a rash, is a result of an infection (usually viral) rather than the antibiotic used to treat that infection.
2. In cases of true penicillin allergy, the reaction rate dissipates about 10%/yr.
3. In children, toxic (nonallergic) maculopapular rash to ampicillin/amoxicillin and to some cephalosporins like Ceclor are common (5% of antibiotic therapies).

In most cases it is advisable to refer the suspected penicillin-allergic patient to an allergist–immunologist specialist for evaluation of the condition. Table 6 lists the peni-

Penicillin Allergy Skin Tests

- β-lactams are the only type of antimicrobial agents in which a suspected reaction (allergic) can be verified by skin tests.
- Of those patients with a history of a prior reaction, only 20% of adults and 10% of children have been found to be skin test positive.
- Positive skin test to penicolloyl-polylysine (Pre-Pen) correlates best with rash(usually urticarial reactions); positive skin test to penicillin "minor determinant mix" correlates with anaphylaxis.
- Skin testing with penicillin G metabolites is usually a measure of potential clinical reactions to the β-lactam ring in amoxicillin and cephalosporins.

Table 6
Penicillin Skin Testing

Reagent	*Type of test*	*Dose*
Penicilloyl-polylsine (Pre-Pen)[a] test strength	Prick/scratch/puncture (intradermal)	1 drop 0.02 mL
Penicillin G, 10,000 U/mL[b]	Prick/scratch/puncture (intradermal)	1 drop 0.02 mL
Penicillin—minor determinant mixture	Not commercially available in the US	

[a]Schwartz Pharma, Kremers Urban Co., Milwaukee, WI.
[b]Serial dilutions (10, 100, 1000 U/mL) advisable in very sensitive individuals.

cillin skin tests bases on commonly available agents. Penicolloyl polylysine (PPL) is an example of the major breakdown product of penicillin drug metabolism coupled to a carrier protein. This test reagent is responsible for positive skin tests in patients with an isolated skin rash (especially urticaria, or urticaria and angioedema). Penicillin G (Pen G) is the parent drug. A positive skin test to Pen G correlates with all types of allergic reactions. A positive minor determinant mixture (MDM) skin test (minor or secondary penicillin metabolites) (*see* Fig. 2) correlates best with more serious life-threatening, systemic anaphylaxis penicillin reactions. Unfortunately, this latter skin test reagent is not available commercially, but is available in some academic centers and large clinics.

In addition, in 2000–2001 and again in 2004–2005, PPL commercial manufacture was suspended. Because of the uncertainty of future supplies, allergists may have to consider preparation of β-lactum antibiotics allergy skin test reagents in their own local laboratories (*see* Suggested Readings, Macy et al. and Verumi et al.).

In studies of penicillin allergic individuals, skin testing with PPL, Pen G, and MDM is safe, can be done electively, and is predictive of the risk of subsequent challenge with penicillin. If all tests are negative, there is only a small risk of a minor skin rash upon challenge. The positive predictive value of skin testing to assess the future risk for allergic reactions to β-lactam antibiotics using only Pre-Pen and Pen G is unclear but has been estimated to be 70–97% reliable (see Suggested Reading).

Penicillin skin testing also tests to reactions directed to the β-lactam ring in cephalosporins and other penicillins. In some cases, individuals may develop sensitivity to the side chain (R in Fig. 1) rather than to the β-lactam ring. Usually this occurs in reaction to either ampicillin/amoxicillin or a specific cephalosporin. Fortunately, this is uncommon in β-lactam-allergic individuals in North America. Allergy skin testing can be done to other penicillins and cephalosporins and if positive, may be helpful information. However, these types of skin tests have not been validated in controlled studies.

In cases in which the skin test results are equivocal or the history of the prior reaction is severe but the skin tests are negative, a graded challenge with a single usual oral dose of the β-lactam antibiotic in question under controlled conditions (see Graded Drug Challenge Test Dosing). In most situations, when MDM skin testing reagent is not available, an oral β-lactam challenge is advised following negative PPL and Pen G allergy skin testing.

In cases in which the individual is found to be allergic (positive history of reaction, confirmed by skin test and/or challenge), all β-lactam antibiotics should be avoided. Usually substitute medications are used to treat subsequent infections.

The overall cross-reactivity rate between penicillin allergy and cephalosporin allergy is estimated to be 4% or less (third and fourth generation) to 10% or more (first generation). Some authorities have recommended the use of third- or fourth-generation cephalosporin in suspected penicillin-allergic individuals. However, most experts feel that all β-lactam antibiotics should be avoided in proven penicillin-allergic individuals.

In select cases, in which individuals who are proven β-lactam antibiotic-allergic and need a β-lactam antibiotic (life-threatening or other serious infections without suitable substitutes available), then penicillin or the appropriate β-lactam antibiotic desensitization may be indicated. In these cases it is advisable to consult an allergist–immunologist specialist.

Table 7 shows an example of an oral penicillin desensitization protocol that can be used as a protocol for desensitization with penicillin and other β-lactam antibiotics. This procedure should be done only in the hospital under controlled conditions, such as an intensive care unit with a doctor present during the entire procedure. Each individual case is different, and published protocols are only guides to the procedure.

The oral route is felt to be safest, but the iv route may be preferable in some cases. Studies have shown that reactions during the procedure should be expected approx 30% of the time. When these occur, the patient should be treated appropriately and stabilized before restarting the desensitization procedure. The next desensitizing dose should be less than the one producing the reaction.

Once the procedure is complete, the patient is usually maintained at a full treatment dose of the medication until the therapy is complete. Once the drug has been stopped for 12–24 h, the patient should be considered to have reverted to his or her previous sensitized (allergic) state.

Sulfonamides and Other Antibiotics

Reactions to sulfonamides (particularly rashes) are common in the general US population. There is marked accentuation of these rates in the patient with HIV infection. In particular, with TMP-SMX, which is frequently used for the treatment and prophylaxis of *Pneumocystis carinii* pneumonitis, the reaction rates are as follows: general population 3%, immunodeficient patients (HIV-seronegative) 12%, AIDS patients (HIV-seroposi-

Table 7
Oral Penicillin Desensitization Protocol

Desensitization dose[a]	*Stock drug, 250 mg/5 mL concentration*	*Oral dose*[a]	
		mL	*mg*
1	0.5 mg/mL	0.05	0.0025
2		0.10	0.05
3		0.20	0.10
4		0.40	0.20
5		0.80	0.40
6	5.0 mg/mL	0.15	0.75
7		0.30	1.50
8		0.60	3.
9		1.20	6.
10		2.40	12.
11	50 mg/mL	0.50	25
12		1.20	60
13		2.50	125
14		5.0	250

[a]Dose increased approximately every 20 min unless reaction occurs; then adjust accordingly.

tive) 29–70%. Sulfa drugs are also likely to be associated with EM minor, SJS, and TEN types of reactions.

The allergic-like reaction to sulfonamides is not felt to be IgE mediated or, for that matter, an immune event. Unfortunately, there is no skin test or in vitro blood test to confirm a suspected reaction. In almost all cases, strict avoidance of the drug is recommended once a presumptive diagnosis has been made.

The exception is life-threatening situations, such as in patients with AIDS with *P. carinii* infection. In some cases the infection can be successfully treated with antimicrobial agents other than the TMP-SMX, such as inhaled pentamidine. In other cases, this is not possible, and TMP-SMX is the optimal drug for treatment of active infection and/or use in *P. carinii* prophylaxis.

In some cases adults with a documented history of a prior rash to TMP-SMX have later been given full doses of TMP-SMX without subsequent reaction. In other cases, serious reactions have resulted from this "full-dose" challenge.

Extended oral TMP-SMX desensitization procedures have proved successful in a limited series of patients: 10–23 d (19/21 patients); 10 d (23/28 patients); 2 d (6/7 patients). Use of full-dose challenge or desensitization is not advised for any patient who has a prior history of drug-associated erythema multiform, SJS, or TEN. The management of these situations is best left to the allergist/immunologist or an infectious disease specialist. Recent evidence would indicate that individuals who develop a rash to sulfonamide antibiotics are not at risk for a reaction to sulfonamide containing nonantibiotic drugs because of cross-reactivity, but may be a risk because of having multiple drugs sensitivity (*see* Suggested Reading, Storm et al.).

Documented allergic-like reactions to other antibiotics are uncommon. Usually they are not life threatening in nature. Most reactions to iv vancomycin result in a red flush ("red man syndrome") resulting from direct histamine release and can be controlled

symptomatically and with adjustment of the iv drug administration rate. Occasionally serious allergic reactions can occur to ciprofloxin, and if this occurs quinolone-type antibiotics should be avoided.

In the case of reactions to other antibiotics, in almost all situations long-term avoidance is usually recommended, and the event is documented in the patient's records. Since there are usually substitute antibiotics available, it is not a problem for most individuals.

In a few individuals, however, multiple antibiotic sensitivities of different types occur. This type of patient presents a problem when the primary care physician tries to treat common infections. In most cases, β-lactam antibiotics are involved, so penicillin skin testing can be done. (Often the tests are negative.) There are no convenient tests for reactions involving other antibiotics. Reproducible reactions of any kind, especially those that are systemic in nature, are unusual. If the history of reaction is minor and the drug is necessary for therapy, a graded oral challenge can usually be done without difficulty to prove the safety of this alternative antibiotic (see Graded Drug Challenge Test Dosing).

Insulin

Approximately 50% of humans given insulin regularly as a replacement therapy, especially the animal-derived forms, develop some IgE antibody to the insulin molecule that can be validated by a positive immediate-reacting IgE skin test. Most of these individuals do not have clinical reactions to insulin. A few, however, do have bothersome local swelling at the insulin injection site.

Management of this local reaction problem consists of the following:

1. Division of the insulin dose in half and administering these doses at different sites
2. Trial of an added oral antihistamine
3. If steps 1 and 2 fail, switching to another commercial type of insulin

Generalized urticaria or systemic anaphylaxis to insulin is very uncommon. Usually the systemic reaction is the direct result of a diabetic discontinuing insulin replacement therapy regularly, for a time, and then resuming regular therapy. About 12 d after restarting of the insulin, systemic anaphylaxis occurs.

Patients who have a systemic reaction to insulin should be hospitalized after treatment of the acute symptoms. If the reaction is mild and the patient is seen within 24–48 h, the total insulin daily replacement can be decreased by one-third and subsequently the dose can usually be safely increased 5 U/dose until therapeutic levels have been achieved.

In the situation in which the reaction is more severe or the interval between reaction time and examination is more than 48 hours, the patient will require specific insulin allergy skin testing by an allergist/immunologist specialist to identify the least reactive insulin type (usually human insulin). The patient then requires desensitization over the course of a week with this new insulin.

Anesthetic Agents

Some patients given local anesthetics complain of allergic-like symptoms. Few if any of these reactions have been shown to be IgE mediated (*see* Mechanism of Reaction). When a patient is confronted with such a problem, the goal is to find one local anesthetic the patient can tolerate. The allergist–immunologist will usually skin test the individual complaining of symptoms with more than one type of local anesthetic, including the one that the surgeon–dentist wants to use.

Drug Challenge and Desensitization

- Graded drug challenges, or drug desensitization, should be done only when necessary, with informed consent, and under controlled conditions by specialists familiar with these techniques
- Any serious (anaphylaxis or anaphylactoid) reactions following drug challenge usually start within 2 h of drug exposure
- Reactions during drug desensitization procedures, such as with β-lactam antibiotics, should be expected to occur in one third of patients.

The specialist will select one of the nonreacting agents and then administer a graded sc injection challenge using dilutions of the local anesthetic at 1:100 (dose: 0.1 mL), 1:10 (dose: 0.1 mL), and full-strength local anesthetic (dose: 0.1, 0.5, 1.0, and possibly 2.0 mL) at 20-min intervals under controlled conditions (*see* Table 5).

Most patients successfully complete the local anesthetic challenge without difficulty. The referring physician is then informed regarding the safety of the drug used in the challenge.

It is common for an allergic-like reaction to occur during the induction of general anesthesia (1:5000 to 1: 15,000 inductions). The symptoms include urticaria, wheezing, rapid heart rate, low blood pressure, and shock. Two types of allergic reactions should be considered should these symptoms occur: (1) reactions to natural rubber latex and (2) allergic reactions to one of the neuromuscular blocking agents used in the induction period (e.g., tubocurarine chloride, alcuronium, gallamine triethiodide, pancuronium bromide, succinylcholine chloride, fluphenazine hydrochloride, thiopental, amytal sodium, and methohexital).

Certain individuals (e.g., health care workers, children with spina bifida or multiple operations, highly allergic individuals, and individuals with atopic dermatitis) are at increased risk for systemic reactions to natural rubber latex. Usually there is a history of prior contact dermatitis or contact urticaria to latex products before the patient has a systemic reaction. Latex proteins can be transferred via aerosol coupled to glove powder, so that severe reactions may occur in very sensitized individuals just by being in a room where latex is being used.

In situations in which systemic anaphylaxis has occurred in an operating room, it is advisable to draw blood from the patient as soon as possible after the event so that in vitro testing can be subsequently be performed for mast cell tryptase (as a sign of mast cell release; *see* General Approaches to Diagnosis and Management) and IgE latex-specific antibodies. If the latex in vitro test is positive, it supports the possibility of a clinical reaction to latex.

No commercial latex allergen is available to allergy skin testing. However, some allergist–immunologists may be able to skin test or challenge selective patients using commonly available natural rubber sources. Although the allergist–immunologist specialist may attempt direct skin testing with various neuromuscular-blocking agents, such a type of testing procedure is not standardized. Positive allergy skin testing to neuromuscular agents would provide helpful information, but a negative skin test result to these agents does not rule out an association between these agents and clinical reactions.

ASA and NSAIDs

There is no skin test or in vitro test available to confirm the presumptive diagnosis of ASA/NSAID intolerance in patients who have a history of allergic-like reactions (e.g., urticaria or asthma). The usual management is to advise the individual to avoid these drugs strictly. A graded drug challenge (beginning with no more than 3 or 30 mg of ASA, depending upon the history of sensitivity, and advancing to 60, 100, 150, and 300 mg at 3-h intervals) can be done under controlled conditions, but such a challenge is usually not advocated in most clinical situations. ASA desensitization has proven successful in patients with ASA-sensitive asthma, but not with most individuals with ASA/NSAID-induced urticaria, angioedema, or anaphylactoid reactions.

Most allergic-like reaction to ASA or NSAID are a result of the COX-1 inhibitor portion of these drugs (*see* Mechanisms of Action). COX-2 inhibitor drugs have been shown to be safe in ASA-induced asthma. However, some individuals who have had urticaria/angioedema or anaphylactoid reactions to ASA/NSAIDs may also react to these new drugs. A graded oral challenge of a COX-2 inhibitor can be helpful to assure the safety of this type of drug in patients known to be sensitive to ASA/NSAIDs.

Adverse Effects of ASA/NSAID

- GI bleeding
- Exacerbation of urticaria/angioedema from any cause
- Asthma; especially in nonatopic adults with chronic rhinitis and nasal polyps
- Anaphylaxis/urticaria-angioedema

RCM

RCM is used in imaging diagnostic procedures, and adverse reactions to RCM are fairly common. Therefore, one allergic-like problem that a primary care physician is likely to face is the patient with a prior history of RCM reaction who needs another diagnostic imaging procedure.

There is no skin test or in vitro diagnostic test that can be done to predict whether or not the patient with a history of prior reaction to RCM will have another reaction. Studies have shown that the chance a patient with a previous reaction to conventional RCM will have another reaction to the same material is approx 30%. This risk can be reduced to 10% by using a preprocedure treatment of prednisone and diphenhydramine (Benadryl). It may be reduced to a risk of 0.5% by using a low-molarity RCM material plus a preprocedure treatment of medications as outline in Table 8.

In spite of these procedure treatments and the use of a low-ionic RCM during the procedure, the individual with a prior RCM reaction is at some risk, and the radiologist should be prepared to treat anaphylaxis should it occur. In addition to the usual treatments, the radiologist should be prepared to treat an unusual but occasionally severe RCM reaction that mimics excess vagal stimulation, inducing bradycardia and resistant shock. Under these special circumstances, the addition of atropine to the anaphylactoid treatment regimen may be lifesaving.

Table 8
Pre-RCM Treatment Protocol for Prevention of Repeat RCM Anaphylactoid Reactions

Time	*Agent/Dose*
18, 12 and 6 h before procedure	Prednisone 50 mg every 6 h for 3 doses (total 150 mg)
Immediately before procedure	Diphenhydrammine hydrochloride (Benadryl) 50 mg po, im, 1 h or iv 5 min before RCM Cimetidine (Tagamet) 300 mg or ranitidine (Zantac) 300 mg po, 1–3 h before, or 5 min before RCM
During procedure	Low-ionic RCM

ACE-IN and AII-RAS

As described under mechanisms of action, ACE-INs can be associated with either a cough or angioedema of the throat, which can be severe and life threatening. The most important aspect of acute management is to recognize the possible relationship between the clinical symptoms and signs of these conditions and the drugs. Long-term ACE-INs should be avoided. Switching to another ACE-IN or to an A-II RAS is not advised since both drug types has been shown to cause the same symptoms in some patients.

The cough associated with ACE-INs (occurs in up to 25% of patients) generally resolves over a few weeks, after the drug is discontinued. Angioedema is more serious but occurs in fewer patients (0.1–0.7%). The symptoms tend to resolve with 24–48 h after discontinuing the drug.

In an emergency situation, life-threatening angioedema usually responds to epinephrine, antihistamines, antileukotrienes, corticosteroids, and possibly anticholinergic drugs. Recently it has been shown that when these conventional medications failed to control ACE-IN-induced angioedema. The patient responded to the infusion of fresh frozen plasma. This therapy may be considered in resistant cases.

Management of Other Drugs Involved in Allergic-Like Reactions

In situations in which a serious, usually systemic allergic-like reaction has occurred to a drug which is critical to the health or survival of the patient, it is not unusual that a subsequent graded drug challenge or desensitization procedure has been attempted. Usually the mechanism of the drug reaction is not clear and often successful results of challenges are only reported in case reports or small members or patients. Excellent management advice in these situations can be obtain by reading the monograph of Grammer and Grenberger (*see* Suggested Reading).

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17 Antihistamines

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SUMMARY

Histamine is widely distributed throughout the body, with the highest concentrations in the lung, skin, and gastrointestinal tract. H_1 receptors are the most important in producing allergic symptoms. Most first-generation antihistamines have a structural resemblance to histamine. The most important side effect of first-generation antihistamines is sedation. As a consequence, increasing numbers of second-generation antihistamines have become available. The activities of second-generation antihistamines are probably related to the fact that each of these mediators act through a G protein-coupled receptor that is analogous in structure to the receptor for histamine. The advantages of second-generation antihistamines include lack of sedation and ease of use (i.e., once-daily dosing). Antihistamines are important in the treatment of various allergic diseases. Antihistamines are the first-line therapy in the treatment of allergic rhinitis. Antihistamines are also becoming increasingly important in the treatment of urticaria, atopic dermatitis, and asthma. The use of antihistamines will likely expand as research into their use continues.

Key Words: Antihistamines; second generation, nonsedating; allergic rhinitis; allergies; treatment.

HISTAMINE

In order to prescribe antihistamines rationally it is important to be familiar with the role of histamine in the production of allergic disease. Histamine is widely distributed throughout the body, with the highest concentrations in the lung, skin, and gastrointestinal (GI) tract. Mast cells and basophils contain the majority of histamine, but it is also found in gastric mucosa, epidermal cells, rapidly growing tissue, enterochromaffin cells, and the central nervous system (CNS).

Histamine exerts its action through four receptors (H_1, H_2, H_3, H_4). The activities of these receptors are shown in Table 1. H_1 receptors are most important in the production of allergic symptoms. H_1 receptor stimulation produces contraction of bronchial smooth

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Table 1
Biological Effects of Histamine Mediated Through Various Histamine Receptors

H_1	*H_2*	*$H_1 + H_2$*	*H_3*	*GPRv53*	*H_4*
Elevates cyclic GMP (cGMP) Induces smooth muscle contraction Increases vascular permeability Stimulates nerve endings Pruritus Vagal irritant receptors (cough and bronchospasm) Induces vasodilatation Direct Stimulation of endothelial cell production of relaxing factors Discharges neuropeptides during axon reflex Increases histidine uptake in basophils Induces epinephrine secretion from adrenal medulla Increases rate of depolarization of SA node Slows rate of atrioventricular (AV) conduction	Increases cyclic AMP (cAMP) Increases gastric acid and pepsin secretion Produces positive inotropic and chronotropic effect on heart Decreases fibrillation threshold of cardiac muscle Immune down-regulation Decreases basophil histamine release Inhibits basophil chemotaxis Inhibits lymphokine and lysosome release Decreases lymphocyte proliferation Inhibits T-cell-mediated cytotoxicity Activates suppressor T-cell Causes lymphocyte production of histamine-induced suppressor factor Decreases monocyte secretion of complement components Inhibits neutrophil superoxide and peroxide generation Modulates neutrophil chemotaxis	Produces vasodilatation Produces flush Produces headache Produces hypotension Modulates eosinophil chemotaxis Alters mucus glycoprotein secretion from goblet cells and bronchial glands (H_1 increases viscosity and H_2 increases amount)	Inhibits histamine synthesis in the central nervous system, lung and skin Reduces peptide release from airway nonadrenergic, non-cholinergic nerves Modulates cholinergic neurotransmission in human airways Affects CNS functioning	Unknown function	Unknown function

muscle, reflex bronchoconstriction through stimulation of the vagus nerve, stimulation of peripheral nerve endings to produce pruritus and pain, and increased vascular permeability.

The most important actions mediated through the H_2 receptor are an increase in gastric acid production, a downregulation of a number of immunological and inflammatory responses, and a direct inotropic/chronotropic effect on the heart. The combination of H_1 and H_2 receptor stimulation is necessary for the maximal expression of effects such as peripheral vasodilatation (producing flush, headaches, hypotension) and the induction of mucus secretion.

The H_3 receptor has been found principally in the CNS. H_3 receptors are located in the hippocampus, the thalamus, the amygdala, and the hypothalamus. Most H_3 receptors are on presynaptic sites on histaminergic nerve terminals. They tend to be "inhibitory receptors." H_3 receptors are also found on peripheral nerve afferent neurons and reduce nerve repolarization when stimulated. H_3 receptors have also been detected in vascular beds.

H_4 receptors are found principally on peripheral blood cells. Their distribution suggests that they might be active in regulation of immune responses. They are also located in the bone marrow, colon, small intestine, and lung.

Histamine has specific effects on target organs. In the vascular tree the overall effect of histamine produces vasodilatation. This results in flushing, a lowering of peripheral resistance, and hypotension. In addition, there is increased vascular permeability, resulting in fluid shifts into the extravascular space. The vasodilatation, as noted, is mediated through H_1 and H_2 receptors, with maximal vasodilatation achieved by stimulation of both. However, the majority of the effects on the vascular bed are mediated through the H_1 receptor, which has a higher affinity for histamine and is stimulated by a lower concentration of the amine.

In addition to the effect of the H_1 and H_2 receptors, H_3 receptors also play a role in vascular phenomenon, as evidenced by animal models of anaphylaxis and nasal challenge studies involving the application of histamine to the human nasal airway. H_3 receptor stimulation of presynaptic terminals of sympathetic effector nerves innervating the heart and systemic vasculature, as well as the nasal vasculature, inhibit endogenous norepinephrine release. Because norepinephrine is involved in correction of hypotension in shock and in the homeostasis of normal airway patency, such stimulation can prevent compensatory sympathetic response to shock and result in an increase in nasal airway resistance as a result of intranasal vascular dilatation. H_3 receptor blockade in animal models of allergic shock thus improve cardiovascular responses, and H_3 antagonists will reverse the intranasal congestion occurring as a result of histamine-induced nasal blockage.

It stands to reason, therefore, that antagonism of all three receptors (H_1, H_2, and H_3) would be beneficial in the context of shock from anaphylaxis, as well as congestion occurring during rhinitis. It has been demonstrated that a combination of H_1 and H_2 antagonism is more effective than either alone in correcting symptoms of flush, headache, and blood pressure changes occurring during intravenous infusion of histamine in human volunteers.

The effects of histamine on the heart are mainly mediated through the H_2 receptor, but the H_1 receptor also plays a role. Vasodilatation is responsible for a reflex tachycardia. In addition, histamine exerts a direct effect on the heart that is both inotropic and chronotropic, with the H_2 receptor increasing the rate and force of both atrial and ventricular contraction. The H_1 receptor speeds the heart rate by hastening diastolic depolarization at the sino-atrial node. In addition, H_1 receptor stimulation contracts coronary arteries.

Smooth muscle contraction in the bronchial tree is mediated solely by the H_1 receptor. The H_1 receptor also produces modest contraction of the smooth muscle of the uterus. Smooth muscle relaxation in the lower airways is increased through H_2 receptors. Resistance in the nasal upper airway is also increased via the H_2 receptor.

Histamine effects on GI smooth muscle vary from species to species, but the predominant effect is contraction, mediated through the H_1 receptor. Effects through the H_2 receptor result in increased secretion of gastric acid.

Glandular secretion is mediated through both H_1 and H_2 receptors. The H_2 receptor increases the amount of mucus glycoprotein secretion from goblet cells and bronchial glands, whereas the H_1 receptor increases the viscosity of mucus.

Various histamine receptors have different roles in the development of pruritus and in the CNS. Pruritus is increased by stimulation of H_1 receptors. Whereas H_1 receptor stimulation increases neurotransmitter release, H_3 receptors decrease the release of neurotransmitters.

Immune Regulation

Histamine regulation of immune and inflammatory responses is mediated through the H_2 receptor and appears to be directly related to an increase in intracellular cyclic adenosine monophosphate. This results in a negative feedback on basophil (but not mast cell) histamine release. It also produces several effects on lymphocytes in vitro, including inhibition of T-cell-mediated cytotoxicity, activation of suppressor T-cells, decrease in immunoglobulin production, and suppression of lymphocyte proliferation and lymphokine production. In addition, H_2 receptor stimulation can decrease monocyte secretion of complement components, inhibit neutrophil superoxide production, and modulate neutrophil chemotaxis.

As noted, it is reasonable to assume that, because H_4 receptors are found on leukocytes, including eosinophils, histamine might well play a role in the immunological inflammatory response. Stimulation of eosinophils by histamine can produce chemokinesis as well as chemotaxis. Those activities are inhibited by an H_4 antagonist. H_4 antagonists also reduce histamine-induced upregulation of adhesion molecules. H_4 stimulation also can cause chemotaxis of mast cells, and thus it can be postulated that the H_4 receptor is active in recruiting mast cells to areas of allergen challenge, amplifying histamine-mediated allergic reactions.

Histamine is widely distributed throughout the body; most is found in mast cells and basophils. H_1 receptors are most important in the production of allergic symptoms. Stimulation of H_1 receptors results in the contraction of bronchial smooth muscle, stimulation of peripheral nerve endings to produce pruritus and pain, and increased vascular permeability.

CLASSICAL, FIRST-GENERATION ANTIHISTAMINES

Structure–Function Relationships

Traditionally all H_1 antagonists were considered to act via the mechanism of competitive inhibition at the H_1 receptor. Recently, the concept of reversed or inverse agonist has been introduced to explain the action of antihistamines. The idea is based on the existence of histamine receptors, at equilibrium, existing in both active and inactive forms. Histamine stabilizes the histamine receptor's conformation, resulting in a predominantly activated state, whereas antihistamines are thought to be agonists of the inactive conformation

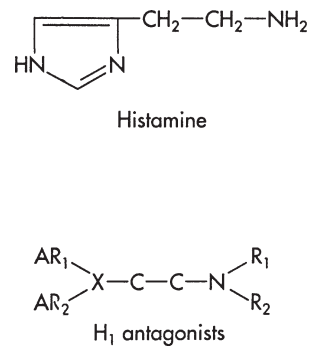

Fig. 1. Structure of histamine compared to prototype structure of first-generation antihistamines.

at the receptor site. Stimulation by antihistamines at the receptor thus results in the abolition of the effects of histamine. Important regarding this concept is that antihistamines induce the downregulation of histamine receptor activity, both in the presence and the absence of histamine. Most, but not all, first-generation antihistamines have a structural resemblance to histamine (Fig. 1) in that they contain a substituted ethylamine moiety. It was previously felt that this structural similarity was necessary for competitive inhibition. However, with the development of newer agents, it has been shown that antihistamine activity can occur without an obvious shared structural relationship between histamine and its antagonist. The proposed difference between the mechanisms of action of antihistamines with an ethylamine moiety (thus exhibiting a structural resemblance to histamine) and those without this entity is that the former group may actually bind to the same site on the histamine receptor as histamine, whereas the latter group binds to the seven-chain, G protein-coupled histamine receptor at other sites to sterically hinder the binding of histamine. In addition, the absence of structural similarities adds credence to the inverse agonist hypothesis.

First-generation antihistamines have classically been separated into categories based on the atom linking the ethylamine grouping to aromatic substituents (Fig. 1). For example, if the link is via oxygen, the drugs are classified as ethanolamines; if via carbon, they are called alkylamines; and if via nitrogen, they are called ethylenediamines (Fig. 2). Certain biological activities have been attributed to these differences, but clinically it is unclear whether or not these are significant. For example, it is said that alkylamines cause less drowsiness in general than do ethanolamines. Examples of first-generation antihistamines classified according to their structural differences are seen in Table 2.

Pharmacokinetics

The pharmacokinetic and pharmacodynamic properties of selected first-generation antihistamines are presented in Table 3.

All first-generation H_1 receptor antagonists are rapidly absorbed and reach peak serum concentration within 3 h when given in liquid form. All are extensively metabolized in the liver, and little, if any, of these drugs are excreted unchanged in the urine. All of these agents are metabolized through the hepatic cytochrome P450 system. Rates vary from patient to patient and are age dependent, with children having shorter, and the elderly having longer elimination half-lives. Severe hepatic dysfunction can prolong the half-life and require dosing adjustments.

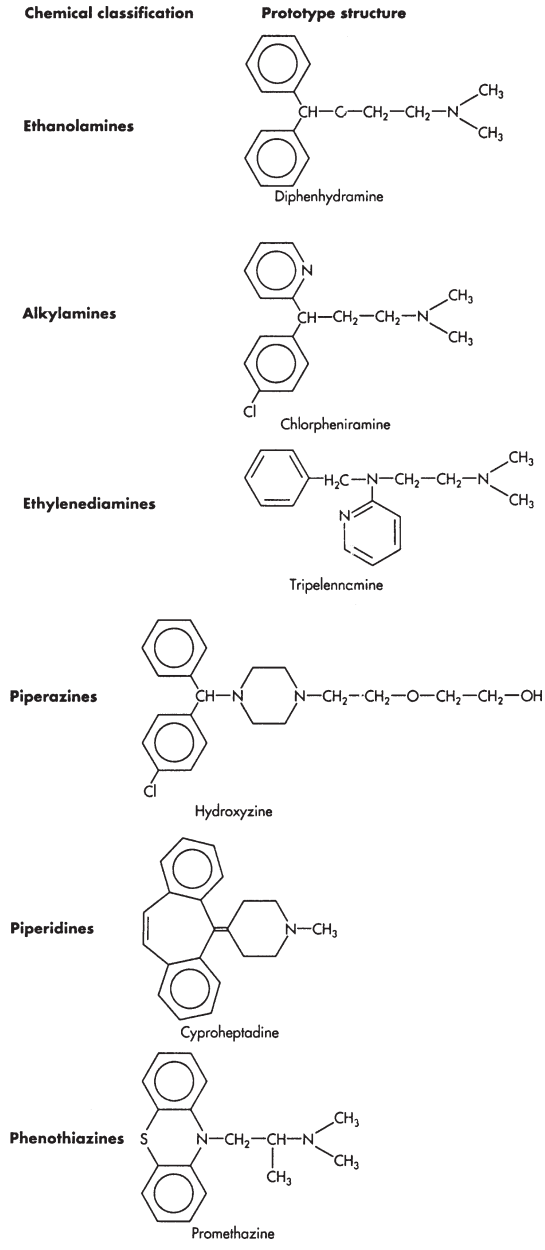

Fig. 2. Structural classification of classic H_1 antagonists.

Pharmacodynamics

An important principle of the pharmacodynamic activity of these drugs is that their tissue effect is delayed relative to peak serum levels and can extend far beyond the life of the drug in the serum. For example, hydroxyzine can suppress histamine-induced wheal and flare for as long as 60 h despite maintaining a negligible serum concentration at this time.

Table 2
Characteristics of Representative First-Generation H_1 Antagonists Based Upon Chemical Classification

Chemical class	*Examples*	*Comments*
Ethanolamines	Diphenhydramine Clemastine Carbinoxamine	Significant antimuscarinic effects. Can be potent sedatives, but sedative potential varies, with clemastine producing the least amount. Low incidence of gastrointestinal side effects. Can have some anti-motion sickness activity. Diphenhydramine and clemastine both available over the counter.
Alkylamines	Chlorpheniramine Brompheniramine Dexchlorpheniramine Tripolidine	Relatively moderate incidence of drowsiness. Moderate anticholinergic effect. No antiemetic or anti-motion sickness activity. Little gastrointestinal side effects. All available over the counter. Occasional paradoxical central nervous system stimulation, especially in children.
Ethylenediamines	Tripelennamine Pyrilamine Antazoline	Mild to moderate sedation. Slight anticholinergic effect. Some local anesthetic effect. Pyrilamine is sold over the counter and is the oldest antihistamine preparation available today. As a group, may have more frequent gastrointestinal side effects.
Piperazines	Hydroxyzine Meclizine Cyclizine	Hydroxyzine has highest sedative activity in group. Meclizine and cyclizine relatively low sedative activity with main use being for vertigo, anti-motion sickness, and antiemetic activity. Hydroxyzine has significant anticholinergic activity.
Piperadines	Cyproheptadine Phenindamine Azatadine	Mild to moderate sedation. Little anticholinergic activity, antiemetic activity, and anti-motion sickness activity. Cyproheptadine has potent antiserotonin effect. As a class, has relatively high incidence of paradoxical central nervous system stimulatory activity.
Phenothiazines	Promethazine Methdilazine Trimeprazine	Usually highly sedating. Strong antiemetic, anticholinergic activity. Main clinical use is as antiemetics.

The tissue effect, however, is delayed compared to peak serum concentrations. For example, with hydroxyzine, maximal suppression of wheal and flare does not occur until 7 h after peak serum concentrations have been achieved. Based on these pharmacodynamic observations, it can be concluded that it is best to administer H_1 antagonists before allergen exposure.

Table 3
Pharmacokinetic and Pharmacodynamic Characteristics of Selected First-Generation H_1 Antagonists

Drug	*Approximate time at which peak serum concentration is reached after oral dose (h)*	*Approximate half-life (h)*	*Approximate duration of biological activity (suppression wheal and flare)*	*Route of metabolism*
Diphenhydramine	0 .75–2.5	8–9	6–10	Liver
Chlorpheniramine	1.5–2.5	20–24	24	Liver
Hydroxyzine	1–2.5	20	36	Liver
Brompheniramine	2–3	24	9	Liver
Tripolidine	1–2	2.1	—	Liver

Other Pharmacological Actions

First-generation antihistamines have a number of pharmacological activities unrelated to their antihistaminic properties. They can exert antimuscarinic, anti-αadrenergic, antidopaminergic, antiserotonergic, local anesthetic, antiemetic, and anti-motion sickness activity.

Side Effects

By far the most common significant side effect of first-generation antihistamines is drowsiness. All first-generation antihistamines cross the blood–brain barrier (BBB). The exact mechanism of production of drowsiness by these drugs is unknown, but may include antihistaminic, anticholinergic, antiserotonergic, and antiadrenergic activities. It should be noted that the antihistaminic activity does not necessarily correlate with the sedative potential, suggesting that this is not the sole cause of this side effect. The degree of sedation depends on many factors, including age, the pattern and quality of nocturnal sleep, and concurrent medication. First-generation antihistamines clearly potentiate the activity of other sedative drugs such as alcohol.

Of importance is the fact that the subjective degree of drowsiness does not necessarily correlate with the objective measurement of central nervous system impairment. For example, drowsiness can occur without impairment and impairment without drowsiness. Although drowsiness can be overcome by the exertion of will, impairment of cognitive functions and psychomotor performance cannot, and will persist until the effect of the drug abates.

Paradoxical CNS stimulation can occur in some individuals, especially children. Other CNS side effects include dizziness, tinnitus, blurred vision, and tremors.

The next most common group of side effects produced by first-generation antihistaminics relate to their antimuscarinic activity. These include dryness of the mouth, urinary retention, blurring of vision, difficulty urinating, and constipation.

Other side effects are uncommon and include loss of appetite, nausea, abdominal pain, and diarrhea. Drug allergy to first-generation antihistamines is extremely rare but has been reported. Leukopenia, agranulocytosis, and hemolytic anemia have all been seen. Teratogenic effects have been noted in animals, but there has been no documentation of this in human beings.

Limitations to the use of the first-generation antihistamines result from their side effects, including sedation, dry mouth, urinary hesitancy, and, in children, paradoxical CNS stimulation.

SECOND-GENERATION ANTIHISTAMINES

An increasing number of second-generation antihistamine products have become available for oral administration in the United States. At this time, these include loratadine (Claritin), cetirizine (Zyrtec), fexofenadine (Allegra), desloratadine (Clarinex), and Azelastine. Fexofenadine and desloratadine are metabolites of other antihistamines, terfenadine and loratadine, respectively. Other products, including levocetirizine and mizolastine, are currently approved in Europe and may be available in the United States in the future. Azelastine is available as a nasal spray (Astelin) and eye drops (Optivar), and levocabastine (Livostin), olopatadine (Patanol), emedastine (Emedine), and epinastine (Elestat) are also available as eye drops. The term second-generation antihis-

tamine is used loosely in this chapter to refer to antihistamines available since 1981. In general, these drugs are distinguished from classical, sedating antihistamines by the fact that they either are considered nonsedating or lesser sedating drugs. However, only three members of this group are classified by the US Food and Drug Administration (FDA) as totally nonsedating: loratadine, desloratadine, and fexofenadine.

Second-generation antihistamines differ from first-generation antihistamines as well by the fact that it is more difficult to classify them by structure (Fig 3). They do not always contain a readily accessible ethylamine side chain as do first-generation drugs. Thus, their structure–function relationships are less well defined. Nonsedating antihistamines are diverse in chemical structure, and many can be considered as drugs with multiple pharmacological effects in addition to their antihistaminic activity. For example, azelastine was originally produced as an antiasthma drug. These multiple pharmacological effects, however, differ from those noted above for first-generation antihistamines. First-generation antihistamines, as noted, have antimuscarinic, antiserotonergic, and anti-α-adrenergic effects. These activities are probably related to the fact that each of these mediators act through a G protein-coupled receptor that is analogous in structure to the receptor for histamine. Thus, the receptor, for example, for α-adrenergic agents differs from that for histamine only by several amino acids. Therefore, these activities of second-generation antihistamines are presumably a result of their nonspecific ability to hinder the effect of other mediators at the receptor site in a manner less efficient than their ability to hinder the activity of histamine. However, the other pharmacological activities of nonsedating antihistamines are termed as "antiallergic effects" and are probably related to more diverse pharmacological activities, as described below.

Another difference between first- and second-generation antihistamines is that some of the latter bind to the $H_{2,}$ as well as the H_1, receptor. This appears to be especially important for azelastine and epinastine. This property could at least be theoretically important in that the capacitance vessels in the nasal turbinates and the conjunctiva respond to the H_2 stimulation by dilating, thus causing nasal congestion and conjunctival erythema. This may explain the observation that azelastine reduces nasal airway resistance, an effect not associated with the administration of an H_1 antagonist.

The most clinically important factor that distinguishes second-generation from first-generation antihistamines is their lack of sedative activity. The most likely explanation for this lack of sedation is the fact that they do not readily pass the BBB. The basis for the failure to cross the BBB likely includes several properties of these agents: (1) a relative lack of lipid solubility compared to first-generation antihistamines; (2) an increased tendency to bind to serum proteins; (3) a relatively large molecular size with larger side chains; (4) their electrostatic charge; (5) and the presence of chemical groups that ionize at physiological PH. In addition, their relative specificity for the H_1 receptor negates the antimuscarinic, antiserotonergic, and anti-α-adrenergic soporific effects of first-generation antihistamines. Finally, these second-generation antihistamines have a greater affinity for peripheral vs central H_1 receptors. Thus, the lack of sedative activity of these agents is probably related to a multiplicity of pharmacological properties—the most important of which is their failure to pass the BBB.

Pharmacokinetics

The pharmacokinetic properties of second-generation antihistamines (Table 4) allow for once- or twice-daily therapy. As with first-generation antihistamines, all second-generation drugs are rapidly absorbed after oral administration. Peak plasma levels occur

Table 4
Comparison of Second-Generation Antihistamines

Drug	*Route of administration*	*Adult dose (mg)*	*Effect of food on absorption (AUC)*	*Plasma protein bound (%)*	*Elimination t1/2 (hours)*[a]		*Onset of action (h)*	*FDA cautionary label*	*Metabolized in liver*	*Pregnancy category*	*Possible cardiac side effects*
					Parent	*Metabolite*					
Loratadine (Claritin)	Oral	10 qd	40%	97–99	12–15	17	1	No	Yes	B	No
Cetirizine (Zyrtec)	Oral	10 qd	0	93	27–10	—	1	Yes	Minimally[b]	B	No
Fexofenadine (Allegra)	Oral	60 bid	NR	60–70	14.42	—	1	No	Minimally[c]	C	No
		180 qd	NR	60–70	14.42	—	1	No	Minimally[c]	C	No
Azelastine (Astelin)	Intranasal	0.137/spray 2 sprays each nostril bid	0	78–88	22–36	42–54	1	Yes	Yes	C	No

[a]Loratadine and azelastine have active metabolites; cetirizine and fexofenadine do not.
[b]Mainly excreted in urine.
[c]Majority excreted in feces.
NR, Not reported; AUC, Area under the curve; NAM, No active metabolite.

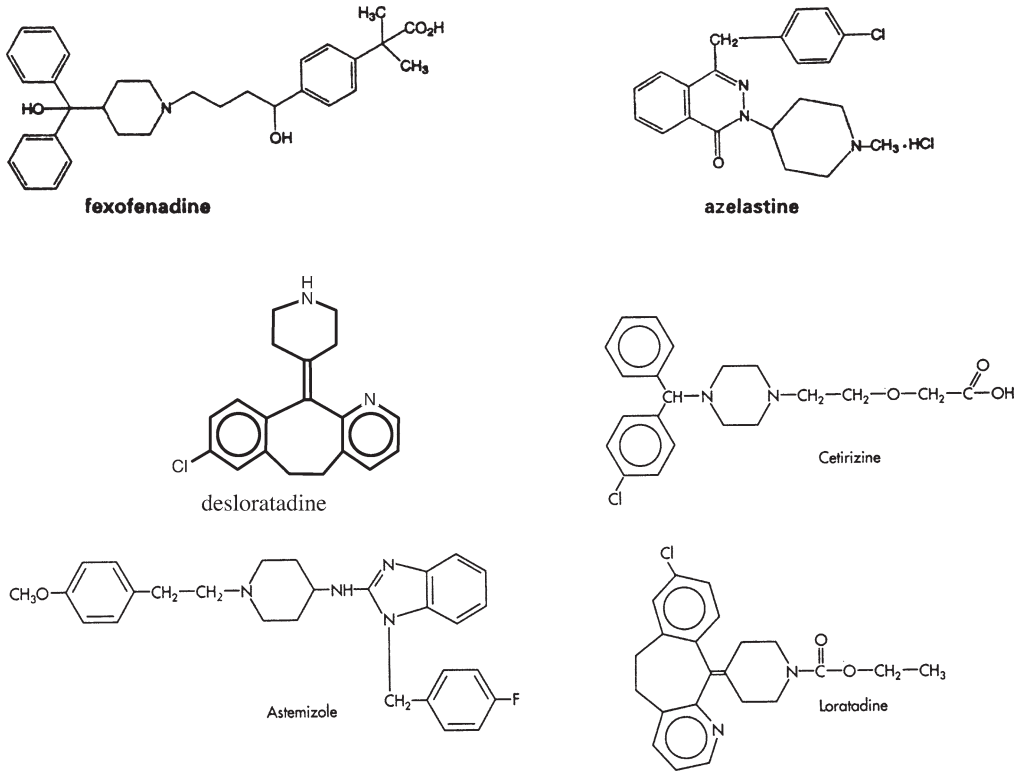

Fig. 3. Structures of representative second-generation H1 antagonists.

1–2 h after administration. Loratadine, desloratadine, and azelastine are all extensively metabolized in the liver through varying cytochrome activities. Cetirizine is partially metabolized in the liver, but is renally excreted for the most part. Fexofenadine differs in that it is, for the most part, excreted unchanged in the feces.

Of these drugs, desloratadine has the longest mean elimination half-life at 27 h. The elimination half-lives of cetirizine and loratadine are between 7 and 10 h, and 12 and 15 h, respectively. Fexofenadine has an elimination half-life of approximately 14.5 h. Loratadine and azelastine have active metabolites. Desloratadine, a metabolite of loratadine, is further metabolized to 3-hydroxydesloratadine, the active metabolite. Fexofenadine and cetirizine have no active metabolite. All of these drugs have strong serum protein-binding activity (Table 4).

Pharmacodynamics

Like first-generation antihistamines, the pharmacodynamic activity of these drugs is relatively unrelated to their serum levels. The peak pharmacodynamic activity is delayed relative to the peak serum levels and can extend far beyond the life of the drug in the serum. The ultimate duration of their antihistaminic activity, therefore, is not predictable solely on the basis of their metabolic half-lives because of the degree of reversibility of receptor binding. Therefore, clinical activity cannot be assessed by measuring serum concentrations.

Anti-Allergic Effects of H_1 Antagonists

Second-generation antihistamines have been shown to have diverse anti-allergic or anti-inflammatory pharmacological activities. The clinical significance of these activities has not been well documented, but based upon their nature, it can be presumed that part of the therapeutic effect of these agents may indeed be related to these properties. The antiallergic activities of second-generation antihistamines include the following: (1) prevention of histamine release from mast cells and basophils; (2) downregulation of intracellular adhesion molecules such as ICAM-1 on epithelial membranes; (3) decreased eosinophil influx into tissues; (4) prevention of the generation of superoxide; (5) prevention of the generation of leukotrienes; and (6) prevention of the production of interleukins. For example, fexofenadine has been shown to decrease the expression of ICAM-1 on epithelial cells and prevent the release of interleukin A and granulocyte-macrophage colony-stimulating factor (GM-CSF). Also, desloratadine inhibits production of interleukin (IL)-4 and IL-13, both cytokines associated with the TH_2, or allergic limb, of the immune response. This is particularly important in the late-phase allergic response.

Sedation and Psychomotor and Cognitive Impairment

It is important to distinguish sedation from cognitive and psychomotor impairment. Sedation refers to the subjective sensation of sleepiness, fatigue, drowsiness, decreased ability to concentrate, and loss of alertness. Of note is the fact that these subjective sensations can occur independent of objective detection of psychomotor and cognitive impairment. For example, patients can feel sedated without being impaired, and can show impairment without being sedated. It has been shown that, in general, all second-generation antihistamines are less sedating and produce less impairment that do first-generation antihistamines. Only three second-generation antihistamines, however, have been deemed by FDA to be totally nonsedating: loratadine, desloratadine, and fexofenadine. Thus these drugs are the only second-generation antihistamines approved by the US Federal Aviation Administration to be taken before or during a flight. Again, it is important to make the distinction between sedation and impairment. Sedation, being subjective, can be overcome by the exertion of will in many circumstances. However, impairment will persist and cannot be overcome through conscious effort. Patients, therefore, may not be aware of impairment when they are not subjectively sedated. The growing recognition of this is reflected in the increased number of states that have enacted laws prohibiting the operation of a motor vehicle while taking sedating medications, including sedating antihistamines. At the time of this writing, a majority of states have enacted such laws.

Perhaps of singular importance regarding the distinction between subjective drowsiness and the objective ability to perform is that in children. It has been shown that the learning capacity of allergic children may suffer during the allergy season, and that a first-generation sedating antihistamine (although improving allergy symptoms) may actually worsen performance. On the other hand, the use of a nonsedating antihistamine will, presumably by controlling symptoms without affecting performance, enhance learning ability in children.

Based on the above observations, it is quite clear that nonsedating second-generation antihistamines such as loratadine, desloratadine, and fexofenadine have a clear advantage over first-generation antihistamines in terms of their ability to relieve symptoms

without affecting performance. However, because of their increased cost, managed care has attempted to reduce their usage by recommending use of a second-generation antihistamine during the day and a first-generation antihistamine at night. Unfortunately, it has been shown, as noted above, that tissue effects of first-generation antihistamines persist beyond their serum level, and it can thus be expected that the performance-impairing activity of a first-generation antihistamine given at bedtime can persist during the following day. Therefore, this strategy may be ineffective in preventing impairment owing to the administration of first-generation antihistamines.

Advantages to the use of second-generation antihistamines are the efficacy and lack of secondary sedation, thus "nonsedating," since most do not cross the BBB. This is particularly important for school-age children to control symptoms, while limiting any impairment in learning. Other advantages include greater affinity to peripheral vs central H_1 receptors and ease of use (once-daily dosing).

Uses of Antihistamines

Rhinitis

It is quite clear that nonsedating second-generation antihistamines are the recommended first line of therapy for patients with allergic rhinitis (Table 5). They are usually sufficient to treat symptoms of sneezing, rhinorrhea, and itching associated with mild to moderate allergic rhinitis. They are also helpful for ocular symptoms. However, with the exception of azelastine, little effect on nasal congestion is seen. There is no distinct difference in the efficacy between first- and second-generation antihistamines for the therapy of allergic rhinitis. However, the lack of effect on performance makes second-generation antihistamines the drugs of choice.

For rhinitis induced by the common cold, second-generation antihistamines are not effective. However first-generation antihistamines, presumably because of their anticholinergic effects, are somewhat beneficial for the therapy of rhinorrhea and sneezing.

Urticaria

As with allergic rhinitis, antihistamines are the drug of choice in patients with urticaria. The primary symptom in urticaria is pruritus. Antihistamines exert their major suppressive activities on this symptom. They are usually less effective in reducing wheal size. For patients with chronic urticaria, daily administration may be most effective. When H_1 antihistamines alone are insufficient, addition of H_2 antihistamines may improve symptom control.

Atopic Dermatitis

There are very few studies examining the use of second-generation H_1 receptor antagonists in atopic dermatitis. Because of the inflammatory nature of this disease, it is expected that they would be less effective than they are in urticaria. Nonetheless, it is customary to use antihistamines in the therapy of atopic dermatitis, and because, at least a portion of the symptoms appears to be related to the release of histamine, there is strong rationale for their use. However, in the treatment of atopic dermatitis, the use of antihistamines is considered adjunctive, rather than first-line therapy.

Asthma

It has long been thought that antihistamines might be contraindicated in the therapy of asthma because of their "drying effect." This is of course untrue. Antihistamines are

Table 5
Indications for Antihistamine Use by Atopic Disease

Allergic rhinitis	First-line therapy. Useful for sneezing, rhinorrhea, itching.
Urticaria	Drug of choice. Efficacious for pruritus.
Atopic dermatitis	Adjunctive therapy for pruritus.
Asthma	Beneficial in treatment by treating rhinitis.
Modulation of the development of atopy	Possible prophylactic role in children with atopy.

certainly not contraindicated and have been shown to have a beneficial effect to some extent in the therapy of this condition. Second-generation H_1 antagonists have been studied extensively in the therapy of asthma. A number of these drugs have been reported to be effective. In patients with both allergic rhinitis and asthma, treatment of the allergic rhinitis symptoms resulted in improved control of asthma.

Antihistamines and Development of Atopy

One study revealed that antihistamines held a preventive role for the development of atopy in children. Recent experimental data obtained from animal models, as well as one study in humans, indicate that antihistamine administration to infants may delay or modify the onset of allergic disease. Studies in mice revealed that treatment with antihistamines prevented inflammation and bronchial hyperresponsiveness. Specifically, decreased eosinophilia in both lower airways and in the tissues, as well as prevention of TH_2 lymphocyte cytokine production was seen, suggesting that histamine participates in the development of a TH_2 lymphocyte profile in childhood. If these early studies are confirmed, there may be a prophylactic role for antihistamine administration in infants born to two allergic parents. There is certainly no reason to withhold these drugs in asthmatics, and in fact, their administration may be helpful.

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18 β-Adrenergic Agonists

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CONTENTS

SUMMARY

Beta-adrenergic agents have been one of the mainstays of asthma treatment over the past several decades. Refinement of these drugs has resulted in the production of selective β-2 agonists with both long and short durations of action. They are the most potent bronchodilators in our therapeutic arsenal. Short-term β-agonists are used in all cases of asthma on an as needed only basis. Long-term β-agonists are reserved for use in those patients simultaneously taking inhaled corticosteroids (stage 3 asthma).

Key Words: Bronchodilators; beta-adrenergic agonists; albuterol; fenoterol; salmeterol.

INTRODUCTION

β-Adrenergic agonists, and especially β_2-adrenergic agonists, are generally prescribed for all asthmatics as backup medication to anti-inflammatory therapy or, in the case of exercise-induced asthma, as the primary drug. Technological advances have led to the development of increased β_2-specific adrenergic agonists of longer duration of action. The effectiveness of β-adrenergic agonists in treating asthma is indisputable. However, the very effectiveness of these drugs causes problems of overuse and consequent side effects, raising issues such as whether other drugs or other parameters should be preferentially utilized.

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β-ADRENERGIC RECEPTORS

Initially, adrenergic receptors were classified as either α or β, based upon the tissue response to various sympathomimetic amines. The receptor population that mediated excitatory responses was called α, and the potency ranking was epinephrine > norepinephrine > α-methyl norepinephrine >α-methyl epinephrine > isoproterenol. The receptor population that mediated inhibitory responses was designated as β, and had an agonist order of potency of isoproterenol > epinephrine > α-methyl epinephrine >α-ethyl norepinephrine > norepinephrine. It later became recognized that although generally correct, this classification was overly simplified, and the α- and β-receptors were further subclassified. For β-adrenergics it is now recognized that there are three receptor groups: β_1, β_2, and β_3. The β_1-adrenergic receptors are primarily located in the brain, the heart, and the pineal gland, the β_2-adrenergic receptors are primarily in the lung and prostate, and the β_3-adrenergic receptors are found in brown and white adipose tissue. Improved techniques to identify receptors have led to the discovery that although these receptors have preferential primary locations, they may also be present in other tissues. The β_2-adrenergic receptor is the predominant β-receptor in the lung, but it is also found in adipose tissue, the brain, heart, and placenta. This is of particular importance in understanding the side effects of the β_2-specific adrenergic drugs.

β_2-ADRENERGIC AGONISTS FOR THERAPY

Advances in therapeutic β-adrenergic agonists have been accomplished by modification of chemical structures of adrenergic agents (Table 1). Although the specific chemical structure determines the specific class of drugs (e.g., catecholamines, noncatecholamines, saligenins), it may be more convenient to consider the available therapeutic agents as first, second, third, and fourth generation, dependent upon the newness of the drug, the β_2 specificity, and the duration of action.

First-Generation Agents (α and β)

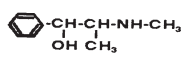
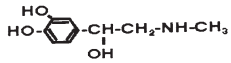
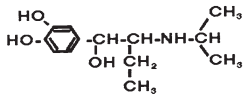
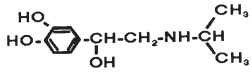
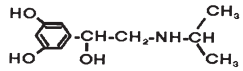
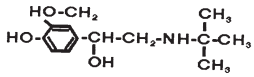
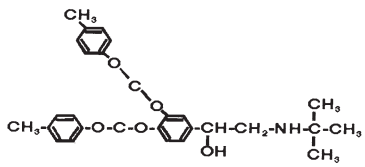
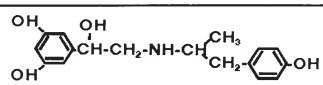
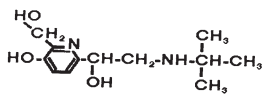
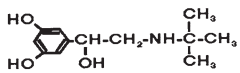
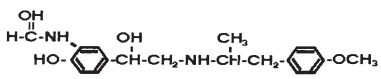
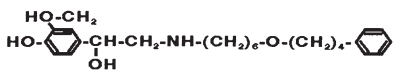
Probably the oldest adrenergic drug is ephedrine, used in China as *ma huang* for centuries before the use of epinephrine. Although ephedrine is rarely used for treatment today, it was commonly combined with theophylline and sometimes a sedative as treatment for asthma until more effective and more specific bronchodilators were developed. The major problem with ephedrine was that it easily crossed the blood–brain barrier, and even modest doses had significant side effects, particularly headache. The amount of bronchodilation was also relatively weak.

Epinephrine has both α- and β-adrenergic actions, which make it the drug of choice for the treatment of anaphylaxis. It is effective as an injection, but not orally, because epinephrine and other catecholamines are rapidly inactivated by the action of catechol-*O*-methyltransferase (COMT), an enzyme present in the gastrointestinal wall. Epinephrine can also be aerosolized, but this particular treatment is more popular for acute laryngobronchitis (croup).

Second-Generation Agents (Relatively β)

Two other catecholamines are of note: isoproterenol and isoetharine. Isoproterenol is available for aerosol administration for asthma, but is also available for sublingual and injectable routes. As an inhaled bronchodilator, isoproterenol has good immediate po-

Table 1
Adrenergic Bronchodilators

Classification	Molecular structure	Formulations in the USA	Duration of effect (h)
First generation			
Ephedrine		Liquid, tablet	2–3
Epinephrine		Injection, MDI	<1
Second generation			
Isoetharine		MDI, nebulizer solution	3
Isoproterenol		Injection, liquid, MDI, nebulizer solution, tablet	1–2
Metaproterenol		Liquid, MDI, nebulizer solution, tablet	3–5
Third generation			
Albuterol		Dry powder inhaler, liquid, MDI, nebulizer solution, tablet	4–6
Bitolterol		MDI, nebulizer solution	6–8
Fenoterol		Not available	6–8
Pirbuterol		MDI	4–6
Terbutaline		Injection, MDI, tablet	4–6
Fourth generation			
Formoterol		Dry powder inhaler	8–12
Salmeterol		Dry powder inhaler	12

MDI, metered-dose inhaler.

Modified from Kemp JP. Making best use of today's bronchodilators. J Respir Dis 1994;15(4 suppl):S21–S27.

tency, usually accomplishing peak bronchodilation within 5 min. However, the effectiveness rapidly declines and usually is lost completely by 2 h. This makes isoproterenol useful acutely, but not for any maintenance bronchodilator therapy or even for prophylactic use before exercise. If high doses are used, cardiac stimulation becomes an unacceptable side effect.

Isoetharine is the first β-agonist that clearly had increased β_2 activity. Because it is also a catecholamine, it cannot be used orally because of deactivation by COMT. It is, however, resistant to monoamine oxidase and so has a slightly longer duration of bronchodilation than the other catecholamines. Its clinical usefulness, however, has been greatly overshadowed by the more specific and longer-acting β_2 drugs.

Metaproterenol is a resorcinol, not a catecholamine. The resorcinol group has a modification in the 3,4 hydroxyl groups of the benzene ring. The hydroxyl groups repositioning from the 3,4 to the 3,5 positions makes metaproterenol resistant to inactivation by COMT, and this leads to the advantage of prolonged duration of action. The side chain of metaproterenol is essentially the same as isoproterenol so, as would be expected, both drugs are similar in their effects relative to heart and lung. Because the relative cardiac effect is similar for both isoproterenol and metaproterenol, metaproterenol is less suited for maintenance bronchodilator treatment or for higher dose treatment than are the third generation of β-adrenergic agonists.

Third-Generation Agents (Highly β, Longer Acting)

The third-generation group are those drugs that are highly β_2-specific with a longer duration of action. These characteristics make these the ideal choice for acute asthma treatment and prevention of exercise-induced asthma.

Albuterol, a saligenin, is resistant to the action of COMT because of the substitution of the 3 hydroxyl group with a hydroxymethyl group. In addition, albuterol has a tertiary butyl group that replaces the isopropyl group seen in isoproterenol and metaproterenol. This increased bulkiness of the side chain has resulted in substantially more selectivity for the β_2 receptor. Albuterol is resistant to degradation by COMT, making it effective orally as well as by aerosol and parenterally. With its high β_2 specificity and its longer duration of activity, albuterol became the standard against which other bronchodilators are compared.

Bitolterol is resistant to COMT because the 3,4 hydroxyl groups are esterified to form a di-$_p$-toluate ester. This modification substantially prolongs the bronchodilator activity; in addition, a tertiary butyl group replaces the isopropyl group, resulting in increased β_2 specificity and protection of the drug against degradation by monoamine oxidase (MAO; which then further increases the duration of activity). Bitolterol is also an interesting bronchodilator because when administered by inhalation, it acts as a pro-drug, which is slowly degraded to the active drug colterol. This gives bitolterol the potential of being much longer acting than the other bronchodilators in this group.

Pirbuterol is resistant to COMT because of the substitution of a hydroxyl methyl group for the 3 hydroxyl group. This plus the increased size of the terminal amino group increases the duration of the bronchodilator action. The side chain is also adequately bulky to account for more selectivity for the β_2 receptor.

Terbutaline is resistant to COMT because of the repositioning of the hydroxyl groups to the 3,5 positions. This modification increases the duration of the bronchodilator action and makes the drug potentially capable of oral administration. The side chain of terbutaline had a tertiary butyl group that increases the β_2 specificity and also protects against

degradation by monoamine oxidase, increasing the duration of bronchodilation. As with the other drugs in this third-generation group, terbutaline is of current usefulness, but it also has unique advantages as the potentially most safe drug for use in pregnancy. It also is used by obstetricians to control premature labor.

Fenoterol is a drug that is not used in the United States but has been part of substantial controversies about the safety of β-agonists. Fenoterol, as other members of this group, is resistant to the action of COMT because hydroxyl groups are located at the 3,5 positions. The side chain in fenoterol is much larger than the other members of this group with the use of a 4-hydroxybenzyl moiety. Nonetheless, in the case of fenoterol, the β_2 specificity is less than those drugs that use a tertiary butyl group substitution. It is this relative decreased β_2 specificity that makes fenoterol a drug that potentially could have more side effects than the other drugs in this group.

Fourth-Generation Agents (Highly β, Extremely Long Acting)

Salmeterol and formoterol induce a long duration of bronchodilation, in some studies reported to be more than 12 h. These two drugs resemble the non-catecholamine-selective β_2-agents, but also posses bulky lipophilic side chains. It is thought that these side chains anchor the molecule next to the β-receptor site. The action of both of these drugs can be reversed by introducing a β-adrenergic-blocking agent, but if the β-blocker is removed, the receptor is restimulated. Because of their long duration of action, these drugs are particularly useful for long-term bronchodilator treatment, but are potentially less useful acutely and may pose problems of toxicity with overuse or increased dosage. Concerns about tolerance to the bronchoprotective properties are raised by studies showing rapid reduction of protection to methacholine or exercise with regular use of salmeterol.

There are some recent suggestions that long-acting β-agonists may induce more than simply sustained bronchodilation. Some work has shown that long-acting bronchodiltors may be involved in apoptosis of inflammatory cells, stabilization of mast cells, and altering expression of cytokines by respiratory epithelium. Furthermore, there has been some suggestion that long-acting β-agonists may upregulate the glucocorticoid receptor, leading to enhanced glucocorticoid responsiveness. The evidence supporting these observations is scant, however, and at this time it is believed that the clinical benefits of long-acting β-agonists primarily derive from their sustained bronchodilatory properties.

There are some interesting differences between salmeterol and formoterol. Formoterol, when given by inhalation, has rapid onset of action, whereas salmeterol has delayed onset of action even when given by inhalation. Formoterol, if given orally, has a duration of activity about equal to albuterol. When given by inhalation, it and salmeterol both have bronchodilation, which persists at least 12 h. However, if the subgroup studied are older nonsmoking asthmatics with some degree of fixed obstruction, formoterol activity can only be measured up to 8 h.

At present, formoterol and salmeterol are recommended for use under very specific guidelines. These include no more frequent use than two puffs two times a day, and warnings that they should be initiated cautiously in patients with worsening or deteriorating asthma, should not be used for acute symptoms, and should not be considered a substitute for oral or inhaled corticosteroids. Thus, experts recommend use of salmeterol concomitantly with inhaled anti-inflammatory therapy and availability of a shorter-acting inhaled bronchodilator for acute symptoms.

METHODS OF ADMINISTRATION

Oral

In general, oral dosing of β-adrenergic agonists requires larger administered doses than in other routes. Consequently, increased likelihood of side effects results. Of course, the only drugs useful orally are those that are resistant to COMT. However, variable absorption is also a concern because of conjugation of the drug in the gut wall or the presence of food in the stomach. Decreased bioavailability may result from rapid metabolism on first passage through the liver. In the case of terbutaline, this results in the bioavailability being only 7–26% when given by the oral route.

Sustained-release formulations have been particularly useful in nighttime asthma but compared to sustained-release theophylline may cause more side effects. Overall the oral route of administration may be useful only for persons who are unable to use other routes of administration, such as very young children or elderly patients. However, nebulizer solutions can effectively be used by these patients.

Parenteral

Both terbutaline and albuterol have been used subcutaneously, by continuous iv infusion, and by bolus iv infusion. Such use has been primarily limited to hospitalized severe asthmatics, but continuing therapy has been reported up to several years. It is interesting that the principal side effect has been problems in sleeping and that tolerance did not occur.

Inhalation

Administration by inhalation is highly recommended, because drug effect is usually rapid and the dose required for adequate bronchodilation is usually accompanied by few side effects. It is interesting that when side effects do occur, these side effects usually are of shorter duration than that of bronchodilation. Overall, the major reasons to primarily recommend inhalation rather than the oral or injectable route of this class of drugs is that the effective dose is less and the side effects are less. In fact, many centers have as part of their protocol for dealing with severe hospitalized asthmatics the use of a continually nebulized selective β_2 bronchodilator as treatment prior to consideration of any more aggressive measures. This is particularly important in view of evidence that isoproterenol iv infusions have been shown to create myocardial injury.

There are, however, substantial problems in the use of the inhalation route if patients are not adequately trained in inhalation techniques. It is absolutely essential that all patients be taught how to use their inhaler or nebulizer and are given an opportunity to demonstrate their competence at each follow-up evaluation. The use of spacers can also improve the efficiency of a metered-dose inhaler, but with the increasing concern of fluorocarbon use, it is expected that self-actuated inhalers will be the standard. Devices such as rotohalers, diskhalers, and turbohalers will make the use of spacers unnecessary.

ADVERSE EFFECTS

Tremor is a specific β2 effect upon skeletal muscles and thus is not separable from the bronchodilator action. However, tremor does decrease with continual use of β-adrenergic drugs. Side effects such as increased heart rate and palpitations are decreased with the

more selective β2 drugs. However, since there are β_2 receptors in the myocardium, and since there is reflex sympathetic stimulation of the heart as a consequence of β_2 relaxation of the vasculature that supports skeletal muscles, there is always some degree of increased heart rate and cardiac output if the dosage of the β_2 drug is high enough. With long-term use, hyperglycemia and hypokalemia may result. Hypokalemia does occur from direct stimulation of the sodium-potassium pump in the cell membrane, and so can occur acutely. Further hypokalemia occurs with steroid or diuretic treatment so that a hypoxemic patient could experience arrhythmias.

Since the 1960s, this class of drugs has been implicated as contributory to asthma deaths. In the 1960s asthma mortality was increased in the United Kingdom at the same time that high-dose isoproterenol metered-dose inhaler sales increased. When these devices were made prescription and subsequent sales were decreased, there was a decline in the number of asthma deaths. In the mid-1970s New Zealand noted a sharp increase in asthma deaths at the same time that fenoterol as a metered dose inhaler went into increased use in this population. In the last few years, studies of pharmacy use and morbidity and mortality in Canada implicated fenoterol and albuterol overuse in death and near deaths from asthma. However, other studies and a meta-analysis of case–control studies noted that a relationship between β-agonist use and death from asthma is a weak relationship. More important may be overuse of medication in patients who are not adequately managing their disease. Consequently, comprehensive overall management of the patient's disease has been emphasized as the most effective way of minimizing potential adverse effects from the medications. Thus, the emphasis on treatment being primarily directed toward the prevention and treatment of inflammation is appropriate. Except for use in preventing exercise-induced asthma, any use of this class of bronchodilators beyond three times per 24 h should be considered reason for re-evaluation of the asthmatic's management program.

Salmeterol carries a warning that it might cause deterioration of asthma in a subset of individuals. The SMART study forms the basis of much of the concern. In stratifying effect of these agents, it was noted that there was a statistically increased incidence of death or life-threatening exacerbations for some. Looking at the African American population, in particular, there was risk ratio of more than 2.8, with incidence increasing from 0.3 to 0.8% for fatal and life-threatening asthma exacerbations. Similar concern has been raised about formoterol. An increased incidence of severe, life-threatening exacerbations was noted in studies of subjects taking formoterol at the 24 μg twice-a-day dosage (not currently approved in the United States). However, under the National Heart, Blood and Lung Institute guidelines, the long-acting β-agonist used in combination with an inhaled corticosteroid still remains the preferred combination therapy for moderate to severe persistent asthma and is highly effective for the majority of asthmatics not controlled on inhaled steroids alone. The fact that a subset of asthmatics seem to have reduced control with the addition of a long-acting β-agonist is a reminder that patients must be cautiously monitored whenever a new agent is added. Furthermore, it is one more suggestion that varying asthma phenotypes have differing responses to interventions.

US OLYMPIC COMMITTEE DRUG RULES

At present, this class of drugs falls under stimulants, so that the US Olympic Committee has banned certain forms of β_2-agonists. Thus, the only β_2-agonists that are permitted are albuterol, terbutaline, and Salmeterol. These are permitted by inhalation only, and

only with written notification from the prescribing physician sent prior to competition indicating its appropriateness of use because of exercise-induced asthma or for asthma. All adrenergic medications by any oral or injectable route are banned, and β_2 agents other than albuterol, terbutaline, and Salmeterol are banned even if given by inhalation. The basic reason for this is that some of the β_2 agents possess anabolic properties, particularly if they are taken orally or by injection. The allowable list of medications is constantly being reviewed by the Committee and constantly revised and changed, so that this information should be checked as to currency on a regular basis (US Olympic Committee Drug hotline phone number: 1-800-233-0393).

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19 Theophylline

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CONTENTS

SUMMARY

Theophylline use in asthma has declined markedly over the last decade with the increase in use of inhaled long-acting bronchodilators. However, it is still a useful drug in some asthmatics. In addition, it is probably the harbinger of improved phosphodiesterase inhibitors, which may become available in the near future. The most prominent limitation in its use is its narrow therapeutic window and the potential of side effects when at higher doses. This characteristic, coupled with the fact that its metabolism is affected by other drugs as well as upper respiratory tract infections, requires that patients be monitored during theophylline therapy. In addition to its bronchodilatory effect, it probably has immunomodulatory effects as well. It has a number of actions unrelated to its phosphodiesterase inhibition, including the antagonism of adenosine receptors.

Key Words: Phosphodiesterase inhibitor; adenosine receptor; calcium influx; antiinflammatory; bronchodilatation; cyclic AMP; diaphragmatic contractility; late asthmatic reaction.

INTRODUCTION

Theophylline was introduced into clinical medicine 65 yr ago for the treatment of asthma. The drug was widely used for 20 yr as a bronchodilator after its introduction; however, following reports of adverse reactions, including death, there was a pronounced decline of theophylline prescribing, particularly for children. In the mid-1960s and the early 1970s, when the pharmacokinetics of the drug began to be elucidated, an increase in the use of theophylline occurred, and it became the most commonly prescribed drug for the treatment of asthma. During the past 15 yr, because of the introduction and widespread use of new potent anti-inflammatory inhaled steroids, doubts about

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theophylline's bronchodilatory activity in acute asthma, and renewed concern about theophylline toxicity (well characterized in the 1950s and 1960s), prescription of theophylline in the United States has substantially decreased. However, even today theophylline is the most widely prescribed drug in the underdeveloped world because of its low cost. During the past 20 yr, evidence first based on in vitro experiences and subsequently on clinical studies has strongly suggested an immunomodulatory role for theophylline even at low (5–10 μg/mL) serum concentrations. Thus, although a relevantly modest bronchodilator, the immunomodulatory or any inflammatory action of theophylline is resulting in re-evaluation of its use in clinical asthma.

Theophylline is a methylated xanthine, closely related to naturally occurring caffeine and theobromine. A theophylline derivative, dihydroxypropyl theophyline (dyphylline), promoted as being safer than theophylline, is no longer marketed in the United States.

Evidence for Anti-Inflammatory/Immunomodulatory and Other Effects In Vitro

- Inhibits phosphodiesterase (PDE) IV receptor
- Reduces histamine release from human mast cells and basophils
- Inhibits T-cell proliferation after antigenic and mitogenic stimulation
- Increases interleukin (IL)-10 release
- Increase in circulating catecholamines
- Inhibition of calcium influx into inflammatory cells
- Antagonizes adenosine A_1- and A_2-receptors
- Inhibits apoptosis of eosinophils and neutophils
- Inhibits production and release of IL-2
- Inhibits generation of eosinophil chemoattractants, e.g., LTB4 and platelet-activating factor, from human monocytes, release of eosinophil basic proteins, tumor necrosis factor (TNF)-2α, and prostaglandins.

MECHANISM OF ACTION

Sixty-five years after the introduction of theophylline into clinical medicine, its mechanism of action is still unclear. Several theories have received the most attention, and it is possible that combinations of mechanisms may be involved.

PDE Inhibition

Theophylline has long been known to be an inhibitor of the PDE enzymes responsible for breakdown of cyclic 3,5-adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP), the intracellular concentrations of which regulate smooth muscle relaxation/contraction. It is now known that the cyclic nucleotide PDEs are a family of at least seven isoenzymes (PDE I–VII). In the context of asthma, selective types III and IV and mixed III and IV PDE inhibitors relax smooth muscle in vitro. Theophylline causes smooth muscle relaxation by nonselective PDE inhibition principally by effect on PDE III. PDE IV is important in the activity of inflammatory cells, including mast cells, eosinophils, and T-lymphocyctes. For example, infiltration and activation of inflammatory cells are attenuated by PDE IV inhibitors. The latter also inhibit cytokine activation of proinflammatory cells and attenuate cytokine release from these cells. The

anti-inflammatory/immunomodulatory effects of PDE IV inhibitors on inflammatory cells that are known to be important in asthma suggest that PDE IV inhibitors might have some role in asthma therapeutics. Several of the PDE IV inhibitors that have been investigated cause dose-limiting nausea and vomiting and have not been shown to have much clinical utility. Very recently Roflumilast, an oral, once daily phosphodiesterase inhibitor, has been reported to show dose-dependent improvement of lung function in patients with asthma. In another study Roflumilast was shown to be well tolerated during a 40-wk safety study in patients with asthma. A third recent abstract reported that a single dose of oral Roflumilast of 100 mg attenuated allergen-test-induced airway hyperresponsiveness. Theophylline has been shown to have a number of important actions on eosinophil and lymphocyte function and as a modulator of cytokine production. Although these inhibiting effects are seen principally at high concentrations of theophylline above the therapeutic range, some of these effects are observed at lower concentrations (5–10 μg/mL) than are thought to be necessary for optimal bronchodilator activity.

Adenosine Receptor Antagonism

Adenosine, a purine nucleoside that occurs naturally, causes contraction of smooth muscle from asthmatics in vitro and bronchoconstriction of asthmatics by inhalation by an indirect mechanism (release of histamine and leukotrienes from airway mast cells). Theophylline is a potent competitive antagonist of the three known types of adenosine receptors, A_1, A_2 and, to a lesser extent, A_3. However, theophylline-induced bronchodilation does not appear to be related to adenosine antagonism, because enprofylline (3-propyl xanthine), which has little inhibitory effect on adenosine receptors, is a potent bronchodilator. The absence of central nervous system (CNS) stimulatory effect with enprofylline suggests that adenosine receptor antagonism is responsible for this (and possibly) other adverse effects of theophylline. Increase of calcium influx into inflammatory cells and antagonism of TNF-α may only be seen at high concentrations of theophylline above the therapeutic range and, therefore, may not be clinically relevant.

Evidence for Anti-Inflammatory/Immunomodulatory Effects of Theophylline In Vivo

- Reduces allergen-induced eosinophil tissue infiltration
- Inhibits airway hyperresponsiveness
- Inhibits the late asthmatic reaction
- Reduces nasal plasma exudates secretion
- Exhibits important diaphragmatic contractility

Theophylline, particularly when given intravenously, causes catecholamine (principally epinephrine) release. Whether this effect is of sufficient magnitude to be clinically significant is doubtful. There are also reports that theophylline increases diaphragmatic and other respiratory muscle contractility and delays onset of fatigue. Because this effect is inhibited by calcium channel blockers and does not occur in the absence of extracellular calcium, it has been suggested that theophylline alters transmembrane calcium flux. This effect is controversial.

PHARMACOKINETICS

Absorption

Rapid-Release Formulations

Theophylline is rapidly absorbed from orally administered liquid and uncoated tablets and from rectally administered (as an aminophylline) solutions. The absorption profile of rectally administered theophylline looks very much like that seen after intravenous (i.v.) administration. Theophylline suppositories (erratically absorbed) are no longer manufactured in the United States. The speed, but not the extent, of absorption is affected to a clinically insignificant degree by concurrent ingestion of food or antacid. For intravenous use, aminophylline continues to be the preferred product. The dose administered needs to be corrected for the fact that aminophylline is 80–85% theophylline.

Slow-Release Formulations

Slow-release theophylline formulations are indicated for patients in whom elimination half-lives are less than 6 h and for enhancing compliance because less frequent dosing is required. Various products differ in terms of rate and extent of absorption. The ideal product releases the drug at a constant rate over the dosing interval. Slow-release formulations vary in rate of the drug released (from slow to slower to ultraslow). With the ultraslow products, the rate of the drug released is typically so slow that the drug may be out of the gut before it is completely absorbed. There is diurnal variation in theophylline absorption, with slower absorption during the night, resulting in higher morning trough concentrations. It has been proposed that host factors, in addition to the drug itself, are responsible for some of the erratic absorption patterns. To minimize fluctuation in serum concentration over a dosing interval, the patient's theophylline elimination characteristics (slow or fast) should ideally be matched to the product's release characteristics (slow, slower, or ultraslow). Most children over the age of 6–8 yr can be treated successfully with 12-h dosing intervals with available slow-release preparations (e.g., Uniphyl, Theo-24, or TheoLair and many generics). Patients with exceptionally rapid theophylline clearance require 8-h dosing intervals to prevent serum concentration fluctuation of more than 100%. On the other hand, individuals (e.g., the elderly) who eliminate theophylline very slowly will maintain therapeutic levels of theophylline with once-a-day dosing of most extended-release products. Food taken concurrently with theophylline has an important effect on the rate of the drug release with some products and minimal or no effect with others. Once-a-day products are more vulnerable to variations in intestinal pH and mobility. The best example of the food effect on slow-release theophylline absorption has been reported with Theo-24. When given with a high-fat-content meal (50% carbohydrate, 20% protein, and 30% fat), about half of the dose of Theo-24 is absorbed in a 4-h period (usually beginning 6–8 h after ingestion), and peak concentrations average two to three times higher than those observed when this drug was given during fasting. This phenomenon of "dose dumping" (defined as more than 50% of the total dose being absorbed in >2 h) is a particular hazard with once-a-day products, in which the total dose is given at one time. Antacids may affect the rate of drug absorption from products with pH-dependent dissolution.

Theophylline Pharmacokinetics

- There is a linear relationship between the log of serum theophylline concentrations and improvements in forced expiratory volume in 1 S (FEV_1) between theophylline concentrations of 5 and 20 μg/mL.
- Anti-inflammatory/immunomodulatory effects occur at serum concentrations in the 5–10 μg/mL range.
- The therapeutic window is relatively small, and toxic symptoms occur when this therapeutic window is exceeded; therefore, monitoring is often necessary.
- Multiple factors affect theophylline metabolism and, consequently, serum theophylline levels. These include age, smoking habits, and other drugs and disease states.
- Each theophylline preparation has its own absorption characteristics, and the physician must be familiar with the preparation utilized, generics, and the three remaining branded products.

Distribution

The pharmacokinetics of theophylline can be characterized by the use of a linear, two-compartment open model, because the multicompartment characteristics of theophylline are not very pronounced. After intravenous administration, theophylline distributes rapidly from the plasma to its site of action in the tissues; this distributive phase is virtually complete within 30 min. The volume of distribution averages about 0.45 L/kg in children and adults (within reasonable parameters of ideal body weight). Protein binding at physiological pH (approx 40%) is not of sufficient magnitude to result in toxicity because of competitive drug interaction. Theophylline passes through the placenta and into breast milk and crosses the blood–brain barrier. Concentrations in the central nervous system (CNS) in children are about 50% of the serum concentration (90% in premature infants). Salivary concentrations are approx 60% of serum levels.

Metabolism/Elimination

Theophylline is eliminated from the body principally by biotransformation in the liver to inactive (with the exception of 3-methylxanthine) metabolites. The enzymes responsible for the metabolism of theophylline (and many other drugs) belong to the cytochrome P450 family of oxidases located in the smooth endoplasmic reticulum of the liver. The isoenzymes involved are designated CYP3A3, CYP2E1 (cause hydroxylation to 1,3-dimethyluric acid), and CYP1A2 (causes *N*-dimethylation to L-methylxanthine and 3-methylxanthine). Initial pharmacokinetic studies of theophylline elimination reported that elimination occurred by a first-order process (i.e., the rate of elimination was proportional to the drug concentration remaining—a log linear decay). However, it is now known that, particularly at high serum concentrations, dose-dependent nonlinear elimination comes into play. This means that there is a disproportionate increase in serum

theophylline concentration for a given percent increase in dose. How many patients being treated with theophylline manifest this dose-dependent kinetics is not known, but in children a 15% incidence has been proposed. Theophylline metabolism is age dependent. In infants, drug biotransformation is slow as a result of immaturity of hepatic microsomal enzymes and slowly increases during the first year of life. By 8–12 mo of age, clearance rates approach those seen in early childhood. From 1 to 9 yr of age, the rate of theophylline metabolism accelerates. There is a gradual decline in the rate of theophylline biotransformation during the adolescent and early adult years. At about 16 yr of age, the metabolic rate approximates that seen in young adults. After 1 yr of age, approx 10% of the drug is excreted unchanged in the urine. In premature infants and normal newborns during the first month of life, 45–50% of an administered dose of theophylline is cleared by the kidney unaltered. At all ages, a small amount (approx 6%) of theophylline is *N*-methylated to caffeine. This minor conversion becomes clinically relevant only in premature infants, in whom caffeine has an extremely long half-life (mean 96 h), which results in its accumulation and pharmacological effect.

Because liver microsomal enzyme activity is not only dependent on age but also subject to the inducing and inhibiting action of a large variety of unrelated environmental conditions and disease factors, it is not surprising that there is intra-individual variation over time in the rate of metabolism of theophylline and resultant serum concentration. Individual variations in theophylline metabolism, however, are small, unless there are changes in disease factors (e.g., fluctuating cardiac function) or changes in concurrent drug therapy. Cigarette smoking causes a dose-related increase in theophylline clearance. Heavy smokers metabolize theophylline twice as fast as nonsmokers. A similar effect is seen with marijuana but to a lesser extent. Ingestion of a high-protein, low-carbohydrate diet accelerates theophylline metabolism, presumably by increasing liver enzyme activity. Dietary intake of methylxanthines, caffeine in particular, affects theophylline metabolism by acting as a competitive substrate for theophylline-metabolizing enzymes. The ingestion of charcoal-broiled meat, presumably because of a stimulating effect on liver enzyme function of polycyclic hydrocarbons produced during the charcoaling process, has been reported to increase metabolism of theophylline. Although of theoretical interest, dietary factors are seldom a clinically significant problem.

Although the data are conflicting, the effect of obesity on theophylline clearance appears to be negligible. Because theophylline distributes poorly into fat, dosage should be based on ideal body weight rather than actual weight.

Theophylline metabolism is affected by various disease states, including hepatic disease, cardiac disease, and viral illnesses. Hepatic dysfunction is a major cause of altered theophylline biotransformation. Patients with decompensated cirrhosis, acute hepatitis, and possibly cholestasis have reduced theophylline clearance. A correlation between slow hepatic metabolism and serum albumin and bilirubin concentration has been made in patients with cirrhosis. Cardiac disease, presumably causing decreased liver microsomal enzyme function by passive congestion of the liver secondary to congestive heart failure (CHF), may have a profound effect on theophylline metabolism. When CHF is treated, theophylline clearance increases. Acute viral illnesses, especially influenza, associated with fever have been reported to prolong theophylline half-life. Symptoms of nausea, vomiting, and headache are commonly observed in children during many viral infections; however, when these symptoms develop in a child receiving theophylline, the physician must consider the possibility of theophylline intoxication. If fever is high and

Table 1
Factors Other Than Drugs That Influence Theophylline Clearance

Factors	*Decreased clearance*	*Increased clearance*
Age	Premature infants; neonates and up to 6 mo; adults over 60 yr	Ages 1–16 yr
Diet	Dietary methylxanthines	—
Habits	—	Cigaret smoking (tobacco or marijuana)
Disease	Liver disease, hypothyroidism, congestive heart failure, acute pulmonary edema, chronic obstructive pulmonary disease, sustained fever usually with viral illness	Cystic fibrosis, hyperthyroidism, diabetes mellitus (poorly controlled)

sustained (e.g., temperature higher than 102°F for more than 24 h), the dosage should be reduced in a patient whose theophylline serum concentration was previously maintained within the therapeutic range (Table 1).

Drug interactions are another factor in altering theophylline elimination. All of the drugs listed in Table 2 caused a change (increase or decrease) of 20% or more (some more than 100%) in theophylline serum concentration. Drugs most likely to be encountered by allergists include cimetidine, macrolide antibiotics (particularly the estolate salt of erythromycin), troleandomycin and clarithromycin, estrogen-containing oral contraceptives, phenytoin, rifampin, and certain quinolone antibiotics (ciprofloxacin, enoxacin, and perfloxacin). Influenza vaccine immunization was originally reported to slow theophylline elimination with a consequent increase in serum levels and the potential for toxicity. More recently, studies have shown no significant effect, and hence, there is no reason to reduce theophylline dose coincident with influenza immunization.

THERAPEUTIC DRUG MONITORING

The rationale for therapeutic monitoring of theophylline serum concentration is that it is a major determinant of both efficacy and toxicity. Theophylline has a narrow therapeutic index, which makes it imperative for the physician to understand that serum concentration may be affected by many factors that affect liver microsomal enzyme function and alter elimination kinetics.

During the treatment of an acute exacerbation of asthma, a serum theophylline level should be determined before administration of an intravenous loading dose of aminophylline if the patient has been receiving theophylline. In this circumstance, the initial bolus may need to be reduced by 25–50%, depending on the result. For a patient who is admitted to the hospital and receives a constant infusion of theophylline after the bolus, it is important to obtain a 1-h level and adjust the serum concentration to the therapeutic range. Thereafter, serum theophylline levels should be monitored every 12–24 h.

The indications for monitoring theophylline serum concentrations in the management of chronic asthma are subject to some controversy. Some authors believe that all patients with chronic asthma should be monitored at regular intervals during the initial phase of theophylline adjustment. These intervals vary, and it is assumed that theophylline clear-

Table 2
Clinically Important Drug Interactions with Theophylline

Decreases theophylline metabolism resulting in increase in serum concentration	*Increases theophylline metabolism resulting in decrease in serum concentration*
Alcohol	Aminoglutethimide
Allopurinol	Carbamazepine
Cimetidine	Moricizine
Ciprofl oxacin	Phenobarbital (PB)
Disulfi ram	Phenytoin
Mexiletine	Rifampin
Propafenone	Sulfi npyrazone
Pentoxifylline	
Propanolol	
Enoxacin	
Erythromycin	
Estrogen-containing oral contraceptives	
Fluvoxamine	
Methotrexate	
Interferon, human recombinant alpha-2a	
Tacrine	
Ticlopidine	
Thiabendazole	
Troleandomycin	
Verapamil	
Zileuton	

ance is stable. Other clinicians reserve monitoring for patients who do not obtain optimal symptom control after an appropriate dose is given and for patients in whom adverse effects develop. In the event of symptoms associated with theophylline toxicity, immediate determination of serum theophylline concentration is mandatory. To interpret serum theophylline concentration properly in clinical situations, a significant amount of information must be provided with a sample, such as characteristics of the patient (age, weight), formulation of the drug (rapid or slow release), dosage, duration of therapy (to ensure steady state for maintenance-dose adjustment), dosing interval, exact timing of previous adjustment, exact timing of blood collection, concurrent drug therapy, and presence of fever or other disease states, such as congestive heart failure or liver dysfunction. With a rapid-release theophylline product (liquid or tablet), a sample obtained 2 h after the dose approximates the peak concentration. The determination of the trough concentration (the sample obtained immediately before the next dose) does not provide much additional information except to show the magnitude of the peak–trough difference. Because of a circadian effect on theophylline absorption, specimens should be drawn during the same dosing interval when more than one measurement is being compared. Various slow-release products differ in their release characteristics. Slow-release products that have pH-dependent dissolution characteristics release drugs at variable rates, depending on whether they are given during fasting or with a meal. Intersubject and intrasubject variability in absorption of slow-release products may be the reason for a

theophylline serum level to be inconsistent or lower than the expected level for a particular dose. An important reason for inconsistent levels of theophylline is poor patient compliance.

PHARMACODYNAMICS

It is well recognized that there is a linear relationship between the logarithm of serum theophylline concentration and improvement in FEV_1. This relationship was first noted in children by Maselli and colleagues, who showed a strong correlation between the intensity of bronchodilator effect (improvement in FEV1) and the logarithm of the amount of drug in the tissue compartment. It was evident from this study that the effect on pulmonary function was not seen until 30 min after the bolus injection of iv aminophylline; this lag represented the time for the drug to be distributed from the plasma to the site of action in the tissues. Because the bronchodilator effect increases and then falls rapidly after a bolus, it is logical to give iv aminophylline by constant infusion rather than by repeated bolus injection after the initial bolus dose. Mitenko and Ogilvie also studied the log serum concentration–bronchodilator relationship in a group of hospitalized adult asthmatic patients and showed a proportionality between the log of the serum concentration and the bronchodilator effect over the 5-20 (g/mL range. Subjects with severe asthma (status asthmaticus) have a rather flat serum concentration–bronchodilator effect curve over the range of 5–20 μg/mL. In patients with mild asthma who may have an FEV_1 of 50–60% of the predicted level, the serum concentration–response curve is steep.

THEOPHYLLINE TOXICITY

Like its bronchodilator activity, adverse effects are related to the logarithm of the serum concentration. Hendeles and associates demonstrated a relationship between serum concentration and symptoms of theophylline toxicity. Few toxic symptoms were noted when the steady-state serum concentration was less than 14.6 μg/mL. Adverse effects appeared as the serum concentration rose beyond 20 μg/mL. These included gastrointestinal, CNS, and cardiovascular effects (Fig. 1). Of all adverse effects, those involving the gastrointestinal tract are most common. Vomiting, particularly if persistent, is very suggestive of theophylline toxicity. Hematemesis has been reported primarily in children; its exact pathogenesis is not clear. Gastrointestinal symptoms occur most often as a result of a central effect of an excessive serum theophylline concentration on the medulla rather than because of a local irritative effect on the stomach. Relaxation of cardioesophageal smooth muscle may lead to reflux and worsening of asthma by reflex stimulation of neural receptors in the distal esophagus or by aspiration of stomach contents into the upper airway and lung.

Theophylline stimulates the nervous system at various levels: the medulla (increased respiratory rate and sensitivity to carbon dioxide, nausea and vomiting), vagal effect (causing bradycardia), the cerebral cortex (restlessness, agitation, tremor, irritability, headache, seizures, difficulty in concentration), the hypothalamus (hyperthermia), and even the spinal cord (hyperreflexia). The mechanism of theophylline's effect on the nervous system is not known, although adensine receptor antagonism is suspected. Although seizures are a prominent manifestation of theophylline toxicity and are often difficult to control, they by themselves do not necessarily lead to death or to irreversible brain damage. Serum concentration associated with seizure activity varies substantially.

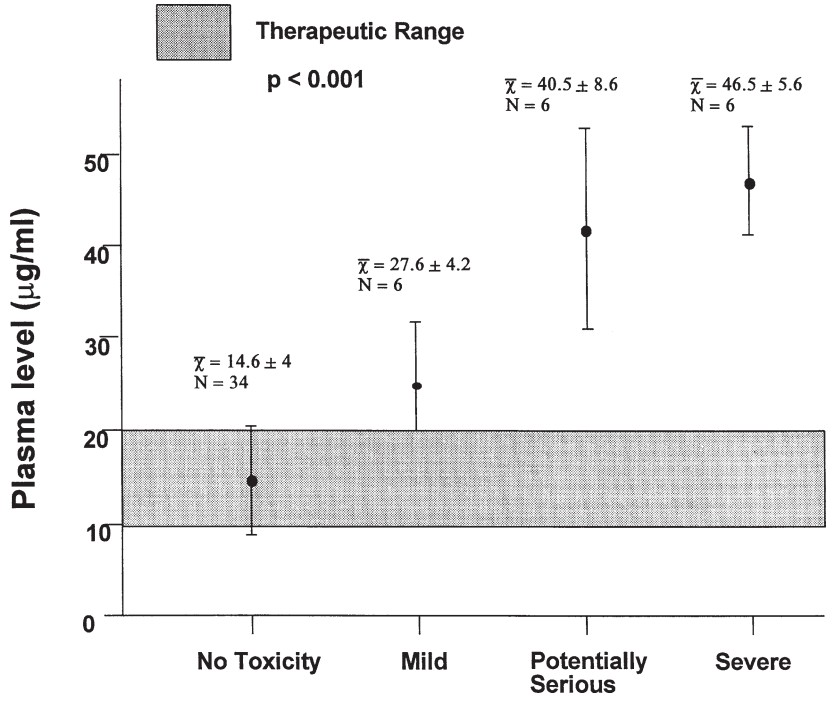

Fig. 1. Frequent toxicity from iv aminophylline infusions in critically ill patients. Modified from Hendeles L, Bighley L, Richardson RH, et al. Ann of Pharmacotherapy 1977;11:12–18.

The combination of seizures and cardiorespiratory arrest leads to the most disastrous consequences of theophylline intoxication. Individuals who are resuscitated and survive show signs of severe anoxic brain injury, much like those who have been resuscitated after drowning or strangulation. A meta-analysis of 12 studies with theophylline and 9 with caffeine showed no effect of either drug on behavior or cognition in children and adolescents. Concern about the effects of theophylline on behavior, particularly learning, was raised in a study by Rachelefsky and coworkers; however, there were many commentaries and critiques of this study. Furukawa and associates, in two studies of theophylline in asthmatic children, also interpreted their results to suggest that theophylline may impair learning and behavior. It is of interest that one important abnormal finding in their initial report was not substantiated in their second study. Creer and McLoughlin, after a critical review of the subject, commented that there is no definitive evidence that theophylline produces any type of learning disability. A similar conclusion was reached by the US Food and Drug Administration Pulmonary/Allergy Drug Advisory Committee in 1987 after a review of studies published until that time.

Theophylline has both inotropic and chronotropic effects on the heart. Although a number of opposing factors (direct effect on pacemaker tissue, effect on catecholamine release, peripheral vagolytic action, stimulation of the medullary center) confound the effects of theophylline on heart rate, the net result is usually tachycardia. In the therapeutic range, the effect of theophylline on the heart rate is modest, in the range of 3–16 beats per minute. On the other hand, tachycardia is an almost constant finding in cases of significant theophylline intoxication. The arrhythmogenic potential of theophylline has

been shown in experimental animals, but data in humans are less clear. Metabolic effects, principally hypokalemia and hyperglycemia, are commonly observed in cases of severe theophylline toxicity.

The appropriate treatment of theophylline toxicity is based on history, clinical signs and symptoms, and theophylline serum concentration determinations. For patients with acute overdose and serum concentrations in the 20–30 μg/mL range, administration of oral-activated charcoal 1 g/kg body weight for adults and monitoring of serum theophylline concentration for 2–4 h after the dose are often all that is needed. In acute overdose situations with serum concentrations between 30 and 100 μg/mL, administration of multiple doses of oral activated charcoal, as indicated above, given every 2 h with serum theophylline concentration monitoring is appropriate. Because patients with theophylline toxicity are almost invariably vomiting, administration of the charcoal must often be via a nasogastric tube. If the oral activated charcoal therapy is ineffective and serum theophylline continues to increase, serious consideration should be given to institution of charcoal hemoperfusion if the facilities are available. In an acute overdose situation with serum concentrations of more than 100 μg/mL, prophylactic anticonvulsive therapy should be considered in addition to multiple-dose administration of activated charcoal 10–20 mg (up to 1 g) divided into two to four doses given at 30- to 60-min intervals. If signs and symptoms of CNS irritation are such that a seizure is anticipated, anticonvulsive therapy should be initiated with an intravenous dose of a benzodiazepine (e.g., diazepam in a dose of 0.1–0.2 mg/kg every 1–3 min until seizure is terminated). If seizure control is not obtained, then a loading dose of phenobarbital 20 mg/kg should be infused over 30–60 min. Of course, monitoring of vital signs and electrocardiogram should be instituted in all cases of significant theophylline toxicity. Recommendations for treatment of theophylline toxicity occurring in patients as a result of chronic overdosage are similar to those for acute overdosage with the following caveat: young patients tolerate acute overdosage much better than older patients, who most often are suffering from chronic overdosage. Serious adverse events are more likely to occur at lower serum concentrations in the chronic overdose situation, and therefore, more aggressive measures are indicated in this setting. In patients older than 60 yr, seizures may occur at levels lower than 30 μg/mL, and therefore, prophylactic anticonvulsive therapy should be instituted earlier than in the young individual suffering from acute theophylline overdosage. Communication with a poison control center should be sought in cases of serious theophylline concentration.

Theophylline Toxicity

- Symptoms of theophylline toxicity generally do not appear until serum concentration exceeds 20 μg/mL.
- Gastrointestinal symptoms (nausea, vomiting) are the most common manifestation of theophylline toxicity.
- Tachycardia almost invariably occurs in instances of significant theophylline toxicity.
- Seizures, often difficult to control, may lead to brain damage if associated with cardiorespiratory arrest.

CLINICAL USE OF THEOPHYLLINE IN ASTHMA

Although intravenous aminophylline has been standard treatment for status asthmaticus since the early 1940s, the value of aminophylline in the emergency room setting for acute asthma has been questioned recently. Various authors have suggested that theophylline adds little in terms of bronchodilator activity while increasing adverse effects when optimal therapy with aerosolized β-agonists have been given. In an early study of the use of intranenous theophylline in the treatment of acute asthma, theophylline was compared with subcutaneous epinephrine in an emergency department. The bronchodilator effect of theophylline was inferior to that achieved by the epinephrine. Subsequent studies have generally confirmed the observation that in acute asthma, the bronchodilator effect of aminophylline is less than that of optimal administration of aerosolized β_2-agonists. However, published data support the addition of intravenous aminophylline in the treatment of patients who fail optimal aerosolized agonist and steroid therapy and who require hospital admission. For example, Pierson and associates showed clinical benefit and pulmonary function improvement in status asthmaticus in a double-blind study of intravenous aminophylline in children with status asthmaticus. An emergency department study of adults with acute airway obstructive disease showed a threefold decrease in hospital admission rates for subjects treated with aminophylline in comparison with placebo recipients. Sakamoto and colleagues reported on results of a study of intravenous aminophylline administration in 12 asthmatic patients with acute episodes varying from mild to moderate to severe. They found progressive improvement in FEV_1 over the range of 5–15 μg/mL; the greatest bronchodilator effect was observed in patients whose initial airway obstruction was of a lesser degree. The possible extrapulmonary effects of theophylline both in improving diaphragmatic function and delaying the onset of muscle fatigue are a useful additional benefit of theophylline administration. For intravenous therapy with aminophylline, some simple calculations can be used to determine the correct loading and maintenance therapy doses. In the case of drugs, like theophylline, that are distributed rapidly from the plasma to the tissues, there is a relationship among plasma concentration (C_p), dose (D) and volume of distribution (V_d) so that

$$C_p = D/V_d \quad (1)$$

If an average V_d of 0.5 L/kg is assumed, it is easy to determine that for each miligram per kilogram (ideal body weight) infused, there will be an increase of approx 2 μg/mL in peak plasma concentration. The loading dose (aminophylline) needed to achieve a given theophylline plasma concentration is determined as follows (in the following equations 0.8 is used in the denominator to correct for the fact that aminophylline is 80% theophylline):

$$\text{Loading dose } (D) = (V_d)\ [\text{desired plasma concentration } (C_p)]/0.8 \quad (2)$$

In this equation, it is assumed that the patient has not previously been receiving theophylline. If theophylline has been taken on an outpatient basis, the loading dose should be reduced unless an immediate serum theophylline determination is available. Once the observed level of theophylline is known, it can be subtracted from the desired level and multiplied by the volume of distribution:

$$D = V_d\ (C_p \text{ desired} - C_p \text{ initial})/0.8 \quad (3)$$

The dose of aminophylline required to maintain a desired steady state of serum theophylline concentration (C_{pss}) may be calculated as follows:

$$\text{Constant infusion rate} = (Cl)\ (C_{pss})/0.8 \quad (4)$$

where Cl is the clearance in L/h/kg and C_{pss} is the average plasma concentration at steady state. A theophylline level determined from a serum sample obtained 1 h after the loading dose is useful in determining the need for an additional bolus loading dose. Therefore, Eq. 1 can be used to calculate the subsequent loading dose if needed. A subsequent determination 4 h after the initiation of a constant infusion shows the trend of the serum concentration; the rate can be either increased or decreased as needed. Additional samples after 12 and 24 h guide further intravenous dosing.

To convert the intravenous dose to an equivalent oral dose, the hourly dose is multiplied by the dosing interval to be used for oral therapy. It is important to correct the aminophylline dose to obtain the theophylline equivalent by multiplying the aminophylline dose by 0.8. In this calculation, it is assumed that the oral product is completely absorbed.

The use of theophylline in chronic asthma is being redefined. Over the 4-yr period from 1989 to 1993, prescriptions for theophylline written by pediatricians decreased from 27 to 7% of all asthma medicines. According to the most recent Expert Panel Report of the National Heart, Lung and Blood Institution's (NHLBI) National Asthma Education of Prevention Program, theophylline has been relegated to a second-line position for patients who fail to respond to optimal β_2-agonist and inhaled steroid treatment. However, abundant data accumulated over the past 20 yr indicate that theophylline is as effective as cromolyn in young children and provides additional control of symptoms even in patients taking inhaled steroids. In several well-designed studies of patients with severe asthma, withdrawal of theophylline resulted in significant deterioration in their clinical condition. In addition, many physicians have noted deterioration of asthma in patients previously well controlled with theophylline therapy in whom the drug was withdrawn as a requirement for a drug study, especially those subjects with moderate to severe asthma. Extended-release theophylline is more effective than extended-release oral β_2-agonists in nocturnal asthma, although β_2-agonists cause less disturbance of sleep architecture. A recent study of twice-daily salmeterol and extended-release theophylline in nocturnal asthma demonstrated no major clinical advantage of one drug over the other. However, there was a small benefit in sleep quality, quality of life, and daytime cognitive functioning with salmeterol.

When theophylline is used for the management of chronic asthma, it is most effectively administered as one of the sustained-release formulations. Use of sustained-release products minimizes the peak-and-trough fluctuation of serum concentration. Depending on an individual's serum theophylline clearance, an 8- or 12-h or even 24-h dosing interval is appropriate. In general, the younger the child (under 9 yr of age), the more likely it is that an 8-h dosing interval will be required to minimize peak-and-trough fluctuations in theophylline concentration. Determination of theophylline serum concentration during the initial weeks of treatment is useful in adjusting the dose and dosing interval. Sustained-release theophylline products that are completely absorbed and whose bioavailability is insignificantly affected by concomitant food administration are preferred. Once-a-day dosing is inappropriate in most children, who, because of their relatively rapid theophylline clearance, show unacceptable peak-and-trough differences in theophylline concen-

Table 3
Dosing Titration (as Anhydrous Theophylline)[a,b,c]

Infants < 1 yr old
Initial dosage
Premature neonates
<24 do postnatal age; 1.0 mg/kg every 12 h
≥24 d postnatal age; 1.5 mg/kg every 12 h
Full-term infants and infants up to 52 wk of age
Total daily dose (mg) = [(0.2 × age in wk) + 5.0] × (kg body wt)
Up to age 26 wk; divide dose into three equal amounts administered at 8-h intervals
>26 wk of age; divide dose into four equal amounts administered at 6-h intervals

Final dosage

Adjusted to maintain a peak steady-state serum theophylline concentration of 5–10 μg/mL in neonates and 10–15 μg/mL in older infants. Since the time required to reach steady state is a function of theophylline half-life, up to 5 d may be required to achieve steady state in a premature neonate, whereas only 2–3 d may be required in a 6-mo-old infant without other risk factors for impaired clearance in the absence of a loading dose. If a serum theophylline concentration is obtained before steady state is achieved, the maintenance dose should not be increased, even if the serum theophylline concentration is < 10 μg/mL

Children (1–15 yr) and adults (16–60 yr) without risk factors for impaired clearance

Titration step	*Children < 45 kg*	*Children > 45 kg and adults*
Starting dosage:	10 mg/kg/d up to a maximum 300 mg/d divided every 8 h	300 mg/d divided every 8 h
After 3 d, if tolerated, increase dose to:	13 mg/kg/d up to a maximum 400 mg/d divided every 8 h	400 mg/d divided every 8 h
After 3 more days, if tolerated, increase dose to:	16 mg/kg/d up to a maximum 600 mg/d divided every 8 h	600 mg/d divided every 8 h

Patients with risk factors for impaired clearance, the elderly (>60 yr), and those in whom it is not feasible to monitor serum theophylline concentrations:

In children 1–15 yr of age, the initial theophylline dose should not exceed 16 mg/kg/d up to a maximum of 400 mg/d in the presence of risk factors for reduced theophylline clearance or if it is not feasible to monitor serum theophylline concentrations. In adolescents ≥16 yr and adults, including the elderly, the initial theophylline dose should not exceed 400 mg/d in the presence of risk factors for reduced theophylline clearance or if it is not feasible to monitor serum theophylline concentrations.

Loading dose for acute bronchodilatation:

An inhaled β_2-selective agonist, alone or in combination with a systemically administered corticosteroid, is the most effective treatment for acute exacerbations of reversible airways obstruction. Theophylline is a relatively weak bronchodilator, is less effective than an inhaled β_2-selective agonist and provides no added benefit in the treatment of acute bronchospasm. If an inhaled or parenteral β-agonist is not available, a loading dose of an oral immediate release theophylline can be used as a temporary measure. A single 5 mg/kg dose of theophylline in a patient who has not received theophylline in the previous 24 h will produce an average peak serum

Table 3 *(continued)*
Dosing Titration (as Anhydrous Theophylline)[a,b,c]

theophylline concentration of 10 µg/mL (range 5–15 µg/mL). If dosing with theophylline is to be continued beyond the loading dose, the above guidelines should be utilized and serum theophylline concentration monitored at 24-h intervals to adjust final dosage.

Final dosage adjustment guided by serum theophylline concentration

Peak serum concentration	*Dosage adjustment*
<9.9 µg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 d for further dosage adjustment
10–14.9 µg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6–12 mo intervals.[d] If symptoms are not controlled and current dosage is tolerated, consider adding additional medication(s) to treatment regimen
15–19.9 µg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated.[d]
20–24.9 µg/mL	Decrease dose by 25% even if no adverse effects are present. Recheck serum concentration after 3 d to guide further dosage adjustment
25–30 µg/mL	Skip next dose and decrease subsequent doses at least 25% even if no adverse effects are present. Recheck serum concentration after 3 d to guide further dosage adjustment. If symptomatic, consider whether overdose treatment is indicated (see recommendations for chronic overdosage)
>30 µg/mL	Treat overdose as indicated (see recommendations for chronic overdosage). If theophylline is subsequently resumed, decrease dose by at least 50% and recheck serum concentration after 3 d to guide further dosage adjustment

[a]Patients with more rapid metabolism, clinically identifi ed by higher than average dose requirements, should receive a smaller dose more frequently to prevent breakthrough symptoms resulting from low trough concentrations before the next dose. A reliably absorbed slow-release formulation will decrease fluctuations and permit longer dosing intervals.

[b]For products containing theophylline salts, the appropriate dose of the theophylline salt should be substituted for the anhydrous theophylline dose. To calculate the equivalent dose for theophylline salts, divide the anhydrous theophylline dose by 0.8 for aminophylline, by 0.65 for oxtriphylline, and by 0.5 for the calcium salicylate and sodium glycinate salts.

[c]Dosing recommendation taken from Hendeles L, Weinberger M, Szefler S, et al. Safety and efficacy of theophylline in children with asthma. *J Pediatr* 1992;120:177–183.

[d]Dose reduction and/or serum theophylline concentration measurement is indicated whenever adverse effects are present, physiological abnormalities that can reduce theophylline clearance occur (e.g., sustained fever), or a drug that interacts with theophylline is added or discontinued.

tration and may become symptomatic toward the end of the 24-h dosing interval. With pellet formulations, the beads should be added to moist food (e.g., applesauce) to ensure their dissolution. Sustained-release tablets should not be crushed because this destroys their slow-release properties. An algorithm for initial dosing and final dosage adjustment based on serum concentration measurement may be found in a recent review of safety and efficacy of theophylline in children with asthma (Hendeles et al.). Because adverse effects of theophylline become manifest as the serum concentration of 20 μg/mL is approached, it is best to aim for the 8–15 μg/mL range in the majority of patients. Also in in vitro animal models and human studies, theophylline has anti-inflammatory/immunomodulatory effects at serum concentrations in the 5–10 μg/mL range. (See dosing recommendations in Table 3.) A recent head-to-head study of oral theophylline vs inhaled beclomethasone showed similar rates of asthma exacerbation in pregnant women with moderate asthma. There were more minor adverse reactions in the theophylline group. The results of this study are consistent with earlier studies in children with mild to moderate asthma, which showed no difference in outcome measures between the two regimens. As noted above, the most compelling evidence for the efficacy of theophylline comes from studies of patients with severe asthma controlled on inhaled steroids and theophylline whose asthma deteriorates when theophylline is withdrawn. In a similar vein, patients with severe asthma poorly controlled on high-dose inhaled steroids improve when theophylline is added. As noted above, theophylline is also effective in nocturnal asthma, but its use in this context has been largely subplanted by the new generation of long-acting β_2-agonists.

CONCLUSION

Theophylline was introduced into clinical medicine 65 yr ago for treatment of asthma. Its role as a bronchodilator is undisputed, but it is not as effective as β_2-agonists in this regard. Most recently it has been discovered, as a result of studies in vitro and in animal and human models, that theophylline has very significant anti-inflammatory and immunomodulatory effects. Most interesting is the finding that these effects are demonstrable at serum concentrations in the 5–10 μg/mL range, significantly lower that what has been considered necessary for optimal bronchodilator effect (10–20 μg/mL). At the lower serum concentrations adverse reactions are rare, and routine monitoring of serum theophylline levels is not necessary. Theophylline with both bronchodilator and anti-inflammatory effects is a truly unique drug. In patients with more severe asthma requiring high-dose inhaled steroids, the combination of low-dose theophylline with an inhaled steroid might allow the steroid dose to be reduced.

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20 Antileukotriene Agents in the Management of Asthma

Sheldon L. Spector, MD

CONTENTS

SUMMARY

Antileukotriene agents are one of the most recent additions to the therapeutic arsenal for asthma. They are very specific in their activity, blocking the action of leukotrienes. However, since these actions can result in multiple adverse effects, antileukotriene agents have the potential to deal with many aspects of the disease, including smooth muscle proliferation, airway hyperactivity, smooth muscle contraction, and eosinophil influx. Antileukotriene agents are indicated for the therapy of asthma from mild persistent to severe.

Key Words: Antileukotrienes; montelukast; zafirlukast; leukotrienes.

INTRODUCTION

The role of inflammation in asthma has been the main theme of various guidelines regarding treatment and is the emphasis of the National Asthma Education and Prevention Program (NAEPP). There are several treatment options when selecting anti-inflammatory agents for managing asthma patients, including corticosteroids, antileukotrienes, cromolyn, and nedocromil.

Although inhaled corticosteroids are associated with considerably fewer side effects than oral corticosteroids and currently are the anti-inflammatory medication of choice, they nevertheless have certain side effects. In the usual doses, they have been shown to be safe and well tolerated. However, with higher doses they can produce adverse effects such as oral candidiasis, dysphonia, osteoporosis, growth retardation (CAMP), and even ocular effects, such as glaucoma and cataract formation.

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Cromolyn and nedocromil are other anti-inflammatory agents that have been used in the treatment of asthma, but these medications are less effective than other available agents. Theophylline also has anti-inflammatory properties; however, potential side effects, a narrow therapeutic range, and requirement for careful monitoring make it less useful in asthma therapy.

The antileukotriene agents represent the newest in anti-inflammatory treatment options in more than 20 yr. The three leukotriene-modifying agents approved for the treatment of asthma include zafirlukast (Accolate®), montelukast (Singulair®), and zileuton (Zyflo®).

When the NAEPP treatment guidelines came out in 1997, the antileukotrienes were mentioned as an alternative to inhaled corticosteroids, cromolyn, and nedocromil, or sustained-release theophylline in patients with mild persistent asthma. More recently, international guidelines suggest their use for the treatment of mild, moderate, and severe asthma. This discussion is concerned primarily with the clinical studies of antileukotrienes and their expanded role in the treatment of asthma.

BIOSYNTHESIS AND POTENCY OF LEUKOTRIENES

Previously identified as slow-reacting substance of anaphylaxis, the leukotrienes are a family of pro-inflammatory lipid mediators derived from arachidonic acid via the 5-lipoxgenase pathway. Their name is derived from leukocytes, which produce them, and the triene-containing chemical structure. The cysteinyl or sulfidopeptide leukotrienes LTC_4, LTD_4, and LTE_4, are so named because each contains a thioether-linked cysteine residue. Another leukotriene, LTB_4, is a similar lipid lacking the thioether-linked peptide.

Many types of inflammatory cells produce cysteinyl leukotrienes (CysLTs), especially eosinophils, mast cells, basophils, and macrophages. A number of signals can stimulate the production of leukotrienes, including trauma, infection, allergen, and inflammation. These stimuli trigger phospholipase A_2-mediated release of arachidonic acid from nuclear membrane phospholipids. The nuclear arachidonic acid binds to 5-lipoxygenase-activating protein (FLAP), a membranous protein that presents arachidonic acid to 5-lipoxygenase. The unstable leukotriene LTA_4 is then formed, which in turn either is hydrolyzed to LTB_4 or is converted to LTC_4 by LTC_4 synthase, depending on the cell type. After conversion of LTC_4 to LTD_4, there is subsequent metabolism to LTE_4.

The CysLTs exert their effects largely through activation of the G protein-linked $CysLT_1$ receptor. Using *in situ* hybridization and immunohistochemical techniques, the $CysLT_1$ receptor has been found uniformly distributed throughout the lung on smooth muscle cells and tissue macrophages. Using a panel of peripheral blood cell markers, the presence of the $CysLT_1$ receptor has also been demonstrated on circulating eosinophils, B-lymphocytes, basophils, monocytes, macrophages, and on $CD34^+$ hematopoietic stem cells.

The CysLTs play an important role in asthma. They are potent constrictors of airway smooth muscle, about 1000 times more potent than histamine in eliciting bronchoconstriction following inhalation. The CysLTs promote mucus secretion, airway edema, and infiltration of inflammatory cells into the airway tissue. More recent data has demonstrated that CysLTs play a role in dendritic cell function, hematopoiesis, cell survival, and expression of inflammatory mediators including cytokines, chemokines, and adhesion molecules. Although LTB_4 has potent chemotactic effects in certain systems, it does not appear to have as much significance in asthma as do the CysLTs.

The role of CysLTs in asthma is also suggested by their detection in bronchoalveolar lavage (BAL) fluid during both the early- and late-phase allergen challenge. Inflammatory cells are typically recruited during the early phase and last throughout the late phase. These cells and the later arriving alveolar macrophage may then contribute to the additional production of leukotrienes. Studies have demonstrated that the elevated CysLTs in sputum are correlated to asthma severity and persist despite treatment with corticosteroids.

Leukotriene-modifying agents can be grouped into those that inhibit leukotriene biosynthesis (i.e., 5-lipoxygenase and FLAP inhibitors) and those that block CysLTs at the subtype 1 ($CysLT_1$) receptor. The only $CysLT_1$ receptor antagonists currently available in the United States are zafirlukast and montelukast; pranlukast is also available in Japan. Zileuton is the only synthesis inhibitor approved in the United States; it blocks the 5-lipoxygenase enzyme. Although it is not being manufactured at the time of this printing there is renewed interest and it probably will reappear in the marketplace.

Various clinical models have been utilized to establish the role of antileukotriene agents in asthma management. Antileukotrienes have been shown to reduce bronchosonstriction produced by a variety of stimuli, including LTD_4, exercise, cold air, sulfur dioxide, and aspirin. These agents also block both the early- and late-phase response to allergen challenge and the subsequent influx of inflammatory cells in BAL fluid. Montelukast and pranlukast have also been shown to reduce sputum, BAL, and peripheral blood eosinophils in clinical trials of patients with asthma. In patients who are aspirin sensitive, antileukotrienes prevent the aspirin challenge-induced production of asthma and rhinitis symptoms, which is consistent with the hypothesis that aspirin sensitivity is medicated in some fashion by CysLTs. Zafirlukast has also been given to patients who were undergoing a desensitization procedure with much difficulty, and it allowed for safe desensitization to occur in such individuals.

ANTILEUKOTRIENES IN CHRONIC ASTHMA STUDIES

The $CysLT_1$ receptor antagonists montelukast and zafirlukast have been shown to improve asthma control in adult and pediatric asthmatics when given alone and in combination with inhaled steroids*. These studies are described here.

The efficacy of montelukast and zafirlukast were demonstrated in placebo-controlled trials submitted to the US Food and Drug Administration for the approval for use in chronic asthma. Compared to placebo, montelukast has been shown to improve pulmonary function (forced expiratory volume in 1 s [FEV_1] and peak expiratory flow rate [PEFR]), daytime and nighttime symptoms, asthma attacks, quality of life, and decrease short-acting β-agonist use and peripheral blood eosinophils in adults. Onset of action occurred on the first day of dosing. A retrospective analysis of seven published studies demonstrated that, compared with placebo, montelukast significantly improved FEV_1 and peripheral blood eosinophil counts in patients with purely mild persistent asthma. Montelukast has also been shown to similarly improve asthma control in children 2–14 yr of age. Montelukast has also been demonstrated to provide protection against exercise-induced bronchoconstriction in adults and children. However, these agents are not to be used to treat acute asthma exacerbations. Zafirlukast also improves exercise-induced bronchoconstriction.

A number of studies comparing antileukotriene agents with other antiasthma medications have also been published. In studies of montelukast vs beclomethasone, montelukast had a quicker onset of action and beclomethasone produced a higher FEV_1, but there was no difference between the two agents with regard to time to first asthma attack. In other studies, moderate doses of corticosteroid aerosols had an effect comparable to montelukast or produced greater improvements in FEV_1. Zafirlukast was also shown to improve symptoms when added to inhaled steroids even in large doses. Antileukotrienes have also showed either equal or greater efficacy than cromolyn, nedocromil and theophylline.

The combination of antileukotriene agents and inhaled steroids has also been studied. The combination of montelukast and beclomethasone or montelukast and budesonide in adults or montelukast and budesonide in children provided improved asthma control vs the steroid alone. In asthmatics previously controlled on inhaled steroids (1000–2000 μg/d), the addition of montelukast allowed for a 47 and 81% reduction in mean inhaled steroid dose with no loss of asthma control. In patients receiving high-dose inhaled corticosteroids (mean beclomethasone doses of 1600 μg/d), the addition of zafirlukast produced significant improvement in pulmonary function and asthma symptoms without affecting the adverse side-effect profile.

The safety of these agents has also been studied. The safety profile of montelukast is comparable to placebo, including incidence of elevated liver enzymes. By contrast, rare occurrences of elevation in liver function tests were reported in the clinical studies with zafirlukast. Many cases of Churg-Strauss syndrome have been reported in association with montelukast and zafirlukast therapy, primarily in patients with severe asthma following reductions in oral steroid usage. The best explanation for the appearance of this unusual syndrome in relationship to administration of these antileukotrienes is the unmasking of a previous condition when oral steroids were tapered because of the introduction of the antileukotriene agent. To support this assumption, the package insert for fluticasone now contains a warning against the possible appearance of Churg-Strauss syndrome upon tapering of oral steroids and introduction of inhaled steroids.

Other studies of these agents for use in asthma are underway. Montelukast has been studied in the emergency room setting and has been found to provide an acute bronchodilator effect. Montelukast has also been shown to reduce post-rhinosyncytial virus asthma exacerbations. However, the prescribing information for montelukast and zafirlukast do not indicate that these agents should be used in this way.

ANTILEUKOTRIENES: WHERE DO THEY FIT IN YOUR PRACTICE?

In the 2002 NAEPP guidelines, antileukotrienes are recommended for therapy in patients who have mild or moderate persistent asthma. In the 2002 Global Initiative for Asthma guidelines, antileukotrienes are recommended for therapy in patients who have mild, moderate, or severe persistent asthma. Montelukast is indicated for use in patients aged 12 mo and older, and zafirlukast is indicated for use in patients aged 5 yr and older with chronic asthma. Montelukast is also indicated for use in patients aged 2 yr and older with seasonal allergic rhinitis.

Although antileukotrienes have a significant bronchodilator effect, they should not be substituted for short-acting β-adrenergic agonists. Patients should always carry a short-acting β-adrenergic agonist to treat exacerbations.

Based on limited data, they are at least as good as and often better than cromolyn or nedocromil, especially with their ease of use and anticipated improved compliance as oral agents. As described above, studies have compared the oral antileukotriene agents with inhaled corticosteroid therapy. Should a patient be experiencing a side effect from corticosteroid therapy, such as hoarseness or thrush, the antileukotriene may very well be preferred. In fact, patient compliance may be better with an oral agent, especially if "steroid phobia" also exists in the mind of the patient.

A particularly attractive concept might be to employ inhaled corticosteroids and antileukotrienes together to minimize the dose of inhaled steroids and thereby mitigate possible steroid side effects. Since the mode of action of inhaled steroids and antileukotrienes is different, it is not surprising that in the studies described above, patients were able to achieve improved asthma control with the combination vs the inhaled steroid alone or able to taper the dose of inhaled steroid with the addition of a antileukotriene while maintaining asthma control.

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21 Cromolyn and Nedocromil

Nonsteroidal Anti-Inflammatory Therapy for Asthma and Other Allergic Diseases

Stephen F. Kemp, MD

CONTENTS

SUMMARY

Both nedocromil sodium and cromolyn sodium are anti-inflammatory drugs that may be used in the therapy of allergic diseases. These diseases include asthma, allergic rhinitis, and allergic ocular disorders. Additional therapeutic uses have been proposed. Nedocromil and cromolyn are both available in the United States for asthma therapy, but only cromolyn is available for the treatment of the other conditions. Recent publications in the evidence-based literature have upheld the safety profile of nedocromil and cromolyn but increasingly suggest that other topical anti-inflammatory agents are more effective and have comparable safety at recommended doses. Nedocromil sodium and cromolyn sodium both can be used prophylactically prior to isolated allergen exposures and must be used regularly for maintenance therapy. No consistent, severe adverse reactions occur with either drug.

Key Words: Nedocromil sodium; cromolyn sodium; asthma; rhinitis; conjunctivitis.

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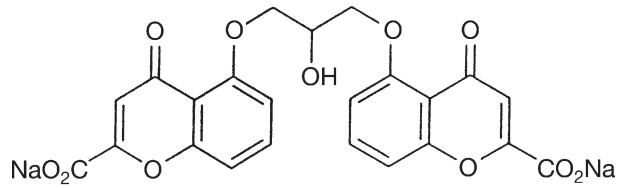
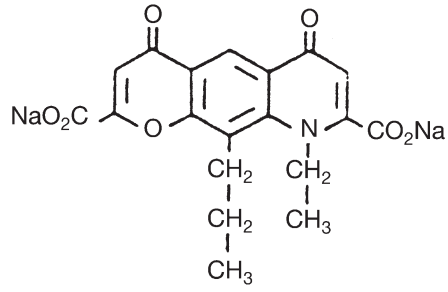


Sodium Cromoglycate



Nedocromil sodium

Fig 1. Structural formulas of cromoglycate (cromolyn sodium) and nedocromil sodium. (From Lieberman P. Nonsteroidal anti-inflammatory drugs for the treatment of asthma and allergic disease. In: Lieberman P, Anderson JA, eds. Allergic Diseases: Diagnosis and Treatment. Totowa, NJ: Humana Press, 1997:315–322.)

INTRODUCTION

Cromolyn sodium and nedocromil sodium are two nonsteroidal anti-inflammatory medications that may be used in the treatment of asthma, allergic rhinitis, and allergic eye disease. They are not, however, chemically or mechanistically related to the prostaglandin synthetase inhibitors commonly known as nonsteroidal anti-inflammatory drugs.

Cromolyn and nedocromil are chromone compounds that were synthesized and developed in 1965 and 1979, respectively. Khellin, a chromone derived and purified from seed extracts of the plant *Ammi visnaga*, had been utilized for centuries in several eastern Mediterranean countries as a diuretic and smooth muscle relaxant. A purified form was noted in the 1940s to provide complete, prolonged relief of asthma.

Cromolyn sodium is a derivative of chromone-2-carboxylic acid, whereas nedocromil sodium is a pyranoquinoline (Fig. 1). Despite their chemical and structural differences, they both exert remarkably similar anti-inflammatory actions. Both cromolyn sodium and nedocromil sodium are water soluble, fat insoluble, and totally ionized at physiological pH. These physical and chemical properties suggest that all biological activities are the result of drug interactions with an unidentified surface receptor.

Since the second edition of this volume, the mechanisms of action have been elucidated further, and several evidence-based studies have compared the efficacy of these compounds separately and together to other anti-inflammatory agents. The salient points will be reviewed here.

Table 1
Mechanisms of Action of Cromolyn and Nedocromil

1. Block chloride channels, thereby decreasing:
   - Mast cell degranulation
   - Activation of eosinophils
   - Nerve conduction through sensory neurons
2. No intrinsic bronchodilatory, anticholinergic, or antihistaminic activity

MECHANISMS OF ACTION

Cromolyn and nedocromil both apparently exert their effects on a variety of chloride channels of cells (Table 1). These channels include a volume-activated chloride channel in endothelial cells, a calcium-independent chloride channel in cultured mast cells, calcium-dependent fluctuations in tracheal smooth muscle, and a calcium- and voltage-dependent chloride channel on airway epithelium. Reduction of neuropeptide release and tachykinin receptor antagonism have been proposed as alternative mechanisms of action. In the rabbit model, nedocromil sodium first activates and then suppresses chloride ion flux in the vagus nerve (mainly composed of nonmyelinated C-fibers). These actions induce a slow, sustained nerve depolarization, thereby reducing sensitivity to subsequent action potentials.

By blocking the activity of chloride channel pathways on cells, such as mast cells, eosinophils, epithelial cells, endothelial cells, fibroblasts, and sensory neurons, these drugs dampen the inflammatory responses associated with allergic disease. This impairment of chloride channels may be related to drug-induced phosphorylation of a 78-kDa protein thought to be associated with the termination of mast cell mediator release. A structurally similar protein, moesin, interacts with the cellular cytoskeleton, and its phosphorylation by cromolyn may help to explain the inhibitory effects of cromolyn and nedocromil on chloride channels. These drugs may imitate a natural inhibitory process, thus accounting for their lack of toxicity.

In summary, the clinical activity of these drugs apparently derives from their downregulation of a variety of cells involved in the inflammatory response, both allergic and nonallergic factors. Of particular importance is their ability to downregulate eosinophil-driven inflammation. Neither cromolyn nor nedocromil has intrinsic bronchodilatory, anticholinergic, or antihistaminic activity.

CLINICAL EFFICACY

Asthma

Nedocromil sodium and cromolyn sodium have demonstrated the ability to prevent asthma exacerbations leading to emergency department visits and hospitalization, especially in children. Nonetheless, the role of chromones in asthma management is still debated. The updated National Heart, Lung, and Blood Institute asthma guidelines, the Cochrane Database Systematic Reviews, and the Childhood Asthma Management Program study suggest that inhaled steroid preparations should be first-line agents in all patients with persistent disease, effectively relegating cromolyn and nedocromil to second-line agents (i.e., they are not “preferred”). The Cochrane Database Systematic Reviews suggests that publication bias has overestimated the beneficial effects of

Table 2
Asthma-Inducing Agents Inhibited by Cromolyn and Nedocromil

Allergens (both early and late responses)
Chemicals (mediators)
Adenosine monophosphate
Hypertonic saline
Neurogenic
NO_2
SO_2
Citric acid
Sodium metabisulfite
Bradykinin
Substance P
Neurokinin A
Capsaicin
Physical factors
Fog
Exercise
Cold air

cromolyn as maintenance asthma therapy and concludes that efficacy of cromolyn over placebo is unproven. Others argue strongly that cromolyn and nedocromil effectively preserve lung function in most patients and have strong safety profiles. Key features of their efficacy are summarized below.

Both cromolyn and nedocromil effectively block the asthmatic response to a variety of stimuli (Table 2). These include not only allergen-induced reactions, but also those related to neurogenic, chemical, and physical factors, such as substance P, bradykinin, nitric oxide, sulfur dioxide, sodium metabisulfite, cold air, citric acid, and fog. In addition, they can prevent exercise-induced bronchospasm. The drugs thus protect against a wide array of asthma-inducing stimuli.

The key features of cromolyn and nedocromil are outlined in Table 3. Their action is clearly anti-inflammatory. Biopsy and bronchoalveolar lavage studies obtained after provocative challenges or during long-term therapy both demonstrate significant reductions in inflammatory markers. Both drugs decrease the number of indolent and activated eosinophils found in bronchoalveolar lavage fluid and biopsy specimens of respiratory mucosa. In addition, cromolyn decreases the amount of albumin present in bronchoalveolar lavage fluid.

Numerous in vitro findings complement these in vivo effects. These findings include inhibition of macrophage release of neutrophil chemotactic factor, decreased eosinophil chemotaxis, and inhibition of eosinophil and mast cell degranulation, among other activities.

Chronic administration of both drugs produces clinical improvement manifested by decreased symptom scores, gradual increases in forced expired volume in 1 s (FEV_1), decreased peak flow diurnal variability, and decreased bronchial hyperresponsiveness following histamine or methacholine challenge. However, acute administration of cromolyn or nedocromil has no effect on bronchoconstriction induced by directly acting spasmogens such as histamine or methacholine. Both cromolyn and nedocromil decrease

Table 3
Key Features of Cromolyn and Nedocromil Use in Asthma

Anti-inflammatory
Decrease bronchial hyperresponsiveness
Block early- and late-phase reaction
Prevent bronchospasm to allergic and numerous, nonallergic stimuli
Maintenance prophylaxis
Major role in mild to moderate persistent asthma
May be corticosteroid-sparing
Excellent safety profile

Table 4
Features Distinguishing Nedocromil from Cromolyn

Nedocromil blocks the late-phase pulmonary response to allergy challenge when given before or shortly after provocative challenge. Cromolyn is only effective if it is given before challenge.
Nedocromil inhalation blocks the release of cytotoxic mediators in aspirin-sensitive asthmatics whose platelets are challenged with aspirin in vitro. Cromolyn inhalation does not.
Nedocromil may be more effective in preventing asthma resulting from nonallergic triggers, such as NO_2, SO_2, metabisulfite, and adenosine monophosphate.
Nedocromil may be more effective in blocking eosinophil chemotaxis.
Nedocromil has a faster onset of action.
Cromolyn may inhibit angiotensin-converting enzyme inhibitor-induced cough through inhibition of sensory nerve activation.
Cromolyn may potentially alleviate refractory atopic dermatitis.
Cromolyn may influence the common cold.
Nedocromil may require less frequent dosing as a maintenance regimen.
Nedocromil is more efficacious than cromolyn in the treatment of vernal keratoconjunctivitis and is effective in patients whose chronic symptoms of allergic conjunctivitis are not controlled fully by cromolyn. Ocular preparations of nedocromil are not commercially available in the United States.

bronchodilator use and also reduce the dosage of inhaled corticosteroids necessary to control asthma. These effects are seen in both allergic and nonallergic asthmatics.

Cromolyn and nedocromil are very similar in their clinical effects, and there are no dramatic differences between these two drugs. However, some minor clinical differences are summarized in Table 4.

Both drugs will prevent the early- and late-phase allergic response when they are administered before an allergen challenge. However, nedocromil will prevent the late-phase response when it is administered after an allergen challenge, whereas cromolyn will not. Both drugs exert their effects on nonallergic asthma stimuli. Nedocromil, however, seems to be slightly more effective in blocking asthma caused by nitric oxide, sulfur dioxide, sodium metabisulfite, and adenosine monophosphate. In addition, nedocromil may be more effective at inhibiting eosinophil chemotaxis. Specifically, nedocromil, but not cromolyn, inhibits chemotaxis of eosinophils induced by platelet-activating factor and leukotriene B_4.

Whether or not these observations result in clinically detectable differences between the two agents is unclear. However, some evidence suggests subtle clinical differences exist between the two drugs:

1. Nedocromil may have a faster onset of action. It exerted its beneficial effects within a few days in one study, while cromolyn effects may take 2–4 wk.
2. The maintenance dosing frequency required for nedocromil may be less than that required for cromolyn. A twice-daily regimen is effective for some patients taking nedocromil. It may also assist in patients, such as adolescents, who may have difficulty adhering to more complex regimens.
3. Nedocromil may be more effective than cromolyn in the treatment of nonallergic asthmatics. The rationale for this statement is its superior effect in blocking nonallergic asthma triggers.
4. Nedocromil may control asthmatic cough more effectively than cromolyn. However, cromolyn may help to reduce the chronic cough associated with angiotensin-converting enzyme inhibitors, presumably due to its inhibition of sensory nerve activation.
5. A certain percentage of patients will not take nedocromil because of an unpleasant taste. Most patients (about 88%) do not taste nedocromil. No unpleasant taste is associated with inhaled cromolyn.
6. Cromolyn sodium is also commercially available in the United States as a solution form for nebulizer usage, whereas nedocromil sodium is not. This may be an advantage for asthmatic patients younger than 5 yr of age. Cromolyn sodium is approved for usage down to age 2 yr. Nedocromil is approved by the US Food and Drug Administration for nebulized usage in children but has never been marketed in this form in the United States.

No consistent difference between the cromolyn and nedocromil exists in clinical trials involving subjects with asthma. Some trials report clinical equivalence, while others report a relative advantage of one over the other in controlling certain asthma features.

It should be emphasized that neither drug is a bronchodilator. Indeed, both drugs seem to have irritative properties that will cause cough or wheeze in some patients whose asthma has not been adequately controlled. As a practical point, therefore, a brief therapeutic course of corticosteroids may be necessary to control active asthmatic inflammation before initiating these drugs.

Both drugs are indicated for maintenance control of mild to moderate persistent asthma and may additionally help to reduce the dependency on inhaled corticosteroids in severe, persistent asthma. Nedocromil is only available in the United States as a metered-dose inhaler (MDI). Cromolyn is available both as a metered-dose inhaler and as a nebulizer solution. Therefore, cromolyn may be used in infants and small children who cannot use a MDI. Cromolyn combined with albuterol (salbutamol) as a nebulizer solution was significantly more effective in a multicenter trial than either agent alone.

The initial dosage frequency for both cromolyn and nedocromil is four times daily once acute asthmatic inflammation is controlled. Dosage reductions to twice daily are almost always possible for maintenance therapy. Prophylactic administration prior to allergen exposure, such as a visit to a relative who resides with a pet to which the patient is allergic, is a unique therapeutic use for both drugs. Both should be administered 30 min before exposure and every 4 h while exposed. Both drugs effectively prevent exercise-induced bronchospasm when administered immediately prior to strenuous exercise. However, neither drug is as effective as a short-acting β-adrenergic agonist. Better

efficacy has been reported for cromolyn when it is inhaled slowly from a large-volume (700 mL) holding chamber rather than a more rapid conventional inhalation. Alternatively, increasing the size of inhaled droplets (dependent on the nebulizer device used) may increase deposition. Results from either modification may be related to more homogeneous pulmonary distribution.

Allergic Rhinitis

Both nedocromil and cromolyn are effective agents in the therapy of both seasonal and perennial forms of allergic rhinitis. However, this discussion will be limited to the use of cromolyn because nasal preparations of nedocromil are not commercially available in the United States. Cromolyn is available in an aqueous form, both with and without prescription, for the therapy of allergic rhinitis. As with asthma, cromolyn administration prevents both the early and late nasal responses to allergen and decreases both activated and indolent eosinophils found in nasal secretions and biopsies.

As in asthma, nasal cromolyn should be administered once the rhinitis is reasonably controlled and it should be given prior to exposure. Thus, therapy for seasonal allergic rhinitis should be initiated before the allergy season begins. This drug can be highly effective in blocking symptoms resulting from isolated allergy exposure when it is administered immediately before mowing the lawn or visiting a relative with a pet.

It is important to remember that cromolyn is a preventive agent that needs to be used regularly during allergen exposure. It has no immediate effect. Its initial dose is two sprays four times daily, but this dosage frequency potentially can be reduced after the first 2–3 wk of therapy.

The safety profile of nasal cromolyn is excellent, permitting its purchase in the United States without a prescription. Therefore, it is an excellent drug for use in children for whom nasal corticosteroids are considered undesirable. Nonetheless, nasal corticosteroids have a superior therapeutic effect compared to nasal cromolyn. Moreover, additional medications are usually necessary to achieve an acceptable clinical response to cromolyn, especially where congestion is a troublesome nasal symptom.

Allergic Eye Disease

Cromolyn may be effective in the management of several allergic eye diseases. All of these disorders appear to involve mast cells and eosinophils. These conditions include seasonal allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis. Nedocromil is more efficacious than cromolyn in the treatment of vernal keratoconjunctivitis and is effective in patients whose chronic symptoms of allergic conjunctivitis are not controlled fully by cromolyn. Ocular preparations of nedocromil, however, are not commercially available in the United States. Current evidence supports preferential use of topical antihistamines (e.g., azelastine, levocabastine, or olopatadine) or mast cell stabilizers (e.g., lodoxamide) for allergic eye conditions.

Seasonal Allergic Conjunctivitis

Ocular cromolyn therapy is virtually as effective as oral antihistamines for seasonal allergic conjunctivitis. It reduces itching, stinging, and photosensitivity. Therapeutic response in seasonal allergic conjunctivitis may be related to allergen-specific IgE antibody levels.

As with other allergic diseases, the drug should be started when the patient is relatively free of symptoms. It is administered at a dose of one to two drops four times daily. Ocular cromolyn is not effective acutely. However, it can also be used prophylactically before specific allergen exposure.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is recurrent, bilateral, interstitial inflammation of the conjunctivae that occurs more frequently in warm, dry climates. Most affected patients develop symptoms before puberty and symptoms usually resolve by 25 yr of age. Symptoms of severe itching, tearing, burning, mucoid discharge, and photophobia may occur perennially but are characteristically worse during spring and summer months. Abnormalities may include giant papillae on upper tarsal conjunctivae, corneal plaques, scarring, and decreased visual acuity.

Several studies indicate that ocular cromolyn is effective for vernal keratoconjunctivitis. Beneficial effects seem to occur within 1 wk of initiating therapy and are manifested by decreased pruritus and mucus secretion. The dosage is one to two drops four times daily. Nedocromil is significantly more effective than cromolyn in treating vernal keratoconjunctivitis and is more effective in controlling keratitis, reducing the need for additional topical corticosteroid treatment.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is the ocular counterpart to atopic dermatitis. However, only a small percentage of patients with atopic dermatitis develop atopic keratoconjunctivitis. Associated symptoms include severe itching, burning, mucoid discharge, and photosensitivity. Cataracts and keratoconus may develop. Double-blind placebo-controlled crossover studies have shown beneficial effects of cromolyn on discharge, photophobia, papillary hypertrophy, and both limbal and corneal changes. In addition, dosage reductions for topical corticosteroids have been reported.

Giant Papillary Conjunctivitis

Evidence suggests that giant papillary conjunctivitis is triggered by an inflammatory response to any foreign substance, such as a contact lens or ocular prosthesis, which irritates the upper tarsal conjunctivae. Because pathological changes are similar to those seen in allergic eye disorders, cromolyn has been employed. A reduction in symptoms and an increased tolerance to contact lens wear has been demonstrated in many patients. The dose is the same as for other ocular disorders. Affected patients should discontinue contact lens wear while the condition persists and should consider switching to disposable contact lenses once it resolves.

Other Therapeutic Uses for Cromolyn or Nedocromil

Atopic dermatitis is an inflammatory, IgE-mediated skin disease characterized by intense pruritus, xerosis, and scaly, licheniform rash with a characteristic anatomical distribution. Therapy is directed at avoidance of inciting stimuli, moisture retention, emollients, antipruritics, and topical corticosteroids.

One report of a placebo-controlled, randomized, crossover study suggests that topical cromolyn may potentially benefit patients for whom the above therapeutic modalities have failed. Cromolyn prepared in an emollient base was applied to the skin of children

and adolescents with moderate to severe atopic dermatitis. All subjects concomitantly applied a mid-potency topical steroid. Objective severity decreased significantly in the cromolyn-steroid group compared to the group treated with steroid alone. The study authors posit an additive anti-inflammatory effect based on the different mechanisms of action employed by corticosteroids and cromolyn.

Nedocromil may inhibit sensory nerve activation to reduce neurogenic itch and flare from histamine but does not modulate wheal diameter. It has not yet been evaluated clinically as a topical preparation.

Other reports have proposed that intranasal cromolyn or nedocromil (not commercially available in the United States as an intranasal preparation) may benefit the common cold. The causative viruses or atypical bacteria may produce a variety of inflammatory mediators, including histamine, cytokines, leukotrienes, and nitric oxide. Compared to placebo, both cromolyn and nedocromil provide a swifter resolution and reduced severity of symptoms in nonallergic subjects. Both drugs also reduce symptoms of virus-induced asthma exacerbations.

Systemic mastocytosis, a disease characterized by mast cell proliferation in multiple organ systems, usually features urticaria pigmentosa (brownish macules that transform into wheals upon stroking them) and recurrent episodes of flushing, tachycardia, pruritus, headache, syncope, abdominal pain, or diarrhea. Because it inhibits mast cell degranulation, orally administered cromolyn has some efficacy in mastocytosis, particularly for symptoms involving the gastrointestinal tract. However, cromolyn does not reduce plasma or urinary histamine levels in patients with mastocytosis.

Similarly, oral cromolyn has been employed as an alternative to an elimination diet in non-life-threatening food allergy, in irritable bowel syndrome, and atopic dermatitis where allergic sensitization to specific foods has been identified.

One group has reported that cromolyn has an antisickling effect in patients with sickle cell disease and concomitant allergic disease. The researchers postulate that the decrease in sickle cells may be a result of inhibitory effects of cromolyn on the calcium-activated potassium Gardos channel, which influences erythrocyte dehydration. Of the studied 18 patients with sickle cell disease, 10 were also taking hydroxyurea, and the report does not mention the duration of treatment or if the hydroxyurea dosage was altered. The clinical effect of reduced sickling activity was also not discussed. Clinical relevance therefore is uncertain.

SAFETY, TOXICITY, AND POTENTIAL SIDE EFFECTS

Nedocromil and cromolyn are two of the safest drugs available for treatment of allergic diseases. They have shown little, if any, toxicity in more than 25 yr of clinical use. Local irritation is the most common side effect. Nedocromil is perceived by some patients (about 12%) to have an unpleasant taste that may limit its use.

CONCLUSION

Both nedocromil sodium and cromolyn sodium are useful anti-inflammatory drugs in the therapy of allergic diseases. These diseases include asthma, allergic rhinitis, and allergic ocular disorders. Additional therapeutic uses have been proposed. Nedocromil and cromolyn are both available in the United States for asthma therapy, but only cromolyn is available for the treatment of the other conditions.

Recent publications in the evidence-based literature have upheld the safety profile of the chromones, but increasingly suggest that other topical anti-inflammatory agents (e.g., glucocorticosteroids or ocular antihistamine preparations) are more effective and have comparable safety at recommended doses. Cromolyn appears to be more effective when combined with a β-agonist. There are no data to support that addition of chromones to inhaled corticosteroids enhances efficacy. Whether other drugs can be utilized with cromolyn or nedocromil to achieve greater effectiveness and comparable safety remains to be seen. Refinements of existing formulations may also achieve greater efficacy. At present, cromolyn and nedocromil appear to be niche drugs that can be of great clinical importance for some patients.

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22 Anticholinergic Agents in Respiratory Diseases

Juan L. Rodriguez, MD

Contents

SUMMARY

Anticholinergic agents play an adjunctive role in the treatment of allergic respiratory diseases. Their formal indication in lung disease is for emphysema. However, they are useful in some asthmatics. In upper airway disease they are very effective agents to treat anterior rhinorrhea of the common cold or due to allergic or nonallergic rhinitis.

Key Words: Ipratropium bromide; tematropium bromide; gustatory rhinitis; chronic nonallergic rhinitis; emphysema.

INTRODUCTION

The origin of the anticholinergic agents is found in the belladonna plants from which atropine and scopolamine are derived. In ancient times, extracts of these plants were used as poisonous agents because of their potent physiological effects. The first recorded use of belladonna alkaloids for the treatment of respiratory diseases comes from India where the smoke of burning jimsonweed (*Datura stramonium*) was used to treat asthma symptoms. British settlers in India introduced the use of belladonna alkaloids into Western medicine in the 19th century. Atropine was isolated in its pure form by Mein in 1831. Although found to be useful for the treatment of respiratory conditions such as asthma and disorders of gastrointestinal motility, these substances were limited by their toxicity, including the effects on the heart and the undesirable side effects such as dry mouth, urinary retention, and pupillary dilation. Recently, there has been an effort to develop anticholinergic substances with little or no undesirable side effects. These efforts have

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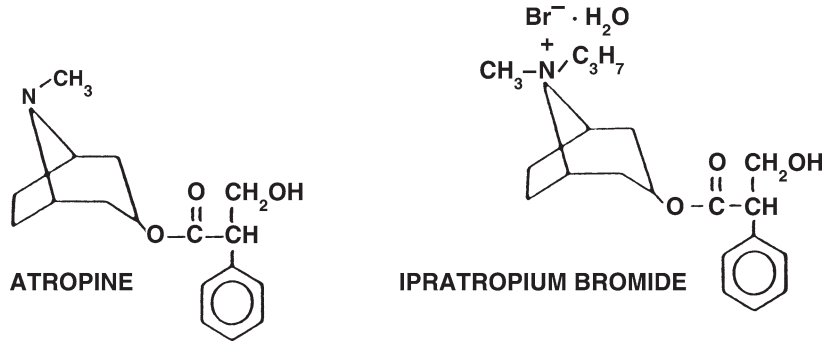

Fig. 1. Structures of atropine and ipratropium bromide.

led to the development of quaternary ammonium compounds of atropine, such as ipratropium bromide and tiotropium bromide, which share with atropine beneficial effects on the respiratory tract with few undesirable effects. The addition of the quaternary ammonium structure makes this medication poorly absorbable through the mucosa of the respiratory and gastrointestinal tract (Fig. 1). This property confers its low potential for side effects.

THE PARASYMPATHETIC NERVOUS SYSTEM AND THE AIRWAYS

The airways are under parasympathetic control via the vagus nerve. Fibers from the vagus nerve synapse with the postganglionic nerves located in the tracheal smooth muscle. Parasympathetic nerves have effects at the level of smooth muscle, airway ciliary epithelia, and mucous glands. Fibers from these postganglionic nerves directly innervate bronchial smooth muscle and glands where acetylcholine is released and its activity mediated via muscarinic receptors. There are five types of muscarinic receptors (M1–M5). The lung contains only M1, M2, and M3 receptors, and the nose contains M1 and M3 receptors. The physiological activity mediated by these receptors is shown in Table 1. Bronchial smooth muscle contains M2 and M3 receptors. Bronchial smooth muscle constricts under the influence of acetylcholine binding with the M3 receptor. Acetylcholine also stimulates M2 receptors, located in the postganglionic nerve endings, which decrease further release of acetylcholine via a negative feedback mechanism. This dual effect of acetylcholine explains why nonspecific blockage of muscarinic receptors could promote smooth muscle relaxation (via M3 antagonism), a desirable effect in asthma, and at the same time promote smooth muscle contraction by blocking M2 receptors and allowing for more acetylcholine release. Most of the parasympathetic innervation of the airways occurs in the upper branches of the respiratory tract with little innervation beyond the terminal bronchioles. This suggests that the parasympathetic activity takes place at the level of the trachea and the large- and middle-sized bronchi, with less influence on small airways and alveoli.

Lung mucous glands and the airway ciliated epithelium appear to be under parasympathetic control. When the airway is mechanically stimulated, the increase in secretions observed is a reflex response mediated by the parasympathetic innervation. This effect is abrogated by atropine. Increased mucous production is seen in asthma and chronic obstructive pulmonary disease (COPD), and the glandular hypertrophy seen in these

Table 1
Location and Function of Muscarinic Receptors in the Airways

Receptor	*Location*	*Function*
M1	Alveoli, glands, ganglia	Enhances transmission
M2	Postganglionic nerves	Negative feedback
	Reduces transmission	
M3	Smooth muscle lung	Contraction smooth muscle
	Glands	Secretion mucous and serous glands

conditions may be the result of chronic cholinergic stimulation. This effect on mucus secretion is mediated by the activity of acetylcholine on M3 receptors. Excessive mucus contributes to the obstruction of the airways seen in these conditions. The clearance of mucus and secretions from the airways depends on the beating of cilia. Atropine appears to decrease ciliary clearance of mucus, but ipratropium does not have this effect, giving this compound an advantage over atropine in the treatment of asthma and COPD.

THE ROLE OF THE PARASYMPATHETIC NERVOUS SYSTEM IN ASTHMA

Denervation of the lungs has been utilized in the past in the treatment of asthmatics. Some studies reported impressive results. In asthmatics, the unstimulated airway tone is increased compared to normal controls. This increased tone can be completely blocked by ipratropium, suggesting a vagally mediated mechanism. Nonspecific airway hyperresponsiveness is characteristic of most patients with asthma. It is believed that the response to many nonspecific stimuli such as exercise, cold air, and sulfur dioxide is partially vagus nerve-mediated because they can be blocked by the intravenous administration of atropine or with the use of adequate doses of inhaled anticholinergic agents in humans. Intravenous or inhaled atropine blocks antigen-induced increases in airway resistance in allergic asthmatics in a dose-dependent fashion. Some studies, on the other hand, have concluded that cholinergic mechanisms are not important in allergic asthma. However, in these studies, low doses of inhaled anticholinergics were used, suggesting inadequate vagal blockade. In exacerbations of asthma resulting from viral infections, vagal mechanisms play an important role. Evidence suggests that in humans the hyperresponsiveness seen in naturally occuring viral infections could be blocked by atropine. This implies a role for increased acetylcholine release as a contributor to hyperresponsiveness. This is most likely a result of loss of function of the M2 inhibitory receptors at the parasympathetic nerve endings allowing for increased acetylcholine release. In nocturnal asthma and in stress-associated bronchospasm, vagally mediated bronchoconstriction also plays a role.

ANTICHOLINERGIC DRUGS IN RESPIRATORY DISEASES

Atropine was the first anticholinergic used to treat respiratory diseases such as asthma. Its role in respiratory diseases is limited by its side effects such as urine retention and dry mouth. It remains widely employed, mostly in anesthesia, where it is used to reduce

Table 2
Comparison of Ipratropium Bromide and Atropine

Ipratropium Bromide	*Atropine*
Synthetic analog of atropine	Botanical origin
Water soluble	Water soluble
No absorption from respiratory tract	Absorbed from respiratory tract
No central nervous system effect	Central nervous system activity
No decrease in mucociliary clearance	Decreased mucociliary clearance

secretions of the upper airways and to reduce laryngospasm. It is still found in some oral preparations used in the treatment of rhinitis. Ipratropium bromide (Atrovent), a quaternary ammonium derivative of atropine, is the anticholinergic currently indicated for use in the treatment of COPD, allergic and nonallergic rhinitis, and the rhinorrea of the common cold. It is also utilized in the treatment of asthma because of its bronchodilatory properties. Table 2 compares ipratropium bromide and atropine characteristics. It is available in an aqueous nasal spray for rhinitis, in an aqueous nebulizer solution for use in COPD, and in a metered-dose inhaler either alone or in combination with albuterol (Combivent). Its inhibition of rhinorrea makes it a useful medication for the symptomatic relief of allergic and nonallergic rhinitis, gustatory rhinitis (onset of rhinorrea induced by eating hot and spicy foods), and the common cold, conditions for which it is also indicated. It is available as a nasal spray in two concentrations. The 0.03% concentration delivers 21 μg of ipratropium per spray, and the dose recommended in chronic rhinitis is two sprays in each nostril two or three times a day. For the treatment of the common cold, it is available in a dose of 0.06%, and the recommended dose is two sprays per nostril three to four times a day. In the treatment of rhinitis, it can be used in conjunction with a topical corticosteroid nasal spray and with an antihistamine (Table 3). It has a rapid onset of action, usually within a few hours. Caution should be taken not to spray it inadvertently in the eyes as it may cause temporary blurred vision.

Other muscarinic receptor antagonists include oxitropium bromide, a derivative of scopolamine, and tiotropium bromide, developed as a long-acting and more bronchoselective anticholinergic agent. Tiotropium was approved for the treatment of COPD in 2004. None of these agents is currently available for use in the United States.

ANTICHOLINERGIC DRUGS IN ASTHMA AND COPD

When ipratropium and tiotropium are compared with β_2-adrenergics in asthma, the adrenergic agents show superior bronchodilation. The bronchodilatory activity of ipratropium is more gradual, although more sustained, than that of albuterol. Thus, ipratropium should not be used alone as a bronchodilator in asthma. However, ipratropium in combination with a β_2-adrenergic agent such as albuterol produces better bronchodilation than either agent alone when delivered by nebulization in the setting of acute severe asthma, especially in the pediatric population. In a study of children who visited the

Table 3
Ipratropium Bromide in Chronic Rhinitis

Approved use	Indicated for symptomatic relief of rhinorrhea in allergic and nonallergic perennial rhinitis
Formulations	Available as a 0.03% solution for perennial rhinitis Available as a 0.06% solution for the common cold
Dosing	The recommended dose for rhinitis is two sprays in each nostril of the 0.03% solution two or three times daily For the common cold the recommended dose is two sprays in each nostril of the 0.06% solution three to four times daily
Side effects	Well tolerated by most patients Avoid contact with eyes
Other uses	Useful in gustatory rhinitis

emergency department with a severe exacerbation of asthma with a peak flow of less than 50% of predictive value, the addition of ipratropium bromide to albuterol and corticosteroid therapy significantly reduced the hospitalization rate. This effect was not seen in those with a moderate (peak flow rate between 50 and 70% predicted) exacerbation. Another study in children with mild and moderate asthmatic exacerbations failed to demonstrate an additive bronchodilatory effect of ipratropium when added to repeated albuterol treatments. Studies of the effectiveness of combination therapy using albuterol and ipratropium bromide in adults with an acute exacerbation of asthma have produced conflicting results. A recent study of adult asthmatics presenting to the emergency department with acute exacerbation of asthma showed that a single dose of ipratropium and albuterol in combination conferred additional bronchodilation as compared to albuterol alone. The patients who exhibited the most benefit from the addition of ipratropium were those who had consumed the least inhaled β_2-agonist before presentation and not those with the most severe asthma. Recent guidelines published by the National Asthma Education Program Expert Panel recommend the addition of ipratropium bromide to high-dose β_2-agonist by nebulization in severe exacerbations of asthma with forced expiratory volume in 1 s (FEV_1) or peak flows below 50%. Because there are asthmatic patients who are going to respond with significant bronchodilation to anticholinergic blockade, a trial with ipratropium should be considered to identify those patients who would benefit from regular treatment in stable asthma. This may be especially true in elderly asthmatic patients with a component of chronic, fixed obstruction or those with longstanding asthma. However, it is important to recognize that most asthmatics do not require or respond to ipratropium in stable asthma. A recent review of the literature suggests that there is insuficient evidence supporting the use of anticholinergic maintenance treatment for chronic asthma in children. Except in elderly asthmatics, its use is not recommended as routine treatment for stable asthma according to recently published guidelines by the National Asthma Education Program Expert Panel. Another group of asthmatics that may benefit from regular use of ipratropium includes those taking concomitant β-blocking medications for other indications. Patients whose asthma is triggered by emotional distress may also respond well to anticholinergic blockade.

It is quite clear that ipratropium and tiotropium are superior bronchodilators compared with β-agonists in patients with chronic bronchitis and emphysema and are the

bronchodilators of choice in these conditions. It offers greater relief of airflow limitation and hyperinflation than albuterol. Its use is indicated for maintenance treatment of bronchospasm associated with COPD. A combination of Atrovent and albuterol (Combivent) in a metered-dose inhaler is now available in the United States and is indicated for the treatment of COPD. Each actuation of Combivent delivers 18 μg of ipratropium and 103 μg of albuterol sulfate. As in the case of asthma, the combination of ipratropium and albuterol offers significantly better bronchodilation in COPD patients than either ipratropium or albuterol given separately. Ipratropium is also available as a solution for nebulization, and it can be administered mixed with albuterol in the nebulizer (Table 4).

Tiotropium (Spiriva), a long-acting anticholinergic agent recently approved in the United States for the treatment of COPD, may become the agent of choice for this condition. It has been found effective in improving dyspnea, improving lung function, and reducing exacerbations in patients with COPD, exceeding the benefits seen with ipratropium. Patients may be able to control their symptoms with scheduled once-a-day treatment of 18 μg of tiotroprium. It is generally well tolerated. The most common adverse reaction reported was dry mouth, which was usually mild and often resolving during treatment.

CONCLUSIONS

New quaternary anticholinergic agents are useful medications to use in the treatment of respiratory conditions of the upper and lower respiratory tract. Their unique mechanism of action and the paucity of side effects give these agents an important role as adjunct therapy in the management of COPD, acute severe asthma, and rhinitis.

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23 Glucocorticoid Therapy in Asthma

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CONTENTS

SUMMARY

Glucocorticoids (GCs) are the most effective therapy we have for the treatment of asthma. Systemically administered GCs are first-line agents for acute severe asthma, whereas topical (i.e., inhaled) GCs are first line agents for the long-term management of all patients with persistent asthma. In the treatment of acute asthma exacerbations, early institution of systemic GCs can prevent further worsening of symptoms, reduce emergency room visits, and hospitalizations. Inhaled GCs are the recommended controller class of medications for all patients with persistent asthma, including children. They are the most effective class of agents in reducing symptoms, improving lung function, and decreasing bronchial hyperresponsiveness, in addition to reducing asthma morbidity and mortality. Long-term administration of oral GCs is associated with multiple adverse effects including adrenal insufficiency, weight gain, increased skin fragility, myopathy, osteoporosis, cataracts, and mood changes. Thus, in patients with chronic severe asthma who require regular systemic GC therapy, all other treatments should be maximized, and the lowest dose sufficient for control should be established through regular monitoring visits. As with oral GC therapy, high-dose inhaled GC therapy can result in systemic adverse effects. Several studies have shown that low-dose inhaled GC therapy, even when administered long term, is unlikely to result in any clinically meaningful adverse effects. By using the lowest possible effective GC dose, as well as maximizing other therapeutic modalities, adverse systemic effects from GCs can be greatly minimized.

Key Words: Acute asthma; persistent asthma; glucocorticoids; inhaled glucocorticoids.

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INTRODUCTION

Glucocorticoid (GC) therapy remains one of the most valuable treatment modalities in the management of both the acute and chronic manifestations of asthma. GCs have been used in the treatment of asthma for more than 50 yr. Initial studies evaluating the effect of cortisone on asthma revealed significant improvements in asthma symptoms and pulmonary function. Unfortunately, much of the early enthusiasm for oral GC use was dampened with the realization that chronic use of this medication resulted in multiple adverse effects. The subsequent development of highly effective inhaled GC preparations has revolutionized asthma care. By virtue of their high topical to systemic potency, inhaled GC therapy has proven to be safe and effective in the treatment of asthma. This chapter will provide a broad overview of the structure, mechanisms of action, pharmacokinetics, efficacy, adverse effects, and current issues associated with both systemic and inhaled GC therapy in asthma.

CHEMISTRY

Synthetic GCs are cortisone-based molecules that have undergone structural modifications designed to enhance their potencies and prolong their durations of action. Anti-inflammatory GCs have a 17-hydroxyl group and methyl groups at carbons 18 and 19. Further modifications to the basic steroid structure have increased the anti-inflammatory while decreasing mineralocorticoid effects; however, it has not been possible to separate the unwanted metabolic effects while retaining the desired anti-inflammatory properties of the synthetic GCs that are systemically administered.

MECHANISMS OF ACTION

Asthma is an inflammatory airways disease. As such, it should come as no surprise that medications with broad anti-inflammatory effects such as GCs are among the most effective classes of medications for asthma. Multiple studies have shown GCs to act at several levels of the inflammatory response (Table 1), with their primary effect coming mainly from their ability to inhibit the expression and/or production of molecules involved in the initiation and maintenance of the inflammatory response. Specifically, they inhibit the upregulation of adhesion molecules on endothelial cells that are required for the adhesion and subsequent migration of inflammatory cells to sites of inflammation. They also inhibit the production of cytokines involved in inflammatory cell recruitment, activation, and proliferation. GCs also display potent vasoconstrictive properties. By decreasing capillary permeability at sites of inflammation, less plasma exudation occurs, resulting in a reduction in the concentration of inflammatory and chemotactic factors and ultimately in a decrease in the inflammatory response. Another salutory effect of GC therapy that is especially relevant to asthma is the upregulation of β-adrenergic receptors on airway smooth muscle cells.

SYSTEMIC GLUCOCORTICOID THERAPY

Pharmacokinetics

The pharmacokinetics of GCs can influence dosing strategies; however, in general, GC dosing regimens are not dependent on pharmacokinetic parameters. Rather, dosing is either empirical or based on the patient's history of prior response. Exceptions to this

Table 1
Mechanisms of Glucocorticoid Action in Asthma

Inhibitory Effects
Inhibition of leukocyte adhesion/migration
Inhibition of leukocyte activation, function, and survival
T-lymphocytes
Eosinophils
Monocyte/macrophages
Inhibition of the production of cytokines important in the differentiation, proliferation, and activation of inflammatory cells
Interleukin (IL)-2, IL-3, IL-4, IL-5,
Inhibition of the production and/or release of inflammatory mediators
Lipid mediators (platelet-activating factor, leukotrienes, prostaglandins)
Cytokines (IL-1, IL-6,tumor necrosis factor (TNF-α)
Eosinophil-derived cytotoxic proteins such as eosinophil cationic protein, major basic protein
Positive Effects
Stimulation of lipocortin expression
Inhibition of arachidonic acid metabolite synthesis
Vasoconstrictive properties
Decreased edema
Less extravasation of pro-inflammatory mediators
Potentiation of β-adrenergic receptor
Heightened response to β-agonists

are when gross abnormalities of absorption or elimination result in a clinically significant reduction of systemic GC exposure. In this scenario, clinical response to treatment would be expected to be diminished. Prednisone, prednisolone, and methylprednisolone are all rapidly and nearly completely absorbed following oral administration, with peak plasma concentrations occurring within 1–2 h. Of interest, prednisone is an inactive pro-drug that requires biotransformation of the 11-ketone group to an 11-hydroxyl group. This conversion to prednisolone (its active form) occurs via first-pass hepatic metabolism.

Once absorbed, GCs bind to serum proteins with prednisolone binding to transcortin, albumin, and α_1-acid glycoprotein, while methylprednisolone binds primarily to albumin. GCs are metabolized in the liver into inactive compounds. The rate of metabolism or clearance of GCs can be altered by drug interactions and disease states. Hyperthyroid patients require higher GC doses because of enhanced clearance and metabolism. With hypothyroid patients, slowed elimination is a concern; however, this has not been well studied. Cystic fibrosis results in enhanced clearance of prednisolone.

GC elimination may also be altered by numerous concomitant medications (Table 2). Drug interactions may result in either reduced or enhanced clearance and consequently an increased risk for adverse effects or a diminished therapeutic response, respectively. The anticonvulsants phenytoin, phenobarbital, and carbamazepine cause an increased rate of elimination for dexamethasone, prednisolone, and methylprednisolone. Of note, methylprednisolone clearance is most significantly affected. Rifampin also enhances the clearance of GCs and can result in diminished therapeutic effect and breakthrough asthma symptoms in the steroid-dependent patient.Other medications can reduce GC elimina-

Table 2
Potential Drug Interactions With Systemic Glucocorticoids.

Glucocorticoid	*Drugs that increase clearance*	*Drugs that decrease clearance*
Methylprednisolone	Carbamazepine	Ketoconazole
	Phenobarbital	Troleandomycin
	Phenytoin	Erythromycin
	Rifampin	Oral contraceptives
Prednisolone	Antacids (decrease absorption)	Ketoconazole
	Carbamazepine	Oral contraceptives
	Phenobarbital	
	Phenytoin	
	Rifampin	
Dexamethasone	Carbamazepine	
	Phenobarbital	
	Phenytoin	

tion. Significant reductions of GC clearance have been noted with concomitant ketoconazole administration. The macrolide antibiotics erythromycin, troleandomycin, and clarithromycin can also delay GC clearance; however, this effect is limited to methylprednisolone. Clearance rates can be reduced 50–70% with the above macrolides. In addition, oral contraceptive and estrogen-replacement therapy can significantly delay prednisolone metabolism.

If a drug interaction that increases clearance is identified, one can simply increase the GC dose. Alternatively, a "split" dosing regimen may be considered, with two-thirds of the total daily GC dose administered in the morning and the remaining one-third administered in the afternoon. This strategy may provide for a more normal plasma concentration vs time curve and could result in better responsiveness. If these changes offer no benefit, a switch to a GC with a longer half-life, such as dexamethasone, could be another option.

Efficacy of Oral Glucocorticoid Therapy in Asthma

Effect on Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness (BHR), or airway "twitchiness," is an essential feature of asthma. BHR has been shown to correlate with disease severity, frequency of symptoms, and need for treatment. Although the precise relationship remains elusive, airway inflammation is thought to contribute to BHR. High-dose prednisone therapy has been shown to improve pulmonary function and BHR in both adults and children with asthma. Reductions in bronchoalveolar lavage fluid eosinophil counts and reductions in the number of T lymphocytes expressing pro-inflammatory cytokines have also been associated with improved BHR following a short course of high dose prednisone. These observations suggest that GCs, by inhibiting cytokine synthesis, inhibit airway eosinophilia and subsequently lessen BHR.

Effects of Systemic Glucocorticoid on Acute Exacerbations of Asthma in Adults

Systemic GC therapy is considered first-line therapy for the treatment of acute severe asthma. Over the past 50 yr, numerous studies have demonstrated the efficacy of systemic

GC therapy in the outpatient clinic, the emergency room, and in hospitalized patients. Short courses of GC administered in the outpatient department have been shown to decrease the rate of asthma relapse, whereas intravenous methylprednisolone administered in the emergency room can decrease the need for subsequent hospitalization. In studies evaluating the effectiveness of intravenous GC therapy in hospitalized patients, GC therapy is superior to placebo with respect to multiple clinical outcomes. Despite their widespread use, the optimal dose of GC in the acute setting has not been firmly established. In one of the few studies that have attempted to determine a dose response, 40 mg of methylprednisolone was found to be as effective as 125 mg administered every 6 h in patients admitted with status asthmaticus (*see* Fanta et al., 1997). In contrast, a study which evaluated three doses of prednisolone (0.2, 0.4, and 0.6 mg/kg/d) for 2 wk in asthmatics requiring a prednisolone burst because of worsening asthma symptoms found the highest dose to be the most effective (*see* Webb, 1986). There is also no consensus regarding the duration of GC treatment for acute asthma. Because duration of treatment is in part related to the severity of the initial episode, recommendations for the length of treatment must be tailored to the individual case. With that in mind, it has recently been recommended to treat patients admitted in status asthmaticus with at least 36–48 h of intravenous therapy with a transition to oral GC therapy when tolerated. The duration of the oral GC taper will depend on the individual's response but should span 4–12 d.

In summary, systemically administered GCs are highly effective for acute asthma. With that said, a clear consensus on the optimal type, dose, route of administration (oral vs intravenous), and duration of treatment does not exist. A number of protocols outlining systemic GC therapy in acute asthma have been published. Keep in mind that therapy should be tailored to the individual patient's condition. The National Heart, Lung, and Blood Institute (NHLBI, 1997) has recently published its revised guidelines established by an expert panel of asthma specialists (*see* Suggested Reading section). This document recommends either prednisolone, prednisone, or methylprednisolone 120–180 mg/d in three or four doses for 48 h, then 60–80 mg/d until peak expiratory flow (PEF) reaches 70% of predicted or personal best for adults. McFadden (1993), in a review of GC therapy in acute asthma, provides a more complete dosing schedule. He recommends administering methylprednisolone 40 mg intravenously every 6 h or prednisone 60 mg orally every 6–8 h for 36–48 h with a taper to 60 mg prednisone per day when the FEV_1 approaches 50% of predicted. This dose is held for the next 4 d prior to instituting a taper in 4-d intervals reaching 0 mg in 12 d.

Acute Asthma in Children

There have been several studies evaluating the efficacy of systemic GC therapy in children. As with the studies in adults, systemic GC therapy has been shown to be effective in the treatment of acute asthma in children with improvements in PER rate (PEFR), FEV_1, PaO_2, decreased frequency of wheezing, or fewer episodes of relapse. Studies evaluating the effect of a single dose of GC (parenteral or oral) in the emergency department setting have uniformly found this therapy to be superior to placebo in decreasing the number of children who ultimately require admission. As all clinicians who care for children know, the administration of intravenous GC requires placement of an indwelling venous catheter, an often difficult task to perform in an agitated wheezing toddler. A recent study that compared the effectiveness of oral prednisone to intravenous methylprednisolone found both treatment modalities to be equally effective (*see* Becker et al.,

1999). Thus, oral GC therapy is an alternative to intravenous GC therapy in children. The liquid forms of prednisone (Prelone®, Pediapred®, Orapred®) can be administered to infants and young children who cannot swallow pills. In addition, the liquid form is very quickly absorbed, with peak serum levels occurring within 1 h compared to 2 h with tablets.

A study published over 15 yr ago demonstrates how early intervention with oral GC therapy during an acute asthma exacerbation can significantly reduce the progression of asthma symptoms (*see* Harris, et al., 1987). In this study, all of patients randomized to receive prednisone improved during treatment, with only one relapse noted following discontinuation of therapy. In contrast, 42% of those randomized to receive placebo developed worsening asthma symptoms requiring rescue intervention. Because continued asthma symptoms often lead to emergency care and/or hospitalization, this classic study supported the early use of oral steroid therapy for acute exacerbations.

As is the case for adults, issues such as the optimal GC dose, the duration of treatment, and the route of administration in children remain largely empirical and depend largely on the severity of the acute exacerbation. A recent study in children with acute asthma found prednisolone doses of 0.5, 1, or 2 mg/kg/d to be equally effective for the outpatient management of acute asthma (*see* Hewer, et al., 1998). Because orally administered GCs are rapidly absorbed and are usually as effective as intravenous GC, oral therapy can be used in many cases. Hospitalized children who require high flow rates of oxygen to adequately treat hypoxemia are obvious candidates for intravenous GC therapy. In this situation, methylprednisolone sodium succinate (Solu-Medrol®) 1–2 mg/kg as a loading dose followed by 0.5–1 mg/kg every 6 h can be administered. Once oral medications are tolerated, a switch to oral prednisone can be made at a dose of 2 mg/kg/d in two divided dose for an additional 2–4 d followed by a taper to 1 mg/kg/d administered in a single morning dose for an additional 2–4 d prior to stopping. For outpatient management of acute exacerbations, we usually recommend a short course of prednisone 2 mg/kg/d (maximum 60 mg/d) in two divided doses for 2–3 d followed by a reduction to 1 mg/kg in a single morning dose for an additional 2–3 d. Of note, the newly revised NHLBI guidelines recommend administering either prednisone, prednisolone, or methylprednisolone, 1 mg/kg/dose every 6 h for 48 h, then 1–2 mg/kg/d (maximum dose 60 mg/d) in two divided doses until PEF is 70% of predicted or personal best.

Oral GC Therapy in the Management of Chronic Severe Asthma

Inhaled GC therapy has allowed the majority of patients with asthma to maintain good control of their disease. In addition, it has allowed a significant number of patients with severe asthma to reduce or even discontinue their maintenance oral steroid. Unfortunately, a small number of asthma patients continue to require regular use of oral GC despite high-dose inhaled GC therapy and are commonly referred to as steroid dependent asthmatics. Studies performed more than 30 yr ago demonstrated that the therapeutic effects of steroids appeared to persist longer than their metabolic effects. Consequently, several dosage schedules were studied, and a single morning dose of oral GC administered every other day was found to be the most effective in optimizing asthma control while minimizing adverse effects. As a result of these pioneering studies, all patients who require chronic oral GCs should be on alternate-day dosing schedules if at all possible.

There are several management issues to consider when caring for patients with steroid-dependent asthma. First, all other asthma therapy should be optimized including inhaled

GC, long-acting β-agonists, and leukotriene-modifying agents, in addition to judicious use of short-acting β-agonists. Second, the diagnosis of asthma should be firmly established. Third, factors such as inappropriate inhalation technique and poor compliance with asthma medications, environmental control (especially in atopic patients), gastroesophageal reflux, and sinusitis, which can contribute to poor asthma control, should be considered and, if present, adequately treated. Last, given the inevitable development of potentially severe steroid-associated adverse effects, every attempt should be made to determine the lowest possible oral steroid dose administered and, if at all possible, administered on alternate days.

To determine the need for and lowest possible required oral GC dose (i.e., steroid threshold), a gradual taper of the GC should be attempted with close monitoring of the patient's symptoms (nocturnal episodes of wheezing/shortness of breath, degree of exercise-induced bronchospasm, frequency of inhaled bronchodilator use), and pulmonary function (PEFR monitoring, spirometry). The daily oral GC dose can be tapered by 5 mg/wk until 20 mg on alternate days is reached or until breakthrough asthma symptoms or declining pulmonary function is observed. Since most of these individuals will be adrenally suppressed, the taper is then slowed with weekly reductions in the oral GC dose by 2.5 mg every other week with periodic measurement of morning cortisol levels to assess adrenal recovery. If during the GC taper the patient develops increasing asthma symptoms and/or diminished pulmonary function, a beneficial steroid effect is documented and a threshold dose is defined. If the threshold dose is more than 20 mg in adults (or more than 10 mg in children) on alternate days, consideration for alternative asthma medications may be indicated. If one fails to derive a beneficial effect of chronic oral GC therapy, every attempt should be made to safely taper the patient off oral GC therapy completely. If this can be accomplished, many of the debilitating adverse effects associated with chronically administered oral GC therapy can be prevented.

Adverse Effects of Systemic Glucocorticoid Therapy

As all nucleated cells in the body have a common GC receptor, all are potentially affected by GC therapy and thus susceptible to the development of untoward effects. These effects can occur immediately (i.e., metabolic effects) or can develop insidiously over several months to years (i.e., osteoporosis and cataracts). In addition, some adverse effects are limited to children (growth suppression) while others appear to require interaction with other drugs (nonsteroidal anti-inflammatory agents and peptic ulcer disease). Most adverse effects occur in a dose-dependent and duration-of-treatment manner, although this has not been uniformly noted. Table 3 lists many of the common adverse effects associated with chronic GC use.

Osteoporosis

Osteoporosis, a significant and common adverse effect, is often overlooked secondary to its insidious onset and the insensitivity of conventional diagnostic methods. All patients who have been on more than 7.5 mg prednisone (or equivalent) daily for at least 6 mo are at risk for developing osteoporosis. Trabecular bone (ribs, vertebrae) appears to be more affected by GCs than cortical bone. Factors that increase the likelihood of the development of osteoporosis include inactivity, sex hormone deficiency, a diet deficient in calcium and concurrent use of drugs such as furosemide, anticonvulsants, and excessive thyroid hormone replacement. Because demineralization of bone is not detectable

Table 3
Adverse Effects Associated With Systemic Glucocorticoid Use

1. Cardiovascular effects
   - Hypertension, atherosclerosis
2. Dermatolic effects
   - Dermal thinning/increased skin fragility
   - Acne
   - Striae
   - Hirsutism
3. Endocrinologic effects
   - Adrenal suppression
   - Growth suppression and delayed sexual maturation in children
   - Weight gain, development of cushingoid habitus
   - Diabetes mellitus
4. Hematologic effects
   - Lymphopenia, neutrophilia
5. Immunologic effects
   - Diminished IgG levels
   - Loss of delayed-type hypersensitivity
   - Potential for increased risk of opportunistic infection/severe varicella infection
6. Metabolic effects
   - Hypokalemia, hyperglycemia, hyperlipidemia
7. Musculoskeletal effects
   - Osteoporosis/vertebral compression fractures
   - Aseptic necrosis of bone (hips, shoulders, knees)
   - Myopathy (acute and chronic forms)
8. Ophthalmalogic effects
   - Cataracts, glaucoma
9. Psychological/neurological effects
   - Mood swings, depression, psychosis
   - Steroid withdrawal syndrome
   - Pseudotumor cerebri

on conventional radiographs until a significant degree of bone mineral density is lost, the diagnosis of osteoporosis is best made using bone mineral densitometry.

Treatment of osteoporosis, as is the case for all steroid-induced adverse effects, consists of attempting to decrease the oral GC dose and/or frequency, increasing calcium intake to 1000–1500 mg of elemental calcium per day supplemented with at least 400 U/d of vitamin D (Table 4), and increasing physical activity (especially gravity-dependent activities such as walking). Avoidance of activities such as heavy lifting, high-impact aerobics, and contact sports (football, wrestling) is recommended as these activities can result in compression fractures of the vertebral bodies (bending, lifting, contact sports) in addition to fractures of the long bones (contact sports). Patients with severe osteoporosis may require treatment with a remitive medication (e.g., bisphosphonate therapy) and a referral to an endocrinologist.

Myopathy

Two distinct types of myopathy can occur with systemic GC therapy. An acute, severe myopathy associated with short-term high-dose parenteral GC therapy has been reported

Table 4
Management of Glucocorticoid-Induced Osteoporosis

1. Minimize oral glucocorticoid dose to ≤ 20 mg in adults and ≤ 10 mg in children (prednisone or equivalent) on alternate days
2. Increase calcium (Ca^{2+})[a] intake to 1000–1500 mg elemental Ca^{2+}/d
   - Increase dietary calcium intake by eating foods high in calcium
   - Consider additonal calcium in the form of a calcium supplement, such as:
     - Calcium carbonate (40% elemental Ca^{2+})
     - Oscal® 500 contains 500 mg elemental Ca^{2+} per tablet
     - Tums® contain 200 mg elemental Ca^{2+} per chewable tablet
     - Calcium citrate (21% elemental Ca^{2+})
     - Citrical® 950 contains 200 mg elemental Ca^{2+}
     - Calcium gluconate (9% elemental Ca^{2+})
   - Vitamin D supplementation—400 IU/d
3. Increase physical activity: gravity dependent activities such as walking/low-impact aerobics are most effective
4. Avoid heavy lifting, contact sports, and high-impact aerobics
5. Other agents used for severe osteoporosis (with consultation from endocrinologist)
   - Calcitonin
   - Bisphosphonates
   - Calcitriol
   - Sodium fluoride
   - Estrogen (indicated for postmenopausal osteoporosis)

[a]Note that Ca^{2+} is in the form of a salt, thus the amount of elemental Ca^{2+} will be a percentage of the total weight of the tablet unless the label specifies the amount of elemental Ca^{2+} per tablet.

in patients hospitalized with severe asthma exacerbations. Fortunately, this presentation is rare. Affected patients often have markedly elevated serum creatine phosphokinase (CPK) levels and diffuse necrosis of skeletal muscle on biopsy. Recovery begins after GC withdrawal, but more than 6 mo may be required for complete recovery. More commonly encountered is the insidious development of proximal muscle atrophy. Patients receiving daily or large alternate-day GC doses for prolonged periods are at greatest risk. Isokinetic muscle testing (Cybex®) of hip flexor strength appears to be the most sensitive and objective measure of proximal muscle weakness. Enzymes of muscle origin such as CPK, aldolase, and lactate dehydrogenase are almost never elevated, and biopsy of affected muscle reveals atrophy rather than necrosis. To correct and/or prevent GC-induced myopathy, every attempt should be made to taper the GC dose, and a program designed to improve muscle strength initiated.

Cataracts

Posterior subcapsular cataracts are a well described complication of chronic GC use with a prevalence rate of up to 29%. GC-induced cataracts are often small, but can at times significantly affect visual acuity, requiring surgical intervention. Although the development of cataracts appears to be related to the daily dose, cumulative dose, and the duration of treatment, there is a significant degree of variability with respect to individual susceptibility to cataract formation. It is not known whether GC dose reduction will result in regression or disappearance of the cataract, although some studies suggest that if recog-

nized early, regression can occur. A yearly ophthalmological exam to evaluate for the presence of cataracts is recommended for all patients receiving maintenance oral GC therapy.

Growth Suppression

Growth suppression is the GC-associated adverse effect that causes the most concern for clinicians caring for children. Regular daily therapy, frequent short courses, or high-dose alternate-day GC therapy often results in suppression of linear growth. Doses of prednisone as small as 0.1 mg/kg administered daily for as short a period as 3 mo has resulted in significant suppression of linear growth. When a GC is administered on alternate days, the degree of suppression may be less, but significant growth suppression can still occur. Complicating the issue of GC-induced growth suppression is the finding that asthma itself can impair growth. This is a significant issue especially as it pertains to whether chronic inhaled GC therapy is associated with growth suppression. Because daily or high-dose alternate-day GC therapy for extended periods of time can result in permanent growth retardation, every effort should be made to decrease the amount of oral GC to less than 20 mg on alternate days. If the child's oral GC dose cannot be tapered to 20 mg or less on alternate days, treatment with recombinant growth hormone (GH) can be considered. GH therapy can increase linear growth in children on chronic GC therapy, but the response is dependent on the dose of GC administered; the higher the daily dose of prednisone, the less effective GH therapy is.

Adrenal Insufficiency

Patients who are adrenally suppressed as a consequence of oral chronic GC therapy are at risk of developing acute adrenal insufficiency at times of stress such as surgical procedures, gastroenteritis resulting in dehydration, or trauma. Patients who develop acute adrenal insufficiency can present with dehydration, shock, electrolyte abnormalities, severe abdominal pain, and lethargy out of proportion to the severity of their presenting illness. This is a medical emergency and requires prompt diagnosis and rapid treatment with intravenous hydrocortisone (2 mg/kg initially followed by 1.5 mg/kg every 6 h until stabilization is achieved and oral therapy is tolerated) and vigorous fluid replacement with normal saline if dehydration and hypotension are present. All patients on chronic high-dose GC therapy should be considered adrenally suppressed and should wear a medical alert bracelet that identifies them as being at risk for acute adrenal insufficiency. All adrenally suppressed individuals should be given hydrocortisone at the time of any surgical procedure (1–2 mg/kg) and every 6 h thereafter for the next 24–48 h with a switch to their usual oral GC dose when oral medications are tolerated. The same recommendations are to be followed at other times of acute stress. Complete recovery from adrenal suppression can take from 6 mo to 1 yr after cessation of long-term GC use. Thus, all patients with a history of chronic GC use should be considered adrenally suppressed and should be managed as such for up to 1 yr following cessation or significant reduction of oral GC therapy.

Other Adverse Effects

Other common adverse effects of chronic GC therapy include increased appetite with weight gain and the development of a cushingoid habitus consisting of a moon facies, buffalo hump, central obesity with wasting of the extremities, atrophy of the skin with the development of striae, and hirsutism. Psychological disturbances from increased emo-

tional lability to frank psychosis can occur, as well as hypertension, peptic ulcer disease, atherosclerosis, aseptic necrosis of bone, and diabetes mellitus. Chronic GC use can also result in immunologic attenuation with loss of delayed type hypersensitivity, diminished IgG levels without change in functional antibody response, potential for reactivation of latent tuberculosis infection, and possible increased risk for infection especially the development of severe varicella.

INHALED GLUCOCORTICOID THERAPY

Effective and safe forms of inhaled GCs were first introduced in the early 1970s with the development of drugs and delivery devices, which provided optimal topical to systemic potency. By effectively delivering small quantities of a potent GC directly into the airway, inhaled GC therapy maximizes the beneficial effects while minimizing the systemic effects associated with chronic GC use. Although these medications had been available for nearly 30 yr, their use, especially in pediatric patients, had been limited to those patients with severe asthma. As our understanding of asthma has changed, with increasing emphasis on airway inflammation even in mild asthma, inhaled GCs are now considered first line therapy in all patients including children with persistent asthma (*see* National Asthma, 2002).

Efficacy of Inhaled Glucocorticoid Therapy

As mentioned previously, BHR is an important feature of asthma. Studies evaluating the effect of inhaled GC therapy in asthma have consistently demonstrated a favorable effect on BHR in both adults and children. Decreases in BHR from two- to sevenfold have been reported within 6 wk of instituting inhaled GC therapy. In addition, associated with the improvement in BHR come reductions in asthma symptoms, improved pulmonary function, less need for supplemental β-agonist use, and fewer exacerbations requiring oral GC therapy. There have now been more than 100 publications demonstrating reductions in airway inflammation after instituting inhaled GC therapy. Specifically, significant reductions in the number of inflammatory cells, the number of cells expressing pro-inflammatory cytokines, and the number of activated inflammatory cells have been noted. In addition, inhaled GC therapy has recently been shown to be effective in decreasing the thickness of the basement membrane of asthmatics. Basement membrane thickening is a characteristic finding in chronic asthma, and although its role in the pathophysiology of asthma is unclear, it may contribute to the development of chronic and potentially irreversible airflow obstruction. In summary, chronic administration of inhaled GC therapy results in improvement in lung function, BHR, symptoms, and need for supplemental β-agonist use, in addition to significant reductions in airway inflammation.

Recent studies have demonstrated inhaled GCs to protect against asthma morbidity and even mortality. Specifically, they have shown inhaled GC therapy to result in significant reductions in need for prednisone, emergency room visits, and hospitalizations owing to acute asthma. Donahue et al. (1997) found asthmatics on inhaled GC to be 50% less likely to be hospitalized with acute asthma compared to those not on inhaled GC. Using frequency of as needed β-agonist therapy as a surrogate marker of disease severity, they found GCs to confer even greater protective effects in patients requiring over eight canisters of albuterol per year with a 70% reduction in the rate of hospitalization noted. Suissa et al. (2000) found inhaled GCs to significantly reduce the risk of death from

asthma in a large epidemiologic study. They found that individuals on low-dose beclomethasone dipropionate (200 μg/d) were 50% less likely to die from acute asthma compared to age- and severity-matched asthmatics not on regular inhaled GC therapy. No other class of asthma medication has been shown to reduce morbidity and mortality to the same extent as inhaled GCs.

Inhaled Glucocorticoids as First-Line Therapy

Inhaled GCs were initially reserved for use in patients with moderate to severe asthma, but as our understanding of this disease has advanced, inhaled GCs are now recommended as first-line therapy in all patients with persistent asthma including children. This recommendation was made in the 2002 Update to the NHLBI Guidelines and was based on a comprehensive review of both the efficacy and safety of long-term inhaled GC use in childhood asthma. This review found inhaled GCs to be the most extensively studied controller class of medications. In addition, studies have consistently demonstrated inhaled GCs to be more effective than the other classes of controller agents. Last, and most important, two landmark studies were published in 2000 that demonstrated the long-term safety of inhaled GC therapy in children with mild to moderate asthma (*see* CAMP study and Agertoft and Pedersen, 2000).

Further support of using inhaled GCs earlier in the course of the disease come from studies that suggest that inhaled GC therapy is most effective if begun within the first couple years of diagnosis. These studies found inhaled GC therapy to be effective in decreasing asthma symptoms and supplemental β-agonist use and improving pulmonary function. More importantly, they found that the longer the individuals had asthma before instituting inhaled GC therapy, the less significant their response to therapy with respect to improvement in baseline lung function and BHR. The results from these studies suggest that the longer the time from the initiation of symptoms and subsequent treatment with inhaled GC, the less effective the therapy will be. Although speculative, the loss of response may be a result of the development of some degree of irreversible airflow obstruction secondary to airway remodeling.

Types of Inhaled Glucocorticoid

There are currently five inhaled GCs available for use in the United States: beclomethasone dipropionate (BDP), marketed as Qvar®, which is available in 40 and 80 μg per actuation, triamcinolide acetonide, marketed as Azmacort®, which delivers 200 μg from the canister but only 100 μg per inhalation from the built-in spacer device, flunisolide, marketed as Aerobid®, which delivers 250 μg per actuation, fluticasone propionate (FP), marketed as Flovent, which is available in three doses—44, 110, and 220 μg/actuation—and budesonide (BUD), marketed as Pulmicort® Turbuhaler (200 μg/actuation) and Pulmicort Respules® (0.5 and 1.0 mg). Recommended dosages for both adults and children for all of the inhaled GCs are listed in Table 5. BUD and FP are thought to be second generation inhaled GCs in that they appear to have greater topical-to-systemic potencies. BUD and FP have recently been shown to have oral GC-sparing effects in adults with steroid-dependent asthma. Few if any studies have attempted to compare the clinical efficacy of the available inhaled GCs. FP is thought to be roughly twice as potent as the other available inhaled GCs. In addition, high dose FP therapy ($\geq$1000 μg/d) has been shown to result in two to four times greater suppression of adrenal function than equivalent doses of BUD. Thus, it appears as if FP may be more potent than the other inhaled GC products on the market in terms of both efficacy and potential for systemic effects at high doses.

Qvar® is the latest product to reach the market. It is unique in that, although the drug has been available for decades, its delivery is novel. Qvar® uses the ozone-friendly propellant HFA, as opposed to chlorofluorocarbon (CFC). BDP, when combined with hydrofluoroalkane (HFA) is present in a solution, as opposed to being in a suspension when a CFC is used as the propellant. This results in a smaller mean diameter size (1.1 μm vs 3.5–4.0 μm) and enhanced lung deposition and greater delivery to the distal portions of the lung. As a result, lower doses of BDP using an HFA-containing pressurized metered-dose inhaler provide equivalent to superior efficacy compared to BDP delivered using the traditional CFC propellants.

Dose/Frequency of Use

The dose of inhaled GC chosen is largely dependent on the clinical situation. The more severe or poorly controlled the asthma, the higher the initial dose (*see* Table 5 for recommended doses). High-dose inhaled GC therapy is often used in an attempt to rapidly optimize pulmonary function and clinical symptoms. Once asthma control is optimized, the dose is tapered, following clinical symptoms and pulmonary function closely. The ideal inhaled steroid dose should be large enough to control asthma symptoms, yet small enough to avoid the potential for adverse systemic effects.

Adverse Effects of Inhaled GC Therapy

Adrenal Suppression

Inhaled GC therapy can result in suppression of the hypothalamic–pituitary–adrenal (HPA) axis. The degree of suppression is largely dependent on the dose and frequency of the inhaled GC delivered, the duration of treatment, route of administration, and the time of day the drug is administered. The preponderance of data would suggest that doses of 400 μg/d or less are not associated with changes in the HPA axis, but as the inhaled dose is increased to over 1000 μg/d, HPA axis suppression clearly occurs. Although FP is thought to have systemic effects comparable to the other inhaled GCs at doses recommended for the treatment of mild and moderate asthma (176–440 μg/d), the same cannot be said regarding high-dose FP therapy (≥1000 μg/d). A number of studies have demonstrated significantly greater HPA axis suppression with FP compared to equivalent doses of BUD. In addition, there have been a few case reports of children who developed acute adrenal insufficiency while on high-dose FP therapy (≥1000 μg/d). Because FP is twice as potent as the other inhaled GCs, one should only use high-dose FP in patients with severe, poorly controlled asthma or in patients with steroid-dependent asthma.

Growth Suppression

Growth suppression is the steroid-associated adverse effect that causes the most concern for clinicians caring for children. Whether clinically significant growth suppression occured with chronic inhaled GC therapy had been until recently inadequately studied. In the late 1990s, a number of studies suggested that doses of as little as 400 μg/d of BDP could result in suppression of linear growth. Unfortunately, these studies were limited by the short duration of the study (1 yr or less). In addition, in many, the pubertal status was not adequately assessed, or baseline growth velocity data was lacking, or there were significant differences in baseline height or age between the different treatment groups at entry into the study. Complicating this issue further was the long known but often

Table 5
Dosage Guidelines Presented in National Asthma Education Program Expert Panel Report Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002

Adults

Glucocorticoid	*Low daily dose*	*Medium daily dose*	*High daily dose*
Beclomethasone CFC 42 μg/puff 84 μg/puff	168–504 μg (4–12 puffs) (2–6 puffs)	504–840 μg (12–20 puffs) (6–10 puffs)	>840 μg (>20 puffs) (>10 puffs)
Beclomethasone HFA 40 or 80 μg/puff	80–240 μg	240–480 μg	>480
Budesonide Turbuhaler 200 μg/dose	200–400 μg (1–2 inhalations)	400–600 μg (2–3 inhalations)	>600 μg (>3 inhalations)
Flunisolide 250 μg/puff	500–1000 μg (2–4 puffs)	1000–2000 μg (4–8 puffs)	>2,000 μg (>8 puffs)
Fluticasone propionate MDI: 44, 110, 220 μg/puff	88–264 μg (2–6 puffs—44 μg) or (2 puffs—110 μg)	264–660 μg (2–6 puffs—110 μg) or (>3 puffs—220 μg)	>660 μg (>6 puffs—110 μg)
Triamcinolone acetonide 100 μg/puff	400–1000 μg (4–10 puffs)	1000–2000 μg (10–20 puffs)	>2000 μg (>20 puffs)

Children

Glucocorticoid	*Low dose*	*Medium dose*	*High Dose*
Beclomethasone CFC 42 μg/puff 84 μg/puff	84–336 μg (2–8 puffs)	336–672 μg (8–16 puffs)	>672 μg (>16 puffs)
Beclomethasone HFA 40 or 80 μg/puff	80–160 μg	160–320 μg	>320
Budesonide Turbuhaler 200 μg/dose	100–200 μg (1 inhalation)	200–400 μg (1–2 inhalations)	>400 μg (>2 inhalations)
Budesonide suspension for nebulization	0.5 mg	1.0 mg	2.0 mg
Flunisolide 250 μg/puff	500–750 μg (2–3 puffs)	1000–1250 μg (4–5 puffs)	>1250 μg (>5 puffs)
Fluticasone propionate MDI: 44, 110, 220 μg/puff	88–176 μg (2–4 puffs—44 μg)	176–440 μg (4–10 puffs—44 μg) or (2–4 puffs—110 μg)	>440 μg (>4 puffs—110 μg)
Triamcinolone acetonide 100 μg/puff	400–800 μg (4–8 puffs)	800–1200 μg (8–12 puffs)	>1200 μg (>12 puffs)

overlooked observation that asthma, especially poorly controlled asthma, can adversely affect growth.

Two long-term studies published in 2000 helped put into perspective the effect of inhaled GCs on growth. In the largest and longest placebo-controlled trial performed to date in children with asthma, the Childhood Asthma Management Program (CAMP;

2002) study found children who had received 4.3 years of BUD therapy to be 1.1 cm shorter than those who received placebo. Of significance, the loss of growth velocity occurred primarily in the first year of therapy, and using the Tanner equation to calculate expected adult height, the expected adult was calculated to be 174.8 cm for both the BUD- and placebo-treated groups. The CAMP study strongly supports the contention that inhaled GC therapy can result in a modest but transient effect on growth that is unlikely to have any adverse effect on adult height.

This point was further strengthened by the article from Agertoft and Pedersen (1998). In this study, the investigators followed 211 children until they attained adult height: 142 treated with BUD (mean dose 412 μg/d for a mean of 9.2 yr), 18 asthmatics not treated with inhaled GCs, and 52 healthy nonasthmatic siblings of the BUD-treated patients. The investigators found no difference in the measured vs the expected adult heights in any of the groups studied. In addition, no statistically significant correlations were found between duration of treatment and cumulative dose of BUD. Of note, these investigators also noted a transient suppression of growth during the first few years of therapy, but it did not adversely impact adult attained height.

Osteoporosis

Despite the fact that osteoporosis can be a debilitating complication of oral GC therapy, there has been a paucity of studies evaluating the effect of inhaled GCs on bone metabolism, and more importantly, bone mineral density (BMD). Some studies have found significant reductions in BMD of the femoral neck of asthmatics treated with inhaled GCs compared to age-matched controls, with significant inverse correlations found between BMD and the dose duration (product of the average daily dose of inhaled GC in grams and the duration of therapy in months) of inhaled GC therapy. Of note, other studies have failed to demonstrate any deleterious effect on BMD.

Given the discrepancy in results among the above studies, Toogood et al. (1995) sought to differentiate between the effect of inhaled GCs compared to the potential effect of other variables such as past or current oral GC use, age, physical activity level, and postmenopausal state on bone density. They found inhaled GC therapy to result in a dose-dependent reduction of BMD with a decrease of approx 0.5 standard deviations for each increment of inhaled GC dose of 1 mg/d. Of surprise, a larger lifetime exposure to inhaled GCs was associated with a more normal BMD. The authors speculated that this "protective effect" was a result of reconstitution of BMD following conversion from oral to inhaled GC therapy. Bone mineral density measurements were performed yearly as part of the CAMP study. At the end of the study there was no difference in the BMD among the three groups studied, suggesting that long-term BUD therapy had no adverse effect on BMD in a large cohort of children with mild-to-moderate asthma. In summary, many factors appear to contribute to the development of osteoporosis, including dose, frequency of administration, and duration of use in addition to time of use above a "threshold" dose.

Cataracts/Glaucoma

Recent reports have suggested that chronic inhaled GC therapy can be associated with the development of cataracts and/or glaucoma. These large epidemiological studies found weak but statistically significant associations between inhaled GC therapy and either cataracts or glaucoma. Of note, these studies evaluated elderly individuals with mean ages of at least 65 yr. In addition, the studies failed to provide any indication of clinical

significance or visual impairment. Agertoft and Pedersen (1998) performed slit-lamp evaluations on 157 asthmatic children on BUD an average of 4.5 yr and in 111 age-matched, asthmatic controls with only one posterior subcapsular cataract identified. This was in a child receiving BUD, but this was a known cataract with the diagnosis made 2 yr before the child was placed on BUD therapy. Upon completion of the CAMP study, all children underwent eye exams for cataracts with one possible cataract identified. Thus, long-term treatment with inhaled GCs in children is unlikely to cause cataracts and ophthalmological surveillance is probably not warranted.

Other Adverse Effects

A number of other adverse effects have been associated with inhaled GC therapy, including hypoglycemia, the development of cushingoid features, opportunistic infections, dermal thinning, and psychosis. Most of these adverse effects have been reported as case reports, with few controlled studies performed to objectively evaluate the potential for and significance of these complications.

CONCLUSION

GCs are an important pharmacological modality in asthma therapy. Systemically administered GCs are first-line agents for acute severe asthma, whereas inhaled GCs are first line agents for the long-term management of all patients with persistent asthma. It is a well-established fact that long-term systemic GC therapy can result in serious adverse effects. Fortunately, inhaled GC preparations have been developed that greatly minimize the systemic adverse effects while retaining beneficial airway effects. Many previously steroid-dependent asthmatics have been tapered off oral GC following institution of inhaled GC therapy. As with oral GC therapy, high-dose inhaled GC therapy can result in systemic adverse effects. Of importance, recent studies suggest that low-dose inhaled GC therapy, even when administered long term, is unlikely to result in any clinically meaningful adverse effects. By using the lowest possible effective GC doses, as well as maximizing other therapeutic modalities, adverse systemic effects from GCs can be greatly minimized.

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24 Anti-IgE Therapy

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CONTENTS

SUMMARY

The development of a drug to affect the basic cause of allergic disease has invigorated practicing allergists' interest in the intricate molecular and cellular processes occurring in allergic reactions. An anti-immunoglobulin (Ig)E antibody is not merely a chemical blocking agent, but possesses potential multiple immunoregulatory effects. A lead product, omalizumab, a recombinant humanized IgG1 antibody with a unique set of binding specificities toward human IgE, has been approved in the United States and Australia for treating adult and adolescent patients with moderate to severe asthma. Applications of this biopharmaceutical in treating allergic rhinitis and for protecting against anaphylactic reactions to peanuts are in active development. It may also have an important role in protection against anaphylaxis during standard antigen specific immunotherapy, providing safety and the ability to more aggressively extend this traditional therapy

Key Words: Omalizumab; humanized antibody; immunoregulatory; receptor downregulation; antigen sweepers; immune balance; anti-IgE; immunotherapy; anaphylaxis.

APPROACH TO ALLERGIC DISEASES

Background

Anti-immunoglobulin (Ig)E is the first commercially available agent designed to interrupt the progression of disease by deactivating antibody IgE to prevent mast cell deregulation and the resulting inflammatory process associated with allergy. Omalizumab, a humanized monoclonal IgG antibody with a unique set of binding specificities toward human IgE, is the first biologic approved for the treatment of asthma. This therapeutic

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anti-IgE binds to free human IgE in blood and in interstitial fluids with very high affinity. However, it does not bind to the IgE that is already bound by the high-affinity IgE.Fc receptors (FcεRI) on mast cells and basophils and to the low-affinity IgE.Fc receptors (FcεRII, also referred to as CD23) on B-cells, granulocytes, platelets, and many other cell types. Unlike an ordinary anti-IgE antibody, this therapeutic anti-IgE does not sensitize mast cells and basophils. Anti-IgE has also the ability to bind to membrane-bound IgE-expressing B-cells, which may downregulate the development new IgE-producing cells. Anti-IgE may have multiple immunomodulary effects other than simply tying up IgE antibody.

Chemistry

Commercially available anti-IgE, omalizumab, is a recombinant DNA-derived humanized monoclonal IgG1 antibody. The basic framework segments in the variable domains and the entire constant domains of γ1 heavy chain and κ light chain are derived from human immunoglobulins. The complementary-determining regions (CDRs), which form the antigen-binding sites, are derived from a parental murine anti-IgE antibody. The CDRs, also referred to as hypervariable regions, are individually unique among antibodies and generally not seen by the immune system. Omalizumab does not induce antibody response in patients, who had received multiple injections of the therapeutic antibody over a period of many months. This is particularly important since recent studies have suggested that mouse antibody sensitization as demonstrated by positive prick tests are seen in as many as 13% of the normal population.

To produce this molecule, a mouse hybridoma cell line was developed that secretes an anti-IgE antibody with the desired set of binding specificities toward human IgE. The anti-IgE products were also screened for their ability to bind to the membrane-bound IgE (mIgE) on the surface of IgE-expressing B-cells, which should include IgE-expressing B-lymphoblasts and memory B-cells. Such a property was regarded as important, because the elimination or downregulation of IgE-expressing B-cells is crucial for anti-IgE to achieve a shift in immune balance and to achieve a longer-term therapeutic effect. The molecular basis for achieving such a unique set of binding specificities is possible because the binding sites on IgE for anti-IgE, FcεRI, and FcεRII are all located on the CH3 domain, overlapping or being in the close vicinity.

The RNA from this hybridoma line was extracted, the genes encoding the variable regions of the antibodies cloned and sequenced, and CDR segments identified. Genes encoding the whole-length humanized γ1 and κ chains were then constructed and inserted into an antibody-expressing plasmid cassette. This was transfected into a Chinese Hamster Ovary (CHO) cell-line host (a mammalian cell line used for the manufacturing of most of the antibody products approved for marketing by the the US Food and Drug Administration [FDA]) for expressing the genes and screened for those that produced the humanized anti-IgE at high yield. The cell lines were then adapted to grow in a serum-free medium for adaptation to culturing in large bioreactor tanks. The commercial omalizumab product is now produced by CHO cell line in 12,000-L bioreactors.

Pharmacodynamics

After subcutaneous injection, the antibody is dissipated in the blood circulation and interstitial space of the entire body in less than 24 h with a bioavailability of approx 60%. Dosing is set to reduce free IgE to10 ng/mL or less. The minimum effective dose to

achieve that goal being 0.016 mg/kg (U/mL) sq every 4 wk adjusted for body weight and baseline IgE antigen load.

Pharmacokinetics and Metabolism

In the absence of reaction with IgE, omalizumab (anti-IgE) has a half-life of about 22 ± 8 d, similar to that of its native human IgG1 framework. The elimination of injected anti-IgE is related to the concentrations of omalizumab and IgE, since the formation of the immune complex by existing and the newly synthesized IgE consumes free omalizumab. As free IgE falls, the concentrations of the immune complexes formed by omalizumab (IgG1) and IgE increase, reaching levels that could result in an apparent IgE level from 3 to 10 times the pretreatment basal levels of IgE. This occurs because currently available measurements read complexed IgE and free IgE identically.

Theoretically, omalizumab, which has two binding Fab arms, and IgE, which has two sites for the binding by omalizumab, can form complexes of very large lattices. It is reassuring that the complexes formed by omalizumab and IgE in the treated patients are small, with the largest containing three omalizumab IgG and three IgE molecules. These complexes are soluble and stable, suggesting the immune complexes do not deposit in kidneys and do not elicit antibody response in the treated patients.

An Entirely New Method of Managing Allergic Diseases

By effectively neutralizing free allergic antibody, anti-IgE is both therapeutic for existing disease and preventive for anticipated allergic states. It does not relieve symptoms immediately like those chemical agents, such as antihistamines, leukotriene receptor antagonists, and bronchodilators, nor is it an anti-inflammatory agent like corticosteroids. However, it chokes off the pathway leading to the sensitization of mast cells, basophils, and activated eosinophils and their discharge of inflammatory mediators. It has also has other regulatory effects, which desensitize the allergic responsiveness.

IGE AS AN ATTRACTIVE THERAPEUTIC TARGET

IgE ss a Mediator for Many Types of Allergic Diseases

The state of atopy of a person toward certain antigens is created by the generation of IgE-specific antibodies for those antigenic substances, but not all IgE in a person reflects specific sensitization. IgE is well known for playing a central role in the pathogenesis of allergic rhinitis and anaphylactic reactions to foods, drugs, and insect stings. In many studies carried out on patients living in communities in the Western world, elevated IgE levels have been shown to be associated with the risk of developing asthma, although its exact role in the pathogenesis of asthma is not clear. A series of clinical trials demonstrated that anti-IgE effectively attenuates the early- and late-phase reactions and improves symptoms of asthmatic patients. These studies have unambiguously confirmed the association of the IgE antibody and asthma.

IgE in Mast Cell and Basophil Sensitization

Mast cells in tissue and circulating basophils in the blood are the two primary cell types sensitized by allergenic molecules to release inflammatory mediators. In nearly all human subjects, these cells express in a resting state on the surface a high density of high-affinity IgE.Fc receptors (also referred to as type I IgE.Fc receptors, FcεRI), which are almost

entirely occupied by IgE. The cells are armed and irritable. When allergenic molecules (antigens) contact the mast cells or basophils, they are bound by FcεRI-bound IgE specific for the allergen molecules. Because an allergenic protein has multiple antigenic sites, the binding by IgE causes the crosslinking of the IgE and hence the aggregation of the underlying FcεRI to almost instantaneously trigger the cells to release the contents of the granules via exocytosis.

IgE Acting Upstream in the Allergic Pathway

The symptoms of an allergic disease may be caused by multiple hypersensitivity reactions involving IgE, other classes of antibodies, and effector T cells. In some allergic states, such as contact skin hypersensitivity, IgE is not the central mechanism. It is understood, however, that in most cases of allergic rhinitis, anaphylactic reactions to foods and drugs, and probably in the majority of cases of allergic asthma (now that anti-IgE has been shown to alleviate the symptoms of allergic asthma in clinical studies), type I hypersensitivity is responsible for the pathogenesis of the disease using IgE as the major mediator.

IgE is an attractive molecular target because it holds a pivotal step upstream in the allergic pathway leading to the discharge of various mediators. Conceptually, targeting IgE would seem more effective than targeting one of the mediators. Mechanistically, a therapeutic intervention can be achieved by targeting the IgE itself and/or the cells or processes that produce IgE. Additional considerations, such as that IgE appears dispensable for normal immune defense (discussed later), have made IgE an attractive target for therapeutic intervention.

HOW ANTI-IGE WORKS

The Unique Binding Properties of Therapeutic Anti-IgE

Antibodies specific for human IgE can bind to IgE, which is already bound by FcεRI and hence can crosslink IgE and sensitize mast cells and basophils even better than allergenic proteins. The anti-IgE therapeutic products can bind to free IgE specifically with high affinity; they cannot bind to and sensitize basophils isolated from even the most sensitive human subjects; they cannot bind to the IgE already bound by the low-affinity IgE.Fc receptors (also referred to as type II IgE.Fc receptors, or FcεRII, or CD23) on the surface of B-cell lines.

Direct Pharmacological Effects of Anti-IgE

Free IgE is reduced to near zero levels. In clinical studies of anti-IgE, free IgE in blood was conservatively reduced to less than 15% of the original level. It is important to note that when the anti-IgE therapy was introduced in the late 1980s, immunologists were generally skeptical of such an approach, arguing that even 1 or 0.1 % of IgE left free would be sufficient to cause the arming and the sensitization of mast cells and. But clinical trials show definite therapeutic response regardless of the minimal levels of IgE remaining free.

The effects on IgE-expressing B cells are not clear: The inhibitory effect was regarded as a key part in the screening of the therapeutic antibodies because if such a mechanism occurs, anti-IgE can then drive the balance between IgE and non-IgE-related mechanism to the non-IgE arena. At the present time, whether anti-IgE actually downregulates the

production of IgE is not clear. This is because the IgE-secreting long-living plasma cells, which express very low levels of mIgE and are not targets of anti-IgE, continue to produce IgE, making the analysis of possible effects of anti-IgE on IgE-expressing B-cells difficult to achieve.

The Downregulation of IgE Receptors

The drastic decrease of free IgE levels produces a profound downregulation of FcεRI on basophils, mast cells, and dendritic cells. Basophils have a life span of only a few days and are continually replenished by new cells. As the new cells are generated, the low levels of free IgE do not signal the cells to express a maintenance level of FcεRI. Thus, in 3 wk, the FcεRI on basophils decreases about 50%, and by 3 mo, to less than 5% of the original levels. The loss of FcεRI on basophils renders those cells insensitive to stimulation by antigens.

Mast cells have very long life spans. The decline of FcεRI on those cells appears to follow a mechanism different from that of basophils. The FcεRI without bound IgE has a faster turnover or reshuffling than FcεRI with bound IgE. Thus, as the proportion of unbound FcεRI increases by only a small fraction, the FcεRI is gradually decreased. It should be noted that while the asthmatic symptoms of most patients treated with omalizumab improve, the skin-test reactivity is variable and remains unchanged in some patients, prompting some to suggest that the downregulation of FcεRI and the loss of sensitivity toward allergens may affect mast cells underlying the mucosal surface and beneath the skin differently.

How Fast Does Anti-IgE Work?

Some patients make significant improvement after 1 or 2 wk of the first treatment with anti-IgE (TNX-901 or omalizumab). The downregulation of FcεRI on basophils and mast cells cannot account for this early response because the decrease of FcεRI on basophils and mast cells will take many weeks or a few months to reach physiologically significantly low levels. Therefore, additional mechanisms must also play important roles in the pharmacological actions of anti-IgE.

The rapid accumulation of IgE–anti-IgE immune complexes to levels of 3–10 times the basal IgE levels during the first 2 wk with anti-IgE treatment may play an important role in the actions of anti-IgE. These immune complexes can still bind allergen molecules and potentially function as an antigen buffer.

Most researchers recommend a trial of 3 mo of anti-IgE be done to assay the clinical efficacy of anti-IgE in asthma.

Anti-IgE Works for Different Allergens and Different Symptoms

Allergic patients are sensitive to their distinctive sets of allergens. However, the cellular and molecular processes leading to the generation of IgE, the sensitization of mast cells and basophils, and the manifestation of symptoms are the same. In contradistinction to specific allergy immunotherapy, anti-IgE is nonspecific.

Another important aspect of anti-IgE therapy is that it works upstream in the IgE pathway at several steps (*see* next section), all of which are above the release of pharmacological mediators. This makes anti-IgE distinct from most existing drugs, such as anti-inflammatory agents and bronchodilators.

Long-Term Therapeutic Effects Still to Be Investigated

The FDA-approved regimen for the administration of omalizumab is once every 2 wk or every month for indefinite periods. During the clinical trials of anti-IgE, some doctors observed that some patients posttherapy seemed to require less pretreatment asthma medication—an observation not yet documented in rigorous fashion. Questions arose whether anti-IgE can modify the allergic disease process. Conceptually, when the IgE pathway is blocked off by anti-IgE, especially if IgE-expressing B lymphoblasts and memory cells are affected, the continual exposure of patients to allergens should cause a shift of immune response to non-IgE-related pathways. If this occurs, the disease process causing allergic states could be modified.

Other direct or indirect effects of anti-IgE are that allergens may be diverted to an antigen presentation pathway that favors IgG response. Allergen–IgE complexes normally bind to CD23 (FcεRII) on B-cells or FcεRI on dendritic cells, favoring IgE responses. Since the tripartite allergen–IgE–anti-IgE complexes can no longer bind to CD23 and FcεRI and will bind to IgG.Fc receptors, immune responses that do not favor IgE production are created.

HUMAN EXPERIENCE WITH ANTI-IGE THERAPY

Clinical Studies

Three forms of anti-IgE antibodies have been studied in human clinical trials, with the majority of studies using omalizumab. Multiple phase 2 and 3 studies were performed on adult and adolescent patients with asthma, pediatric patients with asthma, patients with seasonal allergic rhinitis, patients with perennial allergic rhinitis, and patients with concomitant allergic asthma and persistent allergic rhinitis. Phase 3 studies were done on allergic rhinitis patients with both tree pollen sensitivity in the spring and weed sensitivity in the fall, investigating the effect of anti-IgE in combination with specific immunotherapy. A phase 2 trial was done on patients with severe sensitivity to peanuts and another on patients with sensitivity to latex.

More than 6000 patients have received anti-IgE for 6–12 mo during the various clinical studies with an additional clinical pool of 14,000–16,000 in the first year since approval.

Patient Response

Based on the results of the clinical studies and the experiences of patients using the commercial product, most, but not all patients respond well to omalizumab. Why some patients do not respond well is perhaps the most interesting question in the continual development of the anti-IgE therapeutic concept. Inclusion for clinical studies and the approval for using the commercial product require that a patient must be skin-test positive for a perennial allergen, but the causal relationship of the antigen to the disease process was not established. It is possible that in some allergic patients, the immunological processes causing the tissue damage in the inflamed lung has progressed past IgE-mediated mechanisms, and even though the IgE-mediated process is taken away, the improvement will not be evident for some time, if ever.

Is it also possible that in some of those nonresponders, IgE-mediated type I hypersensitivity is not a primary cause of asthmatic symptoms. Finally, although allergen-specific IgE accounts for very high proportions in total IgE, and although the free IgE concentrations are very low and the densities of FcεRI on basophils and mast cells are also very low, they are sufficient to cause IgE crosslinking and degranulation.

Anti-IgE on Symptoms, Corticosteroids, and Quality of Life

In the earlier phase 3 clinical studies for asthma, patients with moderate to severe symptoms were stabilized with the use of inhaled corticosteroid. In more recent phase 3 trials for asthma, patients with moderate to severe asthma were maintained during the trial period with not only inhaled corticosteroid but also long-acting β-agonists. The goal of the studies was to investigate whether anti-IgE could improve those asthmatic patients whose symptoms were poorly controlled with inhaled corticosteroid or with the combination of inhaled steroids and long-acting βagonists.

The results of the studies indicate that anti-IgE significantly reduces asthma-deterioration-related incidences, which include asthma exacerbations, unscheduled physician visits, and absenteeism from work or school. In most of the clinical studies, anti-IgE was also shown to reduce or eliminate the use of inhaled corticosteroids. In all of the studies performed for asthma, questionnaires were designed for patients and study clinicians to assess the changes in the quality of life of the study patients. Anti-IgE was clearly shown in all studies to significantly improve the quality of life of patients. As a subset of quality of life, improvements in activity were among the most dramatic.

Anti-IgE has also been shown in multiple phase 2 and 3 studies to be efficacious in reducing nasal and ocular symptom scores and the dependence on inhaled corticosteroids and improving the quality of life for patients with seasonal or perennial allergic rhinitis. In a study done on patients with severe sensitivity to peanuts with TNX-901, patients were challenged with oral capsules filled with peanut flour. It was shown that anti-IgE increase the tolerability of patients to much larger amounts of peanuts. Anti-IgE has also been investigated in health care workers with occupational latex allergy, providing a possible partial solution to some with an otherwise insolvable problem.

Adverse Events

The adverse events are related to the injection of a protein substance, and the rates of incidences are similar between anti-IgE- and placebo-treated patients. Two kinds of questions are generally raised for an antibody therapeutic: do the immune complexes cause complications and does the antibody induce immune response? Because the amount of IgE is very small even in patients with relatively high IgE levels and because the immune complexes are small and soluble, the immune complexes of IgE and anti-IgE do not fix complement, cause serum sickness disease, precipitate in the kidney, or cause other complications associated with immune complexes. Antibody response to omalizumab was examined in large numbers of patients during and after the trial period, and no antibody against omalizumab was found in any patient.

Anti-IgE is highly specific for IgE and IgE-expressing B-cells. Therefore, no complication was observed, caused by the inadvertent binding of anti-IgE to other serum component or cells. The question of whether the immune system is compromised because an entire IgE antibody class is depleted will be addressed later.

PATIENTS WHO USE ANTI-IGE THERAPY

FDA Approval of Anti-IgE for Adults with Moderate to Severe Asthma

As the number of patients using anti-IgE increases and the safety profile becomes more established, regulatory agencies and their advisory bodies may become more assured of approval for pediatric asthma patients and for other indications. Also, if anti-IgE is found to modify allergic disease processes and ameliorate underlying disease states or if regi-

mens that may bring about a long-term remission are developed, perhaps less severe patients may also benefit considering overall pharmaco-economic equations. Finally, since the involvement of IgE in the pathogenesis of allergic rhinitis is firmly established, a concept being adopted by increasing numbers of allergists is that those asthma patients with concomitant allergic rhinitis are very suitable patients. This rationale has been backed up by the positive results of a phase 3 trial investigating the effects of omalizumab on patients with both asthma and allergic rhinitis.

Patients Who Benefit Most From Anti-IgE

Within the scope of marketing approval, the patients who can benefit the most from an anti-IgE therapy are those asthmatics whose symptoms cannot be properly controlled by the currently available best standard therapies and whose symptoms are caused entirely or partially by IgE-mediated hypersensitivity reactions. Patients managed with injectable corticosteroids or high doses of inhaled corticosteroids may also be a suitable population to use anti-IgE.

Questions Concerning Skin Tests and Serum IgE Levels

Although radioallergosorbent analysis is a valuable tool for pretreatment analysis, it becomes unusable following anti-IgE treatment because it picks up not only specific free IgE, but also that bound by anti-IgE. Skin testing, on the other hand, may be more useful in both pre- and post-treatment scenarios. Although initial data suggested that prick skin testing decreased dramatically within 3 mo, clinicians report less rapid skin response to treatment even in the face of apparent clinical improvement. This apparent disparity has prompted the notion that the mast cells underlying the mucosal epithelium may be attenuated differently from those underneath the skin. Thus, there is a need to develop a procedure or test better than skin tests to screen patients for anti-IgE therapy.

The label provided with the commercial omalizumab product specifies that the dosing range for IgE must be within 30–1000 U/mL. There is a reason for the upper limit considerating that the provided dose of anti-IgE antibody can only neutralize a certain maximum amount of free IgE over a 2-wk period (presently the shortest treatment interval). However, there is not a convincing reason for setting the lower limit of IgE. While serum IgE levels statistically correlate with the risk of asthma, it is not uniformly correlated with severity, especially in adults. Some severe patients have IgE levels lower than 30 U/mL, and many respond admirably when the clone of IgE-producing disease is neutralized. Those patients, whose allergen-specific IgE may account for high proportions in total IgE, are very attractive target populations for anti-IgE treatment.

WILL ANTI-IGE THERAPY COMPROMISE NORMAL IMMUNE RESPONSE?

The Function of IgE in Defense Against Parasites

One attractive feature of the anti-IgE therapy is its nonspecificity for particular allergens by disabling, in some cases, the entire activity of an immunoglobulin class. However, this ability has caused substantial concerns with respect to whether the therapy will compromise the normal IgE immune functions. The most prevalent thought is that IgE is important for defense against parasites. Naturally, careful assessment of parasite infection was included in the clinical studies.

A thorough analysis of the literature of studies done on parasites and IgE has led us to the understanding that IgE is involved in the defense against helminth infections, especially schistosomiasis and strongyloidiasis. Through many years of research in delineating the roles of IgE in clearing a parasite infection, the most supportive evidence lies largely in the correlation between IgE levels and the timing of parasite infection. In the numerous clinical studies done on anti-IgE, there was no evidence indicating that parasite infection was increased among the patients treated with anti-IgE. A Brazilian trial showed that in patients treated with anti-IgE for 1 yr, the depletion of IgE did not affect the incidence and severity of disease associated with the re-infection of ascariasis.

The Relationship of IgE to Cancer

In what may be a myth, there exists a poorly founded notion among some physicians that allergic people may be more resistant to certain forms of cancer. This concept was initiated by a report of Cockroft et al. in 1979, which summarized a comparative survey of 392 patients with three types of malignancy and 303 controls and concluded that the patients with endodermal neoplasia (lung, gut, bladder, prostate) had lowered forms of allergic disease. The major weakness of the survey was that the sample sizes were too small to be significant. In two other notable surveys done in later years with larger patient populations, the results were largely either contrary to the earlier study or too variable to make definitive conclusion.

An in-depth analysis of the data concerning the occurrence of tumors among patients treated with omalizumab is especially pertinent. Malignancies were found in 20 of 4127 (0.5%) of patients exposed to anti-IgE compared to 5 of 2236 (0.2%) of patients exposed to placebo, which on the surface might cause concern. However, a further analysis found that the majority of the 20 cases occurred in an older patient population, which was not matched with controls, and that at least 5 of 20 had the same cancer before exposure to anti-IgE. The time of exposure to anti-IgE was too short for the tumors to be induced and to grow to the substantial sizes reported. The tumors found were of seemingly random distribution of ectodermal, endodermal, and mesodermal categories. These various observations have led a panel of hemoncologists in a preliminary, blinded analysis to suggest that there should be no concern for causation of malignancy by anti-IgE.

IgE Seems Dispensable

Unlike the other four antibody classes and other components in the human blood and tissue that are generally present in rather defined ranges, IgE exists in an extremely broad range, from less than a few nanograms to more than a few micrograms per milliliter in serum. Some individuals with normal immune function have very low or even undetectable IgE levels in serum. These facts seem to suggest either that IgE does not play an essential role or that IgE plays a beneficial role, but it is dispensable and its roles can be filled by other immune mechanisms when IgE is absent. IgE may have some role in controlling parasites, but if removed, redundancy in the immune system can provide protection.

OTHER POTENTIAL APPLICATIONS OF ANTI-IGE THERAPY

For Pediatric Patients

As data from additional trials on pediatric patients have been reported, the concerns over safety of anti-IgE have gradually subsided. More than 90% of pediatric asthma cases

are known to be associated with allergy, much higher than that (about 70%) for adults. This is probably partly because as the asthmatic disease protracts additional immune factors, expanded inflammatory reactions, and tissue damage may gradually obscure the allergic etiology in some of the asthma cases. If so, it may require anti-IgE to work over a much longer time to allow secondary immune mechanisms to wind down and achieve an improvement.

Pediatric patients who participated in the early clinical studies on asthma had generally mild symptoms controlled with inhaled corticosteroids. However, there is compelling rationale that if anti-IgE is found to be safe, the screening requirement should be somewhat relaxed for pediatric patients to use anti-IgE. These considerations include the fact that anti-IgE can reduce or eliminate the dependence on corticosteroids. Because of smaller body weight, anti-IgE is more affordable and may merit consideration when medication adherence and the decrease in school absenteeism and quality-of-life improvements for the whole family are factored in.

For Allergic Rhinitis and Food Allergy

For almost all patients with a tendency to develop anaphylactic reactions to foods, such as peanuts, egg proteins, wheat proteins, shellfish, and so on, there is not an effective prophylactic treatment other than strict avoidance of the foods containing the allergenic substances. Because severe allergic reactions to foods affect many young children, the fear of developing anaphylactic attacks resulting from accidental exposure to allergenic foods causes tremendous stress for both the young patients and their parents. Anti-IgE can substantially reduce the sensitivity to the problematic foods.

Other Uses, Such as Atopic Dermatitis and Venom Sensitivity

Atopic dermatitis is undoubtedly a very important indication affecting large populations of patients worldwide. The involvement of IgE in atopic dermatitis is persuasive, but not firmly established. Certainly it will be of great interest to investigate whether anti-IgE can ameliorate the symptoms of atopic dermatitis under appropriate clinical trial environments. A result showing efficacy will provide not only a medication for patients affected by this serious disease, but also an answer to the question of whether IgE plays an important role in its pathogenesis .

Insect allergy is of particular interest because the process of therapeutic desensitization is itself fraught with danger. Although not suggested for long-term therapy, a short-term partial disarming of the anaphylactic potential with anti-IgE might allow a safer means of treatment progression.

Combined With Desensitization Immunotherapy

Desensitization immunotherapy is perhaps the most used treatment for patients with severe allergic rhinitis and allergic asthma, offering the possibility of creating a long-term remission with successful therapy. The major limiting factor of specific immunotherapy includes a limitation of dosage to assure safety. A growing interest among allergists is the use of anti-IgE to achieve both an attenuation of symptoms and a tolerable state for allowing accelerated or more vigorous regimens of immunotherapy.

Conceptually, this is a very rational approach. As the IgE pathway is blocked off by anti-IgE, a more vigorous immunization schedule, with increased doses and shortened

immunization intervals, will then induce IgG and other non-IgE-related responses, leading speedily to a shift of the immune balance toward the beneficial side.

A NEW DIRECTION FOR THERAPEUTIC INNOVATION

Developing Anti-IgE of Extremely High Affinity

Anti-IgE therapy has firmly established that IgE is a bona fide therapeutic target for treating a host of IgE-mediated allergic diseases. In more specific terms, it transpires that if free IgE in blood and in tissue can be reduced to near zero concentrations, the cascade of IgE-mediated allergic pathway, such as the release of pharmacological mediators, is reduced and the manifestation of allergic symptoms is attenuated. These findings have stimulated a new direction for therapeutic innovation.

Many new approaches have emerged, including the development of anti-IgE antibodies with much higher affinity than those of omalizumab and TNX-901. The premise is that antibodies of extremely high affinity will require proportionally less drug, reducing cost to the patient. Those patients with very high basal levels of IgE may also be treated.

Targeting B-Cells Expressing IgE

IgE-expressing B-cells are the crucial targets for blocking off the IgE-related pathways and include (1) IgE-expressing lymphoblasts on their way of maturation to become plasma cells and memory cells and (2) IgE-expressing memory B-cells. There are two ways to inhibit, downregulate, and/or eliminate those cells. One is to target the B-cells directly, and the other is to reduce the generation of those cells. Since mIgE is a part of the B-cell receptor and the gate for receiving antigens and initiating signal transduction; it is a target to induce the activation, anergization, and apoptosis of the B cell bearing mIgE. It is possible that anti-IgE, which can bind to mIgE on B cells, may be able to inhibit or downregulate B cells directly.

An extraordinary discovery has also been made that the ε heavy chain of mIgE on human B cells contains an extra domain of 52 amino acid residues, located between the CH4 domain and the membrane-anchoring, C-terminal peptide. This domain, whose amino acid sequence is unique, offers an attractive site for immunological targeting of IgE-expressing B-cells. Other direct approaches include using anti-sense or inhibitory RNA oligonuleotides to disrupt the synthesis of IgE.

Several approaches have evolved to inhibit the generation of IgE-expressing B-cells, including the use of recombinant antibodies or soluble receptors to tie up interleukin-4 or interleukin 5 responsible for the isotype switching of activated IgM-expressing B-cells to IgE-expressing B-cells . An anti-CD23 antibody may also inhibit antigen presentation and related processes that favor IgE responses. Immuno-enhancing oligonucleotides, known as cGp DNA, have also been studied for affecting TH_1/TH_2 balance toward the TH1 arena.

SUGGESTED READING

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25 Environmental Control of Indoor Respiratory Allergens

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CONTENTS

SUMMARY

Exposure to indoor allergens is a common symptom trigger for patients with allergic rhinoconjunctivitis and asthma. Furthermore, scientific studies suggest that effective avoidance of allergens can improve symptom control. The focus of this chapter is to review current concepts regarding the characteristics of indoor allergens and strategies that have been used to decrease allergen exposure in sensitized patients. Specifically, environmental control measures for dust mite, cockroach, animals, and fungi are discussed. In addition, the current evidence regarding the effectiveness of allergen avoidance strategies is summarized. Although indoor environmental control should be discussed with every affected patient, an individualized approach based on a variety of patient characteristics is recommended.

Key Words: Environmental control; dust mite; Fel d 1; Can f 1; fungi; cockroach; alternaria.

POTENTIAL BENEFITS OF ENVIRONMENT CONTROL

Two events occur prior to the development of symptoms in allergic patients. First, the individual has to become exposed and sensitized to a particular allergen with production of allergen-specific immunoglobulin E (IgE). This IgE may become affixed to mast cells that are present throughout the body, but are most prominent at mucosal surfaces. The second event is re-exposure to that allergen, stimulating the mast cells to release their inflammatory mediators and triggering many of the symptoms attributed to allergy.

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Currently, a primary focus of research is to advance the understanding of why some patients become sensitized to allergens and others do not. The complex interplay between genetics and environment plays a key role in determining an individual's susceptibility to allergy. Environmental factors such as exposure to allergen, endotoxin, infections, and foods during infancy seem to be important in the development of the immature immune system. This suggests that there is a potential for the environment to be manipulated to decrease a patient's risk of becoming allergic.

In addition, for previously sensitized patients, avoidance of allergens can prevent allergic symptoms. In many instances, complete avoidance is not possible. However, changes can be made to a patient's environment to decrease exposure to a specific allergen. Which of these environmental manipulations truly improves patient symptoms, outcomes, and quality of life will be the focus of this chapter.

Allergens that accumulate in the respiratory tract share several characteristics. A typical allergen is a small, stable protein that can gain access to respiratory mucosal surfaces and is also soluble so that it can penetrate into the tissue. Many different trees, weeds, molds, grass, arthropods, and animals produce allergens with these properties. Because the average American spends more than 90% of his or her time indoors, the effective reduction of indoor allergen exposure could have a great impact on decreasing symptoms in sensitized patients.

The goal of allergen avoidance measures is to decrease the exposure level to a point that results in decreased symptoms and lowered medication requirements. The exact amount of allergen that is necessary to exceed an individual's symptom threshold is likely both allergen and patient specific. However, we do know that even extremely small (microgram) amounts of these proteins can trigger symptoms in sensitized subjects. What follows is a description of the main indoor allergens, potential environmental control measures for these allergens, and the current understanding of the effectiveness of these measures.

DUST MITE ALLERGEN

Exposure to house dust in sensitized individuals is a common trigger of allergic symptoms. House dust is a complex mixture of materials and contains many different allergens, including products derived from household animals, bacteria, fungi, and insects. One of the major allergen components of house dust is produced by dust mites. Dust mites are microscopic arthropods related to spiders. There are two major dust mite species: *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Dust mites are unable to survive in climates with high altitude or low humidity, so they are less prevalent in mountainous regions. Conversely, they are prevalent in areas with high humidity. *Dermatophagoides* literally means, "skin eater," and they feed on shed skin cells or other organic material. The life span of a dust mite is typically about 6 weeks.

Because of this need for organic matter, large numbers of dust mites are found in areas that can harbor nests. There are several factors predictive of high levels of dust mites in a house. These include older, single-family homes without central air conditioning. Dust mites are prevalent in mattresses, box springs, pillows, quilts, carpeting, stuffed animals, upholstered furniture, and drapes. The primary allergenic protein from the dust mites comes from their bodies or their fecal pellets and are carried on relatively large particles

exceeding 10 μm in diameter. When these particles are vigorously disturbed, they can become airborne. However, because of their size, they again fall to the surface of their reservoir within 15 min and become unmeasurable in the air.

Dust mite products are quite allergenic. Sensitization to dust mite has been shown to occur at concentrations as low as 2 μg of dust mite protein per gram of household dust. Symptoms begin to occur with exposure to concentrations of $\geq$10 μg/g of dust. In additon to symptoms of allergic rhinoconjunctivitis, inhalation of mite particles can cause bronchial hyperresponsiveness (BHR), increased airway inflammation, and asthma.

The importance of decreasing exposure to dust mites has been shown in several studies. In one classic study, dust mite-sensitized asthmatics were moved to very low-dust mite environments for a minimum of 2 months. These patients showed a significant reduction in their BHR as well as reduced asthma symptoms and medication requirements. These parameters returned to baseline when the patients returned to their previous environment. Similar studies in near mite-free environments have yielded comparable results. Thus, effective dust mite control has the potential to be very beneficial for sensitized patients.

In most homes, the highest exposure to dust mites has been shown to occur in the bedroom. Most people spend approximately eight hours a day in bed while breathing air that is in close proximity to bedding surfaces, where household dust contains a high concentration of dust mite allergen. This is the rationale for the focus of dust mite avoidance in the bedroom.

Traditionally, one method of dust mite avoidance has been to obtain dust impermeable covers for mattress, pillows, and box springs. In theory, as long as their pore size is smaller than the dust mite particles, these tightly woven covers should provide a protective barrier between the patient and the allergen inside the pillows, mattress, and box spring. The vast majority of studies show that the levels of dust mite allergen decreases significantly when such measures are taken.

However, two high-profile publications in the *New England Journal of Medicine* suggested that the clinical benefit of using bed covers alone is limited. The first of these studies was a randomized trial of mite impermeable vs "control" bed covers in 1122 adult patients with asthma requiring inhaled corticosteroids. Although there was an effect on the mite content of mattress dust, there was no difference in peak flow rates or asthma medication requirements after a year. Interestingly, both treatment and control groups had equal improvement over the yearlong trial. A similar randomized trial was conducted among 279 patients with allergic rhinitis. This trial again reported lower mite content in mattress dust, but no discernible clinical improvement.

Several concerns over these two high-profile trials have surfaced. Neither trial studied patients sensitized only to dust mites, which raises the possibility that persistent exposure to other allergens may have masked potential benefit from the intervention. Also, because improvement in placebo and bed cover groups was reported, there may have been a masking effect from improved medication use and other uncontrolled interventions. In response to these criticisms, both authors agree that the studies do not suggest that allergen avoidance is ineffective, but that the single intervention of using bed covers is unlikely to produce clinical improvement in a substantial number of multisensitized patients.

In discussing dust mite avoidance methods, there are numerous other measures that should be addressed along with the use of impermeable covers. Frequent, perhaps weekly, washing of all bed and pillow coverings in hot water and detergent for one hour can reduce mite allergen levels. Dust mites are unable to survive temperature extremes, yet thrive at ambient temperatures of 65–80° F. Thus, it is beneficial to wash the bedding in water up to 130°F. Washing will also remove the human skin cells, which can be a food source for dust mites. Drying the bedding on high heat is also recommended. Because very cold temperatures can also be lethal to dust mites, placing small mite-laden objects such as stuffed animals in a freezer has also been suggested.

The removal of carpet in the house can also decrease dust mite exposure, although the clinical benefit of this measure is uncertain. Replacement of carpet with hard flooring would remove a nesting site for the mites, as well as a reservoir that contains their food source. Using this same rationale, upholstered furniture can also contain large amounts of dust mites. It may be preferable for a highly mite-sensitized patient to remove upholstered furniture.

For many patients, the removal of carpeting may not be possible. Currently, two chemicals are being marketed in the United States for the purpose of reducing mite allergen in carpeting. Benzyl benzoate is highly effective in killing mites in a laboratory setting. However, it seems to be only modestly effective when applied to carpets, and that effect is short-lived. Tannic acid can denature dust mite proteins. Again, this effect is diminished when applied to carpet. Although compounds in the future may provide beneficial treatments for dust mite allergen, currently available chemicals appear to have limited clinical efficacy.

Vacuuming removes mite allergen from the carpet but it does not remove live mites. Dust mite-allergic patients should avoid vacuuming if possible, because allergen surrounding the vacuum may become airborne. Similarly, a mite-sensitive patient should avoid recently vacuumed rooms. If vacuuming cannot be avoided, a dust mask and use of a "double-bag" or high-efficiency particulate air (HEPA) filter-equipped vacuum cleaner may be of some benefit.

Environmental humidity is very important to the survival of dust mites. Mites tend to thrive where the ambient humidity exceeds 50–60%. Thus, environmental control measures such as the use of air conditioning or dehumidifiers that keep indoor humidity near levels of 40% have been promoted as a method to decrease mite growth. Successful mite control with dehumidification has been shown in studies performed in areas of very high humidity such as in tropical areas. Its effectiveness in less humid environments needs to be further studied.

When taking into consideration the available data, one realizes that there are many potentially effective methods to decrease mite exposure. Unfortunately, few single methods or combinations of methods have been tested in randomized, controlled trials for their clinical efficacy. The Cochrane Database of Systematic Reviews has summarized the studies done on house dust mite control measures for asthma and perennial allergic rhinitis. According to their analysis, a conclusion cannot be drawn as to the effectiveness of dust mite control measures in the homes of mite-sensitive asthmatics. They did find evidence to suggest that reduction of dust mite exposure in patients with dust mite-allergic rhinitis may be beneficial. Both reviews commented that more studies with larger numbers of patients should be done in order to be able to reach definitive conclusions.

Table 1
Dust Mite-Avoidance Measures

- Encase pillows, mattresses, and boxsprings in impermeable covers
- Wash bed linens, comforters, and blankets in hot water weekly
- Remove stuffed animals
- Vacuum weekly with double-thickness bag or HEPA filter
- Reduce indoor relative humidity to 40–50%
- Remove carpeting or upholstered furniture if necessary

Table 2
Cockroach Allergen-Avoidance Measures

- Exterminate with pesticides
- Vacuum and wash floors and cabinets thoroughly
- Seal portals of entry
- Place trash outside daily
- Wash dishes daily

Summary

The clinical question remains: "What control measures for dust mites should be advised?" The reduction in mite allergen necessary to improve a patient's symptoms is likely to be different for each patient. Because most mite-avoidance measures are safe and relatively economical, I believe dust mite-avoidance measures (Table 1) should be discussed with mite-sensitive patients.

The combination of impermeable pillow, mattress, and box springs covers, frequent laundering of bedding in hot water, removal of dust-laden articles from the bed, and control of humidity should all be considered, depending on symptom severity. For patients with significant symptoms that do not respond to the above recommendations, the removal of carpeting and upholstered furniture can be considered. Although compliance with these instructions requires a highly motivated patient, the potential rewards in highly symptomatic individuals may favor a trial of these measures.

COCKROACH ALLERGEN

Exposure to cockroach allergen can contribute to asthma morbidity in sensitized patients. In the National Cooperative Inner City Asthma Study (NCICAS), children who were allergic to cockroach and exposed to high levels of allergen in their homes had a threefold higher asthma hospitalization rate. It has long been known that cockroach allergen can also trigger allergic rhinoconjunctivitis. Thus, treatment strategies for decreasing cockroach allergen exposure for these patients may be helpful (Table 2).

There are two main species of cockroaches that cause household infestation and allergic sensitization in the United States. Significant crossreactivity is seen between the allergens from the American cockroach and the German cockroach, although most patients are primarily sensitized to the German cockroach. Infestation is most common in inner-city dwellings as well as areas of the United States with a warm, humid climate.

The source(s) of the major cockroach allergens are not completely understood, although they appear to be secreted or excreted proteins originating in the insect's gastrointestinal

tract. Allergens have been detected in the insect's saliva, feces, and other body parts. The highest levels of cockroach allergen is found in the kitchen, although allergen is often detected throughout the home. It is thought that cockroach allergen levels greater than 2 units/gram of dust can cause sensitization, while levels over 8 units can trigger symptoms. Levels greater than 8 units/gram were found in 50% of the bedroom dust samples in the NCICAS study. Although detectable cockroach allergen was found, no visible cockroaches were apparent in 20–48% of inner-city homes. If roaches are seen, especially during the daytime, it is a sign of heavy infestation.

The characteristics of cockroach allergen appear to be similar to dust mite allergen. Like mite allergen, cockroach allergen is present on large particles with a diameter of more than 10 μm. It is detectable in the air only after ground disturbance, settles after several minutes, and is often found in bedding. It has been proposed that the allergen is carried into the bed on feet and clothing. This bedding contamination is very important, as the bed is likely to be an area of significant exposure.

The first step in cockroach allergen avoidance is extermination with insecticides. This is most effective when done professionally. Concomitantly, food sources for the cockroach such as grease, garbage cans, pet food, and open food containers should be cleaned or removed from the environment. This improves the effectiveness of insecticides, since the cockroaches will be more likely to ingest the applied treatments.

Today's pesticides are much safer than the organophosphates, which can cause acute neurological toxicity in large doses. Gel baits such as hydromethylnon that are odorless and colorless are not generally attractive to pets or children. They are also more effective than organophosphates or boric acid. A second application is recommended for adequate extermination in one to two weeks. Cleaning should be delayed during this time to make sure none of the insecticide is removed.

Eradication of living cockroaches is only the first step in depleting the reservoir of allergen. Comprehensive household cleaning is then required to further lower levels of allergen. Cleaning should concentrate on countertops, kitchen cabinets, refrigerators, ovens, and other kitchen appliances. Hard surfaces throughout the house should be scrubbed with detergent and water. Vacuuming carpets and washing clothes and bedding are also important. Because cockroach allergen is difficult to remove and often found in cracks and crevices, it can take up to 6 months to see an 80–90% reduction in cockroach-allergen content of settled dust.

Several studies are currently underway examining whether these cleaning methods are clinically effective. One recent study suggested that inner-city asthmatic children who lived in dwellings that received two cockroach and mouse extermination treatments, allergen-proof bedding, and a HEPA air cleaner in the children's bedrooms, had decreased wheezing, coughing, and asthma symptoms compared to controls. Thus, there is hope that implementing cockroach-avoidance strategies will have a significant health effect on asthmatic patients living in inner cities.

PET ALLERGENS

Humans have kept domesticated animals as pets for thousands of years. In developed countries, pets are often kept indoors in close proximity with their owners. Because of this, we are exposed to large amounts of their secreted/excreted proteins. Unfortunately, many people become sensitized and develop allergic symptoms when exposed to these

Table 3
Pet Allergen-Avoidance Measures

- Removal of pet from home then thoroughly vaccuum, clean and wash all surfaces including walls

If patients choose to keep pet

- Restrict pet to one area of the home
- Do not allow pet into bedroom
- Use allergen-proof bedding covers
- Consider HEPA filter
- Consider removal of carpeting in the bedroom

proteins. It is often quite difficult for these patients to part with the animals that are making them ill. In fact, approximately one-third of all pet-allergic individuals have the offending animal in their home. Cats and dogs are the most common and most studied allergy-inducing pets, but it appears that all fur-bearing animals are potentially allergenic. Allergen-control measures should be similar for all such animals, but the most effective measure is removal of the animal from the home (Table 3)

Cat Allergy

Cats produce several potentially sensitizing allergenic proteins. However, the major allergenic protein, Fel d 1 is implicated in 85–95% of cat-sensitized patients. A single cat can produce 3–7 μg/day of this protein, which is secreted by sebaceous, salivary, and perianal glands. The skin and fur are thought to be the primary reservoirs, with the highest concentration of Fel d 1 found on the cat's face and neck. The function of Fel d 1 is unknown, although it may play a role in epithelial protection or pheromone regulation. Additional cat proteins that may elicit an IgE-mediated response include albumin and Fel d 3. Nearly 10–20% of allergic patients can develop sensitivities to these proteins in addition to Fel d 1.

The production of Fel d 1 is greatly influenced by testosterone, so that male cats produce higher Fel d 1 than females. Castrated male cats produce less protein overall, but still enough to induce symptoms in sensitized patients. There is no evidence to suggest that either secreted Fel d 1 or surface-level allergen is correlated with the length of the cat's hair. Thus, it does not appear that a certain breed of cat, based on hair length, is more or less allergenic than another. However, it has been shown that the degree of variablility in the amount of Fel d 1 that is shed between cats may be greater than 100-fold.

Fel d 1 has several interesting characteristics. The protein itself is carried on both large and small particles. Up to 75% of the total amount will be carried on particles 10 μm or more in diameter, whereas 25% will be carried by particles < 5 μm. Unlike dust mite or cockroach allergen, minimal environment distrubance can cause high levels of allergen to become airborne for long periods of time. Also, the allergen can be quite "sticky," easily adhering to surfaces, clothes, and walls. These factors are important when designing avoidance techniques.

Because pets are ubiquitous in our society, it can be quite difficult to avoid pet allergen. Indeed, recent studies have shown that significant amounts of cat allergen can be found in the majority of houses where cats have never been kept. In fact, dust from 66% of US

homes exceeds the threshold level of cat allergen to cause allergic sensitization, and 35% of homes exceed the level necessary to trigger asthma symptoms. In these homes, the highest levels of Fel d 1 were found on upholstered furniture in the living room. Cat allergen can also be found in public buildings such as airports, schools, theaters, and hospitals. It is generally thought that the allergen is brought to these environments on the clothes of cat owners. Unfortunately, there are no practical avoidance strategies for sensitized patients in these public facilities.

However, effective avoidance measures can be instituted at home. Without a doubt, the highest levels of cat allergen are found in homes with a cat. Concentrations of Fel d 1 are 10–1000 times greater than in catless homes. The highest levels are found in upholstered furniture and carpets, although bedding and mattresses can also have high levels of allergen, especially if that is where the pet chooses to sleep.

The only clearly effective measure for pet allergen avoidance is removal of the pet from the home. This is clearly the correct advice for severely symptomatic patients and should be strongly recommended in this population. A pet produces large amounts of allergen and other control strategies will likely be ineffective. Benefit derived from compromise measures such as designating the bedroom a "cat-free" environment or washing the cat are unproven. Any effect from washing the cat appears transient, as allergen sampling from the animal falls briefly, but often returns to baseline within hours to a few days.

A number of commercial products are available that are designed to spray onto and rub into the cat's fur. Some of these sprays reportedly contain chemicals capable of denaturing Fel d 1. No convincing studies have been published that prove these products have clinical efficacy.

It should be explained that removal is only the first step. Subsequent thorough and repeated cleaning, including washing floors, walls, hard surfaces, and all clothes that have contacted the cat, is required. Removal of carpet, upholstered furniture, and other reservoirs of allergen may also be necessary. Cat allergen will likely persist in mattresses for extended periods after removal of the animal, so the purchase of new bedding or impermeable encasements should also be advised. Because Fel d 1 is often airborne, use of a HEPA air cleaner seems logical. It is important to remember, however, that allergen levels fall quite slowly even with the above measures. It is likely that high allergen levels will be present for months after removal of the cat.

Studies on the clinical effectiveness of instituting the above measures are few. A Cochrane Review evaluating the effectiveness of air-filtration units on asthma concluded that the available trials were too small to provide evidence for or against the use of air-filtration units to reduce pet-allergen levels in the management of asthma induced by pet exposure. Indeed, no clinical trials have tested the effect of removing a pet from the home of a sensitized asthmatic. Thus, studies are greatly needed in this area so that we can confidently counsel our patients on pet-allergen avoidance.

Dog Allergy

Humans develop allergic responses to a variety of proteins that are present in the dander, saliva, urine, and serum derived from dogs. The main identified allergens are dog albumin and a protein named Can f 1. There is some dog breed-specific variability in the production of these allergens, but all dogs have been shown to produce the main allergens. The large number of proteins that are potential allergens and the lack of well-

standardized materials for diagnostic and research purposes have made studies on dog allergy difficult.

Can f 1 seems to have similar properties to Fel d 1. It can be carried on both large and small particles. It can also become airborne quite easily and remain so for extended periods of time. Because of these similarities, the avoidance measures discussed for cat allergy are recommended for patients who are sensitive to dogs.

Similar to Fel d 1, Can f 1 levels can be detected even in homes without a dog. A recent study reported that 98% of homes with an indoor dog and 36% of homes without a dog exceeded the threshold limit for allergic sensitizaiton with Can f 1. In addition, 89% of homes with a dog and 9.3% of homes without a dog exceeded the level necessary to trigger asthma symptoms.

Other Animal Exposures

It is likely that nearly every animal can produce proteins to which individuals could become sensitized if adequately exposed. There are documented cases of allergy to numerous mammals ranging from rodents such as rats and mice to large animals such as horses or cows. Sensitization can also occur to pets such as gerbils, hamsters, guinea pigs, or rabbits. Typically, the urine from these animals contains allergenic proteins that can easily become aerosolized. Therefore, allergic patients should avoid contact with contaminated bedding and avoid cleaning the cages of these animals. Although it is relatively easy to reduce one's exposure to such small caged pets, "natural" exposure to mouse or rat allergen is more common than we would like to think.

Sensitization to rats occurs in up to 30% of laboratory workers who handle these animals, signaling a significant occupational risk. Exposure to increasing concentrations of rat allergen has been associated with increased airway responsiveness in these individuals. However, significant exposure also occurs in many homes. Studies suggest that 20% of inner-city children are sensitized to rats, with one-third of their homes having detectable levels of rat allergen. Interestingly, sensitization was not necessarily associated with the presence of detectable rat allergen in the home. However, a number of asthma morbidity factors such as number of hospitalizations, unscheduled medical visits, and days with limited activity because of asthma were significantly higher in those with both sensitization and exposure to rat allergen.

In the NCICAS study, 18% of the inner-city children were sensitized to mouse. Also, 95% of the homes had detectable mouse allergen in at least one room with the highest levels found in kitchens. However, no statistically identifiable relationship between mouse-allergen exposure and asthma morbidity was seen in the study. Many of the specific characteristics of Mus m 1, the major mouse allergen, have yet to be elucidated, including levels required for sensitization or to trigger symptoms.

Given our present understanding, it would be beneficial for patients with mouse and rat sensitization to minimize their exposure. Our knowledge regarding methods to decrease these allergens is currently lacking, but they are now being studied. A recent study demonstrated that certain measures are effective in lowering Mus m 1 in mouse-infested, inner-city homes. These interventions included filling holes and cracks with copper mesh and caulk sealant, vacuuming with HEPA filters, and cleaning surfaces with mild detergents. Traps and low-toxicity pesticides from professional exterminators were also used. Studies with large numbers of patients will be required to help determine the duration and degree of the clinical effect of these methods.

Table 4
Mold Allergen-Avoidance Measures

- Prevent outdoor mold penetration by closing windows and doors
- Reduce indoor humidity to 40–50%
- Clean washable surfaces with bleach detergent or approved fungicide
- Remove contaminated materials such as wallpaper or carpets

FUNGAL ALLERGEN AVOIDANCE

Avoidance advice regarding indoor fungi or mold allergens is made more difficult by the poorly understood relationship of mold allergen levels and allergic symptoms. One mold in particular, *Alternaria*, seems to be important from recent epidemiological studies. In certain areas of the country, sensitivity to *Alternaria* is associated with increased risk of asthma in children and with sudden, severe asthma episodes in children and young adults. Unfortunately, we have only poorly performing methods to measure fungal exposure levels, which makes the study of fungi and the effectiveness of mold-avoidance measures difficult to study. However, it is clear that damp environments promote the growth of excessive multiple molds, bacteria, or both.

A primary source of indoor mold exposure is the penetration of outdoor fungal spores into the home. Outdoor fungal spores rise during the warm, wet weather months and will significantly decrease during the cold, dry months. During months of high mold exposure, indoor levels can be minimized by simple measures such as keeping doors and windows closed and using air conditioning (Table 4).

Reducing indoor mold growth can be achieved by controlling excess moisture in the home. The primary source of moisture in many indoor environments is from water that leaks into buildings, or from leaky plumbing, dishwashers, or hot water tanks. Thus, proper house maintenance is required for the prevention of excessive fungal growth. Annual inspection of the roof, as well as keeping gutters and drains clear for proper diversion of rainwater is important. Also, keeping the relative humidity in a house near 40% can limit mold growth. Dehumidifers in moist areas, such as basements, are a potentially effective way to accomplish this. Measures such as increasing ventilation in bathrooms or kitchens, with the installation of exhaust fans or venting a clothes dryer to the outdoors, may also be considered. HEPA air filters may be effective in removing some airborne spores.

Carpets are also known to harbor mold spores. The presense of old wall-to-wall carpeting is associated with higher indoor mold levels. Thus, replacing carpet with hard flooring can be considered. If removing the carpet is unacceptable, frequent vacuuming with a vacuum containing a HEPA filter and double-thickness bags may decrease exposure. Wallpaper and paneling can be treated with a mild bleach and detergent solution as well, so that visible mold should be aggressively removed. Walls with more than 10 square feet of obvious surface mold growth may require professional assessment. Highly sensitive patients should wear protective masks when performing such tasks or better yet, have others do it for them.

Window air conditioners or central humidification units are common sources of mold contamination. These devices can circulate spores throughout the house if proper maintenance is not performed. The condensing coils in window air conditioners can be washed

with detergent, and then cleaned with an antifungal agent such as chlorine bleach. Condensation-collection pans should be checked to ensure proper drainage and lack of obstruction to avoid pooling of water. Simple steps such as these can be quite helpful in the treatment or prevention of indoor mold growth. Although studies have yet to be done on the clinical effectiveness of mold avoidance, removal of clearly mold-contaminated materials is important, as these are potential triggers for severe allergy and asthma.

AIR-FILTERING DEVICES

Patients with allergies to indoor allergens often ask whether it is beneficial to buy an air-filtering device. Advertisements for such filters claim improved respiratory health with the use of their devices. Unfortunately, the claims from most of these advertisements have yet to be scientifically substantiated. In addressing this issue with patients, there is no clear answer applicable to every situation. Several factors may play a role in determining the effectiveness of air cleaners on the levels of indoor allergens, and these factors will be discussed here.

As mentioned throughout this chapter, the aerobiology of allergens plays a significant role in determining the extent and location of the allergen in the environment. Many allergens from cockroach and dust mites are carried on relatively large particles that are found on surfaces and only become airborne after significant disturbance. These particles then settle after 10–15 minutes. Therefore, air filters will be of limited use for these allergens, especially in areas with low traffic. The allergens themselves are not in the air long enough to be effectively filtered.

Mold allergens and much of the cat and dog allergens are carried on small particles that can remain airborne for longer periods of time and are more amenable to being filtered from the air. However, only a small percentage of the allergen is likely to be in the air at any one time. Most of the allergen will continue to be found in a reservoir, which can continually replace the airborne allergen. Thus, air-cleaning devices alone are unlikely to provide significant benefit.

Another factor is the type of air filter. There are three basic classifications of air cleaner to consider:

1. Mechanical filters that clean the air by having air pass through porous material, where particles are trapped based on size.
2. Electrostatic precipitators that impart an electrical charge on particles, which then adhere to surfaces that hold the opposite electrical charge.
3. Chemical filters that rely on substances such as activated charcoal to absorb gases and odors.

The most efficient mechanical filters are the HEPA filters. They can remove particles as small as 3 μm at more than 99.9% efficiency. However, as with all filters, only airborne allergens can be removed, and only air from a limited area of the home will be drawn to the filter. The activated charcoal and chemical filters are of limited value in the removal of allergen from the air, although the removal of odors and irritants by these cleaners may be of benefit to some patients.

To date, scientific studies investigating the clinical effects of air cleaners have been inconclusive. A 1997 report by the American Lung Association concluded that if allergen sources were present in a residence, then air cleaning by itself was not effective at reducing allergen particles to levels that would improve symptoms. Thus, it is uncertain

whether air cleaners should be a universal recommendation to patients for control of indoor allergens. If a patient insists on purchasing such a device, the use of a HEPA filter unit can be recommended, as it is likely to capture the relevant allergen particles to some extent. Future studies should focus on the use of these cleaners, along with other environmental control measures, to see if they truly provide additional benefit.

SUMMARY OF AVOIDANCE APPROACHES FOR PATIENTS WITH ENVIRONMENTAL ALLERGIES

When discussing environmental control measures with allergic patients, several factors must be considered. A patient's sensitivity and response to allergens in his or her environment is quite individual. Some might realize improvement by instituting just a few simple measures, whereas others may require extensive avoidance measures. The severity of their symptoms in response to these allergens must also be considered. Avoidance measures are not nearly as important for the patient with mild allergic rhinoconjunctivitis as they are for the patient with severe asthma that is triggered by allergen exposure. Other factors such as the patient's socioeconomic status and ability to manipulate his or her environment are also important. Therefore, advice should be tailored for each individual patient and his or her specific history.

As stated several times throughout this chapter, additional studies currently being completed will help us determine with greater certainty which measures will best help our patients. For the time being, a practical approach includes utilizing simple measures such as allergen-proof bedding, mouse and cockroach extermination, control of indoor humidity, and thorough cleaning practices. More extensive measures should be considered for patients with continuing symptoms or those at high risk of morbidity as a result of exposure to a specific allegen. These avoidance measures, in conjunction with appropriate medications, can be used to achieve optimal patient outcomes and can be an important aspect to the overall management of patients with respiratory allergic disorders.

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26 Allergen Immunotherapy

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CONTENTS

SUMMARY

Allergen immunotherapy is appropriate and effective treatment in patients who have symptoms of allergic rhinitis and/or allergic asthma with natural exposure to allergens and who demonstrate specific IgE antibodies (by skin tests or in vitro tests) to relevant allergens. Allergen immunotherapy is medically indicated in patients with respiratory allergies when symptoms are not controlled adequately by pharmacotherapy and avoidance measures, or when there is a need to avoid adverse effects of pharmacotherapy or a wish to reduce long term use of pharmacotherapy. Randomized, double-blind, placebo-controlled studies show that immunotherapy is effective for the treatment of allergic rhinitis and/or asthma. In patients with moderate to severe respiratory allergies, immunotherapy should be considered.

Key Words: Aeroallergens; vaccine; immunotherapy; pollen; mites; danders; molds; allergic reactions.

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INTRODUCTION

Allergen immunotherapy, a series of allergen vaccine injections over a defined period, results in decreased sensitivity or tolerance to inhaled or injected allergens, which can be measured both clinically and immunologically. Vaccine is used to describe the immune-modifying properties of allergen immunotherapy. Such therapy is used to treat allergic rhinitis (hay fever), allergic asthma, and stinging-insect hypersensitivity. During the first half of the 20th century, efficacy of allergen immunotherapy was based primarily on clinical observations. However, over the past 40 yr, scientific investigations of numerous allergens and of the complexities of the allergic reaction have revealed the immunological changes required for successful immunotherapy. This chapter reviews inhalant allergen immunotherapy utilized to treat allergic rhinitis and/or allergic asthma. Immunotherapy for stinging-insect hypersensitivity is covered in Chapter 6.

When to Consider Allergen Immunotherapy

- Individuals with documented appropriate clinical symptoms, and either skin test or in vitro evidence of IgE-allergen-specific antibody.
- Allergic manifestations of rhinitis, bronchial asthma, or stinging insect venom sensitivity.
- Failure to respond to elimination or control of environmental allergic factors.
- Failure to respond to symptomatic medication or difficulty/inconvenience of using these medications regularly.

ALLERGENS

Sources of aeroallergens include, but are not limited to, pollen, molds, and animal emanations, such as dander, saliva, urine, feces, and other animal parts derived from mammals, birds, insects, and house dust mites. Aeroallergens are able to induce a specific immunoglobulin (Ig)E antibody response. This requires that the aeroallergen is sufficiently abundant in the ambient air to both sensitize and provoke allergic symptoms in an atopic individual.

Ragweed pollen-induced allergic rhinitis is an excellent model for the study of aeroallergen-induced allergic diseases: (1) the pollen is found in the air in sufficient quantities during the predictable fall pollinating season, and ragweed pollen proteins are potent sensitizers; (2) ragweed pollen induces symptoms in the sensitized patient during and immediately following the ragweed pollinating season; and (3) ragweed-induced allergic rhinitis can be diagnosed easily historically and by appropriate in vivo or in vitro testing for specific IgE to ragweed allergens and by provocative challenges.

The immediate effects of allergen exposure are readily observed in the ragweed-allergic patient during the ragweed pollinating season. So too are symptoms in the sensitized patient caused by indoor exposure to allergens such as those derived from dust mites, cat, and dog, although patients may suffer with perennial allergic symptoms from such environmental exposures. Such a temporal relationship is evidence for specific allergen sensitivity; however, allergic symptoms also are caused by various overlapping pollen and mold seasons. Therefore, it is sometimes difficult to ascertain which particular

allergens are the most important as a cause of allergic disease. The physician must know which pollen, molds, and other aeroallergens are most important in a given geographical area in which the patient lives. The American Academy of Allergy Asthma and Immunology has established a North American Pollen Network. Pollen and mold reports in various geographical areas are available by contacting the online service www.pollen.com, or by obtaining patient information from the American Academy of Allergy Asthma and Immunology, 611 East Wells Street, Milwaukee, Wisconsin 53202-3889 (www.AAAAI.org).

ALLERGEN VACCINES

Licensing of allergen vaccines for clinical use in the United States is regulated by the US Food and Drug Administration, Center for Biologics Evaluation and Research, Division of Allergenic Products and Parasitology. Many of the common vaccines used in clinical allergy practice are available as standardized products or are pending standardization. This means that allergen vaccines, as provided by commercial manufacturers, meet standards that assure that the appropriate allergens are included in a given vaccine. However, many allergen vaccines derived from natural sources are not yet standardized, and it is probably not economically feasible or practical to standardize all of those currently available for diagnosis and treatment. Currently, unstandardized allergenic vaccines are labeled on the basis of relative concentration (weight by volume or protein nitrogen units per milliliter) of the respective allergen source.

INDICATIONS FOR ALLERGEN IMMUNOTHERAPY

Allergen avoidance, pharmacotherapy, and patient education form the basis for treating allergic rhinitis, conjunctivitis, and asthma. Allergen immunotherapy is indicated for patients with these diseases who have demonstrated evidence of specific IgE antibodies to clinically relevant allergens and in whom environmental control and pharmacotherapy have failed. The absolute indication for prescribing allergen immunotherapy depends on the degree to which symptoms can be reduced by allergen avoidance, by medication and the amount, type, and length of time medications are required to control symptoms. Immunotherapy, when appropriate, should be used adjunctively with continued environmental control measures and appropriate pharmacotherapy. For stinging-insect-induced anaphylaxis, specific Hymenoptera venom immunotherapy is the treatment of choice.

Controlled clinical studies demonstrate that allergen immunotherapy is effective for patients with respiratory allergies (Table 1). Immunotherapy is specific for the allergen administered, and the content of the treatment vaccine is based on the patient's history and allergy test results. In general, the very young (<5 yr old) and elderly patients (>65 yr old) are not candidates for immunotherapy. The very young patient with respiratory allergic diseases usually responds favorably to environmental control and pharmacotherapy, and an uncooperative child is not the ideal candidate for allergen injections. Theoretically, the young patient may benefit the most by immunotherapy by altering the natural course of a chronic disease. The elderly patient rarely requires immunotherapy for the management of rhinitis and/or asthma. The optimal duration of immunotherapy to achieve the best therapeutic response remains unknown; however, studies indicate that 3–5 yr of immunotherapy is adequate for patients who have had a good therapeutic response.

Table 1
Summary of Controlled Trials of Immunotherapy

						Danders	
	Grass	*Weed*	*Tree*	*Molds*	*Mites*	*Cat*	*Dog*
Allergic Rhinitis	+ +	+ +	+ +	+	+ +	+ +	+
Asthma	+	+ +	+	+/–	+	+ +	+

– No effect
+ Positive effect
+ + Strong positive effect

IMMUNOLOGICAL CHANGES INDUCED BY ALLERGEN IMMUNOTHERAPY

The commonly recognized immunological changes that occur secondary to successful allergen immunotherapy (Table 2) include: (1) a rise in serum IgG-"blocking" antibody; (2) blunting of the usual seasonal rise of IgE followed by a slow decline of IgE over the course of immunotherapy; (3) increase in IgG- and IgA-blocking antibodies in the respiratory secretions; (4) reduction in basophil reactivity and sensitivity to specific allergens; (5) reduced production of inflammatory mediators during both early- and late-phase responses to allergen exposure; (6) decreased mast cell numbers and eosinophil recruitment; and (7) reduced lymphocyte responsiveness (proliferation and cytokine production) to specific allergens and a shift of T-cell subsets away from a TH2 type (producing IL-4 and IL-5) in favor of a TH1-type T-lymphocyte response (interferon [IFN-γ]).

The hallmark of asthma and allergic rhinitis is allergic inflammation of the mucosa and submucosa, predominantly caused by eosinophils. TH2 lymphocytes amplify and prolong allergic inflammation and late-phase reactions. TH1 cytokines, i.e., IFN-γ and IL-2, inhibit production of TH_2 cytokines. Successful immunotherapy is associated with a shift in IL-4/IFN-γ production (from IL-4 to IFN-γ) either as a consequence of downregulation of the TH_2 response or increase in the TH_1 response by regulatory T cells screting interleukin (IL)-10 and transforming growth factor (TGF)-β.

Not all immunological changes associated with effective immunotherapy occur in all subjects, although there is general correlation between clinical improvement and favorable alterations from baseline immunological parameters. Reduction in biological sensitivity to specific allergens has been demonstrated in allergen immunotherapy trials to such allergens as ragweed, mixed grasses, birch and mountain cedar pollen vaccines; the molds, *Alternaria* spp and *Cladosporium* spp; and cat dander and house dust mites. Successful allergen immunotherapy ameliorates, but usually does not completely eliminate, the respiratory symptoms of allergic rhinitis and allergic asthma.

CLINICAL TRIALS AND SCIENTIFIC STUDIES

Allergic Rhinitis: Overview

Many randomized, double-blinded controlled trials for allergic rhinitis in reaction to airborne pollens, animal allergens, and house dust mite aeroallergens demonstrate efficacy of allergen immunotherapy based on subjective symptoms scores and medication diaries. Favorable immunological changes include decreased basophil histamine release,

Table 2
Proposed Sequence of Events for Successful Immunotherapy

Step 1.	Suppression of the inflammatory cells' response to allergen prior to measurable immunological changes
	Reduced cellular activation and mediator release
	Rapid changes in target organ mast cells, basophils and eosinophils
Step 2.	Production of IgG blocking antibodies
	IgG1 subclass antibodies early in the course
	IgG4 subclass antibodies predominate later in the course
Step 3.	Suppression of IgE response to seasonal and other allergens
	Blunting of seasonal rise of IgE
	Gradual decline of specific allergen IgE
Step 4.	Alteration of the controlling T-cell lymphocytes
	Down-regulation of TH_2 lymphocyte cytokine profile
	Down-regulation of IgE antibody production and eosinophil activation
Step 5.	Reduction of target organ hypersensitivity and mast cell and basophil cellular sensitivity
	Reduced cellular hypersensitivity
	Reduced biological responses

reduced skin test allergen reactivity and increased allergen-specific IgG blocking antibody. A significant reduction in CD4+ IL-4+ cells is seen in the highest dose with immunosuppressive properties being linked to induction of CD4+CD25+ regulatory T-cells producing Il-10, TGF-β, or both.

Pollen

Nasal challenge studies enable investigators to measure the allergic response in the upper airway following allergen immunotherapy. Such research demonstrates that there is a dose response to ragweed allergen immunotherapy, i.e., an optimal dose above which little or no additional improvement occurs. The first of these studies involved 12 ragweed-sensitive subjects who received immunotherapy, Antigen E (AgE, now known as Amb a 1, the principal ragweed pollen allergen) injections for 3–5 yr, and results were compared to those in 27 untreated control subjects. Nasal provocation studies of treated subjects revealed that AgE immunotherapy decreased the clinical response to ragweed and decreased the allergic inflammatory mediator responses (histamine, prostaglandin D2 [PGD2], TAME-esterase, and kinins) to an intranasal ragweed challenge. In a later study, 26 previously nonimmunized, ragweed-sensitive subjects were randomized to three different dosage regimens (low to high doses; 0.6–25 (μg AgE/injection) and their responses to ragweed nasal challenges compared. The low-dose immunotherapy regimen provided no protective effect, whereas the moderate dose and high dose caused significantly reduced mediator release from the nasal mucosa following ragweed nasal challenge. Symptom scores, recorded by the moderate- and high-dose-treated subjects over three ragweed seasons, also improved significantly and correlated with the decreased release of inflammatory mediators. There was no significant difference in the degree of clinical improvement between the moderate- and high-dose groups. An example of a typical immunotherapy schedule needed to achieve an optimal immunotherapy dose is found in Table 3.

Table 3
Illustrative Dose Schedule for Short Ragweed Allergen Immunotherapy

			Dose	
Dose	*Vial*	*Dilution of 1:10 w/v concentration*	*mL*	*Ragweed Amb a 1 (AgE) (μg)*
1			0.05	
2			0.1	
3	D	1:100,000	0.2	
4			0.3	
5			0.4	
6			0.05	
7			0.1	
8	C	1:10,000	0.2	
9			0.3	
10			0.4	
11			0.05	
12			0.1	
13	B	1:1000	0.2	
14			0.3	
15			0.4	
16			0.05	
17			0.1	Desirable Dose
18	A	1:100	0.2	Range of 3–12 μg
19			0.3	
20			0.4	

1:10 Weight by volume (w/v) means that 1 g of pure pollen is diluted in 10 mL of diluent. 1:10 w/v of standardized ragweed vaccine contains 400 μg *Amb a 1* (Antigen E)/mL. Maintenance dose of immunotherapy is administered on a weekly to monthly schedule and can be altered on an individual basis. The above schedule represents a weekly injection schedule (week 1–20). More rapid build-up can be accomplished by giving the injections twice weekly or by utilizing a "rush" immunotherapy protocol that achieves maintenance doses in days rather than weeks.

Nasal challenges also confirm that such therapy attenuates both the immediate- and late-phase allergic responses by decreasing mucosal membrane cellular influx and mediator production. Ragweed immunotherapy for 3–5 yr is required to achieve clinical remission. Both mixed- and single-grass pollen immunotherapy studies for hay fever result in significantly decreased symptom-medication scores during the grass pollen season and responses to grass skin testing and nasal challenge testing. Increases in grass-specific IgG-blocking antibody occurs in subjects successfully treated with mixed-grass immunotherapy. The size of both the immediate- and late-phase skin tests to timothy grass vaccine were diminished in a timothy allergen immunotherapy study.

Mountain cedar tree pollen immunotherapy decreases symptom-medication scores during the cedar tree pollen season, reduces the late-phase skin test reaction to mountain cedar pollen diagnostic vaccine, and increases the specific IgG and decreases the seasonal rise in specific IgE during the mountain cedar pollination season. Similar clinical and immunological results were obtained in birch pollen allergen immunotherapy trials. In addition, birch pollen nasal provocation studies show inhibition of allergic symptoms and reduced chemotactic activities for eosinophils and neutrophils in nasal secretions after allergen immunotherapy.

Mites, Molds, and Animal Danders

House dust mite allergen immunotherapy results in significantly decreased nasal symptom scores, responses to nasal allergen challenge, and size of the skin test reaction. The same changes in specific IgG and IgE as observed with pollen studies were found. *Alternaria* spp mold immunotherapy produced similar decreases in nasal symptom-medication scores, allergen provocative challenges in the skin and nose, and increased serum IgG. Cat allergen immunotherapy results in reduced nasal symptom scores of subjects exposed to a cat in a study room.

Allergic Asthma: Overview

More than 50 controlled immunotherapy trials have been performed with a variety of allergens for seasonal, perennial and animal-induced asthma. Vaccines of rye grass, mixed grasses, ragweed, birch, mountain cedar, *Alternaria* spp, *Cladosporium* spp, house dust mites, cat, dog, and cockroach have been used in these trials. Collective analysis of these studies provides important insight, but comparisons among studies are difficult because of varied study designs. Of these studies, 42 demonstrated significant clinical improvement in treated subjects; 23 of these showed a significant increase in the bronchoprovocation threshold to the allergen used for immunotherapy. Of the trials in which immunological parameters were monitored, 16 demonstrated an increase in allergen-specific IgG-blocking antibody, and one showed a decline in specific IgE. Nine reported decreased skin test reactivity to the allergen used for immunotherapy, and two demonstrated reduced in vitro basophil histamine release following allergen challenge. An overall analysis of controlled studies in the treatment of asthma with allergen immunotherapy indicates clinical efficacy in allergic asthmatics.

A meta-analysis of most published, controlled trials of allergen immunotherapy in asthma reviewed in the Cochrane Database (2003) indicates that allergen immunotherapy is effective in the treatment of allergic asthma, provided that the clinically relevant and unavoidable allergen can be identified. Between 1954 and 1997, 54 published randomized controlled trials satisfied the strict inclusion criteria of the Cochrane Database. There were 25 studies reporting immunotherapy for dust mite allergy, 13 studies of pollen allergy, 8 studies of animal dander allergy, 2 studies of allergy to the mold *Cladosporium* spp, and 6 studies that attempted simultaneous immunotherapy for multiple aeroallergens. A review of 75 additional studies by the Cochrane Database (1996–2001) indicates benefits from immunotherapy in asthma treatment. It was found that allergen-specific immunotherapy significantly reduced asthma symptoms and medication requirements, but there was no consistent effect upon lung function. Allergen immunotherapy reduced allergen-specific bronchial hyperreactivity to a greater extent than nonspecific bronchial hyperreactivity. It is not possible to compare the size of improvement with immunotherapy to that obtained with other therapy for asthma. Immunotherapy must be considered for use when asthma is extrinsic or allergic and unavoidable clinically relevant allergens are identifiable. The arguments favoring immunotherapy are especially strong in the case of younger patients requiring year-round medical management. If allergen immunotherapy is utilized, it should be administered in sufficiently high doses of vaccine to maximize the benefits. With these optimal doses, there is the expectation of a reduction in medication requirements and symptom scores in the majority of treated patients.

The National Heart, Lung, and Blood Institute (NHLBI) in 2001 sponsored an expert panel to establish guidelines for the diagnosis and management of asthma. This national asthma education and prevention program states that 75–85% of asthmatic patients are

allergic, and immunotherapy should be considered in such patients when avoidance of allergens and treatment with appropriate medications does not control the disease. Immunotherapy decreases asthma medications, offsetting its own cost, and it may further reduce costs by decreasing need for concurrent treatment of allergic rhinitis.

Pollen

Allergic asthmatic subjects often experience increased bronchial hyperactivity during a specific pollen season. The effect of birch pollen allergen immunotherapy on bronchial reactivity, as measured by methacholine provocation, was investigated in subjects with birch pollen asthma induced during the birch pollen season. Untreated subjects had increased bronchial hyperreactivity to methacholine, whereas those receiving birch pollen immunotherapy did not. In addition, eosinophil cationic protein, an inflammatory mediator derived from eosinophils in the bronchoalveolar lavage fluid, was decreased in subjects receiving birch pollen immunotherapy. Other studies using mixed grasses, cedar, birch, mugwort, and ragweed pollen vaccine immunotherapy demonstrate reduced bronchial responses to methacholine or histamine.

The benefits of immunotherapy are specific for the allergen(s) used in treatment. Some studies have shown that single-pollen allergen immunotherapy, such as derived from one grass species, may provide incomplete relief of asthmatic symptoms because of multiple grass sensitivity or because other sensitivities exist, for example, to molds. Similarly, a highly purified standardized ragweed allergen vaccine containing only a single protein allergen, such as ragweed AgE or Amb a 1, may provide incomplete relief of symptoms in ragweed-sensitive asthmatic subjects because they are sensitized to several ragweed proteins besides the allergenic protein in the vaccine.

The IgE immune response of asthmatic subjects is different in the polysensitized vs the monosensitized subject. Patients sensitized to a single allergen have significantly lower total serum IgE levels than those allergic to multiple allergens. The lymphocytes from the polysensitized subject, when challenged with allergen, release significantly more IL-4 (favors IgE production) and CD23 (low-affinity IgE receptor) in vitro than those from the monosensitized subject, although the lymphocyte IFN-γ in vitro production is the same in both groups.

A double-blind placebo-controlled study during the pollen season compared the efficacy of immunotherapy in monosensitized (orchard grass pollen) and polysensitized (multiple pollen, including orchard grass) asthmatic subjects. Subjects allergic to grass pollen were treated with an optimal maintenance dose of a standardized orchard grass pollen vaccine, whereas those allergic to multiple pollen species, including grass, received the same biologically equivalent dose of all standardized allergens to which they were sensitized. The results indicated that monosensitized subjects with orchard grass pollen allergy, but not polysensitized subjects, were significantly protected during the respective pollen season during this study. Higher doses of standardized vaccines over a prolonged treatment schedule are probably required to demonstrate efficacy in polysensitized allergic patients.

A 5-yr study of the role of immunotherapy in ragweed-induced asthma was published in 1993. Clinical parameters (symptom diary scores, medication usage, peak expiratory flow rate [PEFR] measurements and physician evaluations) and other end points (skin test sensitivity, serological parameters, and bronchial sensitivity to ragweed and methacholine) were monitored. A standardized, maintenance dose of ragweed vaccine contain-

ing Amb a 1, 10 μg/injection, was used to immunize ragweed-sensitive subjects. Both clinical and objective parameters improved, again demonstrating that the use of an appropriate therapeutic dose is necessary to achieve a good clinical response.

Creticos et al. in 1996 examined the efficacy of allergen immunotherapy for asthma exacerbated by seasonal ragweed exposure; 64 patients completed 1 yr of the study treatment, and 53 completed 2 yr. These patients were not exclusively ragweed sensitive. The immunotherapy group had reduced hay fever symptoms, skin test sensitivity to ragweed, sensitivity to bronchial challenges, and increased IgG antibodies to ragweed as compared with the placebo group. The seasonal increase in IgE antibody to ragweed allergen was abolished in the immunotherapy group after 2 yr. Patients received doses of 4 μg/injection of Amb a 1 the first year and 10 μg/injection the second year. Although positive effects were observed in the immunotherapy asthma group, the clinical effects were limited. Both groups (immunotherapy and placebo) had some improvement in asthma symptoms during the study.

Role of Allergen Immunotherapy in Asthma Management

- A consideration in asthmatics who are allergic: 80% of children over age 2 yr; 50% of adults.
- A possible therapy in asthmatic, with concomitant significant allergic rhinitis—uncontrolled with environmental allergen elimination, plus rhinitis medication.
- An adjuvant therapy in moderate–severe asthmatics who are not well managed with environmental allergen elimination plus asthma medication.

Adkinson et al. in 1997 performed a controlled trial of immunotherapy for asthma in allergic children. A placebo-controlled trial of multiple-allergen immunotherapy in 121 allergic children with moderate to severe perennial asthma was conducted over 2 yr. The median medication score decline was not significantly different between the immunotherapy group and the placebo group. The number of days patients received oral corticosteroids were similar in the two groups. There was no difference between the groups in the use of medical care, symptoms, or peak flow rates. Partial or complete remission of asthma occurred in 31% of the immunotherapy group and 28% of the placebo group. The median PC20 for methacholine increased significantly in both groups, but there was no difference between the two study groups. Optimal doses of immunotherapy, ranging from 4.3 to 26 μg/injection, resulted in a mean 8.8-fold increase in the levels of allergen-specific IgG to *Dermatophagoides pteronyssinus* and *D. farinae* mites, short ragweed, oak, and grass. A 61% mean reduction in wheal diameters by prick skin testing to each respective allergen was observed. The group that benefited from immunotherapy was made up of children with milder disease (no inhaled corticosteroids) and younger children (<8.5 yr) with a shorter duration of disease. The data indicate that there is no discernible benefit from immunotherapy in allergic children with perennial asthma who already are receiving appropriate and optimal medical treatment from asthma experts.

Mites

Several studies of immunotherapy with vaccines of standardized aqueous *D. pteronyssinus* and/or *D. farinae* house dust mites demonstrate significant benefit. A study by Bousquet et al. revealed that among subjects allergic only to *D. farinae*, children show significantly greater improvement than adults. As expected, patients with severe, chronic asthma ($FEV_1 \geq 70\%$ of predicted), other perennial allergen sensitivities, aspirin intolerance, or chronic sinusitis achieve the least benefit from immunotherapy.

A later study by Bousquet et al. analyzed immunotherapy to *D. pteronyssinus* in 74 mite-allergic asthmatics. It demonstrated a significant dose-dependent increased tolerance to the standardized *D. pteronyssinus* allergen, Der p 1, on bronchial allergen challenge in each of the immunized groups vs no change in the control group. A significant reduction in histamine bronchoprovocation hyperresponsiveness also was observed, with the greatest reduction in the highest-dose group. The rate of systemic reactions was lowest in the low-dose and highest in the high-dose group, and since the 7 and 21 μg/injection schedules were equally effective, the 7 μg/injection dose was recommended as the appropriate target dose.

Danders

Several controlled studies found that cat and dog immunotherapy effectively increases the threshold dose of cat or dog dander vaccine, respectively, needed to induce a positive bronchial challenge in subjects with cat- or dog-specific allergic asthma. Such therapy also results in a reduction of symptoms after dander exposure in a challenge room. Many subjects are given cat or dog immunotherapy, at their own request, in an effort to better tolerate the presence of a pet in their home. However, confirmation of clinical efficacy, under such circumstances, is needed, and elimination of the animal from the environment in which the subject lives is the preferable mode of therapy. There is increasing evidence that the allergens of fur-bearing pets are ubiquitous in many homes and other indoor locations, even where no animals reside. It is being passively introduced into these locations because of the prevalence of such animals in US homes. Including cat and/or dog allergens in the vaccine of a patient with positive skin tests to cat and/or dog may become more commonplace.

Molds

Molds that trigger asthma are numerous, diverse, and contain multiple allergens, and mold vaccines available for use in the United States are not standardized. Controlled immunotherapy trials with standardized vaccines of *Alternaria* spp and *Cladosporium* spp demonstrate efficacy in the treatment of asthma. One such trial of 1 yr of treatment with *Alternaria* spp resulted in ablation or a reduced late-phase response upon *Alternaria* spp allergen challenge in 8 of 10 subjects. Increased concentrations of allergen and methacholine also were required to induce bronchial constriction. *Cladosporium herbarium* vaccine immunotherapy produced significant decreases in symptom-medication scores and response to bronchial challenge tests.

REASONS FOR LACK OF BENEFIT FROM IMMUNOTHERAPY

The reasons for lack of benefit from allergen immunotherapy include: (1) inappropriate treatment with such therapy of non-IgE-mediated disease, such as chronic nonallergic rhinitis or vasomotor rhinitis; (2) utilization of low-potency allergen vaccines; (3) administration of inadequate doses of allergen; (4) ineffective environmental control resulting in continued excessive exposure, for example, to cat or dog dander; (5) a coexistent medical problem, such as sinusitis and nasal polyps, which accounts for most of the

symptoms; (6) the allergen vaccine lacks important allergens because of undiagnosed or unrecognized sensitivities.

OVERVIEW OF PRACTICAL ASPECTS

Specific allergen immunotherapy is effective treatment for specific patients with allergic rhinitis and allergic asthma. Careful selection of the patient and the relevant allergen(s) for immunotherapy requires expertise and knowledge about the pathophysiology of allergic diseases and regional outdoor and indoor allergen sources. Allergen immunotherapy is indicated for symptomatic patients in whom an adequate trial of environmental control and avoidance and appropriate pharmacotherapy has failed. Reduction of symptoms and the amount of medications required occurs in patients who received optimal maintenance doses of specific immunotherapy for a 3- to 5-yr period.

Local Reactions to Allergen Immunotherapy

- Redness and swelling (usually dime–quarter sized) are not uncommon and easily managed with an ice pack, with or without an antihistamine.
- Larger reactions may require an antihistamine as well as short term oral corticosteroids.
- Significant local reactions may require adjustment of subsequent allergen immunotherapy doses.

DURATION OF IMMUNOTHERAPY

Clinical trials and observations indicate that immunotherapy can be stopped after 3–5 yr of successful therapy. The results of grass, tree and ragweed immunotherapy trials demonstrate efficacy for several years after cessation of such therapy. In one ragweed study, the immunological parameters and nasal lavage mediators remained unchanged 1 yr after the treatment vaccine was stopped. House dust mite immunotherapy administered for 1–6 yr and then discontinued was found to be most effective after discontinuation if it had been administered for at least 3 yr. The effect of immunotherapy on the reduction of the skin test end points at the conclusion of the treatment was correlated with the duration of efficacy after immunotherapy cessation. Efficacy of a 3-yr course of animal dander immunotherapy was assessed 5 yr after its discontinuation, and one-third of these subjects continued to demonstrate tolerance to cat exposure. When relapses occur after the immunotherapy is discontinued, a good response to restarting such therapy occurs more rapidly than occurs during the initial course of immunotherapy.

ADVERSE REACTIONS

Local Reactions

Patients receiving allergen immunotherapy often experience reactions at the site of the injection (erythema and edema) that cause some local discomfort. No adjustment in vaccine dose is necessary for reactions less than 4 mm in size. Large local reactions, 4 cm or greater in diameter, occur less frequently and may cause more discomfort and persist for 24 h or longer. There is a concern that subsequent increases in the dose of the vaccine following a large local reaction may result in a systemic reaction; however, there is little

Key Words:

evidence that such local reactions, whatever their size, place the subject at increased risk for a systemic reaction. This local discomfort can be controlled with cold compresses and oral antihistamines. When such reactions occur, the subsequent allergen immunotherapy dose usually is reduced to the previously tolerated dose and subsequently increased. If large local reactions persist, either the dose has to be divided into two doses given at separate sites or the same dose maintained, if tolerated, or the dose decreased. Large local reactions do not predict the onset of a subsequent systemic reaction, and most systemic reactions occur in the absence of previous large local reactions.

Risk of Systemic Reactions to Allergen Immunotherapy

- Risk rate: 1 per 2000 injections.
- Most reactions begin within 30 min of injection—thus, a minimum of 30 min waiting time is advised.
- More systemic reactions occur:
  - In highly allergic patients.
  - With use of pollen-allergen vaccine, especially during the pollen seasons.
  - During initial dose "buildup" phase, especially with accelerated programs.
- The risk of more serious reactions is increased:
  - In allergic asthmatics.
  - With patients taking concomitant β-blocking drugs

Systemic Reactions

Systemic reactions occur rarely; they may range from mild, manifested as generalized pruritus, urticaria, or symptoms of allergic rhinitis and conjunctivitis, to life threatening, with upper and lower airway obstruction and/or anaphylactic shock. Fatalities are rare but do occur. A retrospective survey by questionnaire of allergy specialists in the United States for the period 1945–1983 reported 46 fatalities either from skin testing or immunotherapy. The data from 30 questionnaires allowed further evaluation of the fatalities; 6 were caused by skin testing and 24 by immunotherapy. A later extension of this study included reports of an additional 17 deaths between 1985 and 1989. Further reporting has disclosed another 41 fatalities related to immunotherapy from a survey from 1990–2001.

The incidence of systemic reactions from immunotherapy over a 10-yr period at the Mayo Clinic was 0.137%; most were mild and responded to immediate medical intervention. There were no fatalities. The estimated fatality rate from allergen immunotherapy in the United States was approximately one per 2–2.8 million injections. Some factors cited that increased the likelihood of a systemic reaction are an incorrect injection technique or erroneous dose. This type of mishap was not the cause in all systemic reactions. Other observations were (1) mite-sensitive individuals had more immunotherapy-related asthma reactions than those who were pollen sensitive; (2) fewer reactions occurred with maintenance doses than during the build-up phase; (3) excluding the severe or unstable asthmatic from receiving the immunotherapy injections significantly reduced the rate of systemic reactions.

PRECAUTIONS

No allergen vaccine should be considered completely safe for an allergic subject, and immunotherapy should be carried out only by trained personnel who know how to admin-

ister immunotherapy injections, to adjust doses, and to manage adverse reactions in a setting where appropriate equipment for such management is immediately available. A detailed protocol to adjust for missed injections and for reactions to immunotherapy is necessary. A protocol for the management of anaphylaxis is indicated, and personnel who administer injections should be trained in the appropriate treatment of anaphylaxis. Prompt recognition and immediate administration of epinephrine in systemic reactions are the mainstays of therapy.

Patients at higher risk for severe life-threatening systemic reaction include those with:

1. Unstable or symptomatic asthma.
2. Significant seasonal exacerbation of their allergic symptoms, particularly asthma.
3. A high degree of hypersensitivity (by skin testing or specific IgE measurements).
4. Accelerated schedules of immunotherapy, particularly during the initial build-up period.
5. High-dose maintenance regimens in highly sensitive allergic patients.
6. Concomitant use of β-blockers (which makes treatment of anaphylaxis more difficult with epinephrine). β-Blockers should be discontinued, when possible, prior to initiation of immunotherapy.
7. Injections from new vials.

Patients who become pregnant while already receiving immunotherapy may be maintained at their current or a reduced dose during pregnancy. Immunotherapy should not be started during pregnancy unless a life-threatening situation exists, e.g., Hymenoptera hypersensitivity. Relative contraindications for immunotherapy include: (1) serious immunopathological and immunodeficiency diseases; (2) malignant disease; (3) severe psychological disorders; (4) poor compliance; (5) patients who are noncompliant; (6) severe uncontrolled asthma or irreversible airway obstruction, <70% predicted FEV1; (7) significant cardiovascular diseases, which increase the potential side effects from epinephrine; (8) children under 5 yr of age; and (9) systemic mastocytosis.

The risk of systemic allergic reactions and fatal reactions should be reduced and, it is hoped, eliminated by (1) avoiding errors in dosing; (2) utilizing preventive protocols to minimize risk, such as measuring peak flow rates in patients with unstable asthma; (3) reducing doses when injections are given from new vials; (4) reducing doses when injections are given during a particularly high pollen- or mold-induced seasonal exacerbation; and (5) by using standardized allergen vaccines.

Any physician who administers immunotherapy, regardless of specialty, should be present when the injections are given. The patient should be required to wait 30 min following the injection. A longer wait is indicated for high-risk patients. In the event of any adverse reactions or uncertainity about the dose, the allergist should be consulted prior to administration of another dose of allergen vaccine.

TREATMENT OF ALLERGIC REACTIONS: MEDICATIONS AND EQUIPMENT

Physicians prescribing and/or administering such therapy must be aware of the potential risks and institute appropriate clinic procedures to minimize them. Prompt recognition of signs and symptoms of a systemic reaction and immediate use of epinephrine (subcutaneously or preferably intramuscularly) to treat such a reaction are the mainstays of therapy. The following equipment, medications, and reagents should be available: (1) stethoscope and sphygmomanometer, (2) tourniquets, syringes, hypodermic needles, and large-bore (14-gage) needles, (3) aqueous epinephrine HCl, 1;1000 w/v, (4) equipment

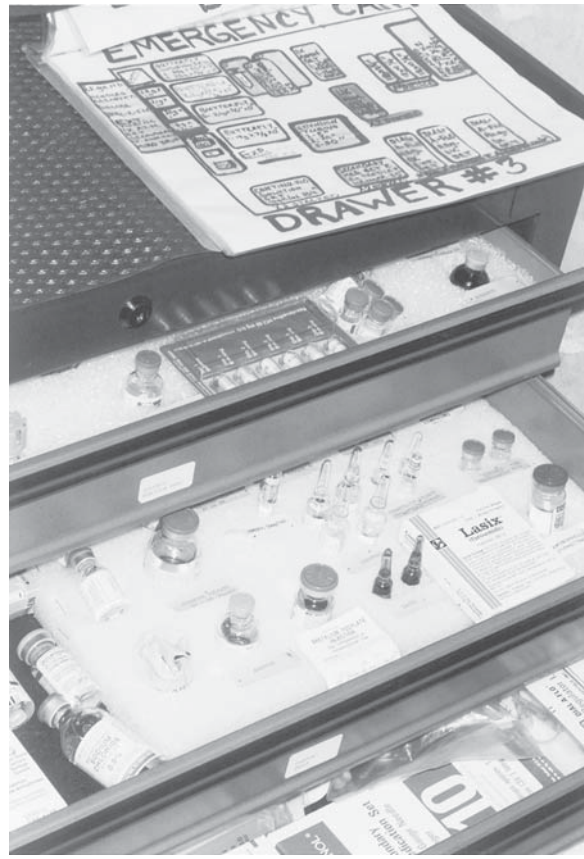

Fig. 1. Emergency medications and supplies as included in a code cart. Office or clinic physicians and staff personnel should be familiar with its contents.

to administer oxygen,(5) equipment to administer intravenous fluids, (6) oral airway, (7) antihistamine,(8) corticosteroids, and (9) injectable vasopressor. The rare situation in which invasive procedures (electrical cardioversion, tracheotomy, intracardiac injection of drugs) might be essential does not justify the risk of their being available for use under less than ideal circumstances. It is impractical to insist that these procedures be available in every clinic situation.

FUTURE TRENDS IN IMMUNOTHERAPY

New technology and advancement of knowledge in the basic mechanisms and pathophysiology of allergic diseases will completely change allergen immunotherapy in the future. These advances should result in new, safer, and substantially more effective methods of manipulating the human immune response. Several approaches may be used: (1) novel delivery systems, such as sublingual immunotherapy (the World Health Organization accepts this type of immunotherapy as a valid alternative to the subcutaneous route for allergic rhinitis and asthma); (2) allergen fragments or peptides (devoid of anaphylactic potential) for active immunotherapy; (3) IgE-binding haptens of major allergens for passive saturation of effector cells and induction of blocking antibodies; (4) plasmid DNA immunization; (5) allergen-specific antibodies and antibody fragments for

Fig. 2. Careful inspection of the patient's injection dosage sheet and vials of allergen vaccines. Draw up exact amount of the vaccine into a syringe. Document the injection site (right or left arm) and if a local or systemic reaction occurs.

passive therapy, i.e., to be used by inhalation into the nose or lungs; and (6) immunotherapy with humanized anti-IgE monoclonal antibody (Xolair™), which reduces total IgE, making immunotherapy safer.

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27 Controversies in Allergy and Allergy-Like Diseases

Abba I. Terr, MD

Contents

SUMMARY

Evidence-based diagnostic and therapeutic practices are currently available to allergists for use with nearly all patients suffering from allergic disease. However, unproved and controversial methods and theories of allergy abound and may appeal to even the most knowledgeable and sophisticated patient. It therefore behooves the practitioner to be aware of these unconventional techniques and concepts in order to counsel those patients who would be tempted to pursue them.

Key Words: Controversial; unproven; unconventional; experimental; alternative medicine; complementary medicine.

INTRODUCTION

The management of allergic diseases is accomplished most successfully and cost-effectively by the patient's primary care physician in collaboration with a specialist in allergy/immunology. It is critically important to use methods of diagnosis and treatment that are based on sound scientific principles and that have been validated by proper clinical trials. Physicians who treat allergic patients, therefore, must be aware of the plethora of unproven and controversial methods that are currently promoted by a small group of practitioners, and they should understand the faulty rationale on which they are based. These unproven techniques and their unscientific, or even antiscientific, theories are sometimes deceptively labeled as alternative or complementary forms of medical practice. This implies some measure of efficacy that in fact does not exist.

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Table 1
Unproven Allergy Theories

Allergic toxemia
Environmental illness
Food-additive sensitivity
Multiple food allergies
Multiple chemical sensitivities
Candida hypersensitivity

In contrast to the scientifically rigorous immunopathological foundation underlying our present knowledge of human allergy, the theories advanced by the proponents of the controversial methods described in this chapter lack experimental proof. These theories frequently arise from misinterpretations of chance empirical observations.

UNCONVENTIONAL THEORIES OF ALLERGY

The principal theories on which most of the unproven allergy practices are based are listed in Table 1. So-called allergic toxemia is the basis for a number of these practices. It is comprised of two mistaken components. It postulates that allergens are inherently toxic and that virtually any subjective symptom in the absence of objective evidence of pathology can be attributed to allergy. In fact, most allergens are nontoxic in the usual dosage and manner of exposure necessary to either induce or elicit an allergic reaction. The presence or absence of potential toxic properties of an allergen is irrelevant to its ability to evoke an allergic immune response. Furthermore, the manifestations of allergic illness result from inflammation and not toxicity. In contrast, proponents of allergic toxemia in its various forms diagnose this condition not in patients with allergic symptomatology, but rather in patients with multiple vague complaints that usually include fatigue, anxiety, cognitive difficulties with memory and concentration, and a variety of physically unexplained pains and other bodily discomforts.

The allergic toxemia concept originated with patients who attributed their multiple medically unexplained symptoms to their diet. This led (i.e., misled) to the idea that multiple food allergies in a single individual can produce an unlimited number of symptoms and that the specific symptoms and implicated foods are variable and changeable. Other ingested substances, such as food additives and prescribed medications, particularly antibiotics, are often included as causes of allergic toxemia. To explain unpredictable symptom responses, the concepts of masking and overload were devised to rationalize the absence or presence, respectively, of unexpected symptoms. The current terminology for unexplained absence/presence of symptoms is adaptation/de-adaptation. It is clear that these terms are merely descriptive and have yet to be explained by their advocates in a physiologically meaningful way.

Environmental illness and multiple chemical sensitivities are names applied to a condition described as allergic toxemia, but in this case the cause is attributed to numerous common everyday environmental chemicals. In most cases these chemicals include pesticides, solvents, perfumes, new carpets, plastic materials, new clothing, and virtually any synthetic chemical or commercial product with an odor. Occasionally, electromagnetic fields generated by nearby electric power lines or even household appliances are

included as causes of symptoms. Some patients believe that their multisystemic polysymptomatic illness represents hypersensitivity to numerous chemicals, foods, and drugs. The term given to this condition is universal allergy. Because symptoms in these patients have never been shown to be in fact related to chemicals, the term idiopathic environmental intolerance is more accurate. The clinical presentation of this condition is often indistinguishable from that of chronic fatigue syndrome and other controversial subjective conditions.

Periodically over the past century, this clinical condition has also been ascribed to the effects of a specific microorganism, usually one that enjoys a normal symbiotic or commensal relationship with the human organism. Formerly called autointoxication, presumably from normal gastrointestinal microbial flora, this concept has reappeared as a presumptive chronic viral disease. In this case, according to one unproved theory, the persistence of a virus such as the Epstein-Barr virus or human herpesvirus 6 (HHV-6) was postulated to cause chronic "activation" of the immune system. There is no substantiated evidence or even a clear definition of what activation means in this context, and there is no proof currently that persistence of any virus can explain the pattern of symptomatology experienced by such patients. A variant of this theory is the so-called *Candida* hypersensitivity syndrome, attributed to the existence of *Candida albicans* on certain mucous membranes of many healthy individuals. Recently, toxins from indoor molds have been implicated.

CONTROVERSIAL METHODS OF ALLERGY DIAGNOSIS

To select the most appropriate methods for diagnosis and treatment, the clinician should be familiar with the underlying principles of both legitimate and unproved methods. Controversial diagnostic and treatment procedures will be discussed separately (Tables 2 and 3). Some of these procedures are of no proved worth under any circumstance, whereas others may have a legitimate place in some conditions, although not in allergic disease.

The provocation–neutralization procedure consists of "testing" the patient with a small amount of a substance in liquid form administered by either intradermal injection or by sublingual drop. The patient records any symptoms or sensations for a period of 10 min thereafter, and any symptom, regardless of its nature or intensity, is taken as indication that the test is "positive." If the patient reports no symptom, the test is repeated using the same test substance at a different concentration until there is a "positive" result. Next, the same substance is tested at lower concentrations until the patient again reports no symptom, at which point the allergy (i.e., the symptom) is said to be "neutralized." The neutralizing dose of the substance is then prescribed as treatment.

Numerous substances are tested, including the common atopic allergens, food extracts, chemicals, drugs, and hormones. Because each test substance must be administered separately to elicit symptoms, testing to multiple substances is extremely time-consuming. It has been shown, however, that patients cannot distinguish test extracts from placebo controls by this procedure, so the basis of a positive test is merely the power of suggestion. It is therefore worthless for diagnosis, and there is the potential danger that delivery by the sublingual route of an allergen to a patient with a true IgE-mediated allergy might cause life-threatening angioedema of the buccal mucosa or even systemic anaphylaxis.

Table 2
Unconventional Diagnostic Methods

Provocation–neutralization
Cytotoxic test
Pulse test
Applied kinesiology
Electrodermal testing

Table 3
Unconventional Treatment Methods

Neutralization
Food avoidance
Chemical avoidance
Vitamins and other supplements
Enzyme-potentiated desensitization
Acupuncture
Homeopathy

The cytotoxic test consists of applying a drop of the patient's blood onto a microscope slide containing a minute quantity of a food or drug. The unstained blood sample is then inspected microscopically for alterations in the morphology of the leukocytes, which is claimed to indicate allergy to the food or drug. There is no standardization for criteria indicating a positive result, time of incubation, pH, temperature, or any other variable that might affect leukocyte viability. There is no reasonable theory linking changes in blood leukocyte appearance and allergic disease. There have been no studies to correlate the result of this test with a rigorous independent proof of allergy, such as the double-blind, placebo-controlled oral food challenge.

The pulse test for food allergy is performed by measuring the pulse rate of the patient before and after food ingestion. Remarkably, advocates of this "test" have claimed at various times that an increase or a decrease is diagnostic of food allergy. There is no independent verification that a pulse change correlates with allergy, nor is there a cogent theory to explain such a phenomenon. The pulse test is an example of a valid medical diagnostic procedure—quantitation of the pulse rate—being misused as an allergy test.

Applied kinesiology is a purported system of health practice that is based on the bizarre concept that a variety of diseases, especially allergy, cause a reduction in the strength of skeletal muscle. The diagnosis of food allergy consists of subjectively testing the ability to resist the forced movement of the patient's outstretched arm during exposure of the patient to a food. Incredibly, the exposure to the presumed food allergen is usually carried out by placing the food in a container that the patient simply holds during the muscle-strength testing. Not surprisingly, there is no experimental proof of either the diagnostic efficacy of the procedure or validation of its theory.

The suggestive power of a mechanical or electrical apparatus in medical diagnosis is illustrated by electrodermal diagnosis. In this case a device to measure the electrical resistance of the skin is inserted into a circuit that includes a metal container of a food item and a probe applied to the patient's skin. The probe presumably explores various points

on the body surface, and a change in the galvanic resistance of the skin is believed to indicate allergy to that food. The use of a computer-generated printout gives the "results" an aura of high-technology precision.

CONTROVERSIAL TREATMENTS FOR ALLERGY

Treatment regimens that are based on unsubstantiated theories of allergy or unreliable diagnostic tests are clearly not in the patient's best interest. Those discussed here are listed in Table 3. The fact that a patient might seemingly benefit from a particular form of treatment, especially if the illness is largely or completely subjective, does not validate the treatment. Clinical efficacy and safety can be evaluated only by a properly designed and executed controlled trial with appropriate measurements and analysis.The controversial forms of allergy "treatment" described here have either failed critical tests of efficacy and safety or they have not been evaluated because of the lack of any compelling reason to do so.

Neutralization therapy is an extension of the provocation–neutralization testing procedure. The so-called neutralizing dose of the test substance is prescribed for self-administration by the patient either to relieve current symptoms or to prevent symptoms when they are believed to be imminent because of an anticipated environmental exposure. The treatment is also recommended on a regular schedule as an ongoing maintenance program. The neutralizing solution is taken by either sublingual drops or subcutaneous injections. There is no evidence of any therapeutic result other than a placebo response.

Avoidance therapy is frequently recommended as a feature of most controversial forms of allergy practice, as it is in conventional practice. The differences, however, are profound with respect to the underlying rationale and the extent and consequences of the recommended program The unreliable diagnostic tests described here invariably "uncover" an extensive list of nonexistent allergies, leading to the unnecessary elimination of numerous foods and the avoidance of environmental items that are ubiquitous in today's world. Extreme elimination diets are obviously dangerous, so proponents of the concept of multiple food allergies usually advise their patients to eat (or to avoid eating) specific foods on a prescribed schedule, usually as a 4- or 5-d rotational diet. Proponents of the rotational diet also claim—without substantiation—that such a diet actually prevents the development of food sensitivities. Chemical avoidance for patients with so-called multiple chemical sensitivities may be so extreme that major lifestyle changes are necessary to avoid any possible exposure to all synthetic products and all items that can be detected by odor. Fortunately, most of those individuals in whom multiple food and chemical sensitivities have been diagnosed eventually compromise on these extreme recommendations.

Dietary supplements are frequently a component of these irrational approaches to allergy management. Although there is neither theoretical nor experimental evidence that allergy pathogenesis involves a deficiency of any nutrient, clinicians and others who promote any of these "alternative" programs usually advise their patients to take supplemental vitamins, minerals, amino acids, chemical antioxidants, or some combination of these.

A number of nonmedical, unscientific, and unproven systems of practice offer to help persons with a variety of illnesses, including allergy. The most prevalent today are acupuncture, chiropractic, homeopathy, and naturopathy, but there is also a long list of boutique "therapies" such as crystal therapy and herbalism. In general, each of these treatment-based systems employs a similar if not identical treatment procedure, regard-

less of the nature of the disease. Needless to say, needling of the skin, spinal manipulation, ingestion of herbs, or any of the other maneuvers embraced by these entities are inconsistent with the known mechanisms of allergy, and proponents of them cannot cite any evidence of effectiveness.

Many of the unconventional treatments discussed above are recommended for patients with presumed allergy in whom the existence of a true hypersensitivity disease is questionable. Recently, an unproved "modification" of allergen immunotherapy for patients with atopic allergy has surfaced. It is called enzyme-potentiated desensitization, and it consists of a single preseasonal subcutaneous injection of a conventional pollen extract mixed with a minute quantity of the enzyme β-glucuronidase. It is claimed to be superior to the usual extended course of immunotherapy that requires graduated increasing doses of allergen leading to a successful long-term maintenance program. Although a single low-dose injection of an allergen is certainly less likely than conventional immunotherapy to cause a systemic reaction, there is no evidence that enzyme-potentiated desensitization favorably affects atopic disease, whereas there are now dozens of well-controlled clinical trials confirming efficacy of the conventional high-dose form of treatment.

DISCUSSION

The superficial similarity of many of these unproven methods to scientifically based procedures of diagnosis and treatment of allergic diseases is an opportunity for exploitation by their proponents and a trap for the unwary clinician. The allergic population is very large, and the primary care physician is the first medical contact for most of them. Practitioners of these unconventional procedures are readily available both within and outside the medical profession. They often advertise their services with promises that most physicians cannot and do not make. Only by knowing the specifics of these methods and their claimed theoretical basis can the clinician make an informed decision and give proper advice to the patient about their use. Some of the more common ones are described here.

With the exception of sublingual allergen administration, the methods reviewed in this chapter are not likely to pose an immediate hazard to health. Rather, their danger is more subtle, pervasive, and profound. An incorrect diagnosis made by an unreliable test creates the risk that another disease—physical or psychiatric—will remain undiagnosed and untreated. Diagnosing allergy in a person who truly has none may create a lifelong disability characterized by unnecessary avoidance behavior. An extreme form of this unfortunate iatrogenic phenomenon is seen in patients who accept the idea that they have multiple sensitivities to foods and/or chemicals. Some of these individuals live a life of social and material isolation from which they may never recover. Most allergists would agree that it is far easier to treat an allergy than it is to disabuse a patient of his or her fear of an allergy that does not exist.

The problem of unconventional methods in allergy is of concern to a number of professional societies. In particular, the American Academy of Allergy, Asthma and Immunology has published position statements about many of these procedures. These publications also provide literature citations to appropriate studies and evaluations that document their lack of effectiveness.

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28 The Patient With 'Too Many Infections'

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CONTENTS

SUMMARY

Perhaps the most common complaints in the primary care physician's office are related to the common cold. The miseries induced by the common cold virus prompt patients afflicted to seek medical care with expectations of relief prompted by the fact that physicians can successfully transplant hearts, cure cancer, and heal a number of other more severe maladies. Thus, expectations are perhaps unrealistically high for relief of the less threatening and more mundane miseries associated with upper respiratory tract infections. This fact, coupled with the frequency of occurrence of such infections, makes the "cold season" (usually stretching from late October until mid-May) one of the busiest for all primary care physicians and allergists/immunologists as well. It is of course imperative to be able to distinguish those recurrent infections which are benign from those which represent a distinct immunological deficiency syndrome. The nature of the infection is key not only to making this distinction but also in establishing the type of immunological abnormality.

Key Words: Immunodeficiency; Bruton tyrosine kinase; chronic granulomatous disease; severe combined immunodeficiency; immunoglobulin IgA deficiency; T-cells; interferon-γ; chronic granulomatous disease; leukocyte adhesion deficiency.

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INTRODUCTION

The cornerstone of the practice of primary care medicine is the ability to recognize unusual or distinct manifestations of disease and to separate these from those that are routine or expected. Immunodeficiency should be suspected immediately when a patient has an opportunistic infection or the features of one of the immunodeficiency syndromes. However, the primary care provider must more commonly grapple with the question: How many routine infections are too many? Answering this question involves the consideration of factors that influence immune function, such as environment and age. This chapter provides an overview of the immune deficiency disorders, the differential diagnosis to be considered for the patient with recurrent infection, and a diagnostic approach for the patient suspected of having immunodeficiency.

The Child With "Too Many" Infections: Important Findings

- Age of child and onset of infections
- Type/location of infections
- Number of infections
- Failure to thrive
- Family history of serious infections or early death
- Environmental influences (i.e., passive smoke, daycare)
- Atopic disease symptoms that may mimic infection
- Signs of cystic fibrosis, AIDS, gastroesophageal reflux

PRESENTATION

Age influences immune function. The immune system of a newborn is functionally inferior to that of an older child. For example, children under 2 yr of age routinely mount a poor antibody response to the polysaccharide antigens found on encapsulated organisms like pneumococcus and *Haemophilus influenzae*. Serum immunoglobulin concentrations as a whole are lower in the infant than in the older child and adult. Also, the infant and young child have not yet developed the memory immune responses that occur as a result of exposure and infection. For the premature infant, the immaturity of the immune system is magnified. Often, neutrophil and complement function are depressed. Serum concentrations of immunoglobulin G (IgG) antibody are often further reduced for the preterm infant because two-thirds of transplacental transmission of IgG antibody occurs in the third trimester.

While the infant gains in immune function with age, the elderly lose immune function. The primary immune response weakens and the production of naïve T-cells by the thymus slows considerably. The consequence of these changes results in the exclusive presence of memory T-cells. Additional changes in the T-cell population include the accumulation of cells with signal transduction defects and changes in the T-cell response to cytokines and their development to T-helper type 1 and type 2 effector cells. Age influences the functional potential in monocyte-macrocyte immune responses. The end result of all of the changes observed in the elderly is a dysregulation of immune function and an increased risk of infection and malignancy.

Environment dramatically impacts the incidence of infection, as seen in infants exposed to infection, as in a daycare setting, who have more infections than infants who stay at home. Passive cigarette smoke inhalation also predisposes to illness, including otitis media, pneumonia, and bronchitis. Hygiene of the patients, caretakers, and family members impacts the frequency of such infections as impetigo and furunculosis. For the allergic patient, exposure to indoor allergens such as dust mites and molds often worsens congestion and predisposes to sinusitis and otitis.

The expected frequency of infection varies with the type of infectious organism. It is unusual for a normal host to have even a single infection with an opportunistic organism; however, we are all subject to repeated viral infections of the upper respiratory tract. The question about the expected frequency of recurrent upper respiratory tract infections (URIs) is not easily answered. Some normal individuals experience six to eight URIs per year. This number is increased in children who are exposed to an older sibling or to other children in school. Normally, URIs are mild and last only a few days, and recovery is complete between infections.

In contrast, chronic or severe infection, including pneumonia, chronic bronchitis, otitis, mastoiditis, and sinusitis, is often found in individuals with immunodeficiency. Infections may be difficult to clear with oral antibiotics, resulting in prolonged duration of infection and dependency on antibiotics. Unexpected complications may result from infections in the immunodeficient host.

FAMILY HISTORY

The family history is helpful to explore for an individual with recurrent infections, since evidence of primary immunodeficiency disorders can been seen in family members. Many immunodeficiencies are inherited as a result of mutations in genes on the X chromosome, and others are autosomal recessive in inheritance. Autoimmune processes, history of early infant deaths, and recurrent infections in other family members appearing in the family history are important considerations in the evaluation of a patient for a primary immunodeficiency disorder.

THE IMMUNODEFICIENCY DISORDERS

For the sake of ease of discussion, dividing the immunodeficiency disorders into categories of primary and secondary is helpful. The genetic abnormalities have been described for many of the primary immunodeficiency disorders, and examples of these disorders, the genetic lesion, and typical presentation are listed in Table 1. In general, the primary immunodeficiency disorders result from inherent defects in immunity. Secondary immunodeficiency disorders occur when some external force disrupts normal immunity.

Secondary causes of immune dysfunction must be considered when one is evaluating for immunodeficiency, since secondary disorders occur much more commonly than the primary disorders (Table 2). For the individual with recurrent sinusitis and pneumonia, disorders resulting in impairment of mucus clearance from the respiratory tract such as cystic fibrosis and ciliary dysfunction should be considered. Similarly, the chronic congestion associated with perennial allergic rhinitis can predispose to URI. Opportunistic infection and wasting are hallmark findings of AIDS; however, recurrent bacterial infection is common in HIV infection, especially in children. Immunodeficiency related to a single site that is associated with loss of protein in the stool or urine should trigger an

Table 1
Examples of Genetic Defects Known to Cause Primary Immunodeficiencies

Disorder	*Chromosomal location*	*Known affect on immune response*	*Typical clinical findings*
X-Linked agammaglobulinemia	Xq22	Absence of Bruton's tyrosine kinase results in arrest of B-cell development	Recurrent, serious pyogenic infections
Autosomal recessive agammaglobulinemia	14q32.3(_ chain); 22q11.23 (_5/14.1) 19q13.2 (Ig-α); 10q23.2-23.33 (BLNK)	Defects in Ig receptor proteins results in arrest of B-cell development	Recurrent, serious pyogenic infections
X-Linked hyper-IgM syndrome	Xq26	CD40 ligand (CD154) is not expressed on T-cells	Recurrent, serious pyogenic infections; also opportunistic infections
NEMO deficiency	Xq28	Defective signaling and activation of nuclear factor κ-B	Recurrent bacterial and mycobacterial infections of respiratory tract, soft tissues, and GI tract
DiGeorge anomaly	22q11.2, 10p13	Absence of thymus	Hypocalcemic seizures due to hypoparathyroidism, cardiac disease, abnormal facies, opportunistic infection
X-Linked SCID	Xq13	Absence of the common γ chain of the receptor for cytokines 2, 4, 7, 9, 15	Failure to thrive, opportunistic infection, rash
SCID–CD8 lymphocytopenia (*Zap*-70 Deficiency)	2q12	Deficiency of T-cell kinase involved in thymic T-cell maturation and in intracellular signal transduction	Failure to thrive, opportunistic infections, rash
SCID-T-B+NK+	5p13	Defective IL-7 receptor expression	Failure to thrive, opportunistic infection, rash
*Jak*3 deficiency	19p13.1	Disruption of T-cell intracellular	Failure to thrive, opportunistic infection, rash signal transduction
Adenosine deaminase deficiency	20q13.11	Lymphopenia and poor T-cell function due to toxic effect of adenosine metabolites	Opportunistic infection, poor growth, skin rash
Purine nucleoside phosphorylase deficiency	14q13.1	Abnormal purine metabolism	Opportunistic infection, poor growth, skin rash
Recombinant activating gene (RAG)1 and RAG2 deficiency	11p13	Defects result in an inability to make DNA double-strand breaks durng V(D)J recombination in T- and B-cells	Opportunistic infection, poor growth, skin rash

Artemis deficency	10p13	Defects in repairing the DNA double-strand breaks made during V(D)J recombination	Opportunistic infection, poor growth, skin rash increased sensitivity to ionizing radiation
X-Linked lymphoproliferative syndrome	Xq25	Unregulated stimulation of B-cells by EBV leading to malignant transformation	Lymphadenopathy, hepatosplenomegaly, recurrent opportunistic infections
Wiskott-Aldrich syndrome	Xp11.22–p11.23	WASP is abnormal; abnormalities are seen in the cytoskeleton structure of T-cells	Thrombocytopenia with bleeding and bruising, eczema, recurrent infection with encapsulated organisms
Ataxia-telangiectasia	11q22–23	Defective DNA-dependent kinase involved in cell cycle control and DNA recombination. Specific etiology of immune system defects still under study	Chronic sinopulmonary disease, cerebellar ataxia, malignancy oculocutaneous telangiectasia
Nijmegen breakage syndrome	8q21	Deficient DNA repair and cell-cycle control due to the loss of function of nibrin	Chronic sinopulmonary disease, facial dymorphism, mental retardation, and microcephaly
Chronic granulomatous disease	Xq21.1($gp91^{phox}$), 16q24 $gp22^{phox}$), 7q11.23 ($gp47^{phox}$), 1q25 ($gp67^{phox}$)	Phagocytes cannot generate respiratory burst because of lack of a component needed for oxidative metabolism	Deep-seated infection, abscess especially with catalase-positive organisms
Leukocyte adhesion deficiency 1	21q22.3 (CD18)	Absence or poor upregulation of adhesion molecules	Recurrent serious bacterial infections, especially on mucosal surfaces or wound sites; poor wound healing, lack of pus

IL, interleukin; EBV, Epstein-Barr virus, GI, gastro intestinal

Table 2
Secondary Immunodeficiency

Category	*Examples*
Malnutrition	Developing country, associated with chronic disease
Organ system dysfunction	Nephrotic syndrome, protein-losing enteropathy, diabetes mellitus, uremia
Immunosuppressive agents	Corticosteroids, cytotoxic drugs, cyclosporine, radiation
Infectious diseases	HIV infection, mycobacterial infection, EBV infection, cytomegalovirus infection
Infiltrative disease	Malignant disease, histiocytosis, lymphoproliferative disease, sarcoidosis, multiple myeloma
Surgery and trauma	Burns, splenectomy, head injury
Hereditary diseases	Down syndrome, chromosomal instability syndromes, congenital asplenia, hemoglobinopathies, storage diseases, galactosemia

EBV, Epstien-Barr virus.

evaluation for a structural or anatomical problem that may have occurred during fetal development or surgery or that may be secondary to trauma. Also, foreign bodies, for example, nasogastric tubes and intravenous catheters, predispose to infection. Several specific systemic diseases that result in immunodeficiency are listed in Table 2.

ANTIBODY DISORDERS

Immunodeficiencies primarily affecting IgG antibody production usually do not result in recurrent infection until after maternal antibody wanes at 6–12 mo of age. Bruton's disease or X-linked agammaglobulinemia (XLA) is a primary immunodeficiency that is characterized by an inability to produce antibody because of the absence of mature B-cells. The defect resides in a gene, labeled the *btk* gene for Bruton tyrosine kinase, which is located on the X chromosome. Bruton tyrosine kinase is necessary for signal transduction in B-cell differentiation. Mutations in μ heavy-chain and components of the surrogate light chain of B-cells results in defective B-cell maturation. Autosomal recessive agammaglobulinemia (ARA) is a phenotypically similar primary immunodeficiency. Defects in the B-cell linker protein (BLNK) and the transmembrane signal transducer Ig-α (CD79a) prevent B-cell development and cause ARA. The functional loss of these receptor proteins in ARA and *btk* in XLA blocks B-cell development at the pro-B-cell stage. The lack of antibody production in individuals who have agammaglobulinemia leads to decreased protection from infection, especially with encapsulated bacteria. Common infections include pneumonia, otitis media, sinusitis, septic arthritis, or gastrointestinal tract infections. Infections may be systemic, such as septicemia or meningitis. However, patients are also susceptible to central nervous system infections with viruses, especially enteroviruses, which may prove fatal. XLA and ARA are characterized by low or undetectable levels of IgG, IgM, and IgA in serum. In addition, mature B-lymphocyte markers, CD19 and CD20, are found on less than 2% of lymphocytes. Patients are commonly observed to have small or absent lymph nodes and tonsils. Milder

Type of Infections Common in Selected Immunodeficiency Diseases

Immunodeficiency disease	*Example of infections*
T-cell	Viral/fungal/opportunistic
B-cell	Bacterial
XLA	Bacterial after age 1–2 yr
Severe combined immunodeficiency disease (SCID)	Opportunistic
Chronic granulomatous disease (CGD)	*Staphylococcus*, *Serratia*, *Aspergillus*
Complement	*Neisseria*
AIDS	Opportunistic
Common variable immunodeficiency (CVID)	Late-onset bacterial, *Giardia lamblia*

phenotypes have been observed, and disease may present later in life. Prognosis is good for individuals receiving aggressive antimicrobial treatment and routine monthly intravenous immunoglobulin (IVIG)-replacement therapy.

Hyperimmunoglobulin M (HIGM) syndrome is classically thought of as an antibody production disorder, although the disorder manifests itself with opportunistic infection with *Pneumocystis carinii* pneumonia (PCP) and neutropenia as well as with recurrent bacterial infection. For the X-linked form (HIGM1 or XHIGM), the problem resides with the T-cell instead of the B-cell and occurs because of failure to upregulate the CD40 ligand (CD40L) on the activated T-cell. The CD40L, also labeled CD154, interacts with the B-cell co-receptor CD40 to activate the transcription factor nuclear factor κ B (NF-κB). This interaction is necessary to provide a second signal in T-cell, B-cell communication for class switch recombination (CSR) in B-cells, initiating the change from production of IgM to that of another class of antibody. Defects in the gene encoding CD40 lead to the autosomal recessive form of HIGM or HIGM3. Another form of HIGM, HIGM2, results from mutations in activation-induced cytidine deaminase (AID) or uracil nucleotide glycosylase (UNG). AID and UNG play a critical role in the deamination of cytidine to uracil and excision repair of uracil, respectively, during CSR and somatic hypermutation. The action of AID and UNG are important for B-cells to properly change from production of IgM to that of other immunoglobulin classes. Thus, high IgM levels and low levels of IgG and IgA are characteristic of HIGM syndrome. Patients with defects in AID and UNG also present with enlarged tonsils and lymph nodes with aberrantly large germinal centers. Prognosis is good for individuals given monthly IVIG infusions, although the incidence of autoimmune disorders and malignant disease are increased. Bone marrow stem cell transplantation (BMT) has proven curative.

Mutations in the gene coding for NF-κB essential modulator (NEMO) results in immunodeficiency associated with ectodermal dysplasia (ED) or NEMO deficiency. A few cases of NEMO without ED have been discovered. NEMO functions as a regulatory and structural protein subunit of the IKK (IκB kinase) cell-signaling complex, which plays an integral part in the activation of the NF-κB-signaling pathway. Activation of the

IKK complex leads to the degradation of the complex and release of IKK1 and IKK2, which actively phosphorylate IκB, allowing the release of NF-κB. Mutations in the NEMO result in the null release of the transcription factor NF-κB, a known regulator of genes involved in immune and stress responses, inflammatory reactions, cell adhesion, and human development. Clinically, ED is associated with abnormal development of ectoderm-derived structures (i.e., abnormal or missing teeth, sparse hair, null development of eccrine sweat glands, and failure to thrive). Immunodeficiency frequently presents with recurrent and severe infection (bacterial and mycobacterial) of the lower respiratory tract, soft tissue, bones, and gastrointestinal tract along with defective immunoglobulin class switching recombination in response to CD40L. Laboratory findings include hypogammaglobulinemia with elevated levels of IgM and low serum IgG levels. Defective polysaccharide-specific antibody responses are quite common along with poor inflammatory and cellular response to interleukin (IL)-1β, IL-18, and tumor necrosis factor (TNF)-α. Gross defects in activation of natural killer (NK) cell cytotoxicity have also been shown. IVIG therapy has proven effective in reducing the rate of bacterial infections.

An antibody deficiency disorder that occurs occasionally in older children (>2 yr) and mostly in adults, common variable immunodeficiency (CVID), results from waning ability to produce antibody. Defects in early stages of B-cell development and the regulation of immunoglobulin expression are suspected to cause the defects in some CVID patients. Mutations in the human leukocyte antigens (HLA) class II and major histocompatibility complex (MHC) class III regions have also been implicated in CVID. In some patients, defects in the inducible costimulator (ICOS) on T-cells that signal B-cell activation are thought to lead to the development of CVID. Although the true etiology of CVID is uncertain, approx 1:50,000 individuals suffer from CVID. Typically, encapsulated bacteria cause chronic or recurrent infection of the middle ear, sinopulmonary tract, and respiratory tract. Bronchiectasis is not infrequent in this disorder. Patients commonly have gastrointestinal complaints, including malabsorption and diarrhea, that result from infection or autoimmune disease. Gastrointestinal tract infections with *Campylobacter jejuni* or *Giardia lamblia* are common. Other autoimmune problems and lymphoreticular malignant disease are more common than in the general population. Hypertrophy of lymphoid tissues can occur and may manifest as lymphadenopathy, splenomegaly or occasionally hepatomegaly. Antibody levels, especially IgG and IgA levels, are typically low and specific antibody production (i.e., isohemagglutinins and/or responses to vaccines) is commonly impaired. The recommended treatment for CVID is IVIG.

A more common form of antibody deficiency that has been linked to CVID is selective IgA deficiency (SIGAD). The incidence of SIGAD is 1:700 individuals and is a result of low levels or absence of serum IgA with normal IgG and IgM serum levels. Affected individuals may have recurrent sinopulmonary tract infections that are intractable to usual therapies. Medical histories that include placement of pressure-equalizing tubes, chronic tympanic membrane perforation, mastoiditis, and previous sinus surgery are not uncommon. However, some healthy individuals have very low IgA values and are not subject to recurrent infections. Some SIGAD patients have developed CVID later on in life. An increased risk of autoimmune diseases and IgG2 subclass deficiency has also been associated with SIGAD.

Four subclasses of IgG exist, namely IgG1-4, and many patients have been reported who have recurrent sinopulmonary infections and a low level of one or more of the IgG subclasses. However, asymptomatic individuals have also been found in association with

selective IgA deficiency. Antibody synthesis following a challenge of protein and polysaccharide antigens must be tested to know the clinical relevancy of a low IgG subclass level.

Patients have been described with normal IgG and IgG subclass levels who have a specific inability to respond with antibody production following challenge with polysaccharide antigens such as pneumococcal polysaccharide antigens; they are labeled as having antigen-specific antibody deficiency (lacunar defect).

Transient hypogammaglobulinemia (THI) of infancy represents a delay in the attainment of normal antibody levels for age. When the immune system is evaluated, these infants typically are found to have low antibody levels. Production of antibody to diphtheria and tetanus toxoids and to isohemagglutinins is normal. IVIG is not indicated for this condition, and antibody levels normalize with time.

T-CELL AND COMBINED DISORDERS

Primary disorders of T-cell function and combined T-cell defects come in many forms. One combined immunodeficiency, Wiskott-Aldrich syndrome (WAS), results from defects in the gene for the WAS protein (WASP), encoded on the X chromosome. WASP is a complex protein that functions in phagocytosis of microorganisms and apoptotic cells and regulation of cytoskeletal architecture in T-cells and platelets. WAS results in to profound humoral and cellular deficiency hallmarked by eczema, excessive bleeding, and thrombocytopenia. Patients usually have elevated levels of IgE and IgA accompanied by low levels of IgM. Atopic dermatitis and recurrent infections, including otitis media, pneumonia, sinusitis, meningitis, or sepsis, with pneumococci or other encapsulated bacteria present during the first 12 mo. BMT from HLA-identical siblings or HLA-matched unrelated donors have resulted in complete correction of both platelet and immunological abnormalities.

DiGeorge syndrome (DGS) is a primary immunodeficiency commonly caused by deletions on chromosome 22 or 10 and presents as a heterogeneous group of disorders with variable degrees of penetrance. Afflicted individuals often present with conotruncal cardiac defects, cleft palate, hypocalcemia, speech delay, musculoskeletal defects, thymic hypoplasia, and immunodeficiency. The highest degree of penetrance or complete DGS is associated with the absence of T-cells. Patients with the milder phenotype or partial DGS have low to normal T-cell levels and a highly variable T-cell proliferative response to stimuli. T-cell serum concentrations have been shown to change during the course of disease, requiring long-term assessment of T-cell numbers in DiGeorge patients. In partial DGS, an increased incidence of IgA deficiency has been reported, but normal immunoglobulin levels with good antibody responses to pathogens are more common. In contrast, patients with complete DiGeorge present with severe infections with opportunistic pathogens and require BMT.

An immunodeficiency also associated with physiological abnormalities, ataxia–telangiectasia (AT), is characterized by both humoral and cellular deficiency in conjunction with cerebellar ataxia, ocular and skin telangiectasia, and a marked predisposition to the development of lymphoid malignancies. AT is autosomal recessive in inheritance, wherein the genetic defect is located on chromosome 11 and codes for the ATM (AT, mutated) protein. The ATM protein has been implicated in the control of cell cycle checkpoints, DNA repair, and maintaining telomere length. The thymus is often

poorly developed or absent and patients present with a predisposition to sinopulmonary infections. Patients commonly have low or absent IgA, IgG, and IgE levels along with an increased percentage of monomeric forms of IgM. AT patients frequently present with an inverted $CD4^+$:$CD8^+$ ratio as a result of low numbers of $CD4^+$ cells and elevated α-fetoprotein and carcinoembryonic antigen levels in serum. Long-term prognosis is poor, and most individuals die because of neurological deterioration or malignant disease by the second decade, although some have reached adulthood.

A variant of AT, Nijmegen breakage syndrome (NBS), is also characterized by T- and B-cell defects as well as radiosensitivity and a predisposition to cancer. NBS is unique in presenting with moderate mental retardation, facial dysmorphism, and an increased frequency of microcephaly while lacking telangiectasia and progressive ataxia. The defect results from mutations in the gene that codes for nibrin, a protein similar to ATM in that it functions in DNA repair and cell-cycle control. Blood $CD4^+$ T-cell counts are low with an inverted CD4:CD8 ratio and low or absent IgG and IgA while NK cell and IgM levels are elevated.

Severe combined immunodeficiency (SCID) represents a diverse group of genetic defects and the most severe group of primary immunodeficiencies. This group of disorders often presents within the first 6 mo of life with failure to thrive, diarrhea, skin rash, otitis, sepsis, and severe infections. T-cell development is greatly impaired in all SCID, whereas defects in B- and NK cell development varies from one form of SCID to the next. The most commonly recognized genetic defect, X-linked SCID (XSCID), is the result of mutations in the gene that encodes the common γ-chain receptor subunit shared by interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The common γ-chain receptor subunit functions as a signal transducer through interactions with cytokines and intracellular kinases. As a whole, total lymphocyte counts are markedly decreased with low percentages of T- and NK cells. B-cell percentages are usually elevated. Tonsils are absent, and frequently the thymus gland is hypoplastic and devoid of lymphocyte precursors. As a result, no thymic shadow is present in chest radiograms. Survival is dependent on HLA-matched and HLA-haploidentical T-cell-depleted BMT, which has been shown to be curative; however, patients still may not make antibody appropriately and require IVIG-replacement therapy.

Defects in Janus-associated kinase 3 (Jak3), an intracellular signal transducer, results in an autosomal recessive SCID phenotypically similar to XSCID, called Jak3 deficiency. Jak3 functions in the activation of signal transducers and activators of transcription factors downstream from receptors containing the common γ-chain. Another form of SCID, in which T-cells are absent but both B- and NK cells are present, has been shown to be due to defects in α-chain of the IL-7 receptor.

Aberrant mutations in the gene encoding another tyrosine kinase, Zap-70, leads to the autosomal recessive ZAP-70 deficiency, resulting from a block in signal transduction from CD8 receptors. T-cells do not undergo normal maturation. ZAP-70 deficiency is characterized by the absence of $CD8^+$ T-cells with elevated percentages of $CD4^+$ T-cells in the peripheral blood. Defects, upstream from ZAP-70, in protein subunits of the CD3 T-cell receptor result in CD3 deficiency characterized by depressed levels of TCR/CD3 expression. A mutation in the gene coding for the common leukocyte surface protein CD45 has resulted in a receptor defect that presents with the SCID phenotype as well. Other defects include T-cell antigen receptor defects, cytokine deficiencies, and the bare lymphocyte syndrome (BLS), in which major histocompatibility antigens are not expressed on peripheral blood lymphocytes.

An important part of T- and B-cell growth involves the development of Ig and T-cell receptor (TCR) variable domains. Variable domains are composed of variable (V), diversity (D), and joining (J) elements. The selection of these elements during DNA transcription, processing, and recombination is has been termed V(D)J recombination and allows for the vast antigen receptor diversity of Ig and TCR. Some patients present with SCID as a result of a block in V(D)J recombination. Defects in recombinase-activating genes, RAG-1 or RAG-2, lead to the arrest of T- and B-cell maturation at early stages of development. Another aberrant mutation has been found in the Artemis gene that codes for a novel V(D)J recombination/DNA repair factor necessary for repairing the double-stranded cuts made by RAG1 or RAG2 gene products. Both RAG deficiencies and Artemis deficiency are autosomal recessive and present with low or absent levels of T- and B-cells.

Adenosine deaminase (ADA) deficiency is an autosomal recessive disorder in which this enzyme is not produced, and metabolites of adenosine, which are toxic to lymphocytes, cause immunodeficiency. Lymphocyte numbers are very low. The diagnosis is made by demonstrating absent or low levels of ADA, typically in erythrocytes, or in granulocytes if the patient has received red blood cell (RBC) transfusion. In addition to the recurrent and severe bacterial, viral, fungal, or parasitic infections, affected individuals have skeletal and rib-cage abnormalities. HLA-identical and HLA-haploidentical T-cell-depleted BMT has been curative for the T-cell defect. Replacement enzyme injections with polyethylene glycol conjugated, bovine adenosine deaminase can improve lymphocyte function. Gene therapy has been successful in a few patients, but there is a need to improve the efficacy of the therapy.

Another enzyme defect, purine nucleoside phosphorylase (PNP) deficiency, results in the clinical picture of SCID; however, the attrition of lymphocyte function is slower than in ADA deficiency, and these patients may be several years of age before the disease is noted. PNP levels are low, and lymphocytes numbers are low. BMT is the current treatment of choice.

The X-linked lymphoproliferative syndrome (XLP or Duncan disease), which results in unregulated B-cell proliferation secondary to Epstein-Barr virus (EBV) infection, is now known to be a result of an X-chromosome defect in the gene that codes for signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) found on T-cells. SAP is an inhibitor of T-cell–B-cell interactions induced by SLAM. XLP typically presents with fulminant infectious mononucleosis, lymphoma, and/or dysgammaglobulinemia. IVIG can provide some degree of protection, whereas BMT is curative.

In contrast to the unregulated lymphoproliferation in XLP, autoimmune lymphoproliferative syndrome (ALPS) results from defects in programmed cell death or apoptosis. As an essential feature of the immune system, apoptosis allows the negative selection of autoreactive lymphocytes and the removal of activated cells after an immune response. Apoptosis may be induced through the activation of the Fas pathway. Fas, a member of the tumor necrosis factor (TNF) receptor superfamily, is one of the main receptors used by the immune system to control the peripheral lymphocyte pool. Binding of Fas (CD95) by the Fas ligand leads to the activation of the caspase 8 and 10, triggering the caspase cascade, activation of caspase 3, 6, 7, and cell death. Patients with defects in the Fas pathway commonly present with autoimmune diseases and lymphoproliferative disorders or ALPS. The most common defect in ALPS patients results from the mutations

in the intracellular domain of the Fas receptor. However, defects in the Fas ligand, caspase 8, and caspase 10 have also been shown to cause ALPS. Patients commonly present with malignant and nonmalignant lymphoproliferation that results in lymphadenopathy, splenomegaly, and hepatomegaly early in life. Autoimmunity in ALPS commonly results in anemia, thrombocytopenia, or neutropenia. Autoimmune manifestations not involving hematological lineages are also quite frequent. Lymphocyte counts are elevated with an increased percentage of CD4-CD8- T-cells in the peripheral blood. Elevated levels of IgG and IgA are also quite common in ALPS patients. Although there is no specific treatment for ALPS, for some individuals treatment with steroids, mycophenolate mofetil, or pyrimethamine and sulfadoxine has aided in control, while BMT has proven curative in several patients with Fas deficiency and severe disease.

PHAGOCYTIC DEFECTS

Disorders involving phagocytic cells most commonly present with recurrent cutaneous abscesses, periodontitis, pneumonia, osteomyelitis, or sepsis. The most common problem in this category of immunodeficiency is neutropenia. Neutropenia is often the result of decreased production of neutrophils in reaction to medications, such as antibiotics, or to infection, such as those of viral origin. Other acquired causes of neutropenia include autoimmune diseases, aplastic anemia, toxins, antineutrophil antibodies, glycogen storage disease type IB, and infiltrative disorders such as neoplasia or myelofibrosis. Notable viral causes include parvovirus and HIV infection.

Points to Remember About Immunodeficient States

- Severe congenital T-cell deficiency is most likely to occur during early infancy. AIDS and B-cell deficiency may occur at any age. Deficiency of the white blood cell phagocyte or complement system is usually evident in childhood.
- Chronic sinusitis, multiple pneumonias, sepsis, meningitis, and recurrent skin abscesses are types of infections associated with the most common type of immunodeficiency, antibody deficiency.
- Failure to thrive in an infant or "wasting" in an older child/adult, with increased susceptibility to infection (of any kind), should be an indication for screening for HIV and other immunodeficiencies.
- Recent onset of persistent sinopulmonary disease and/or diarrhea in an older child/adult may be a sign of common variable immunodeficiency.
- Severe combined immunodeficiency should be considered when there is a low lymphocyte count on the complete blood count in early infancy.

Congenital neutropenia, Kostmann syndrome, is a result of maturation arrest of myelopoiesis in the bone marrow. Patients early in life have recurrent pneumonia, gingivitis, otitis, or urinary tract infections and severe neutropenia. Patients respond to recombinant human granulocyte colony-stimulating factor (G-CSF) with increased neutrophil counts.

Cyclic neutropenia is a disorder in which individuals have regular fluctuations in the number of peripheral blood neutrophils, with neutropenia occurring approximately every

3 wk. Typically, symptoms occur cyclically during times of neutropenia and include fever, malaise, periodontitis, mucosal ulcers, impetigo, sore throat, or lymph node enlargement. Clinical improvement has been seen with use of G-CSF.

Chronic granulomatous disease (CGD) occurs as the result of a decrease in the granulocyte's ability to kill specific types of microorganisms because of dysfunction of the cytochrome enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Recurrent, severe, life-threatening infections are often a result of organisms such as *Staphlyococcus aureus*, gram-negative enteric bacteria like *Serratia marcescens*, *Proteus*, *Klebsiella*, *Escherichia coli*, and other organisms, including *Pseudomonas cepacia*, *Nocardia* species, and *Aspergillus* species. Common types of infections include adenitis, abscesses including perianal abscesses, pneumonia, and osteomyelitis. Lymphadenopathy, hepatosplenomegaly, and ulcerative stomatitis are not uncommon findings. Granuloma formation may lead to obstruction in the gastrointestinal tract. Both systemic and discoid lupus erythematosus have been described in CGD. Inheritance pattern is both X-linked and autosomal recessive.

Other disorders of intracellular killing include myeloperoxidase (MPO) deficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency. MPO deficiency is the most common neutrophil granule defect. This enzyme deficiency leads to immune problems resulting from low levels of MPO activity; however, immunodeficiency is usually mild. The clinical manifestations of the disease are usually seen in association with diabetes mellitus. Defective killing of *Candida albicans* results in increased susceptibility to infection with *Candida*.

Leukocyte adhesion deficiency (LAD) is a result of impaired ability of cells to adhere to the vascular endothelium and migrate out of the intravascular space. LAD-1 is caused by aberrant mutations in the β_2-integrin family common chain (CD18) that leads to low levels or absence of leukocyte adherence glycoprotein expression, a heterodimer composed of CD11 and CD18. Affected individuals have severe bacterial infections such as pneumonia, otitis, gingivitis, septicemia, and recurrent skin infections. Periodontal disease, poor wound healing, and leukocytosis are also common. Umbilical cord separation may be delayed and omphalitis can develop. The diagnosis is confirmed by abnormal expression of adhesion markers on cell surfaces. LAD-2 is due to a defect in fucose metabolism that blocks expression of sialyl-Lewis^X, which impairs selectin-mediated leukocyte rolling along the vascular endothelium. Afflicted individuals commonly present with severe mental retardation, short stature, and the Bombay blood phenotype, a disorder of blood group antigens that results in an inability to express the precursor H antigen and therefore lack of expression of A or B antigens on red blood cells. Infections are similar to those found in LAD-1. LAD-3 has been suggested to be a result of defects in G-protein-coupled receptors that interact with endothelial-displayed chemokines to stimulate leukocyte attachment to the vascular endothelium. Treatment includes very aggressive evaluation and treatment of infections.

Defects in the IL-12 and IFN-γ receptors results in an immunodeficiency that presents with an increased risk to mycobacterial infections. Normally, consumption of mycobacteria by the macrophage leads to the production of IL-12. IL-12 binds to the IL-12 receptor (IL-12R) on T- and NK cells, leading to the production of IFN-γ. Binding of IFN-γ to the heterodimeric IFN-γ receptor (IFN-γR) activates the signal transducer and activator of transcription 1 (STAT1) complex, an important promoter of TNF-α and other

activities necessary for killing mycobacteria and intracellular microorganisms. Patients with the autosomal recessive (AR) defect in the IFN-γR (AR IFN-γR deficiency) lack the ability to mount an effective defense against nontuberculous mycobacteria and commonly present with severe infections early in life with a high mortality rate. Viral infections with parainfluenza, respiratory syncytial virus, and cytomegalovirus, and poor granuloma formation have also been seen in IFN-γR deficiency. In contrast, the autosomal dominant (AD) IFN-γR deficiency presents in childhood and adolescence with fewer mycobacterial infections than the AR form, and affected individuals have an excellent chance of survival. Defects within the IL-12R lead to IL-12R deficiency and presents with a milder phenotype than that seen in IFN-γR deficiency. Although patients are at an increased risk of mycobacterial infection in early childhood, the risk wanes later in life. For patients with IL-12R deficiency and AD IFN-γR deficiency, subcutaneous treatment with IFN-γ has been shown effective at controlling infections. However, for patients with AR IFN-γR deficiency, IFN-γ treatment is ineffective and BMT should be considered.

COMPLEMENT DEFECTS

Complement deficiencies are rare and represent only 2% of the primary immunodeficiency disorders. Deficiency of one of the early components of the classic pathway (C1q, C1r, C1s; C4; C2; or C3) is associated with systemic lupus erythematosus-like symptoms, glomerulonephritis, and pyogenic infections. Deficiency of alternative pathway components, factor D, properdin, factor I, or factor H is also associated with recurrent pyogenic infections. A third complement pathway, the lectin pathway, has been shown to bind to the mannan used in bacterial cell membranes. Defects in the regulation of lectin production leads to mannose-binding lectin (MBL) deficiency and an increased risk of viral and bacterial infections. Recurrent serious infection with neisserial organisms is the classic presentation for a complement deficiency and is seen with deficiency of one of the terminal components common to the classic, lectin, and alternative complement pathways and with properdin deficiency. Hereditary complement component deficiency is autosomal recessive in inheritance and results in the absence of the component. The CH_{50} assay is a good screen for the presence of the entire classic pathway of complements and for the terminal components of the alternative and lectin pathway of complement. The CH_{50} titer ranges from very low to 0 when one of these components is missing. The CH_{50} assay should be performed when the active infection is resolved, because neisserial as well as other infections cause consumption of complement and can result in low values. If a complement component deficiency is suspected, testing for specific component levels is available.

DIAGNOSTIC TESTS

The evaluation for immunodeficiency revolves around a complete and reliable medical and family history. The evaluation should be tailored to reflect likely disorders given the historical background. Secondary causes for recurrent infection should be sought. For individuals with recurrent pneumonia, a sweat chloride test or test for mutation in the cystic fibrosis gene should be carried out to look for cystic fibrosis. The differential diagnosis should also include gastroesophageal reflux (GER), and consideration should be given to evaluation for GER and for ciliary dysfunction. If allergy is thought to be the predisposing factor for the individual's recurrent sinopulmonary infection, an allergy evaluation should be undertaken, possibly including immediate hypersensitivity skin

testing to evaluate for specific hypersensitivity to common allergens. IgE measure by itself has poor negative predictive value for allergy.

The hallmark finding of wasting or failure to thrive and opportunistic infection without evidence of a systemic disorder such as malignant disease should trigger an extensive evaluation for a T-cell disorder. For the infant and young child, SCID should be suspected. For all ages, the evaluation should include a test for HIV infection (nonantibody test <18 mo of age). An evaluation of the adhesion markers on peripheral blood granulocytes is needed for the patient with poor wound healing or gingivostomatitis along with a high white blood cell (WBC) count without a malignant or metabolic disorder. Recurrent, serious neisserial infection should trigger an evaluation for a late component complement defect. The typical presentations for immunodeficiency disorders and tests used in evaluation are listed in Table 3. If suspicion for an immune problem is high because of, for example, opportunistic infection or severe, recurrent bacterial infection, early involvement of an immunologist is advisable for an expedient detailed evaluation.

The complete blood count (CBC) gives extensive information regarding the immune system and should be a part of every evaluation of the immune system. Lymphopenia occurs in many types of SCID. Leukocytosis occurs in CGD and in LAD. Depending on the clinical context, neutropenia sometimes reflects autoimmune disease or bone marrow suppression that can accompany immunodeficiency such as HIV infection. Alternatively, neutropenia may be a reflection of cyclic neutropenia. Rarely, an infant might have a congenital form of neutropenia. Other findings include anemia, often accompanying chronic illness or autoimmune disease, and thrombocytopenia, also a result of autoimmune disease. Thrombocytopenia with small platelets is a hallmark of WAS. Abnormal WBC forms from the blood smear can indicate absence of the spleen (Howell-Jolly bodies), malignant disease or HIV infection (atypical lymphocytes), Chédiak-Higashi syndrome (large granules in granulocytes), and MPO deficiency (unusual staining of granulocytes). Eosinophils are increased in allergy, in some infections that accompany immunodeficiency such as PCP or parasitic infection, and in some forms of SCID.

Antibody should be studied as part of the immune workup of the individual with recurrent sinopulmonary tract infection (Fig. 1). Quantitative immunoglobulin levels are helpful in this evaluation. However, immunoglobulin levels do not evaluate directly for antibody production, and antibody deficiencies do exist in individuals with normal immunoglobulin levels. Also, a percentage of the normal population has low antibody levels, produces specific antibody normally when challenged, and does not benefit from intravenous antibody replacement therapy. To evaluate antibody production, the level of antibody produced to known antigenic exposures should be measured. Isohemagglutinins are antibodies produced to blood group antigens that are not present on the individual's RBCs. When a person is exposed to antigens that are present in the environment, the normal response involves production of antibody against the antigens that are not recognized as self. Isohemagglutinin titers are detected in most individuals over 1 yr of age. In the individual with both A and B blood group antigens, both A and B antigens will be recognized as self and isohemagglutinins will not be produced.

Immunization elicits an antibody response, and measuring this response is another routine test of antibody production. Previous response to the tetanus vaccine is evidenced by expected titers of antibody to diphtheria and tetanus toxoid. A challenge normally elicits at least a twofold increase in individuals with low baseline titers. A fourfold response or greater is typical. Response to tetanus toxoid challenge is usually measured 2 wk following immunization.

Table 3
Evaluation and Referral

Disorder group	*Example presentation*	*Screening tests*	*Detailed evaluation tests*	*Specialist referral*
Antibody deficiency	Recurrent or severe infection with encapsulated bacteria	CBC with differential and platelets IgG, IgA, IgM Antibody titers to tetanus toxoid, diphtheria, pneumococcus	Response to immunization (required to exclude an antibody deficiency) Isohemagglutinins IgG subclasses in select cases B-cell and T-cell number in peripheral blood Bacteriophage ϕX174 Stool for α1-antitrypsin; urinalysis if protein loss is suspected	Helpful in performance and interpretation of tests, especially when suspicion for deficiency is strong or detailed evaluation is required For family testing and genetic testing and counseling Consult AI[a] specialist for management
T-cell deficiency or combined deficiency	Recurrent or severe infection with bacteria or with opportunistic organism Wasting, failure to gain weight, or diarrhea Dermatitis	CBC with differential and platelets HIV, ELISA IgG, IgA, IgM, IgE Delayed hypersensitivity skin test (>6–12 mo)	T-cell numbers and percentages in the peripheral blood B- and NK-cell numbers and percentages in the peripheral blood Lymphocyte proliferation to mitogen and antigen stimulation	Diagnosis of a T-cell or combined immunodeficiency, except HIV infection, should be done with the help of specialist trained in the diagnosis and management of the suspected disorder. If the patient is an infant, urgent referral is required.
Phagocytic cell deficiency	Organ abscesses, recurrent skin infection or abscesses, lymphadenitis, periodontitis Poor wound healing	CBC with differential (sometimes serial monitoring is required) Nitroblue tetrazolium (NBT) test Dihydrorhodamine oxidation (DHR) test	Adhesion marker presence and up-regulation Chemiluminescence Chemotaxis Bactericidal activity Granulocyte production and margination	Helpful in performance and interpretation of tests, especially when suspicion for deficiency is strong or detailed evaluation is required For family testing and genetic testing and counseling Consult AI[a] specialist for management
Complement deficiency	Systemic lupus (C1, C4, C2) Recurrent pyogenic infections (early classic and alternative pathway) Recurrent neisserial infections (C5–C9)	Serum total hemolytic complement (CH_{50})	Specific complement component levels Alternative pathway total hemolytic complement (AH_{50}) Lectin ELISA	Helpful in performance and interpretation of tests, especially when suspicion for deficiency is strong or detailed evaluation is required For family testing and genetic testing and counseling Consult AI[a] specialist for management

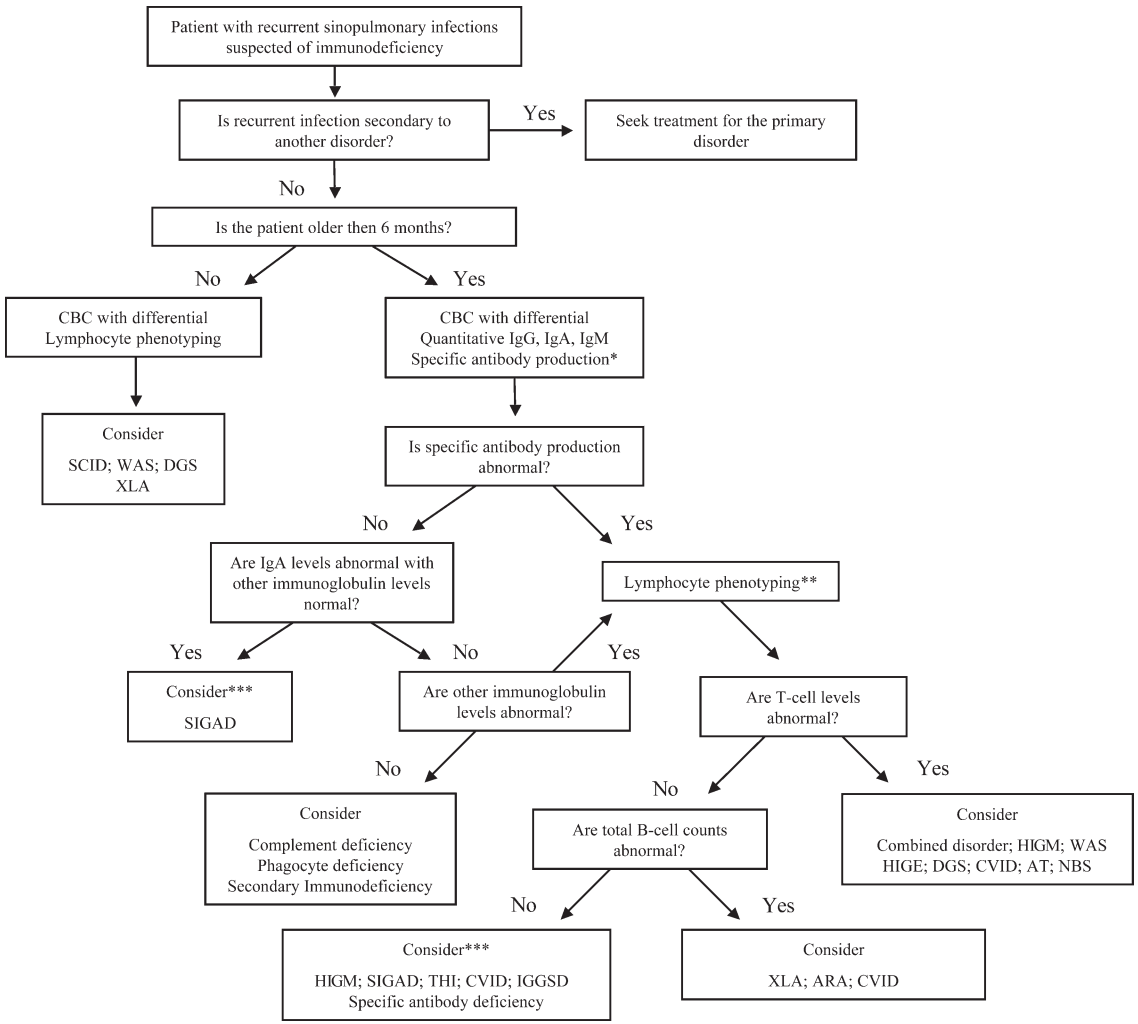
[a]AI, Allergy and Immunology
CBC, complete blood count; ELISA, enzyme-linked immunosorbent assay; NK, natural killer.

Response to polysaccharide antigens can be measured by challenge with the unconjugated pneumococcal vaccine. Expected results using a reliable laboratory would include a twofold to fourfold increase in antibody to at least one of the serotypes of pneumococcus contained in the vaccine, although many experts look for a rise in antibody to 50% of the vaccine antigens tested. Some pneumococcal serotypes are more antigenic than others. Pneumococcus type 3 is one of the more antigenic serotypes present in the unconjugated vaccine. The test for response to pneumococcus is best done with a preimmunization specimen sent along with a specimen drawn 3–4 wk following immunization for processing on the same day to control for day-to-day variability in results. In normal children less than 2 yr of age, the response is not reliably present using the unconjugated vaccine. The pneumococcal vaccines containing a protein antigen conjugate rather than the pure polysaccharide antigen is routinely indicated for children as part of their routine immunization schedule to protect them from pneumococcal disease in early childhood.

The delayed hypersensitivity skin test (DHST) measures T-cell recall response and is a cost-effective measure of T-cell function. This intradermal skin test is commonly performed using 0.1 mL of an antigen such as *C. albicans* (1:200 dilution), tetanus toxoid (1:10 dilution), or mumps. A positive test requires induration. The reported criteria for interpreting a DHST response as reactive vary. The usual indication of a positive DHST reaction is 10 mm of induration recorded at 48–72 h; however, a recent study suggests that using a 2-mm cutpoint of DHST induration is useful for determination of immunocompetence in adult women with HIV infection.

For individuals suspected of having a disorder involving T- and/or B-lymphocyte dysfunction, in vitro study of lymphocyte function is in order. This testing is often done in specialized centers. Enumeration of peripheral blood lymphocyte surface markers is utilized to look for deficiencies or patterns suggestive of described disorders. For example, the presence of B-cells with the near-absence of helper and cytotoxic T-cells in an infant is suggestive for X-linked SCID. Likewise, the absence of B-cells with normal numbers and percentages of T-cells is found in X-linked agammaglobulinemia. CD40 ligand is not upregulated on T-lymphocytes in hyper-IgM syndrome. Routine in the evaluation for degree of immunodeficiency and as a predictor of prognosis in HIV infection is the measure of the percentage and number of CD4 lymphocytes in the peripheral blood.

In vitro functional studies of lymphocytes measures of the proliferative response of the lymphocytes following stimulation. This test is performed by quantification of the radiolabeled thymidine incorporated into the nucleus of cultured lymphocytes. Proliferation following mitogen stimulation occurs independent of the T-cell receptor. Antigen stimulation tests the T-cell recall response and requires recognition of the processed antigen on the antigen-presenting cell by the T-cell receptor complex. Experimental tests of lymphocyte responses to cytokine stimulation are also available at specialized centers. The nitroblue tetrazolium (NBT) test is routinely used to test for CGD. When superoxide generation is normal, the NBT dye is reduced and the granulocytes on the test slide change from having a yellow-appearing cytoplasm to blue. The blue is not present in the cytoplasm of CGD patients. Similarly, the dihydrorhodamine oxidation (DHR) test provides a sensitive and highly quantitative way to assess NADPH oxidase activity upon stimulation with phorbol myristate acetate (PMA). PMA induces the production of H_2O_2 and O_{2-}, which oxidize DHR to rhodamine. This molecule emits florescent light when stimu-


Patient with recurrent sinopulmonary infections suspected of immunodeficiency
Is recurrent infection secondary to another disorder?
Yes
Seek treatment for the primary disorder
No
Is the patient older then 6 months?
No
Yes
CBC with differential Lymphocyte phenotyping
CBC with differential Quantitative IgG, IgA, IgM Specific antibody production*
Consider SCID; WAS; DGS XLA
Is specific antibody production abnormal?
No
Yes
Are IgA levels abnormal with other immunoglobulin levels normal?
Lymphocyte phenotyping**
Yes
No
Yes
Consider*** SIGAD
Are other immunoglobulin levels abnormal?
Are T-cell levels abnormal?
No
Yes
No
Consider Complement deficiency Phagocyte deficiency Secondary Immunodeficiency
Are total B-cell counts abnormal?
Consider Combined disorder; HIGM; WAS HIGE; DGS; CVID; AT; NBS
No
Yes
Consider*** HIGM; SIGAD; THI; CVID; IGGSD Specific antibody deficiency
Consider XLA; ARA; CVID

lated with blue light. Sample analysis is performed by flow cytometry. Other tests for granulocytes, available at specialized centers, include chemiluminescence, a direct measure of superoxide production and energy release, and chemotaxis, an in vitro measure of granulocyte movement in the direction of chemoattractants. Testing for LAD involves the measurement of the presence and upregulation of adhesion markers on the surface of the granulocytes. MPO deficiency is diagnosed by measure of the MPO content of granulocytes and is easily diagnosed with a routine CBC since the automated differential WBC counters identify granulocytes by MPO content. G6PD deficiency is diagnosed by a measure of the G6PD enzyme level.

The CH_{50} is an excellent screening test for complement component deficiencies of the classic pathway components and of the terminal components of both the lectin and alternative pathways. Consumption of components can result in a low value during active infection; therefore, to avoid spuriously low results, individuals should be tested while recovering and not during active infection. Each of the specific components can be tested if the CH_{50} is confirmed to be low. A similar test, the AH_{50} is available at specialized centers for use in individuals for whom an alternative pathway early component deficiency is suspected. Individual component testing for alternative pathway components, such as properdin, is available as well. Deficiency of the MBL pathway may be tested by ELISA, in which in serum concentrations of lectin and its mannan binding ability are assessed.

Genetic studies are available for some of the inherited immunodeficiency disorders. Fluorescence *in situ* hybridization (FISH) analysis of genetic material is widely available to probe for the genetic deletions found in DiGeorge anomaly. Select research centers offer genetic evaluation for immune disorders for which the genetic defect is known or can be mapped in a family, such as Wiskott-Aldrich syndrome, XLA, ADA-deficient SCID, other forms of SCID, X-linked lymphoproliferative syndrome, and AT. Genetic counseling for families with a member who has an identified inherited disorder is imperative.

The rapid diagnosis of common immunodeficiencies is important and has become possible as a result of both clinical and laboratory advances. Identification of novel immunodeficiencies may become easier as scientific understanding of the molecular and cellular pathways of the adaptive and innate immune systems expands. The potential is high for other defects in Toll-like receptors and in the development and signaling of lymphocytes. An immunodeficient patient with an unknown defect may present with a unique phenotype that represents a new primary immunodeficiency and would require an immunologist for diagnosis and treatment.

Fig. 1. *(opposite page)* Theoretical algorithm for the diagnosis of a patient with recurrent sinopulmonary infections suspected of a primary immunodeficiency. *, specific antibody production in response to tetanus, diphtheria, and pnemococcal antigens; **, lymphocyte phenotyping assess the percentages of T- and B-cells and their subsets in the peripheral blood; ***, any patient with low immunoglobulin values and recurrent infections may have an evolving problem that should be followed over time. CBC, complete blood count; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; DGS, DiGeorge syndrome; XLA, X-linked agamaglobulinemia; HIGM, hyper-IgM syndrome; HIGE, hyperimmunoglobulin E; AT, ataxia-telangiectasia; NBS, Nijmegen breakage syndrome; SIGAD, selective IgA deficiency; CVID, common variable immunodeficiency; IGGSD, immunoglobulin G subclass deficiency; ARA, agammaglobulinemia.

TREATMENT

Treatment options for the primary immune deficiency disorders and HIV infection are complex and require the expertise of a specialist trained in the management of the suspected or proven disorders. Precautions regarding exposures to infection, an aggressive search for the source of infections, and judicious use of antibiotics for infection are required in the management of these individuals. For children with a severe form of immunodeficiency, caretakers are cautioned to limit exposures to infections. Practical advice includes frequent hand washing and bathing. PCP prophylaxis with trimethoprim and sulfamethoxazole is indicated for individuals with severe T-cell deficiencies. In HIV infection, guidelines exist for other types of prophylaxis, such as antibiotics to prevent infection with *Toxoplasma* and *Mycobacterium* in the severely immune compromised.

Live viral vaccines are to be avoided for individuals with severe immunodeficiency. However, in HIV infection, the measles, mumps, and rubella vaccine is recommended for routine use, but should be avoided in severely immunocompromised patients. Varicella vaccine should be considered for HIV-positive children when $CD4^+$ T-lymphocyte counts are above 25%. In contrast, routine immunizations and other vaccines, mainly the influenza vaccine and the pneumococcal vaccine, which are not live viral vaccines, should be used in individuals with immunodeficiency who have the capacity to mount a protective response.

The small number of T-cells that are given with packed RBC transfusions can cause graft vs host disease in individuals with T-cell immunodeficiency. Therefore, blood products should be irradiated. Also, individuals with very low IgA levels may make IgG antibody against IgA. Packed RBCs should be washed to remove the IgA for these individuals. Other products containing IgA such as intramuscular immunoglobulin, plasma, and some of the IVIG products can cause severe reactions in individuals who have made anti-IgA antibody.

Replacement of the missing component of immunity or correction of the immune defect is prescribed whenever possible for the management of the immunodeficiency disorders. For HIV infection, combination antiretroviral therapy has been shown to restore $CD4^+$ T-cell numbers and to prevent deterioration of the immune system in individuals with susceptible virus. IVIG has been lifesaving for individuals with immunodeficiency involving poor IgG antibody production. This therapy is reserved for individuals who have a proven deficiency of antibody production. The usual replacement does is 400–600 mg/kg given every 4 wk. A higher dose or a shorter dosing interval is sometimes necessary for prevention of infection or during infection. CGD patients have fewer infections when injections of IFN-γ are used in the treatment regimen in addition to antibiotic prophylaxis against staphylococcal infection. Stem cell transplantation has been used successfully to correct the underlying immune defect for particular primary immunodeficiency disorders, including SCID and WAS. When gene therapy is perfected, this therapy may be possible for use in those disorders for which the gene defects have been described.

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