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HANDBOOK OF
CLINICAL ALLERGOLOGY

Textbook for students of high medical educational establishments

Библиотека ВГМУ

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The content of «Handbook of clinical Allergology» is update, believed to be
reliable coben checked coith sourceo and is in accordance coith simple language and in
stepcoise manner, cobich coil create interest – and enthusiasm to cearn and develop the
concept in clinical Allergology.

This book gives a new arientation to the subject of Allergology so that the
student appreciate the great importance and significance of application of allergology to
medicine.

Autbors welcome comments and suggestion from faculty students and other
readers to make improvement in the next edition.

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Symbols and abbreviations

ADA	adenosine deaminase
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
APC	antigen-presenting cell
APGS	autoimmune polyglandular syndrome
APS	anti-phospholipid syndrome
BAL	bronchoalveolar lavage
BCG	bacille Calmette-Guerin
Td	twice a day
BM	bone marrow
cAMP	cyclic adenosine monophosphate
C-ANCA	cytoplasmic ANCA
CIDP	chronic inflammatory demyelinating polyneuropathy
CK	creatine kinase
CMI	cell-mediated immunity
CMV	cytomegalovirus
CNS	central nervous system
ConA	concanavalin A
COPD	chronic obstructive pulmonary disease
CPD	continuing professional development
Cr & E	creatinine and electolytes
CRF	chronic renal failure
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSF-1	colony-stimulating factor-1
CSS	Churg-Strauss syndrome
CT	computed tomography
CTD	connective tissue disease
CTL	cytotoxic T lymphocyte
CTLp	cytotoxic T-lymphocyte precursor
CV	coefficient of variation
CVA	cerebrovascular accident
CyA	cyclosporin A
DAF	decay accelerating factor
dATP	deoxyadenosine triphosphate
DBPC	double-blind, placebo-controlled
DCT	direct Coombs test
DH	dermatitis herpetiformis
DIC	disseminated intravascular coagulation
DIF	direct immunofluorescence
DM	dermatomyositis
DNA	deoxyribonucleic acid
DNA-PKcs	DNA protein kinase catalytic subunit
DRL	drug-related lupus
dsDNA	double-stranded DNA
DTH	delayed-type hypersensitivity
DV	designated value
DVT	deep vein thrombosis
EA	early antigen
EAA	extrinsic allergic alveolitis
EBNA	EBV nuclear antigen
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECP	eosinophil cationic protein
EDTA	ethylenediaminetetraacetic acid
EGF	epidermal growth factor
EIA	enzyme-linked immunoassay
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
ENA	extractable nuclear antigen
ENT	ear, nose, and throat
EPD	enzyme-potentiated desensitization
FAST	fluorescent allergosorbent test
FCAS	familial cold autoinflammatory syndrome
FcR	Fc receptor
FIA	fluorescent immunoassay
FISH	fluorescent *in situ* hybridization
FITC	fluorescein isothiocyanate
G-CSF	granulocyte colony stimulating factor
GGT	gammaglutamyt transferase
GI	gastrointestinal
GLP	good laboratory practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GN	glomerulonephritis
GP	glycoprotein
GPC	gastric parietal cell
G6PD	glucose 6-phosphate dehydrogenase
GPI	glucosylphosphatidylinositol
GS-ANA	granulocyte anti-nuclear antibody
HAE	hereditary angioedema
H & E	haematoxylin and eosin
HANE	hereditary angioneurotic oedema
Hb	haemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEP	histamine equivalent potency
HEp-2	human epithelial cell line
HGV	hepatitis G virus
HHV	human herpesvirus
Hib	*Haemophilus influenzae* type b
HIGE	hyper-IgE syndrome
HIGM	hyper-IgM
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
Hsp	heat-shock protein
HSP	Henoch-Schonlein purpura
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine (serotonin)
HTLp	helper-T lymphocyte precursor
HUV	hypocomplementaemic urticarial vasculitis
ICAM	intercellular adhesion molecule
ICOS	inducible co-stimulator
ID	intradermal
IDDM	insulin-dependent diabetes mellitus
IDT	intradermal test
IEF	Immunoelectrophoresis
IF	intrinsic factor
IFN	interferon
Ig	immunoglobulin
IIF	indirect immunofluorescence
IL	interleukin
IM	intramuscular(ly)
IMIg	intramuscular immunoglobulin
IPF	idiopathic pulmonary fibrosis
U	intensive care unit
IU	international units
IV	intravenous(ly)
JCA	juvenile chronic arthritis

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JDF	Juvenile Diabetes Foundation	Pr3	proteinase 3
KIR	killer-cell Ig-like receptors	PrP	prion protein
LAC	lupus anticoagulant	PRU	Protein Reference Unit
LAD	leucocyte adhesion defect	PSS	progressive systemic sclerosis
LAK	lymphokine-activated killer cell	PUPP	pruritic urticaria and plaques of
LDH	lactate dehydrogenase		pregnancy
LE	lupus erythematosus	PV	pemphigus vulgaris
LFA	lymphocyte function antigen	RANA	rheumatoid-associated nuclear
LFT	liver function test		antibodies
IG	lymphomatoid granulomatosis	RAST	radioallergosorbent test
LPS	lipopolysaccharide	RBCs	red blood cells
mAbs	monoclonal antibodies	RFT	respiratory function tests
MAOI	monoamine oxidase inhibitor	RhA	rheumatoid arthritis
MAST	multiple allergosorbent tests	RhF	rheumatoid factor
MBL	mannan-binding lectin	RIA	radioimmunoassay
MBP	mannan-binding protein	RID	radial immunodiffusion
MCP	macrophage chemotactic peptide	RNA	ribonucleic acid
MDP	muramyl dipeptide	RNP	ribonucleoprotein
MPA	microscopic polyarteritis	rRNP	ribosomal ribonucleoprotein
MPGN	membranoproliferative	SC	subcutaneous(ly)
	glomerulonephritis	SCID	severe combined immunodeficiency
MPO	myeloperoxidase	SCIg	subcutaneous immunoglobulin
MRA	magnetic resonance angiography	Scl	scleroderma
MS	multiple sclerosis	SIRS	systemic inflammatory response
MTX	methotrexate		syndrome
NARES	non-allergic rhinitis with eosinophilia	SLA	soluble liver antigens
NB	*nota bene*	SLE	systemic lupus erythematosus
NBT	nitroblue tetrazolium test	SPT	skin-prick test
NCAM	neuronal cell adhesion molecule	SSc	systemic sclerosis
NF-AT	nuclear factor of activated T cells	ssDNA	single-stranded DNA
NK	natural killer	T3	triiodothyronine
NRL	natural rubber latex	T4	thyroxine
NSAIDs	nonsteroidal anti-inflammatory drugs	TAME	tosyl-L-arginine methyl ester
OCP	oral contraceptive pill	TB	tuberculosis
od	once a day	Tcr	T-cell receptor
P450 sec	P450 side-chain cleavage enzyme	TdT	terminal deoxytransferase
PA	pernicious anaemia	TFT	thyroid function tests
PACNS	primary angiitis of the CNS	TGF	T-cell growth factor
PAF	platelet-activating factor	TGSI	thyroid growth stimulating antibody
PAN	polyarteritis nodosa	Th1	T helper-1
P-ANCA	perinuclear ANCA	Th2	T helper-2
PBC	primary biliary cirrhosis	TIA	transient ischaemic attack
PCNA	proliferating cell nuclear antigen	TNF	tumour necrosis factor
PCP	*Pneumocystis carinii* pneumonia	TPMT	thiopurine methyltransferase
PCR	polymerase chain reaction	TPN	total parenteral nutrition
PDC	pyruvate dehydrogenase complex	TPO	thyroid peroxidase
PDGF	platelet-derived growth factor	TRAB	thyrotropin receptor antibody
PE	pulmonary embolism or	TRAPS	TNF-receptor-associated periodic
	phycoerythrin		syndrome
PEFR	peak expiratory flow rate	TREC	T-cell receptor excision circle
PFAPA	periodic fever with aphthous	TSH	thyroid stimulating hormone
	ulcers, pharyngitis, and cervical	TSH-R	thyroid stimulating hormone receptor
	adenopathy	TSI	thyroid stimulating antibody
PGE2	prostaglandin E2	TTP	thrombotic thrombocytopenic
PHA	phytohaemagglutinin		purpura
PM	polymyositis	UC	ulcerative colitis
PMR	polymyalgia rheumatica	UV	ultraviolet
PNH	paroxysmal nocturnal	VCA	viral capsid antigen
	haemoglobinuria	VCAM	vascular celt adhesion molecule
PNP	purine nucleoside phosphorylase	VCF	velocardiofacial syndrome
PNU	protein nitrogen units	VEGF	vascular endothelial growth factor
PPD	purified protein derivative (of	VIP	vasoactive intestinal polypeptide
	tuberculin)		

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1. IMMUNOLOGY OF ALLERGIC DISORDERS

Hypersensitivity indicates a heightened or exaggerated immune response that develops after more than one exposure to a given antigen. *Hypersensitivity* is usually considered synonymous with *allergy*. An antigen responsible for an allergic reaction is an allergen. The term *allergy* was introduced by Clemens Von Pirquet in 1906 to designate an altered reactivity to a foreign substance after prior experience with the same material, whether this response was helpful or harmful to the host. This concept of allergy, popularized by Gell and Coombs, may have merit in that it permits an organized and systematic approach to the pathogenesis of immunologic diseases. Nevertheless, the term allergy, as commonly used in clinical practice, indicates an adverse reaction and describes the pathophysiologic responses that result from the interaction of an allergen with antibodies and/or lymphocytes in a patient previously exposed and sensitized to that allergen. This immunologic definition of allergy is accepted by most but not all allergists, as nonimmune processes can influence the pathogenesis of allergic diseases with recognized immune etiologies.

The terms *atopy* and *atopic* are frequently used in reference to allergic diseases. Derived from the Greek word meaning "strange," they were introduced by Coca and Cooke in 1923 to describe allergic diseases, such as asthma, allergic rhinitis (hay fever), and atopic dermatitis (infantile eczema), that showed a familial predilection and an implied genetic predisposition. Other allergic diseases, such as contact dermatitis and serum sickness, showed no familial tendency and were referred to as nonatopic. It was also recognized that serum from these allergic individuals contained a factor subsequently described as a skin-sensitizing antibody. This heat-labile serum factor could passively sensitize the skin of a nonsensitive individual and, after imradermal challenge with a specific allergen, the passively sensitized skin showed a positive wheal-and-flare reaction within 20 minutes. This passive transfer test, also known as the Prausnitz-Kustner, or PK, test, provided documentation of the presence of a specific serum antibody important in the pathogenesis of allergic diseases. More than 90% of these antibodies are now identified as immunoglobulin (Ig) E. Many allergists use the term atopic instead of allergic to identify those families and patients with hereditary predisposition toward asthma, hay fever, and/or infantile eczema.

CLASSIFICATION OF IMMUNOLOGIC REACTIONS IN ALLERGIC DISEASES

The manifestations and expressions of allergic disease are dependent on many variables, which include the genetic constitution of the sensitized individual, the nature of the allergen involved, the route of allergen administration to the sensitized subject, the biologic properties of the antibodies or sensitized cells, and the local tissue response to the allergen-antibody interaction. If a suspected allergen is applied to or injected into the skin of a previously sensitized allergic subject, several different responses occur. The allergic or hypersensitivity cutaneous reactions can be classified as immediate hypersensitivity (IgE early- and late-phase) reactions and T-cell (48 hours) hypersensitivity reactions.

IMMEDIATE HYPERSENSITIVITY RESPONSES

The immediate cutaneous hypersensitivity reaction usually develops within 20 minutes of challenge with the antigen and is manifested as a wheal-and-flare skin response. Studies have demonstrated that an antibody (typically IgE immunoglobulin) present in either serum or tissues binds to the specific antigen and initiates secretion of mediators of inflammation and cytokines that are responsible for the immediate hypersensitivity response.

Biopsy and microscopic examination of an immediate cutaneous hypersensitiviiy reaction at 15 to 30 minutes reveals little cellular infiltrate - perhaps a few neutrophils and occasional eosinophils and some local edema. It is the immediate hypersensitivity reaction that is the basis for much of the allergy skin testing performed by clinical allergists and immunologisls.

LATE PHASE AND DELAYED RESPONSES

Depending on IgE antibody and allergen concentrations, a subset of allergy patients shows a late (2 to 6 hours) cutaneous allergic IgE response in addition to the immediate (15 to 30 minute) reaction. Biopsy of the late-phase IgE reaction reveals moderate cellular inflammation and an increased number of neutrophils and lymphocytes, with many basophils and eosinophils.

The T-cell-mediated cutaneous delayed hypersensitivity reaction typically peaks 48 to 72 hours after antigen challenge and is characterized by local erythema and induration. This delayed reaction is not dependent on a serum antibody but rather on a cell-mediated immune reaction involving sensitized T-lymphocytes. Microscopic examination of a cutaneous biopsy of delayed hypersensitivity skin reaction reveals moderate mononuclear cellular infiltrate, consisting primarily of small lymphocytes. These different IgE- and T-cell-mediated cutaneous manifestations are not mutually exclusive and may be elicited in the same host, depending on the variables listed previously.

GELL AND COOMBS CLASSIFICATION SCHEMA

To better comprehend the concepts of allergy, including the cutaneous immediate and delayed hypersensitivity reactions, Gell and Coombs proposed a classification of the immunopathologic mechanisms. They separated the reactions by which a specific antigen can induce cellular and tissue injury into four groups: Type I (immediate or anaphylactic), Type II (cytotoxic or cytolytic), Type III (antigen-antibody complex), and Type IV (delayed or cell mediated) (Fig. 1-1). These four reactions patterns are not mutually exclusive; often, more than one of them occurs in the same patient. Hence, some immunologists do not accept or utilize this schema. For example, there may be several allergic immune reactions to penicillin. Urticaria may develop, representing a Type I response involving IgE. In other patients, a hemolytic anemia can result from the formation of an immune complex composed of penicillin, IgG antibody, and complement (Type III). Further, contact dermatitis, mediated by sensitized T-lymphocytes reacting to the penicillin (Type IV), may also arise. Appreciating that these inconsistencies exist, the authors feel that this classification is helpful for the clinician in understanding the pathogenesis of allergic and immunologic diseases.
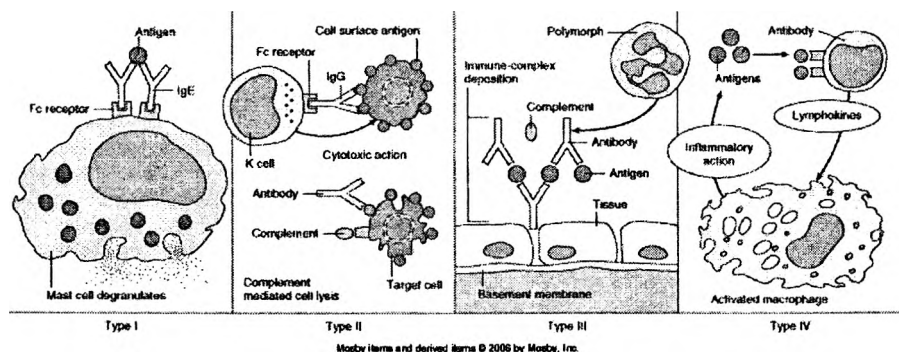

Figure 1-4. Summary of the four types of hypersensitivity reactions. Type I: Mast cells bind immunoglobulin E (IgE) via Fc receptors. On the encountering antigen, the IgE becomes cross-linked, inducing degranulation and release of mediators. Type II: Antibodies are directed against antigens on an individual's own cells (target cells). This may lead to complement-mediated lysis or cytotoxic action by killer cells. Type III: Immune complexes are deposited in the tissues, complement is activated, and polymorphs are attracted to the site of antigen deposition, causing local damage. Type IV: Antigen-sensitized T-cells release lymphokines following a secondary contact with the same antigen. Lymphokines induce inflammatory reactions, activating and attracting macrophages, which release mediators.

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Type I Reaction

The Type I reaction of Gell and Coombs is referred lo as the immediate, anaphylactic, or homocytotropic antibody reaction. This reaction might also be called an atopic phenomenon, and it is responsible for many of the common allergic diseases. Clinical examples include asthma, hay fever, urticaria, angioedema, and anaphylaxis.

In the Type 1 reaction, mast cells or peripheral blood basophil leukocytes are passively sensitized by homocytotropic IgE antibodies, which are synthesized by plasma cells on stimulation by appropriate allergens. The binding of IgE to the mast cells involves the Fc portion of the IgE molecule and a receptor on the cell surface. During this initial sensitization phase, there is no overt deleterious host reaction. On subsequent challenge, however, this same allergen combines with its specific IgE antibody at the cell membrane of the sensitized mast cell and/or the blood basophil. This combination of allergen and antibody results in a sequence of energy-dependent enzyme reactions, with alteration of the cell membrane that initiates the synthesis and release of the specific pharmacologic mediators of the Type I immediate hypersensitivity reaction. These mediators may be preformed and stored in the mast cell granules or generated from phospholipids of the mast cell or basophil membrane. The preformed mediators include histaminc and eosinophil chemotactic factor (ECF-A). The newly synthesized mediators of anaphylaxis include metabolites of arachidonic acid, especially including the prostaglandins, which are products of the cyclo-oxygcnase pathway, and the leukotrienes, which are the result of the lipoxygenase pathway.

The Type I reaction usually occurs within minutes of exposure to an appropriate antigen but may be sustained for 2 to 6 hours without additional antigen contact as a late-phase IgE reaction. After the mast cells and basophils have been through a refractory period of several hours, they resynthesize the pharmacologic mediators of hypersensiliviiy and once again become capable of responding to a specific allergen.

The specific intracellular biochemical events that occur during the Type I response arc not entirely understood on a molecular level, but in vitro studies suggest that mediator release is promoted by those processes that decrease intracellular cyclic adenosine monophosphate (cAMP). It has been noted that adrenergic agents, especially the more selective beta-adrenergic agents, increase intracellular cyclic adenosine monophosphate and thereby inhibit histamine release. Cyclic adenosine monophosphate is normally catabolized by phosphodiesterase; if phosphodiesterase is inhibited by a phosphodiesterase inhibitor, intracellular cyclic adenosine monophosphate is increased, and less histamine and other mediators may be released. Theophylline, a methylxanthine derivative, is a phosphodiesterase inhibitor. Calcium and magnesium appear to be essential to the release of histamine from sensitized mast cells and basophils in vitro.

Interaction of IgE antibodies and an allergen at the mast cell membrane does not appear to be capable of activating the complement sequence by the classic pathway; however, complement activation by the alternative pathway may occur. In most situations, the immunologic effectors of the Type I immediate hypersensitivity allergic reaction have been shown to be IgE antibodies; it should be emphasized, however, that it is the inflammatory mediators (e.g., histamine, prostaglandins, and leukotrienes) that are responsible lor the pathophysiologic changes observed in the patient.

Type II Reaction

The Type II reaction as described by Gell and Coombs is referred to as the cytotoxic or cytolytic reaction. In this allergic situation, circulating IgG and IgM antibodies react with antigens that may actually be portions of cells, such as erythrocytes and their membranes, or with an unrelated antigen, such as a drug that has become associated with these cells. The fact that the antigen is a cell or a cell constituent indicates that this reaction may be expressed as a form of autoimmunization or isoimmunization in clinical situations. In most cases, both IgM and IgG are involved in this reaction, as is the complement system. The complement-activated mediators are responsible for an inflammatory reaction. The cell that functions as the antigen or carries the appropriate antigenic determinant is usually destroyed or altered; there may be injury to erythrocytes, leukocytes, and platelets, and other cytotoxic reactions may be involved in this mechanism. Clinical examples of

Type II reactions include autoimmune hemolytic anemia; transfusion reactions; hemolytic disease of the newborn; Goodpasture's syndrome; and drug-induced, antibody-dependent hemolytic anemia, leucopenia, and thrombocytopenia. It is the destruction or alteration of a target cell that differentiates this type of immunologic injury.

Type III Reaction
The Type III reaction is referred to as immune-complex injury or tissue damage. In this immunopathologic reaction, serum IgG antibodies interact with an antigen but not necessarily at a cell surface or membrane. Antigen-antibody complexes are formed, usually in moderate antigen excess, when antigen and antibody concentrations are appropriate. These microprecipitates or complexes aggregate in and near blood vessels. They induce inflammation in the tissues in which they are deposited, which leads to vascular damage and thrombosis. Frequently, these antigen-antibody complexes are formed in areas of high blood flow, with deposition occurring in such tissues as the kidneys, lungs, and walls of small blood vessels.

The antigen-antibody complexes activate the complement system, and components C5, C6, and C7 attract polymorphonuclear leukocytes to the reaction site. Phagocytosis of the complexes by these leukocytes, as well as other macrophages, result in the release of enzymes, cytokines, and other mediators responsible for the observed inflammation and tissue destruction. Clinical examples of this Type III reaction include serum sickness syndrome, acute poststreptococcal glomerulonephritis, and certain collagen vascular diseases, especially systemic lupus erythematosus.

Type IV Reaction
The Type IV reaction of Gell and Coombs is the T-cell-mediated immune response or delayed hypersensitivity reaction. The immunopathologic response in the Type IV reaction appears to be dependent on sensitized small T-lymphocytes and their cytokines; serum antibodies to the appropriate antigens have not been implicated in the pathogenesis of this immune reaction. Many of these cytokines are identified as interleukins. There is no apparent interaction of the antigen with humoral antibodies, either at the cell membranes or in tissues, and it has been proposed that the antigens react directly with the sensitized lymphocytes.

After challenge with an antigen, the cell-mediated immune reaction results in the accumulation of mononuclear cells at the site of tissue inflammation within 24 to 48 hours. Activation of dendritic cells, local proliferation of lymphocytes, and additional release of cytokines are important in the development of the delayed hypersensitivity, cell-mediated immune reaction.

Complement does not appear to be involved in this reaction. Cell-mediated delayed hypersensitivity represents the pathophysiologic basis for contact dermatitis, as well as for many aspects of organ transplant and skin graft rejection phenomena. In certain pulmonary diseases (e.g., tuberculosis, fungal diseases, and sarcoidosis), the observed tissue damage and inflammation appear to be due to cell-mediated, delayed hypersensitivity responses of the host to various antigens.

IMMUNOGENETIC ASPECTS OF ALLERGIC (ATOPIC) REACTIONS
The familial nature of allergic diseases has been recognized for years, and a positive family history of atopic disease has been reported in approximately 75% of allergic patients. Though the tendency for developing allergic disease is clearly familial, the specific clinical allergic reaction is not directly inherited, since the host response is dependent on the appropriate environmental exposure. If there is no exposure to the allergen, there is no allergic disease, regardless of familial predisposition. Family studies comparing the allergic high-IgE phenotype to the nonallergic low-IgE phenotype suggest a recessive inheritance for high-IgE levels. However, studies of IgE levels in monozygotic and dizygotic twins were not conclusive. Although a major portion of the variation in IgE levels is genetic, other environmental factors are likely to be involved.

Investigations of inbred animals suggested that specific antibody synthesis to a well-characterized antigen is controlled, in part, by immune response (Ir) genes linked to the major tissue histocompatibility locus antigen (HLA). Analogous Ir genes linked to HLA have been described in

humans. Ragweed hay fever symptoms and a positive skin test for the purified ragweed antigen E correlated highly wilh a particular HLA haplotype in successive generations of allergic families. The observed haplotype varied from family to family, suggesting that the Ir genes for this response were linked to (not associated with) HLA. The responses to complex multiple allergens, such as those used in clinical practice, may be dominated by the general level of IgE production rather than by the presence of specific HLA-linkcd Ir genes. Recently, a dominant autosomal trait was uncovered in allergic families, through use of restrictive enzymes, and the IgE immune response gene has been linked to chromosome 11. However, these results were not universal in other populations, and other studies suggest the gene is located on chromosome 5. In the past 10 years, there have been other linkage and association studies examining genetic susceptibility to allergic disease. A mullifactorial mode of inheritance also has been proposed, and many investigators feel that several loci are involved in the expression of allergic disease; interaction with environmental exposures is also important.

Parents often become concerned with the risk of having allergic children if one or both of them have allergic problems or if they already have an affected child. Retrospective family studies suggest that when both parents are affected, allergic disease is present in about 60% of the offspring, and when only one parent is affected, about 30% of the children are allergic. When environmental exposure is probably the same for siblings in a given family, the risk of developing allergic disease is probably the same for each pregnancy, unless the family initiates preventive tactics to reduce antigen exposure. Many clinicians suggest breastfeeding during the first year of life to reduce the possibility of cow's milk allergy. It remains to be proven that avoidance of inhalant allergens during infancy reduces the incidence of respiratory allergy.

2. ALLERGENS

Allergens are those antigens responsible for clinical allergic diseases. They are usually proteins or glycoproteins capable of inducing synthesis of immunoglobulin (Ig) E antibodies, thereby sensitizing the potentially allergic person. Upon reexposure to the same allergen, the previously sensitized patient manifests the signs and symptoms of allergy, as the allergen reacts with cell-related IgE tissue antibody, and the cells generate the mediators of inflammation.
As shown in Box 2-1, allergens can be classified on the basis of the nature or manner in which the patient is exposed.

Box 2-1. Classification of allergens according to the route through which they enter the body
Inhalants
  • Outdoor
  • Indoor
Ingestants
Contactants
Injectants

Those allergens responsible for allergic respiratory diseases, including allergic asthma and allergic rhinitis, are principally inhalants. These aeroallergens, which can be present outdoors or indoors, are responsible for the majority of all allergic diseases. Foods and other ingestants, including drugs, are also important, especially for allergic gastrointestinal and skin diseases. The contactants are principally responsible for allergic contact dermatitis. In addition to drugs, the injectant group includes the venom and saliva of insects. This chapter is limited to a discussion of the inhalant allergens, as the other allergens are described in the separate chapters on food allergy, drug allergy, contact dermatitis, and anaphylaxis. The inhalant allergens can be grouped as outlined in Box 2-2.

Box 2-2. Classification of inhalant allergens
Pollen
Fungi (molds)
Animal products
  • Mammalian
  • Arthropod
Dusts
Algae

Pollens were the earliest known causes of allergic respiratory diseases, being identified as such in the 19th century. They remain the most commonly recognized today. The spores of fungi, often referred to as molds by clinicians, are especially important when airborne in those environments in which the humidity supports their growth. Animal products, both mammalian and arthropod, have been increasingly recognized during the 20th century as being causative factors in allergic diseases, as have other organic and inorganic dusts to which sufferers are exposed in the home and workplace. Algae are relatively uncommon inhalant allergens.

ALLERGEN DETECTION
The detection and quantification of aeroallergens have provided the clinician with the basis for understanding the etiology of allergic respiratory illnesses. The methods of aeroallergen detection and measurement are listed in Table 2-1.
An environmental survey based on the history given by the patient or visual inspection of the environment provides valuable information regarding potential aeroallergen sources and can

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provide clues as to the source of the allergen. Direct microscopic examination is the most widely employed means of detecting and counting pollen and fungal spores. The quantification of pollens has been traditionally performed by collecting the pollen grains onto greased microscope slides using the Durham gravity system. Only during the past two to three decades have impact samplers (Rotorod) and suction samplers (Burkard, Kramer-Collins and Andersen) been used, providing truly quantitative ways of measuring these allergens. Recently, immunochemical techniques have been developed that can identify the soluble allergen constituents of ragweed pollen, as well as other allergens such as dust mites. These types of studies have become very important in finding other amorphous airborne allergens that cannot be identified using microscopy. Propagation of viable microorganisms in culture media can be used depending on the material under study and the type of data desired.

Table 2-1. Aeroallergen detection and measurement

Methods	Application
Visual inspection or retrospective	Clinical environment survey (no sampling device)
Microscopic analysis	Identification and enumeration of pollen grains and fungal spores
Immunoassay	Specific allergen detection and measurement
Propagation (culture)	Identification of viable microorganisms

ALLERGEN NOMENCLATURE
The Allergen Nomenclature Committee of the International Union of Immunological Societies (IUIS) has devised a unified nomenclature system for purified allergens. Allergens are phenotypically designated by the first three letters of the genus followed by a space, the first letter of the species, another space, and finally, an Arabic number; occasionally an additional letter must be added to either the genus or the species, designation. Allergens are genotypically designated with italics; for example, the two genes encoding the two polypeptide chains of the major house cat *(Felis domesticus)* allergen *Fel d 1* are designated *Fel d 1A* and *Fel d 1B*. A complete and updated Internet-based listing of purified allergens is maintained by the IUIS.

POLLENS
Pollens are the viable male germinal cells that are essential for the reproduction of most seed plants. The sources of pollens include trees, grasses, and weeds. Because of this seasonal variation in atmospheric pollen, the patient who develops pollen allergy manifests a seasonal symptomatology. In some tropical and subtropical regions of the world, however, climatic conditions show little annual variation, and pollen prevalence may be perennial. Guidelines for the characterization of those pollens that can become potent allergens were initially postulated by Thommen in 1931 (Box 2-3).

Box 2-3. Factors that contribute to the allergenicity of pollens
Wind-borne (anemophilous)
Buoyant (of small particle size)
Produced in large quantity
Potent antigen

In general, pollens that are wind-borne (anemophilous) are of greater clinical relevance than those carried by insects (entomophilous). Thus, the pollens of attractive, brightly colored flowering plants are infrequently the cause of allergic diseases. These insect-borne pollens tend to be heavy, sticky, and less numerous. For example, the pollens of roses and goldenrod are often incorrectly incriminated as important inhalant allergens, since their flowers bloom in temperate climates at the

height of the grass pollen and ragweed pollen seasons, respectively. However, florists, landscapers, hobbyists, and others whose occupational or recreational pursuits increase their exposure do become sensitized to the pollens of flowering plants.

The buoyancy, relative size, and density of a pollen can contribute to its dispersion. Ragweed pollen has a long wind-borne range and has been detected many miles offshore of lakes and oceans. Certain plants are widely distributed and produce large amounts of pollen - a single ragweed plant may release a million pollen grains in one day. Trees, especially conifers such as pine, may release clouds of pollen, but these are generally less allergenic than ragweed.

Typically, the onset of pollination for many pollens is predictable to within a margin of a week or less, a characteristic that is important for clinical diagnosis. Clinicians should know the most prevalent pollen allergens in their area of the world, as well as their seasonal occurrence. Even though the seasonal appearance of the pollen is predictable, the amount produced in a given season varies, depending on climatic conditions. Extended dry periods during plant development and growth reduce the eventual pollen production. Also, a rainy day during the pollen season reduces the amount of airborne pollen on that day, whereas a dry, windy day increases the airborne concentration.

In addition to allergen exposure, the allergenicity of the pollen is another important factor. It is not known what accounts for certain pollens being more potent-sensitizing allergens than others. Only a subset (10% to 20%) of the population become sensitized and show allergic symptoms, even though the entire community is exposed to the allergens.

WEEDS

The pollens of weeds are common causes of seasonal allergic rhinitis. The most prevalent allergenic ragweeds are the short *(Ambrosia artemisiifolia)* and giant ragweeds *(Ambrosia trifida);* the latter can reach a stately 12 feet (3.7 m) in height. Its pollen is released in temperate areas from mid-August to mid-September. In the southern and southwestern states, ragweed pollen can be airborne throughout the spring, summer, and fall.

Botanically, ragweed is a member of the same *Asteraclae* composite family as many flowering plants, including chrysanthemums, marigolds, asters, some daisies, and sunflowers. These others, however, are only bothersome to those such as florists or gardeners who handle them regularly. Pyrethrum is an insecticide made form the flower heads of certain chrysanthemums, and inhalation of this compound can provoke symptoms in ragweed-allergic patients. The major allergens of ragweed have been isolated and characterized as *Amb a I* (antigen E) and *Amb a II* (antigen K). Commercial extracts of ragweed pollen used in clinical allergy testing and immunotherapy are now required by the U.S. Food and Drug Administration (FDA) to be standardized to *Amb a I* content.

The most common weeds throughout the world are similar. These include nettle, plantain, dock, sage, mugwort, lamb's quarter, and pigweed. Depending on the climate and the local geography, the pollination of weeds frequently coincides with that of grasses in many temperate areas of the world.

GRASSES

In Europe, South America and North America, Asia, and Africa grasses are the most important causes of pollen allergy. Allergic rhinitis was described initially in England in 1889 by Blackley as *hay fever* because of the association of nasal symptoms with the harvesting of the forage grass, timothy, which is used to make hay. Most of the grasses are cultivated either agriculturally or ornamentally and are prevalent where people live. The pollens of the different grasses vary in size from 20 to 40 μm, and they all have a single germinal pore, which makes them difficult to distinguish microscopically.

Only about a dozen of the more than 5000 species of grass are important allergens, as many of the grasses do not produce abundant pollen. The bulk of the airborne grass pollen in the Northern Hemisphere, United States, Canada, Europe, and northern Asia is present in the late spring and

height of the grass pollen and ragweed pollen seasons, respectively. However, florists, landscapers, hobbyists, and others whose occupational or recreational pursuits increase their exposure do become sensitized to the pollens of flowering plants.

The buoyancy, relative size, and density of a pollen can contribute to its dispersion. Ragweed pollen has a long wind-borne range and has been detected many miles offshore of lakes and oceans. Certain plants are widely distributed and produce large amounts of pollen - a single ragweed plant may release a million pollen grains in one day. Trees, especially conifers such as pine, may release clouds of pollen, but these are generally less allergenic than ragweed.

Typically, the onset of pollination for many pollens is predictable to within a margin of a week or less, a characteristic that is important for clinical diagnosis. Clinicians should know the most prevalent pollen allergens in their area of the world, as well as their seasonal occurrence. Even though the seasonal appearance of the pollen is predictable, the amount produced in a given season varies, depending on climatic conditions. Extended dry periods during plant development and growth reduce the eventual pollen production. Also, a rainy day during the pollen season reduces the amount of airborne pollen on that day, whereas a dry, windy day increases the airborne concentration.

In addition to allergen exposure, the allergenicity of the pollen is another important factor. It is not known what accounts for certain pollens being more potent-sensitizing allergens than others. Only a subset (10% to 20%) of the population become sensitized and show allergic symptoms, even though the entire community is exposed to the allergens.

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early summer from May to July. Whereas in the Southern Hemisphere, including Australia, South America, southern Asia, and South Africa, the seasons are reversed. The important early grasses include sweet, vernal, and orchard, which are followed by timothy, bluegrass, fescue, redtop, and perennial ryegrass. All of these grasses show considerable allergen cross-reactivity, but they are allergenically distinct from the southern grasses. In the subtropical and tropical areas of the world, including the southern United States, Bermuda grass is found nearly all year round, and Johnson and salt grasses also have long seasons. In southern Europe and the Mediterranean areas, grasses may pollinate from February to October.

TREES

Tree pollens are prevalent worldwide, but because of a shorter pollen season in most countries, they do not produce as much allergic disease as do the grasses and weeds. The fruit-bearing trees, such as apple, pear, and peach, are insect pollinated, and their entomophilian pollens are not relevant in most clinical allergy. In much of North America, Europe, and temperate areas of the world, the pollen seasons for trees typically precede those of the weeds and grasses, sometimes making these early-onset symptoms easy to relate to the tree pollens. There is less antigenic cross-reactivity among the tree pollens than among the grass pollens.

In the Mediterranean region and southern Europe, cypress and hazel tree pollens can appear as early as January, whereas in the northeastern forests of North America and Europe, the earliest tree pollens appear in March and April, with the release of pollen from birch, elm, maple, ash, alder, and hazel trees. Birch is a major allergen in Scandinavian countries. Oak trees shed more pollen than many other plants and are present in all of Europe and North America except Alaska, Hawaii, and other hot, tropical, or very cold climates. In the Northern Hemisphere, airborne oak pollens are present in April and May, whereas in the Southern Hemisphere, these and others can initially appear during August and September. In general, conifer (pine) trees produce large amounts of pollen but cause modest allergic symptoms, with the exception of the mountain cedar in Texas and the Japanese cedar in California, Japan, and other parts of Asia.

FUNGI (MOLDS)

Fungi are saprophytic organisms that are present throughout most of the world. Most fungi produce airborne spores that can become important inhalant allergens. As allergens, fungi can be detected both outdoors and indoors and may show seasonal or perennial presence. Their numbers increase in the air during the warm months and decrease when hard frost prevents growth, and they are absent when the ground is snow covered. In those areas of the world without a winter season, outdoor fungi spores can be perennial aeroallergens. *Alternaria* and *Cladosporium (Hormodendrum)* species are the most numerous in late summer and early fall in the Northern Hemisphere. These molds are saprophytic fungi and grow on decaying leaves and dead plants. They are often increased atmospherically in the daytime. Some, such as *Drechslera (Helminthosporium)*, grow abundantly on grasses and cereal crops and in the soil and are more numerous in subtropical climates.

Water (humidity) is the primary controlling factor for fungal growth, both outdoors and indoors. In cool weather, warmer moist indoor air diffuses through walls and on contact with cold vapor barriers forms condensation with growth of fungi. In this fashion, molds such as *Aspergillus, Penicillium,* and *Stachybotrys* can grow indoors with a humidity lower than 85%. These are the organisms most typically found in sheds, barns, and homes, especially in basements and crawlspaces. *Aspergillus* is also commonly found in barns associated with stored grains or vegetables. *Penicillium* is the green "mildew" seen typically on items stored in damp basements. *Stachybotrys* is often referred to as the "black mold." *Epicoccum* can be found both in storage areas and outdoors as a seasonal aeroallergen. Fungi can also often be found in damp bathrooms and on houseplants. Vaporizers, humidifiers, and air conditioners that have water storage units can be contaminated with fungi and then become a source of aerosolized mold spores. The potential of

fungal allergy should not be ignored, as recent studies have indicated that many asthmatics in large cities had positive immediate skin tests to *Alternaria* and *Penicillin.*

Unfortunately there are no generally accepted standards for interpretation of fungal levels in indoor or outdoor air. At present, the best approach to indoor fungal control is moisture control in the indoor environment.

INDOOR ALLERGENS

Airborne indoor allergens are important causes of clinical allergy. It has been known for years that indoor exposure to dusts, either through household or occupational exposure, can provoke respiratory allergy (Box 2-4).

Box 2-4. Selected indoor allergens
Acarids
Dust mites
Mammals
Cat, dog, rabbit, ferret, guinea pig, gerbil, mouse, rat
Insect
Cockroach (Blatella germanica, Periplaneta Americana,Blatta orientalis)
Fungi
Aspergillus, epicoccum

For years, the source of the allergen in house dust was debated, but in 1967, its principal allergenic component was shown to be a mite. House dust or mattress mites *(Dermatophygoides),* as well as other mite species, are found worldwide. *D. pteronyssius* is more common in Europe, along with *Euroglyphus maynei, D. farinae,* and *D. pteronyssius,* which are both found in the United States and Japan.

The tropical mite *Blomia tropkalis* has been detected in Brazil, Venezuela, Puerto Rico, and Florida and is probably present in many tropical areas. These eight-legged, sightless arthropods cannot be observed without magnification, but they can be identified microscopically with lower-power lenses.

They feed on human or animal epithelium and other high-protein debris found in human environmental dusts. The highest concentrations of mites have been found in mattresses, pillows, rugs, upholstered furniture, and vacuum sweepings. Mites do not search for or drink water but absorb water from ambient humidity. For optimal propagation, mites require temperatures of 25°C to 30°C and humidity greater than 50%. In temperate climates, they attain their maximal numbers in early fall, but they can survive for many months at lower temperatures and humidity as well. Temperatures greater than 130°F (54°C) or less than 32°F (0°C) can kill the mites. They are rarely found in arid or arctic climates or at high altitudes.

The major mite allergen has been found in the spherical mite fecal particles. Their shape and size (10 to 35 μm in diameter) make these particles comparable to many pollens. Moderate amounts of mite allergen are found in the body cuticle. The two major allergens in dust mites have been purified and are identified as *D. pteronyssius* allergen I *(Der p 1)* and *Der p 2* and *D. farinae (Der f 1* and *Der f 2).* These purified *Der p 1* allergens have homology with cysteine proteinases with enzyme activity and are cross-reacting allergens with *Der f 1.* However, these purified *Der p* and *Der f* allergens only partially cross-react with the tropical dust mite *(B. tropicalis).* In the United States and England, 10% of the population and 80% to 90% of allergic asthmatics have positive immediate skin tests to the purified dust mite allergen. Reductions in mite exposure by reducing the environment concentration of mites lead to lower levels of specific IgE antibody and fewer allergic symptoms. About 10% of allergic patients who are symptomatic indoors in the United States do not react to skin testing with dust mites; they are reactive to another allergenic constituent in their environmental house dust.

Another important indoor aeroallergen is the cockroach, which can introduce important aeroallergens into the household dusts of certain environments. Studies comparing air samples in crowded New York tenements versus suburban middle-class homes showed comparable concentrations of house dust mite allergen but remarkably higher- levels of German cockroach allergen in the older urban apartments, with a significant association of cockroach IgE antibodies with asthma. As with the dust mite, the major cockroach allergens are related to the gastrointestinal tract or the feces and are greater than 10 μm in size.

MAMMALIAN ANIMAL ALLERGENS

Domestic pets are a very common source of indoor inhalant allergens that provoke significant respiratory complaints and disease in many patients with asthma and allergic rhinitis. Allergic symptoms can occur not only in owners, family, and friends of dogs, cats, or other pets but also in veterinarians and farmers, as well as laboratory workers exposed to horses, cattle, sheep, and rodents, including rabbits, rats, mice, and guinea pigs. The desquamated epithelium, also known as dander, that is attached to the hair becomes aerosolized and is the potent allergen. Epithelial desquamation is a constant process in mammals and is a continual source of aerosolized, highly allergenic proteins, as well as body excretions (Table 2-2).

Table 2-2. Common inhalant allergens from animal sources

Epidermal	Excretions
Dander (desquamated epithelium)	Saliva
Cuticle (body)	Urine
	Feces

It is common for animal-allergic individuals to develop urticaria at sites where they have been licked by a cat or dog or scratched by its claws or teeth. Among the house pets, cats seem to cause the more prominent symptoms. However, dogs do spend more time out of doors and are less frequently kept in bedrooms or beds and may be groomed more frequently than cats. Recent studies have shown that cat allergens are found in the skin, saliva, and sebaceous glands of the skin. It has also been suggested that cat urine can become aerosolized from litter pans, and urinary proteins can act as allergens. Dog allergens have been shown on fur and in dander, saliva, and serum proteins. It has been suggested that some breeds of dog are less allergenic than others, but this may be more quantitative than qualitative and related to frequency of grooming.

The main cat allergen, *Fel d 1,* has been purified from both cat washing solutions and pelt. The allergens prepared from pelt extracts are thought to be less representative of natural exposure because they contain a relatively large concentration of cat tissue proteins (e.g., albumin). When cats are washed repeatedly, the allergen recovered decreases progressively. These observations lead to the clinical recommendation that washing cats is a method of reducing exposure to allergen in cat-allergic patients. However, not all cats tolerate washing, and this effect is short lived - less than a week. To be effective, washing of cats or dogs needs to be repeated frequently, at least once a week. The major dog allergen *(Canf1)* has also been purified. Identification of the major cat and dog allergens has enabled specific environmental immunoassays. Using these assays, significant levels of both cat and dog allergens have been documented, not only in homes of pet owners but also in dust from schools. Recent reports suggest that persistent daily exposure to the allergens from dogs or cats from early infancy may result in statistically less allergic inhalant symptoms than intermittent or daily exposure as an older child or adult. These observations need to be confirmed and may provide future means to induce immune tolerance to animal allergens.

OTHER ENVIRONMENTAL DUSTS

A variety of inhalant airborne allergens include organic dusts, such as baker's flour, grain mill dust, and enzymes used in laundry detergents, as well as trimellitic anhydride, plicatic acid from

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wood dust, toluene di-isocyanate, and the salts of nickel, chrome, and platinum. Kapok, a plant fiber from the Kapok tree, is very resilient and has been used in pillows and upholstered furniture. It is impervious to water, making it a useful material for boat cushions and life jackets. When pulverized and airborne, kapok is a potent allergen. It is being replaced by various synthetic polymers in pillows and cushions.

Occasionally, foods become aerosolized allergens during booking. If inhaled by a sensitive person, certain food allergens may provoke severe respiratory allergy. However, most food-allergic individuals manifest their reactions, which can include respiratory symptoms, after ingestion of the specific food.

Many clinicians feel that respiratory complaints related to our environment have increased in the past several decades. Terms such as *sick building syndrome* have been coined to describe allergies that might be related to exposure to inhaled substances from closed environments with inadequate ventilation. Such nonantigenic irritants, which can exacerbate allergic respiratory disease, include sulfur dioxide, cigarette smoke, cold air, auto exhaust fumes, hairsprays, perfumed aerosols, and solvent vapors.

These substances may directly provoke the activation of mediators of inflammation, such as histamine or leukotrienes, which then cause respiratory symptoms without any mediation by an IgE antibody and allergen reaction. If combined with exposure to an allergen such as dust mites or fungi, these nonallergic irritants can potentiate or exacerbate an allergic respiratory disease.

3. THE ATOPIC DISEASES: APPROACH TO DIAGNOSIS

Introduction

Allergic diseases are common: it has been estimated that 15% of the population will suffer from some sort of allergic reaction during their lifetime. It is clear that there has been an increase in atopic diseases since the Second World War. The precise cause of this change is unknown but undoubtedly reflects changes in lifestyle, in particular 'improvements' in housing, rendering houses more heavily colonized with dust mites. A reduction in breastfeeding may also have contributed, particularly to atopic eczema. The evidence for air pollution, particularly car exhaust fumes, contributing to the increase is conflicting. It is also likely that the improvements in public health, leading to elimination in the Western world of parasitic infections, may contribute through a lack of physiological function for the IgE-mast cell axis. This has been formalized in the hygiene hypothesis ('dirt is good for you!').

The atopic diseases are processes mediated by or related to IgE-immediate hypersensitivity. (The terms atopic and allergic are frequently interchanged. In its broadest sense, the term allergy has been used in the past to describe any immunologic alteration in the capacity to react following contact with a foreign substance. Atopic, on the other hand, characterizes conditions produced only by the action of IgE.)

Genetic factors play an important role in the susceptibility to these diseases. The association of the atopic diathesis with the inheritance of histocompatibility (HLA) antigen haplotypes in families has been demonstrated and suggests that immune-response genes associated with the major histocompatibility complexes may genetically determine or define the atopic state. An IgE response occurs normally in all individuals, but the presence of immune-response genes may be needed for antigen specificity and clinical manifestations of the atopic state. The expression of this potential response may clearly be altered by factors such as dose, route, and timing of antigen exposure, drug therapy, and concomitant illnesses.

I. Anaphylaxis, the most dramatic and devastating form of atopic disease, is the systemic manifestation of immediate hypersensitivity. The implicated antigen is often introduced parenterally such as by injection of penicillin or a bee sting. Oral exposure may also produce anaphylaxis, although less frequently. The activation and degranulation of mast cells systemically, with massive mediator release, results in the clinical picture of bronchospasm, urticaria, and anaphylactic shock.

II. Allergic rhinoconjunctivitis is the most common atopic disorder, affecting approximately 15% of the United States population. Like anaphylaxis, allergic rhinoconjunctivitis is a well-documented model of immediate hypersensitivity pathophysiology. It is mediated by IgE produced locally under the mucosal surfaces of the nose and eye. Airborne antigen comes into contact with mast cells sensitized by the locally produced IgE and produces mast cell degranulation, with the resulting picture of "local anaphylaxis" of the nasal or conjunctival membranes, or both.

III. Urticaria and angioedema. Immediate hypersensitivity may express itself in a cutaneous form of disease: urticaria, or angioedema, or both. Allergic urticaria-angioedema is often self-limited, lasting less than 6 weeks, and is frequently related to the ingestion or administration of foods or drugs. If urticaria persists longer than 6 weeks, the causative agent is not often determined.

IV. Asthma is the expression of immediate hypersensitivity reactions in the lung. Inhaled intact pollens, deposited heavily in the nose and pharynx, probably do not reach the small or even the large airways. Although bronchial challenge studies may provoke bronchospasm, they employ large doses of antigen (e.g., aerosolized aqueous extract of pollen). On the other hand, bronchospasm develops after natural exposure to pollen antigens. The definite role of inhaled antigens has not been completely elucidated.

The antigens may also be ingested in the mucous membrane of the oropharynx, their active allergens eluted and subsequently absorbed, with hematogenous spread producing symptoms. Pulmonary manifestations alone, without cutaneous or nasal symptoms, may follow antigen exposure. The reason for this differential expression of target organs in atopic patients is unknown .

V. Gastrointestinal allergy. The gastrointestinal tract is an unusual site for the expression of localized immediate hypersensitivity disease. Nausea, abdominal cramps, vomiting, and diarrhea may follow food exposure within a matter of minutes to hours, but these reactions are usually not mediated by IgE. Although the gastrointestinal tract contains large numbers of IgE-forming plasma cells, there is little documented evidence to support the common belief that IgE-mediated hypersensitivity reactions occur there frequently. The presence of increased numbers of eosinophils in the small intestine on biopsy after food challenge is suggestive, but not definite, evidence of immediate hypersensitivity.

VI. Atopic dermatitis is an eczematous cutaneous eruption associated with the previously mentioned atopic disorders of asthma and allergic rhinitis. The incidence in the general population is up to 10%. Several features suggest its classification as an atopic disorder: familial association with allergic rhinitis and asthma; markedly elevated serum levels of IgE; frequent hypersensitivity to environmental allergens; eosinophilia; evidence for a beta adrenergic-receptor defect in atopic dermatitis patients similar to that described in asthmatic patients; and the association of allergic rhinitis and asthma in patients with atopic dermatitis. In contrast, the presence of atopic dermatitis does not correlate with immediate hypersensitivity skin tests and antigen exposure, does not respond to immunotherapy, and has histopathologic features that do not resemble those of the usual atopic states.

Approach to the Patient

I.   **Allergic history.** A comprehensive allergy history produces the best data base for the diagnosis and management of patients with allergic disease. A **standardized allergic history form** (Table 3-1) allows the physician to obtain a comprehensive picture of the patient's problem as it relates to allergic disease and exposures.

Table 3-1. Allergy history guidelines

I. Name: _____ Date: _____ Age: _____ Sex:_____

II. Clinical Illness

A. Present illness

     1. Nature of illness
     2. Age of onset
     3. Frequency of attacks
     4. Duration of attacks
     5. Changes in nature, frequency, or duration of attacks
     6. Previous evaluation and treatment
     7. Present treatment

B. Family history

C. Past medical history

III. Environmental Reactions

A. Time of year and day of symptoms

B. What produces symptoms?

C. What relieves symptoms?

D. Symptoms at home, work, vacation

E. Reactions to dusty or moldy environments, pets, odors, foods, medicines, insects, colds, change in weather, smoke, exercise, emotion, mowing lawn

IV. Environmental Survey

A. Occupation, where employed, unusual exposures

B. Place and type of residence, basement, heating, air conditioning, etc. C Carpets or rugs in home, type and matting

D. Pillow, blanket, and mattress, type and age

E. Exposure to barns, dead leaves, or other moldy environments

F. Pets in home (indoors and/or outdoors), number and type

G. Exposure to chemicals, insecticides, etc.

H. Hobbies

I. Medications

J. Cigarettes

The principles of history taking are similar to those for any medical history, but certain aspects of the history require particular attention and expansion, namely, noting the **temporal** and **spatial** relationships of symptoms as related to possible allergen exposures.

Historical details should include the following:

A. The **time relationships** of symptoms should include the time of day, time of the week (all week or weekends only), and time of the year, as well as the duration of symptoms.

B. Do the symptoms occur at home, at work, or on vacation, when the patient is away from his or her work or home environment?

C. Does sensitivity occur to known allergens (e.g., dust, animals, grass cuttings) in addition to possible exposures to unsuspected allergens (e.g., room humidifiers, jute carpet pads)?

D. Do symptoms relate to physical changes (cold, heat, dampness) or activities (e.g., smoking, exercise, or painting)?

E. Does past or current use or abuse of antiallergic therapy (medication, immunotherapy, environmental controls) change allergic symptoms?

F. Since atopic diseases have a strong propensity for familial incidence, a careful history to detect possible atopic disorders in other family members is necessary.

G. The patient should estimate the degree of difficulty or impairment experienced from the allergic symptoms. **This is the primary factor in determining the extent of further evaluation and treatment.**

H. The presence of any concomitant medical conditions should be noted, since these conditions may mimic allergic disease or alter its expression (e.g., pregnancy, hypothyroidism).

II. Physical examination. A complete physical examination is mandatory. Specific attention should be directed to areas where atopic diseases are manifested: the skin, the conjunctiva, the nasopharynx, and the lungs. A more complete discussion of the physical findings in each specific atopic disorder is found in subsequent chapters. However, certain principles bear emphasis at this time.

A. The **entire skin** should be examined for important physical changes (e.g., lichenification in the flexor areas or other chronic alterations of the skin) that may not be mentioned by the patient who feels that they are unimportant, unrelated, or embarrassing.

B. The **conjunctiva** should be carefully examined for hyperemia and edema (chemosis) involving both the palpebral and bulbar membranes. The presence of increased or abnormal-appearing secretions in the palpebral fissures should be noted. The fundus should be examined, because cataracts are often associated with both atopic disease and corticosteroid treatment.

C. The **middle ear** is often a site of secondary complications of allergic disease, such as serous or infectious otitis media. Similarly, the frontal and maxillary sinuses should be examined by palpation and transillumination.

D. The **nose** is the most accessible area to observe the physical alterations resulting from the pathophysiologic features of immediate hypersensitivity disease.

1. A transverse line across the **top of the nose,** the **allergic crease,** may occur as a result of chronic upward nose rubbing **(allergic salute),** especially in children.

2. The **interior of the nose** should be assessed using adequate illumination and exposure as provided by a head mirror and nasal speculum. An otoscope with a large speculum provides an alternative method. The examiner must be careful **not to distort the anatomy** of the nasal vestibule.

a. The **mucosa** and the structures it overlies (septum, turbinates) should be examined carefully.

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b. The quantity and quality of **nasal secretions** should be assessed.

c. The presence of **polyps** or **foreign bodies** should be noted.

d. The **patency** of the nasal passages is assessed by having the patient sniff through one nostril with the other lightly occluded.

E. The **mouth** and **oropharynx** are examined with a bright light source and tongue blade. Because the mucosa of the oropharynx is continuous with the nasal mucosa, in allergic rhinitis the posterior lateral pharynx and uvula may often be erythematous, or edematous, or both. A narrow, high-arched palate, narrow chin, and elongated maxilla with overbite occasionally result from chronic allergic disease in childhood **(allergic facies).**

F. The **chest** should be examined by visual inspection, palpation, percussion, and auscultation. The findings in allergic disease vary from normal during symptom-free intervals to marked hyperinflation, accessory muscle use, and marked wheezing during acute asthma attacks. The changes of chronic lung disease (e.g., increased anteroposterior diameter) may result from severe asthma or may be a complication of repeated infections or immune injury (e.g., hypersensitivity pneumonitis).

III. Diagnostic tests of allergic and clinical immunologic disordes

The results of laboratory studies do not make the diagnosis of allergic disease. They strengthen or weaken various diagnostic possibilities suggested by the history and physical findings. They are also an aid in patient management - in monitoring both the complications of allergic disease and the effects of therapy.

A. Complete blood count with differential. The white blood cell count is usually normal except during states of increased catecholamine input (endogenous or exogenous) or intercurrent infection. Eosinophil percentages between 5 and 15% are nonspecific but do suggest atopic disease. Corticosteroids cause eosinopenia and may mask eosinophilia.

    1. Moderate eosinophilia (15-40% of peripheral blood leukocytes) may be found in allergic disorders, but other causes should be considered, namely, parasitic infections, drug exposure, malignancy, and immunodeficiencies. Radiation therapy, congenital heart disease, peritoneal dialysis, cirrhosis, periarteritis nodosa, and dermatitis herpetiformis also are associated with moderate eosinophilia.

    2. Exaggerated eosinophilia (50-90% of peripheral blood leukocytes) is commonly observed in visceral larva migrans, seen especially in children, and in the idiopathic hypereosinophilic syndrome, seen in adults. In disorders generally associated with moderate eosinophilia (parasites, Hodgkin's disease, periarteritis nodosa, drug hypersensitivity) the eosinophilic response may occasionally be exaggerated.

B. Total eosinophil count. Although the number of eosinophils per cubic millimeter of blood can be estimated from the differential and total leukocyte counts, more accurate counts can be obtained by the use of special diluting fluids that hemolyze the erythrocytes and stain the eosinophils. The eosinophils can then be counted directly in a counting chamber. Normal values for absolute eosinophil counts are 0 to 450 cells/cu mm for adults, 50 to 700 cells/cu mm for young children, and 20 to 850 cells/cu mm for newborns.

C. Smears for eosinophils. The nasal secretions, conjunctival secretions, and sputum of atopic patients usually reveal eosinophils. During symptomatic periods, eosinophils predominate in these secretions. Intercurrent infection may produce a prominent neutrophil response. Repeat smears after treatment of the infection reveal the characteristic eosinophilic nature of the cells. Conjunctival secretions are obtained by a cotton swab. Nasal secretions are secured by having the patient blow the nose in a piece of wax or nonabsorbent paper. In younger children, nasal secretions may also be obtained with a bulb-suction apparatus, a syringe with feeding tube, or cotton-tipped applicator. Sputum is obtained by inducing a deep cough. Eosinophils are best demonstrated by Hansel's stain; alternatively, Wright's stain may be used. If clinically indicated, these secretions may be stained and cultured for bacteria and fungi.

D. Total serum IgE levels. An elevated total serum IgE level supports the diagnosis of atopic disease. However, there is an overlap of IgE values between atopic and normal persons; a normal IgE level does not exclude the diagnosis of an allergic disorder. Newer techniques, such as the direct sandwich radioimmunoassay (paper radioimmunosorbent test [PRIST]) are more sensitive, especially for low levels (< 50 Units/ml). Accurate interpretation of IgE levels must be based on knowledge of the test assay and normal values for each laboratory. Using a PRIST method, approximately 63% of adults with asthma, or hay fever, or both will have an IgE value above the 2 S.D. limit for healthy adults. In children with high serum IgE levels, 96% are found to have significant allergy. Patients with atopic dermatitis and respiratory symptoms often have a markedly elevated IgE level (> 1000 Units/ml).

    1. The following are the current clinical indications for IgE determinations (laboratory kits for IgE determinations are commercially available):

        a. Differentiation of atopic and nonatopic asthma and rhinitis (especially in young children)
        b. Differentiation of atopic and nonatopic eczema (especially in children)
        c. Prediction of allergy among children with bronchiolitis
        d. Initial laboratory screening for allergic bronchopulmonary aspergillosis
        e. Evaluation of immunodeficiency
        f. Evaluation of drug reactions
        g. Paraprotein evaluation in patients with multiple myeloma

    2. Parasitic infections, a common cause of marked IgE elevations, must be excluded. Diseases with known elevations of IgE are listed in Table 3-2.

Table 3-2. Disorders associated with elevated serum IgE levels

Common disorders
        Atopic diseases
        Parasitic infections
        Laennec's cirrhosis
        Mononucleosis
Less common disorders
        Selective IgA deficiency
        Gluten-sensitive enteropathy
        Pulmonary hemosiderosis
        Drug-induced interstitial nephritis
        Minimal change nephritis
        Bullous pemphigoid
        Acral dermatitis
        Mucocutaneous lymph node syndrome (Kawasaki disease)
        Wegener's granulomatosis
        Polyarteritis nodosa
Rare disorders
IgE myeloma
T-Cell deficiency (DiGeorge syndrome, Wiskott-Aldrich syndrome, Nezelof syndrome)
Job-Buckley syndrome
    Bone marrow transplantation (immediate post-transplantation period)

E. Skin tests for immediate hypersensitivity
    Skin testing is the tool used most widely to diagnose clinical allergies. As the antigen combines with immunoglobulin (Ig) E antibody fixed to mast cells, mediator substances, particularly histamine, are released from the mast cells. The mediators cause local vasodilation and increased capillary permeability. Wheal-and-flare reactions appear within 15 to 20 minutes. A

typical scoring system is listed in Table 3-3. If the negative control comes up positive, or if the histamine control produces no reaction, the tests are impossible to interpret.

Test results greater than the 'positive' negative control might be considered positive: this is risky, and confirmatory blood tests should be undertaken.

Table 3-3. Commonly used scoring system for grading the response to hypersensitivity skin testing

Grade	Wheal	Erythema
0(-)	< 3mm	0-5 mm
1+	3-5 mm	0-10 mm
2+	5-10 mm	5-10 mm
3+	10-15 mm	>10 mm >20 mm
4+	> 15 mm or with pseudopods	

The immediate wheal-and-flare reactions are often followed by late-phase reactions. There is evidence that if high enough concentrations of antigens are presented, 100% of immediate reactions will go on to late phases. These late-phase reactions in the skin are also manifested in the nasal mucosa and bronchi.

There are two types of skin tests - the epicutaneous, also referred to as scratch, puncture (SPT), and prick technique, and the intracutaneous, or intradermal test (IDT).

Indications for testing

• SPT is the gold standard for allergy diagnosis and should be considered as the first choice for testing.

• Testing should be driven by clinical symptoms: the use of routine panels of allergens on every patient is wasteful and can be misleading (irrelevant positives).

• Where no commercial antigens are available, direct SPT (prick to prick) with allergens such as foods may be desirable. This is the test of choice for fruit and vegetable allergens that are labile.

• IDT is used to follow-up SPT, particularly for drug allergy investigations.

Limitations

• If patients cannot stop their antihistamines, then blood tests may be the only way of diagnosis.

• It is advisable to avoid any form of skin testing in patients known to have had a severe systemic reaction to any of the proposed test agents. The small amount of allergen introduced during SPT may be enough to trigger a reaction in a susceptible individual.

Precautions. Several precautions should be observed during skin testing procedures.

a. Testing should be deferred during periods of symptomatic bronchospasm to prevent worsening of the clinical status.

b. Epicutaneous tests (scratch or prick tests) are done initially. This type of testing can detect the sensitive patient with minimal risk of systemic reaction.

c. Emergency treatment materials - syringes, and needles should be readily available to treat systemic reactions.

d. A trained technician or nurse may perform skin tests, but **a physician must be immediately available.**

e. The back is preferable for prick or scratch testing because its flat surface permits the performance of many tests.

Methods of skin testing
EPICUTANEOUS SKIN TESTS
Prick skin tests

1. Procedure. Cleanse the skin with isopropyl or 70% ethyl alcohol and allow it to dry by evaporation. Using a pen or inked stamp, mark future test sites 2 cm apart to prevent coalescence of positive test reactions. Every fifth site should be coded to recheck the test order. Then place a drop

of allergic solution at each mark, and insert a sterile 26-gauge needle, a sterile sewing needle, or a blood lancet through the drop into the superficial skin and withdraw with a slight lifting of the skin. Do not draw blood. Because blood lancets and sewing needles are not hollow, they can be simply wiped with sterile gauze after testing at each site. Alternatively, a fresh disposable needle can be used for each test site. After 15 to 30 minutes, observe the test sites for erythema and wheal formation. The average (greatest and smallest) or largest diameter of the wheal in millimeters should be noted and compared with controls. If a large wheal (> 15 mm) appears in less than 15 minutes, wipe the allergen solution from the test site.

2. Because stored **allergen solutions** lose potency within weeks to months, extracts, especially diluted preparations, **must be regularly renewed**. Most suppliers place a 2- to 3-year expiration date on concentrated allergen solutions. The half-life of an allergen solution decreases with increasing dilution and increasing temperature. Properly stored allergen solutions (2 to 8°C) at 1:100 dilution or stronger may maintain antigenicity up to 1 year, but more dilute (1:1000 or weaker) solutions may lose antigenicity in 2 to 6 months (less in very weak solutions).

3. A test using **diluent solution** alone (a **negative control**) should be included to assess skin reactivity to mechanical trauma. (This diluent is usually a phosphate-buffered physiologic saline at pH 7.4 with 0.4% phenol added to inhibit bacterial growth.)

4. If patients with **dermatographia** are detected, reactions greater than those in the control site may be considered positive.

5. A 0.1% **histamine solution** (histamine phosphate) can serve as a positive control. This histamine control aids in interpreting skin tests (a "standard" 3+ reaction) and demonstrates diminished or absent skin reactivity, which is commonly found in very young or very old patients or in patients taking medications such as antihistamines.

Scratch tests employ the same principles as prick tests but are less sensitive and more time consuming. There are, however, minor technical differences.

1. After the skin is cleansed and marked, a 2-mm skin scratch without bleeding is made with small scalpel, needle, or punch scarifier.

2. The test controls and allergen solutions are aseptically dropped onto and gently rubbed into the scratch areas, using a clean toothpick for each allergen.

3. Allergen solutions are wiped off and reactions read after 15 to 30 minutes.

The epicutaneous method has many advantages. It is easy and safe to perform and causes little discomfort. It is inexpensive, and test solutions are stable because they are suspended in 50% glycerine. Positive epicutaneous tests correlate well with clinical symptoms (Table 3-4).

Table 3-4. Advantages of epicutaneous versus intracutaneous

Epicutaneous	Intracutaneous
Easy to perform	More reproducible
Safe	More sensitive
Little discomfort	
Inexpensive	
Stable test solutions	
Correlates well with symptoms	

One possible disadvantage to this method is that it can result in false-negative reactions due to a lack of sensitivity (Table 3-5).

Table 3-5. Disadvantages of epicutaneous versus intracutaneous

Epicutaneous	Intracutaneous
Less sensitive	More time consuming
	More difficult to perform
	More discomfort
	Increased risk of systemic reaction
	More false-positive result

INTRACUTANEOUS SKIN TESTS

Following scratch or prick testing, intradermal skin testing is done to allergens that did not elicit clearly positive reactions. Because intradermal skin testing employs a larger antigen challenge than does scratch or prick testing (between 100-fold and 1000-fold, depending on the concentration of antigens), marked local or systemic reactions can occur if intradermal testing is performed with the same antigens that produced positive prick or scratch reactions. In patients with five or less positive epicutaneous skin tests, intradermal tests can be done immediately following the reading of scratch or prick tests. If the number of positive epicutaneous tests is large, intradermal tests should be deferred to another day. In sensitive patients it is best to divide cross-reactive groups (especially grasses) into separate testing sessions since many strongly positive reactions may yield systemic symptoms. Careful antigen selection correlated with the geographic area and history will minimize the number of tests.

Intracutaneous skin tests are more reproducible than epicutaneous tests and are 100 to 1000 times more sensitive. Thus, they are associated with fewer false-negative reactions. The drawbacks to intradermal tests are that they are time consuming and tedious to perform and are often associated with discomfort and an increased risk of systemic reactions. Even more important, they are more likely to produce false-positive results because of their increased sensitivity. Mildly positive intradermal reactions are not considered clinically relevant.

The sequential steps in intradermal testing are as follows:

Use a 1:500 or 1:1000 (weight to volume) dilution of allergen, a 0.01% histamine base solution (histamine phosphate) as a positive control (3+ reaction), and a buffered saline diluent as a negative control.

The upper half of the volar surface of the forearm and the lateral aspect of the upper arm are choice test sites. The skin of the back may be used. This site precludes the use of a tourniquet in case of systemic reactions. Intradermal skin testing in young children (2-5 years of age) is easier on the back because tests can be applied with better control than on a moving arm.

With the patient comfortably positioned, cleanse the skin and mark test sites approximately 2.5 cm apart.

Fill sterile plastic disposable 1-ml tuberculin syringes with approximately 0.1 ml of test solution. To avoid misleading "splash" reactions from injected air, **expel all air bubbles.**

Stretch the skin taut and introduce the needle into the skin at a **45-degree angle** with the bevel facing **downward.** Advance the needle until the entire bevel of the needle is into the skin.

Inject the smallest amount of allergen solution that will raise a 1- to 3-mm wheal (approximately **0.02 ml** of solution). If no wheal forms immediately after injection (either the needle is too deep, with subcutaneous fluid injection or too superficial, with a fluid leak), withdraw the needle and repeat the injection at a different site.

Read the skin test reactions after 15 to 30 minutes. Measure the size of the erythema and the size of the wheal with a millimeter ruler. As in scratch or prick tests, this may be done by measuring the greatest and smallest diameter of each reaction and taking the average. Alternatively, only the greatest diameter can be used. **Pseudopods** (protrusions from the wheal) should be noted. A helpful method of measuring wheal size is to stretch the skin taut between the fingers. The wheal will appear as a definite blanched central area that can be easily measured.

TEST RESULTS

The value of skin tests, like that of any diagnostic procedure, depends on the knowledge of their interpreter. To be informative, the tests must be related to the clinical context of the patient's history and physical examination. The selection of antigens and the administration of tests require

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experience and knowledge. The physician must be aware of the many reasons for false-positive and false-negative reactions to properly interpret test results.

False-Negative Results
Several circumstances may account for negative skin test results in a patient who truly has an IgE-mediated allergic disease (Box 3-1).

Box 3-1. Reasons for false-negative skin test results
Improper storage of antigen
Improper administration
Inherent host factors
- Age
- Skin area
- Time of day
- Skin temperature

Refractory period
Inhibiting drugs

The antigen in solution - a protein - if improperly stored may lose potency with time or exposure to heat, thereby causing a false-negative result. Antigen solutions must be refrigerated and replaced at appropriate intervals.

A false-negative result may also occur due to the improper administration of a test. Too superficial a scratch or prick of the skin or too deep an intracutaneous injection will prevent the allergen solution to reach the skin area in which mast cells are located.

The patient's age must also be considered when a skin test result is negative. In general, the skin of infants and elderly persons is less reactive than that of other age groups. In the same individual, the skin on the forearm is less reactive than the skin on the back, and responsiveness is lower in the early morning than later in the day.

The refractory period of a test may also contribute to a false-negative result. Soon after a systemic reaction to an allergen, such as insect venom, penicillin, or food, the patient enters a refractory period during which a skin test reaction to that substance may be negative. The reason is that specific IgE is consumed by the severe allergic reaction, so a 3- to 4-week period is needed for the allergic antibody to build back up to its prereaction levels. Therefore, if a patient has a systemic reaction to an allergen, it is best to wait a full 4 weeks before performing skin tests.

As sensitization is dependent on circulating IgE reaching the mast cells at the test site, it is possible, where the allergic reaction is highly localized, to get negative results, as insufficient IgE is present in the circulation.

Finally, a number of drugs, particularly antihistamines, may inhibit skin reactivity and therefore should be discontinued at least 72 hours before skin testing. Whenever a skin test is performed, histamine should be included as a positive control. If the histamine skin test is negative, further testing should be deferred. A more complete list of drugs that can inhibit immediate skin reactivity is provided in Box 3-2.

Box 3-2. Drugs that may inhibit immediate skin test reactivity
- All H1-blocking antihistamines
- Ranitidine
- Amitriptyline
- Desipramine
- Nortriptyline
- Imipramine
- Protriptyline
- Trimipramine
- Triavil

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Corticosteroids, theophylline, cromolyn, leukotriene modifiers, beta agonists, and decongestants are not presently known to be inhibitory.

False-Positive Results
When a skin test is positive in the face of a negative clinical picture, several explanations may be offered (Box 3-3).

Box 3-3. Reasons for false-positive skin test results
- Improper preparation and administration of allergen solution
- Nonspecific histamine release
- Dermographism
- Remnant of past sensitivity
- Harbinger of future sensitivity
- Disparity with clinical sensitivity

Many factors contribute to the production of nonspecifically irritating skin test solutions. Deviation from a physiologic pH or from the correct osmolarity may cause a false-positive skin test result. Extracts may contain low-molecular-weight irritants, and it is necessary to dialyze these materials before utilizing them as skin testing agents. Glycerine, commonly used as a preservative in allergy extracts, causes nonspecific irritation at a concentration of 6% if injected intradermally. Injecting too large a volume of extract intradermally may also cause false-positive reactions. The optimal injection volume is 0,02 ml.

Allergen solutions to a wide range of allergens are available commercially from several manufacturers. They should be checked regularly to see that they are still within date. False-positive tests may often be found to food allergens, although the rate is lower with SPT than IDT. Where commercial food allergens give an unexpected false-negative, use of the fresh food may be possible. Where no commercial antigens are available, direct SPT (prick to prick) with allergens such as foods may be desirable. This is the test of choice for fruit and vegetable allergens that are labile.

Materials that are urticariogenic may cause a wheal and erythema skin test response in all subjects on a non-IgE-mediated basis. Examples are morphine and codeine. Some food extracts, particularly those from cheese, have a high histamine content and I may cause false-positive reactions.

Dermographism also may be responsible for a false-positive test result. It is present in 5% to 20% of the population, depending on the degree of pressure applied. Skin testing should also include a negative saline control to ensure that the patient is not dermographic. A positive response to saline obviously makes other positive skin test reactions suspect.

Positive skin test reactivity may persist in an individual whose clinical sensitivity has disappeared either spontaneously or through the use of immunotherapy. Additionally, false-positive results are often harbingers of future sensitivity. The risk of developing an allergic condition is considerably greater for individuals with positive skin test results.

Perhaps the most important reason for the false-positive skin test reaction is the physician's failure to recognize that a positive skin test is not necessarily an indicator of clinical sensitivity.

PRINCIPLES OF PATCH TESTING
The purpose of patch testing is to identify type IV hypersensitivity, usually in the context of contact hypersensitivity to environmental agents.
- As for skin-prick testing, an area of normal skin is required: the upper and mid zone of the back is usually appropriate.
- Allergens are made up in petrolatum jelly or in aqueous solution on a filter paper and applied under occlusion in a small metal chamber (Finn chamber), which is secured firmly to the back with hypoallergenic tape.
- Chambers are left in place for 48 hours and the patients are told not to wash the area.

• When the chambers are removed, the application areas are inspected for erythema, vesiculation, and evidence of cellular infiltrate.

There may be false-positives at this stage due to reactions of types I and III.

The sites should be re-read at 72-96 hours.

False-positive reactions at 48 hours will have disappeared on the later reading.

• It is usual for a standard panel to be used in the initial screen, unless there are clear indications of the most likely allergens (e.g. through the occupation and exposure history, site of eczema, etc.). Standard panel will include metals (nickel, chromium), preservatives, fragrances, rubber mix, lanolin, formaldehyde, balsam of Peru, and colophony.

• Where there are positive reactions to one of the mixed reagents (rubber mix, fragrances) there are usually supplementary panels of the individual ingredients.

• If the patient is exposed to an unusual substance, then it or its contents may be made into extemporaneous patch tests, provided that appropriate safety data can be obtained from the manufacturers.

• Some allergens only cause reactions when there is concomitant exposure to sunlight. This can be reproduced in the clinic using a photopatch test.

Here duplicates of each allergen are applied and, after 14-48 hours, one of the pair is taken off and the back exposed to UV-A light (10 joules).

The other one of the pair is then taken off and the sites read as for an ordinary patch test.

The unexposed member of the pair serves as the control.

Indications for testing

Contact eczema or dermatitis.

Tests are only appropriate for delayed hypersensitivity (type IV).

Patch testing for drugs may be valuable where reactions are atypical and delayed.

Interpretation

•Results can be roughly graded as:

0, no response;

1+, erythema and oedema;

2+, erythema, papules, and small vesicles;

3+, marked erythema, induration, and large blisters;

•Grades 2+ and 3+ are positive.

•Antihistamines have no effect on the responses, but topical steroids applied to the sites of application or systemic steroids will significantly reduce or abolish the responses.

F. PROVOCATIVE CHALLENGE TESTING

The skin test and measurement of total serum IgE and specific IgE antibody levels in the serum are indirect assays of an allergic state. Direct challenge, either by inhaling or ingesting antigens may be of greater diagnostic use. It is wise to avoid challenging someone who has had a severe systemic reaction, or who has pre-existent severe asthma, with allergens. Challenge tests are potentially dangerous and should be carried out by experienced staff prepared to deal with any adverse reactions that may arise. Informed consent should always be sought from the patient prior to the test.

In addition to the antigen challenge, the general hyperresponsive state of the airway associated with asthma may be evaluated by exercise or by inhalation of chemical substances to which asthmatic individuals are more sensitive than are nonasthmatics.

NONSPECIFIC TESTS

Exercise

Physical exercise is a major precipitant of bronchial asthma. The diagnosis of asthma can usually be made after 6 to 8 minutes of exercise and pre- and postpulmonary function testing (Fig. 3-1).
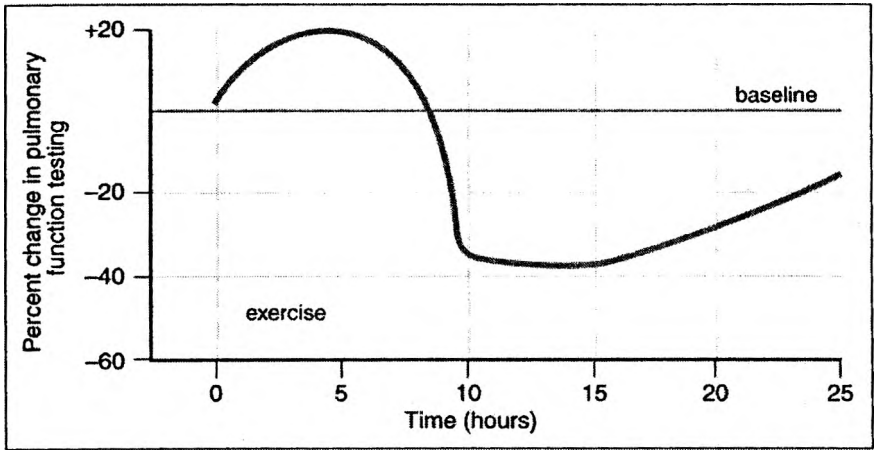
Figure 3-1. A classic response in exercise-induced asthma.

Initially, the patient exhibits a bronchodilation effect, along with an increase in the forced expiratory volume in one second (FEV_1). In the patient with exercise-induced bronchoconstriction, 6 to 8 minutes of exercise is generally followed by a 20% or greater fall in FEV_1.

Bronchial Challenges

Asthma is characterized by enhanced bronchial hyperreactivity. This hyperreactivity can be manifested clinically by the asthmatic's adverse response to cold air, cigarette smoke, fumes, weather changes, and other stimuli that have little or no effect on a non-asthmatic patient. In the doctor's office setting, hyperreactivity can be demonstrated by the patient's response to a bronchial challenge, such as the inhalation of methacholine or histamine (Fig. 3-2).
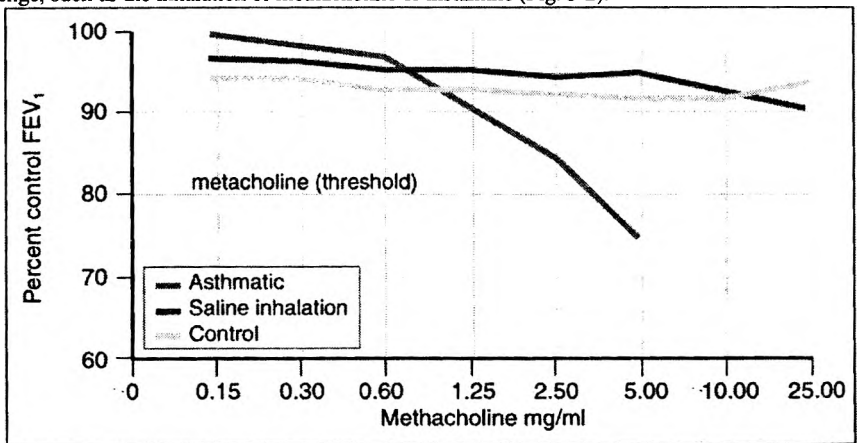

Figure 3-2. The effect of methacholine inhalation on an asthmatic patient. The asthmatic subject shows a greater than 20% fall in FEV_1 after inhalation of methacholine 5 mg/mL. Saline inhalation results in no change in FEV_1. A control patient inhales methacholine through a concentration of 25 mg/mL and shows no change in FEV_1.

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A greater than 20% fall in FEV_1 after the inhalation of a methacholine solution at a concentration of less than 25 mg/mL is indicative of a positive response.

SPECIFIC TESTS

Bronchial Challenges

Specific airway reactivity can be assessed by measuring the patient's bronchial response to the inhalation of certain allergen solutions. There is evidence that skin test results generally correlate well with bronchial-provocation test results. Therefore, bronchial-challenge testing with specific allergens is generally not necessary in everyday practice. There may be special instances, however, such as with occupational asthma, or in investigative work when specific bronchial-challenge testing is indicated. Several bronchial responses have been documented after the inhalation of antigen solutions. Figure 3-3 illustrates the immediate, dual, and late-phase responses that are seen.
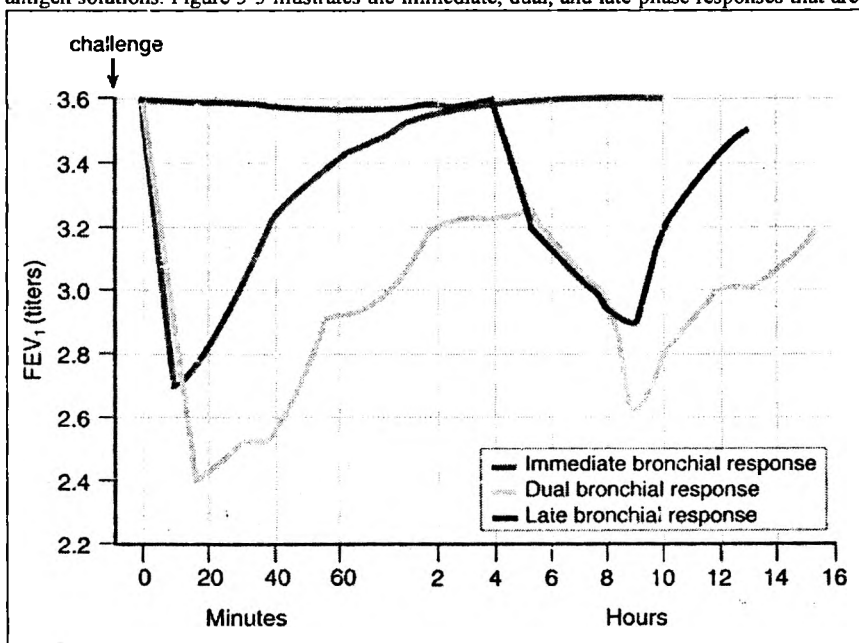
Figure 3-3. The different patterns of bronchial response after a bronchial challenge.

The "classic" asthmatic response to inhaled allergens had been thought to be immediate, occurring in all cases within minutes, but it is now estimated that approximately 50% of allergic asthmatics demonstrate a dual immediate and late-phase response (may occur 6-8 hours after the challenge): the patient must be kept under observation for this period. An isolated late-phase bronchial response is seen largely in instances of occupational asthma.

Pretreatment with different medications may alter the bronchial responses to antigen inhalation. Beta agonists block the late reaction but have no effect on the immediate response, and pretreatment with cromolyn inhibits both bronchial responses.

Enthusiasts may carry out endobronchial challenge through a bronchoscope, which allows them to observe the changes in the bronchial mucosa and also to carry out bronchoalveolar lavage to look at the release of mediators and the cellular response. This is important in research but not for routine diagnosis.

Nasal Challenges

Inhaled antigen solutions can also be used to challenge the nasal mucosa, to diagnose allergic rhinitis. Usually performed by spraying a diluted solution (1:1000 of SPT solution) of the test allergen into one nostril, while spraying a similarly diluted solution of the buffer only into the other nostril.

Patient's symptoms are recorded (running nose, sneezing, itching eyes, etc.) and the nasal mucosa inspected for signs of inflammation and oedema. Each nostril is inspected.

The response can be gauged by the measurement of nasal airway resistance through anterior or posterior rhinomanometry or by changes in the cellular or mediator content of the nasal mucus. The nasal challenge technique is useful in studying the pathophysiology of the nose, the action of drugs, and instances of occupational rhinitis.

Oral Challenges

In instances when a suspected allergen is ingested, an oral challenge can be performed. The challenge can be open, in which case both the physician and the patient know the content of the substance ingested; single blind, with only the doctor knowing the content; or double blind, with neither the patient nor the physician knowing the content of the challenge. The food or drug can be administered either whole or in a lyophilized preparation contained in an opaque capsule.

Oral challenges serve several purposes. First, double-blind, placebo-controlled food challenges (DBPC) have proven useful in discerning IgE-mediated food sensitivities. Second, oral challenges can also help diagnose sensitivity to ingested substances, such as aspirin or sulfites, in which the sensitivity is not on an IgE basis. In such instances, skin testing or measurement of serum specific IgE levels would be of no use.

For open incremental food challenge, incremental doses of food are given at 15 minute intervals, with monitoring of BP, PEFR, and symptoms before each increment. Steps are: food on lip (may be omitted), 1%, 4%, 10%, 20%, 20%, 20%, 25% of a normal portion (this may be variable!). Over the course of the challenge, 100% of the normal portion size is administered.

Where multiple foods are suspected, an oligoallergenic (elimination) diet may be instituted for a period to see whether symptoms remit. If symptoms persist, food allergy/intolerance is not the cause.

If symptoms improve, foods may then be reintroduced as open challenges one at a time and the patient's symptom response noted. This should ideally be followed by a DBPC challenge where the patient, on an oligoallergenic diet is challenged with the suspect food concealed in opaque gelatin capsules, interspersed with identical capsules containing an innocuous substance, in a random sequence, determined by the dietician but unknown to the patient and doctor.

This is time-consuming, as some food allergic symptoms may require exposure for several days before they appear and, equally, may take several days to disappear when the food is withdrawn. There needs to be a wash-out period between the placebo and the active capsules.

Injections

A naturally occurring injection in the form of a *Hymenoptera* family insect sting has been carried out at some medical centers. This has been performed to determine whether a preceding course of immunotherapy with venom of that particular insect had been successful. At present, this is an experimental technique that should only be performed under the most carefully controlled conditions.

Drug allergy testing

• Type I reactions are investigated by skin prick and intradermal testing.

Some drugs are irritant and provoke non-specific reactions on intradermal testing.

Some drugs (opiates, radiocontrast media) cause direct histamine release from mast cells.

• There is only a limited range of tests available for in vitro testing for IgE to drugs; many of the drug allergens are unvalidated in clinical practice.

• Flow cytometric assays of basophil degranulation/activation are available, but appear to correlate poorly with SPT/IDT testing.

• Type IV reactions are investigated by patch testing.

- Reactions of types II and III are more difficult to investigate.
- Open and blinded challenge tests may be appropriate for atypical reactions.

!Patients with Stevens-Johnson reactions must not be tested— reactions may be severe.

- Testing is time-consuming.
- The table 3-6 shows starting concentrations and usable dilutions for SPT and IDT.

Table 3-6. Starting concentrations and usable dilutions for SPT and IDT

Drug	SPT at dilution			IDT at dilution		Comment
	1/10 mg/ml	Neat mg/ml	1/1000 µg/m	1/100 µg/ml	1/10 µg/ml	
Quaternary ammonium compounds						
Succinylcholine (suxamethonium)	5 mg/ml	50 mg/ml	50 µg/ml	—	—	Irritant IDT >1/1000
Benzylisoquinolones						
Atracurium	1 mg/ml	10 mg/ml	10 µg/ml	—	—	Irritant IDT >1/1000
Cisatracurium	0.2 mg/ml	2 mg/ml	2 µg/ml	20 µg/ml	200 µg/ml	
Mivacurium	0.2 mg/ml	2 mg/ml	2 µg/ml	—	—	Irritant IDT >1/1000
Galtamine	4 mg/ml	40 mg/ml	40 µg/ml	400 µg/ml	—	
Doxacurium*						
Aminosteroids						
Pancuronium	0.2 mg/ml	2 mg/ml	2 µg/ml	20 µg/ml	200 µg/ml	
Vercuronium	0.4 mg/ml	4 mg/ml	4 µg/ml	40 µg/ml	400 µg/ml	
Rocuronium*	1 mg/ml	10 mg/ml	10 µg/ml	100 µg/ml	—	
Rapacuronium						
Local anaesthetics						
Articaine	1 mg/ml	10 mg/ml	10 µg/ml	100 µg/ml	1000 µg/ml	
Bupivacaine	0.25 mg/ml	2.5 mg/ml	2.5 µg/ml	25 µg/ml	250 µg/ml	
Citanest with Octapressin	3 mg/ml	30 mg/ml	30 µg/ml	300 µg/ml	3000 µg/ml	
Lignocaine	1 mg/ml	10 mg/ml	10 µg/ml	100 µg/ml	1000 µg/ml	
Pritocaine	0.5 mg/ml	5 mg/ml	5 µg/ml	50 µg/ml	500 µg/ml	
Procaine	1 mg/ml	10 mg/ml	10 µg/ml	100 µg/ml	1000 µg/ml	
Induction agents						
Etomidate	0.2 mg/ml	2 mg/ml	2 µg/ml	20 µg/ml	200 µg/ml	
Propofol	1 mg/ml	10 mg/ml	10 µg/ml	100 µg/ml	—	Irritant IDT >1/100
Thiopental	2.5 mg/ml	25 mg/ml	25 µg/ml	250 µg/ml	2500 µg/ml	
Analgesics						
Alfentanil	50 µg/ml	500 µg/ml	—	—	—	Mast cell degranulator
Fentanyl	5 µg/ml	50 µg/ml	—	—	—	Mast cell degranulator
Morphine	1 mg/ml	10 mg/ml	—	—	—	Mast cell degranulator
Pethidine	5 mg/ml	50 mg/ml	—	—	—	Mast cell degranulator

* - Information not available. Based on information collated by Dr. Mansour Karadsheh.

• Open drug challenge uses incremental doses:

1%, 4%, 10%, 20%, 20%, 20%, 25% of a standard oral dose at 15-minute intervals, with observation of BP, PEFR, and symptoms before each incremental step.

Over the period of the challenge, the challenge administers 100% of the normal dose.

Indications for testing

• Suspected drug allergy, where testing will alter clinical management.

• Do not test where there are readily available and safe alternatives (i.e. do not test all 'penicillin-allergic' patients).

Interpretation

• Interpretation of testing requires the demonstration of wheal and flare. Reactions to drugs will usually be much smaller than the typical reactions on SPT/ID to inhalant antigens. Photographing the results for the medical records is desirable.

• Knowledge of irritant concentrations is required. This may require testing on non-atopic volunteers.

• Clear goals are required for testing:

testing to prove causality;

testing to prove safety of alternative drugs.

• Information must be provided to patient as well as referring doctor (and GP if referred by other specialist).

• Advice to patient on the use of medical alert bracelets may be required.

Limitations

• Preparation of drug dilutions is time-consuming: assistance from pharmacy is required. Preparation of dilutions in clinical areas is not recommended.

• Where testing is carried out with controlled drugs, appropriate steps must be taken to account for receipt and disposal of the drugs, according to local regulations.

G. Passive cutaneous transfer testing

Passive cutaneous transfer testing (Prausnitz-Kustner [P-K] testing), now more of historical interest, provided the first demonstration of a substance (reagin) in the serum of allergic persons that is capable of sensitizing the skin of nonallergic persons. In the past, P-K testing was used in patients with dermatographia or generalized skin eruptions. Currently, it is impractical even in these selected patients because in vitro testing for specific IgE antibodies (radioallergosorbent test [RAST]) provides the same information without the risk of transferring serum from one person to another. If P-K testing is done, the donor serum must be screened for the presence of hepatitis B antigen-antibody and for syphilis. The P-K test involves the following: Inject allergic serum (0.1 ml) intradermally into a carefully marked site on the forearm of a nonallergic person. After 24 to 48 hours this site is challenged with intradermal allergen (0.02 ml) and observed for an immediate positive wheal-and-flare response not present on the control site.

H. In vitro tests of antigen-specific IgE

In vitro allergy tests do not substitute for clinical history-taking, examination, and direct patient testing (SPT, patch tests, challenges).

Allergen-specific IgE

• Units: 1 IU/ml = 1 kU/l.
• Range:

<0.35 IU/ml	=	RAST score 0;
0.35-0.70 IU/ml	=	RAST score 1;
0.70-3.50 IU/ml	=	RAST score 2;
3.50-17.5 IU/ml	=	RAST score 3;
17.5-50.0 IU/ml	=	RAST score 4;
50.0-100 IU/ml	=	RAST score 5;
>100 IU/ml	=	RAST score 6.

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Principles of testing
* Detection of allergen-specific IgE in the blood is by sensitive RIA, EIA, or fluorescent assay. There are numerous acronyms for this process, depending on the method (RAST, MAST, FAST tests).
* Radioimmunoassay is now little used.
* Principles of all the tests are identical, with allergen bound on to a solid phase that is then incubated with a labelled anti-IgE antibody.
* Pharmacia Unicap/immunocap system is most widely used system in the UK.
* Tests are expensive due to costs of purification and standardization of allergen.
* CE marking requirements have reduced the number of commercially available allergens.
* EQA and international standards are available.

Indications for testing
* Skin prick testing remains the gold standard.
* *In vitro* EIA assays may be used on patients with a high risk of anaphylaxis (SPT contraindicated), on drugs that interfere with SPT (antihistamines, calcium channel blockers, antidepressants), or with extensive skin disease, and on small children.
* Patients with a total IgE <20 kU/l have a low (but not zero) probability of having positive specific IgE tests.

Interpretation
* The assays are carried out quantitatively and reported in units.
* It is more usual for the results to be graded on a scale of 0-6, where 0-1 represent no or minimal specific IgE and 2-6 represent increasing levels of positivity.
* RAST scores of 0 and 1 are usually considered to indicate a negative result.
* High total IgE levels (>1000 kU/l) may cause false-positive tests for allergen-specific IgE, due to non-specific binding of IgE to the solid phase: this is less common with newer systems, but applies particularly to food allergens.
* Units are standardized against an international standard for birch pollen allergen, but this cannot validly be applied to reactions with other allergens.
* Attempts are being made to standardize allergens in terms of defined proteins and protein nitrogen. With a potentially limitless list of allergens, this is a slow process.
* The important clinical implication is that the detection of a grade 3 response to two different allergens does not indicate that the same amount of IgE is present against both and that equivalent clinical reactions might be expected.
* There is no close relationship between the grade and the severity of reactions (either past or future).
   * The presence of allergen-specific IgE is a marker only of exposure. Positives may be detected where there is no evidence of any clinical reaction.
   * Levels will fall with time if the offending allergen is avoided over a long period, so low or negative results may be obtained even with sensitized patients.
* As with skin-prick tests, if the allergic reaction is highly localized, there may be insufficient spill-over of specific IgE into the circulation to be detected, leading to a false-negative.
* Results must always be interpreted in the light of the clinical history (blood tests are not a substitute for proper history-taking!).

Limitations
* Few allergens are available for robustly identifying IgE to drugs.
* Reagents for penicillin contain major but not minor determinants: a negative result does not exclude significant allergy, and SPT and IDT are required with a minor determinant mixture.
* Reagents for labile food allergens such as fruits are unreliable: use SPT with the fresh fruit.
* If there is a good history for type 1 food allergy and an unexpected negative result, consider SPT with fresh food.
* 15% of NRL-allergic patients will be negative by specific IgE testing.

Churg-Strauss syndrome (acute active disease).
• Synovial fluid levels are increased in:
rheumatoid arthritis;
ankylosing spondylitis.
• Urine levels are increased by carcinoma of the bladder. CSF levels are increased by malignant but not benign tumours. Levels correlate with the degree of underlying inflammation. Assay requires timed separation of samples, although the assay itself uses very similar methodology to that used for detecting allergen-specific IgE.

ECP may be released during the coagulation process.

This significantly limits the usefulness of the test.

Eosinophil count
• Units: cells x 10^9/L
• Normal range:
Newborn, $<0.85 \times 10^9$/l;
Children 1-3 years, $<0.70 \times 10^9$/l;
Children >3 and adults, $<0.44 \times 10^9$/l.

Principles of testing Routinely on the newer automated haematology counters, which are capable of providing a five-part differential. Where older counters are used, an additional manual differential with special stains may be required.

Indications
Allergic disease, including drug reactions;
Lymphoma;
Vascutitis;
Pulmonary infiltrates;
Parasitic infection.

Interpretation
• Raised eosinophil counts are not specific for allergic disease; counts >10 x 10^9/l are not due to allergy or parasitic disease.
• Moderate elevations are seen in:
parasitic infestations;
drug reactions;
lymphoma (especially Hodgkin's lymphoma);
after radiation therapy;
vasculitides (Churg-Strauss vasculitis, polyarteritis nodosa);
dermatitis herpetiformis;
primary immunodeficiencies (Omenn's syndrome, materno-fetal engraftment);
hepatic cirrhosis.
• Exceptionally high eosinophil counts are seen in:
• larva migrans;
• hypereosinophilic syndromes;
• severe vasculitis (CSS, PAN) and occasionally in lymphoma and cirrhosis.

Eosinophil count is reduced by acute infection, stress, fasting for more than 24 hours, and by corticosteroids.

Examination of nasal and conjunctival secretions for the presence of eosinophils may provide confirmatory evidence for an allergic cause for local symptoms.

Eosinophilia of nasal secretions may be seen in non-allergic rhinitis (non-allergic rhinitis with eosinophils—NARES).

Flow-CAST® and CAST-ELISA®
These commercial assays rely on activation of basophils either directly or via specific IgE in the patient's serum.

CAST-ELISA® measures the release of sulphidoteukotrienes by activated basophils by EIA.

Assay is extremely slow and time-consuming and is impractical for a busy diagnostic laboratory.

The Flow-CAST® uses flow cytometry to identify basophils, labelled with anti-IgE-FITC, and then anti-CD63-PE, a marker of activated basophils, which identifies basophil degranulation.

Manufacturer provides an array of specific allergens including food additives and drugs.

Both assays work well for normal inhalant allergens, but appear less useful for drugs and additives.

Modification of the Flow-CAST® assay using anti-CD203c in place of anti-CD63 improves the characteristics of the assay.

Results for drug allergens compare poorly with those from IDT.

The assays cannot therefore be recommended as a non-invasive way of testing for drug allergy.

Assays are more expensive and labour-intensive than standard EIA for routine inhalant allergens.

Histamine-release assays

In vitro release of histamine by basophils in response to stimulation by cytokines or by allergens is a complex test. Measurement of free histamine is required (difficult as it is labile in serum/plasma).

Assays are of value in the research setting. In the clinical setting assays have been used for investigating the histamine-releasing properties of certain drugs. Like all bioassays, they suffer from difficulties in standardization.

Immunoglobulin E (total IgE)

. Units: kU/l.

• Normal ranges:

. age <1 year,   <11 kU/l;
. age <2 years,   <29 kU/l;
. age 2-3 years,   <42 kU/l;
. age 4-5 years,   <52 kU/l;
. age 6-7 years,   <56 kU/l;
. age 8-10 years,   <63 kU/l;
. age 11-12 years,   <45 kU/l;
. age 13-14 years,   <70 kU/l;
. age >14 years,   <100 kU/l.

Principles of testing

• Usually the same as for allergen-specific IgE (RIA, EIA).

• Some nephelometers have the capacity to run total IgE.

Indications for testing

• Allergic disease (as screen for atopic tendency).

• Lymphoma.

• Vasculitis (Churg-Strauss vasculitis).

• Primary immunodeficiency.

• Myeloma.

Interpretation

• Measurement of total IgE may be helpful in diagnosing allergic disease.

• Normal range is very wide and levels correlate poorly with clinical disease.

• High level of specific IgE to a single allergen may occur with a total IgE within the 'normal' range.

• In asthmatic patients, a level of >150 kU/l is suggestive of an allergic basis, while a level <20 kU/l is very much against it The severity of asthmatic symptoms correlates very poorly with total IgE (but better with eosinophil count).

• In the investigation of dermatitis, a level of >400 kU/l is usual while a level of <20 kU/l is against atopic dermatitis.

• Very high levels of IgE are seen in atopic eczema, allergic bronchopulmonary aspergillosis (ABPA), parasitic infections (larva migrans, hookworm, schistosomiasis, and filariasis), lymphoma (especially Hodgkin's disease), and liver disease.

• Levels may be elevated in EBV infection, the Churg-Strauss syndrome, systemic sclerosis, and bullous pemphigoid, although this is a poor marker of disease activity.

• Some primary immunodeficiencies are associated with raised IgE, such as Wiskott-Aldrich syndrome and Omenn's syndrome.

• Highest levels are seen in the hyper-IgE syndrome (Job syndrome, Buckley's syndrome): here levels frequently exceed 50 000 kU/l, a level rarely, if ever, seen in atopic disease.

• IgE myeloma is exceedingly rare: diagnosis will have been made on electrophoresis and immunofixation.

• Levels are often higher in Asians, although it is not clear whether this is just due to a higher risk of parasitic diseases.

Limitations

• Specific IgE testing becomes inaccurate with very high levels of IgE (>1000 kU/l), due to non-specific binding.

• Conversely, where the total IgE is very low, it is not useful to perform tests for specific IgE.

Serial monitoring

• Justified in ABPA (a rise in the level of IgE precedes relapse, and the level falls with appropriate therapy).

• Justified in Churg-Strauss syndrome (responds to therapy).

IgE autoantibodies/IgE **receptor antibodies**

• These have been reported in patients with allergic problems.

• Antibodies to the IgE receptor have been reported as a possible cause of chronic urticaria, although the evidence is very weak.

• Routine assays are not available at present and the clinical utility needs to be confirmed in further studies.

IgG to food allergens

• IgG antibodies to food allergens are available (UniCAP$^®$/ImmunoCAP$^®$).

• It has been suggested that these may be valuable in the investigation of irritable bowel syndrome (IgG to wheat, milk).

• IgG to food allergens occur frequently in healthy individuals, especially against bovine, ovine, and porcine proteins.

• Clinical value remains to be determined.

Mast cell tryptase

• Units: µg/l.

• Normal adult range: 2-14 µg/l.

Sample Serum, preferably on several occasions within a 24 hour period after an acute reaction (tryptase is stable in serum).

Principles of testing Measured by Pharmacia UniCAP$^®$ system (EIA). **Indications for testing**

• Confirmation of mast cell degranulation (is a specific marker of mast cell granules).

• Investigation of atypical 'allergic' reactions.

Interpretation

• Does not distinguish between anaphylactic and anaphylactoid reactions.

• Relatively stable in serum, being catabolized in the liver with a half-life of approximately 3 hours.

• Levels may be significantly raised for 24 hours after an acute reaction involving mast cell degranulation.

• Good correlation between plasma histamine and mast cell tryptase makes mast cell tryptase the preferred marker for mast cell activation.

• Persistently elevated levels may be seen in patients with urticaria pigmentosa and systemic mastocytosis.

• Elevated levels may also be detected in nasal and bronchial lavage fluids after allergen challenge.

• In order to assess the significance of a result taken during an acute reaction in a given patient, it is important to have a sample taken when the patient has fully recovered.

Thromboxanes and prostaglandins

• Assays of these short-lived mediators are available in the research setting but do not have much applicability to the routine management of allergic problems at the present time.

• Assays are usually by RIA.

Urinary methyl histamine

Histamine release from mast cells is a key feature of acute severe allergic reactions.

It is rapidly cleared destroyed in the circulation: measurement of free histamine is therefore difficult and limited to research settings.

The urinary metabolite, N-methyl histamine, is stable and is therefore useful in determining whether mast cell degranulation has taken place in an acute reaction.

The commercial assay and consequently the routine clinical service from the Supra-Regional Protein Reference Units has been withdrawn.

Mast cell tryptase is available as an alternative.

Renal function must also be known to evaluate results.

Venom-specific IgE and IgG

Measurement of specific IgE to bee and wasp venom is an essential investigation in suspected insect-sting allergy.

This is carried out as for other allergen-specific IgE tests.

Negative results may occur with the *in vitro* assays.

SPT with incremental concentrations of venom may be required.

Incremental SPT for bee and wasp can be carried out with solutions of 10, 100, and 300 µg/ml. IDT with diluted venom may occasionally be required.

10-fold steps from 0.0001 µg/ml to 1 µg/ml.

Measurement of venom-specific IgG may be helpful in determining the success of desensitization.

I. Pulmonary function testing

1. Measurement of pulmonary function is employed in patients with allergic pulmonary disease to aid in the differential diagnosis of obstructive airway disease, to evaluate bronchial challenge objectively, and to determine the clinical severity and monitor the results of therapy. Although complete spirometry before and after the use of bronchodilators is performed initially, a simple measurement such as peak expiratory flow rate or forced expiratory volume at 1 second is used to follow patients routinely. Arterial blood gases are the best guides to gas exchange abnormalities. In severe asthma they should be assessed frequently to predict the onset of respiratory failure.

2. Spirometric measurements of nasal airflow and resistance are technically difficult and are not commonly employed in clinical practice.

J. X-ray examinations

1. X-ray examination of the chest is indicated during the initial evaluation of allergic pulmonary disease. The chest x-ray film in asthma is usually normal; accentuation of the bronchovascular markings, thickening of the bronchi on end, or hyperinflation may be noted in patients with chronic disease. During acute exacerbations, an x-ray can exclude complications such as pneumonia, atelectasis, or pneumothorax.

2. Tomography and, in selected cases, **bronchography** are helpful in patients with suspected bronchiectasis or other lesions not revealed by routine chest radiography.

3. Sinus x-rays are indicated for suspected acute or chronic sinusitis, a common complication of upper respiratory allergy.

K. Miscellaneous studies

1. Urinalyses and serum chemistries are usually normal in atopic patients.

2. Stool specimens should be examined for **ova** and **parasites** in cases of unexplained urticaria, eosinophilia, or elevated serum IgE. A **duodenal** or **small-bowel aspirate** can uncover parasitic infestation in a patient with negative stool findings (e.g., giardiasis).

3. The erythrocyte sedimentation rate is normal in uncomplicated atopic disease. An elevated rate suggests an alternative or additional diagnosis or infectious complications.

4. Alpha-antitrypsin level and phenotype should be assessed in patients showing irreversible obstructive airway disease.

5. Serum quantitative immunoglobulins, especially IgA, can be deficient in patients with symptoms suggestive of allergy. In immunodeficiency, however, wheezing is not usually the predominant presenting symptom.

6. Quantitative sweat chloride test values are elevated in cystic fibrosis, a disease primarily affecting children but occasionally seen in adults. Symptoms of poor growth, chronic pulmonary infection, and malabsorption should prompt performance of this test.

4. ANAPHYLAXIS

The term *anaphylaxis* has been used to define the allergic adverse reaction characterized by systemic clinical manifestations that occur in an individual who had been primarily sensitized to a foreign substance on subsequent reexposure by any route, whether inhalation, oral, or injection, of the same material. The term *anaphylaxis* was derived from the Greek words *a-* (against) and *-phylaxis* (immunity protection). The terms *anaphylactic* and *anaphylactoid* refer to similar if not identical syndromes but have been utilized in the past by some clinicians as meaning IgE-mediated or non-IgE-mediated systemic reactions, respectively.

Anaphylaxis represents the most severe type of allergic reaction and a medical emergency.

IMMUNOLOGICAL FEATURES
- Sudden massive degranulation of mast cells, releasing histamine.
- Mast cells are stimulated to produce leukotrienes (cause of late reaction).
- Degranulation can be mediated by bound IgE-allergen cross-linking on the surface or direct, IgE-independent, mast cell degranulation (anaphylactoid reaction) responses. Mechanism is calcium-dependent.
- Involvement of IgE requires prior exposure to sensitize the patient. In childhood sensitization to peanut may occur via formula milk, which may contain peanut oil. Following sensitization, only tiny amounts may be required to trigger subsequent reactions.
- Reaction is an example of type I hypersensitivity, dependent on the presence of specific IgE. Other reactions may mimic the clinical symptoms but without the involvement of IgE.
- Repeated challenge at short intervals may lead to progressively more severe reactions, but otherwise the severity of a reaction does *not* predict the severity of subsequent reactions.
- Symptoms occur as a result of mast-cell release of histamine, which is responsible for bronchoconstriction, increased airway mucus secretion, stimulation of gut smooth muscle, hypotension due to increased vascular permeability, and vasodilatation and urticaria/angioedema.
- Other mediators include mast-cell tryptase and chemotactic factors for eosinophils. Activated mast cells also synthesize prostaglandins and leukotrienes, which reinforce the effects on smooth muscle. Tosyl-Larginine methyl ester (TAME) has a similar effect. Platelet-activating factor (PAF) causes the activation of platelets, leading to the release of histamine and serotonin and augmenting the effects on vascular tone and permeability.
- Mast-cell numbers at sites of allergen exposure are critical. It is speculative that there are variations in the output of mast cells from bone marrow that influence the possibility of developing reactions.
- Complement and kinin systems are activated (basophils release kallikrein when activated). Bradykinin, C3a, and C5a all act as smooth muscle constrictors and increase vascular permeability.
- Reactions may recur after 2-6 hours, despite successful initial treatment, due to the continuing synthetic activity of mast cells and the release of leukotrienes.
- Those with underlying atopic disease are said to be more at risk of developing serious allergic responses.

SUBSTANCES CAUSING ANAPHYLAXIS
Any substance may cause anaphylaxis, but the most common causes are:
- venoms: bee and wasp venoms;
- legumes: peanuts (and related legumes, soya, and other beans/peas);
- true nuts (walnut, almond, cashew, hazelnut, etc.);
- shellfish (crustacea, prawns, shrimps, crab, lobster) and fish;
- latex (and related foods: banana, avocado, kiwi, chestnut, potato, tomato);
- egg, milk;

- antibiotics: penicillin, cephalosporins, other antibiotics;
- anaesthetic drugs: neuromuscular blocking agents (e.g. suxamethonium, vercuronium);
- peptide hormones (ACTH, insulin);
- heterologous antisera (antivenins, antilymphocyte globulins, monoclonal antibodies).

In some cases a cofactor is required for the reaction, such as concomitant aspirin ingestion with the food, or exercise. It is probable that these cofactors alter the amount of allergen entering the circulation.

PATHOGENESIS
IMMUNE MECHANISMS
IgE-Mediated Reactions
A wide variety of agents are potentially responsible for IgE-mediated anaphylaxis (Table 4-1).

Table 4-1. Examples of Agents Causing Anaphylaxis via Immune Mechanisms

IgE Mediated	
Antimicrobial agents (haptens)	Penicillin, cephalosporin, tetracydine, aminogfycoside, streptomycin, amphotericin-B, nitrofurantoin, sulfamethoxazole
Hormones	Insulin, thyroid-stimulating hormone, corticotrophin, progesterone, adrenocorticotropic hormone
Enzymes	Streptokinase, penicillinase, chymotrypsin, trypsin
Antiserum	Tetanus, diphtheria, antitoxins, antithymocyte, antilymphocyte globulin
Venoms (and saliva)	*Hymenoptera* (bee, vespid and wasp, fire ant), *Chrysops* (deer fly), triaroma (kissing bug)
Vaccines	Tetanus, egg-containing vaccines (influenza), allergen vaccines
Foods	Milk, egg, wheat, fish and shellfish, legumes (peanuts), nuts (tree); exercise with foods
Miscellaneous	Latex, seminal fluid; animal or human proteins; polysaccharides
Complement Mediated	Transfusion reaction associated with IgA deficiency
	Cytotoxic (cell-fixed antigen, transfusion reactions to cellular elements, IgG, IgM
	Aggregate (intravenous immunoglobulins)

Antibiotics, such as the penicillins and cephalosporins, cause anaphylactic reactions through a hapten-protein-initiated IgE antibody-mediated mechanism. Proteins - including insulin, chymotrypsin, and venoms - as well as therapeutic agents - such as allergy vaccines and various other vaccines - can also be responsible. Foods are a significant source of IgE-mediated anaphylaxis, reactions most commonly occurring with eggs, shellfish, and nuts.

Non-IgE-Mediated Mechanisms
Anaphylaxis may occur during the administration of blood and blood products through a non-IgE immune complex (probably IgG) mechanism. These reactions are provoked by the development of antibodies to the red blood cell antigen or plasma protein (such as immunoglobulin), are presumed to be mediated by activation of complement, and can also induce anaphylaxis via fixation of complement. However, administration of blood products containing IgA to selective IgA-deficient patients may induce the development of IgE antibodies to IgA, which could mediate an anaphylactic reaction.

NONIMMUNE MECHANISMS
Table 4-2 lists agents that cause anaphylaxis via nonimmune mechanisms.

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Table 4-2. Examples of Nonimmune Mechanisms: or Conditions Causing Anaphylaxis (Immunoglobulin E Independent)

Direct histamine-releasing agents	Muscle relaxants, ciproflaxin, vancomycin, pentamidine, radiocontrast media, angiotensin-converting enzyme inhibitor, opioids, plasma expander polysaccharides (Dextran)
Arachidonate mediated	Aspirin and nonsteroidal anti-inflammatory drugs
Physical	Exercise, temperature (cold, heat)
Idiopathic	
Undifferentiated somatoform idiopathic anaphylaxis	Nonorganic symptoms mimicking anaphylaxis

Direct mast cell degranulating agents, such as opiates, curare muscle relaxants, plasma expander polysaccharides (dextran), certain antibiotics, and iodinated radiocontrast media, have been noted to release histamine from basophils and mast cells. Aspirin is also known to cause anaphylaxis through uncertain mechanisms. Aspirin-sensitive patients may also show intolerance to other nonsteroidal anti-inflammatory agents, including ibuprofen, indomethacin, and tolmetin. The role of tartrazine and other dyes in producing anaphylaxis is a matter of controversy. Patients with systemic mastocytosis can also manifest reactions resembling anaphylaxis due to release of histamine and other mediators from the abundant and excessive mast cells without an overt immune mechanism.

IDIOPATHIC ANAPHYLAXIS

A number of patients are also recognized as having idiopathic anaphylaxis, during which symptoms occur in the absence of any identifiable inciting agent. It is thought that this type of reaction may represent the most severe form of a spectrum of immediate-type reactions due to abnormal and inappropriate mast cell or basophil activation. Exercise-induced anaphylaxis may be included in this category. These individuals have been described as developing anaphylaxis more readily after eating certain foods, such as celery, just prior to exercise. Another subgroup of patients with idiopathic anaphylaxis has been classified as having an undifferentiated somatoform disorder, because the patient history mimics idiopathic anaphylaxis but lacks correlating objective physical findings and has no response to appropriate therapy.

PATHOLOGY

The principle anatomic and microscopic findings in fatal anaphylaxis include pulmonary emphysema, laryngeal edema, visceral congestion, pulmonary edema, intraalveolar hemorrhage, urticaria, and angioedema. These findings result from hypoxia and hypovolemia. Autopsy findings may be complicated by therapeutic measures (iatrogenic procedures).

Microscopic evidence that suggests myocardial infarction, pulmonary hemorrhage, edema, increased bronchial secretions, peribronchial vascular congestion, and eosinophilic infiltration of the bronchial walls can be found. There is accumulation of thin noninflammatory fluid in the lamina propria of the hypopharynx, epiglottis, and larynx in as many as two thirds of fatal cases. Other less-specific findings associated with systemic anaphylaxis include liver, spleen, and other abdominal visceral congestion, with an increased number of eosinophils in the red pulp of the spleen. Hemorrhagic gastritis also may be seen.

CLINICAL PRESENTATION

Usual features are:

- generalized giant urticaria;
- angioedema, often involving face, lips, tongue, and larynx, causing stridor;
- bronchospasm;
- hypotension with loss of consciousness;
- gastrointestinal symptoms (nausea, vomiting, abdominal cramps, diarrhoea).

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Not all symptoms will be present during an attack and only 50% of patients will have a rash. Onset is rapid after exposure, usually within minutes, although some agents (foods and latex) may lead to a slower onset. Agents that are injected (drugs, venoms) give the fastest reactions.

Reaction should be graded:

- **Mild:** a feeling of generalized warmth, with sensation of fullness in throat, some localized angioedema and urticaria, but no significant impairment of breathing or features of hypotension.
- **Moderate:** as for mild, but with more widespread angioedema and urticaria, some bronchospasm, and mild gastrointestinal symptoms.
- **Severe:** intense bronchospasm, laryngeal oedema, with severe shortness of breath, cyanosis, respiratory arrest, hypotension, cardiac arrhythmias, shock, and gross gastrointestinal symptoms.

DIAGNOSIS

The diagnosis of systemic anaphylaxis has been based on recognition of the *clinical features*.

History is all-important, particularly the timing of reaction in relation to the suspected trigger. If the trigger is not clear, a detailed review of all exposures over the preceding 24 hours is required.

Confirmation of the nature of the reaction may be obtained by taking blood for *mast-cell tryptase* (levels will be elevated for up to 12 hours and it is stable). This is valuable where there is doubt about the nature of the reaction; *urinary methylhistamine* is an alternative, but is not now routinely available.

Evidence should also be sought for activation of the complement system (measurement of C3, C4, and C3 breakdown products). Measurement of *C3a and C5a* is possible but requires a special tube, which is unlikely to be available in time.

Total IgE measurements are of no value.

Tests for specific IgE (RAST, etc.) may give negative results in the immediate phase, even when it is quite clear what has caused the reaction, due to consumption of the IgE. Repeating tests 3-4 weeks later may be helpful.

A complete blood count may show an elevated hematocrit secondary to hemoconcentration, but usually there is no acute abnormality.

Blood chemistries. If myocardial damage has occurred, elevations of serum glutamic-oxaloacetic transaminase (SGOT), creatine phosphokinase (CPK), and lactic dehydrogenase (LDH) enzymes are present.

Skin-prick testing may be sufficient to trigger a further systemic reaction and should be undertaken with great caution and only in a situation in which full facilities for cardiopulmonary resuscitation are immediately available.

Chest x-ray. With bronchial involvement, the chest x-ray shows hyperinflation with or without areas of atelectasis. In some cases, pulmonary edema is evident.

Electrocardiogram. Unless myocardial infarction has occurred, ECG changes are usually transient and can include S-T wave depression, bundle branch block, atrial fibrillation, and various ventricular arrhythmias.

DIFFERENTIAL DIAGNOSIS

Attention must be paid to other conditions that may appear similar clinically:

pulmonary embolus;

myocardial infarction (but this may follow anaphylaxis in those with pre-existing ischaemic heart disease);

hyperventilation;

hypoglycaemia;

vasovagal reactions;

phaeochromocytoma; . carcinoid;

systemic mastocytosis;

rarely the symptoms may be factitious (typically occur in those who also have true anaphylaxis).

Table 4-3 presents characteristic features of the most common conditions confused with anaphylaxis.

Table 4-3. Differential Diagnosis of Anaphylaxis by Clinical Features

Condition	Anaphylaxis	Anaphylactoid Reaction	Insulin Reaction	Myocardial Infarction	Vasovagal Reaction
Pallor	+	+	+	+	+
Diaphoresis	±	±	+	+	+
Altered consciousness	+	+	+	±	+
Urticaria, angioedema	±	±	-	·	-
Dyspnea	+	+	-	+	±
Wheezing	±	±	-	±	-
Hyperinflation	+	+	-	-	-
Stridor	+	+	-	-	-
Hoarseness	+	+	-	·	-
Tachycardia	+	+	+	+	-
Hypotension	+	+	±	±	+
Arrhythmias	±	±	±	+	-
ECG and enzyme abnormality	±	±	-	+	·
Hypoglycemia	-	-	+	-	-

+ = usually present; ± = may be present; - = usually absent.

Vasovagal reactions and syncopal attacks often occur with injections. The pulse is slow, and cyanosis usually does not occur. Although the blood pressure is low, it is usually easily detectable and generally higher than in anaphylaxis. Pallor and diaphoresis are common features.

Myocardial infarction. The predominant symptom in myocardial infarction is chest pain, with or without radiation. Respiratory difficulty, developing more slowly, results from a restrictive abnormality without air trapping or other evidence of bronchial obstruction. There is no upper airway edema or obstruction.

Insulin reactions are characterized by weakness, pallor, diaphoresis, and unconsciousness. Airway obstruction and respiratory distress do not occur; the blood pressure is usually only moderately depressed.

In *hysterical reactions*, there is usually no objective evidence of respiratory distress, hypotension, or cyanosis. Paresthesias are more common than pruritus. Syncope can occur, but unconsciousness is momentary. Rapid assessment of vital signs and neurologic status will differentiate this condition from anaphylaxis.

TREATMENT OF ANAPHYLAXIS

The treatment of anaphylaxis can be life saving. Prompt recognition is essential, as death may occur within minutes. Box 4-1.

Box 4-1. Physician-Supervised Management of Anapnylaxis

1. Assess rapidly (airway, breathing, circulation, and adequacy of mentation).
2. Place in recumbent position and elevate lower extremities.
3. Discontinue inciting agent or allergen.
4. Inject epinephrine 1:1000, 0.01 ml/kg (max 0.3-0.5 ml) intramuscularly, preferably into the anterolateral thigh or arm (deltoid). Repeat every 5 min as necessary to control symptoms

and blood pressure. Epinephrine 1:10,000 dilution may be utilized intravenously in moribund subjects.

The initial treatment of anaphylaxis with epinephrine is crucial in:

- Supporting blood pressure

- Decreasing bronchospasm, which helps maintain an effective airway

- Decreasing laryngeal edema, especially when given as a racemic epinephrine aerosol

- Slowing the absorption of injected agents if promptly used to infiltrate the site of injection

A tourniquet can also be applied above the injection site, because this can reduce and compress venous return at the site of an injection and decrease systemic absorption of antigen. It should be released for 1 of every 3 minutes.

Never give IV bolus adrenaline to a conscious patient with anaphylaxis under any circumstances.

5. Establish and maintain airway. May need racemic epinephrine by nebulizer into a tracheal tube.

6. Provide supplement oxygen if needed (6-8 L/min)

7. Establish IV to maintain blood pressure with IV fluids (saline or volume expanders), pressors (dopamine hydrochloride 2-10 μg/kg/min or norepinephrine bitartrate 2-4 μg/mln). Support blood pressure with IV fluids (colloid or crystalloid): persisting hypotension may require further vasopressor agents.

8. Give diphenhydramine 1.25 mg/kg (max. 50 mg) IV over 3-5 min. Antihistamine should be given intravenously (chlorphenamine 10 mg).

9. Ranitidine, 50 mg (1 mg/kg in children), may be diluted in 5% dextrose to a total of 20 ml and injected intravenously over 3-5 min. Inhaled β-agonists (albuterol or levalbuterol) or amlnophyfline 5 mg/kg over 30 min (may be helpful for severe bronchospasm 0.3-1 mg/kg/hr)

10. Provide hydrocortisone 5 mg/kg (max. 100 mg) IV q 6 hr or methylprednlsolone 1-2 mg/kg per 24 hr. A bolus of hydrocortisone (100-200 mg) should be given. The latter has no effect on the immediate reaction but reduces the possibility of a late reaction. Use hydrocortisone sodium succinate; do not use hydrocortisone phosphate as this is frequently associated with severe burning genital pain which makes a sick patient feel much worse.

11. Tracheotomy may be required if there is major laryngeal oedema. Admission for observation is required (risk of late reactions); a period of 8 hours is usually adequate.

It is essential to move the patient as soon as possible to an emergency room or intensive care hospital facility that can manage major complications, such as cardiac arrhythmias, cardio-respiratory arrest, seizures, myocardial infarction, hypovolemia, and obstruction of the airway. Antihistamines (H_1 and H_2 blockers) are suggested and may decrease the potential for cardiac arrhythmias and peripheral vasodilation, as well as possibly urticaria/angioedema and gastrointestinal symptoms. Corticosteroids, although requiring several hours to exert beneficial effects, are indicated and may prevent late-phase reactions. Recurrent or biphasic anaphylaxis occurs 8 to 12 hours after the initial attack in as many as 20% of subjects who experience anaphylaxis.

If a patient who is on therapy with a beta-adrenergic-blocking agent, such as propranolol for hypertension, vascular headaches, mitral valve prolapse, or cardiac arrhythmias, develops anaphylaxis, the management may be compromised by the propranolol. Treatment may require massive infusing of fluid (saline or colloid solutions) to support the circulation compromised by the decreased peripheral resistance. In addition, judicious administration of epinephrine for alpha-adrenergic activity and isoproterenol to attempt to overcome the beta blockade may be indicated, Glucagon 1 to 5 mg (20-30 μg/kg [maximum, 1 mg] in children) administered intravenously over 5 minutes, followed by an infusion of 5 to 15 μg/minute may be used when beta-blocker therapy complicates treatment.

Cardiopulmonary arrest occurring during anaphylaxis may require a high dose of epinephrine administered intravenously (1:10,000 dilution). Rapid volume expansion is also mandatory, as is the use of atropine and transcutaneous pacing.

Indications for prescription of adrenaline for self-injection
(Epipen.Anapen®)

Adrenaline for self injection should be given when:
- patient has had a severe allergic reaction;
- there is a risk of re-exposure or the allergen cannot easily be avoided;
- patient has had a moderate reaction, but access to rapid medical assistance is impossible;
- patient has asthma - reactions are likely to be more severe;
- pregnancy is not a contraindication, as the risk to the fetus from hypoxia due to anaphylaxis is greater than the risk of adrenaline.

Adrenaline should not be given when:
- reaction is mild (urticaria or urticaria with minimal angioedema not involving throat);
- allergen is avoidable;
- patient is unable to use injection device;
- patient has or is at risk of ischaemic heart disease; this may include the elderly;
- patient is on beta-blockers, this is a relative contraindication and there is some evidence that the effect is not significant, however, it is recommended that the dose of adrenaline be halved in patients on beta-blockers, to avoid paradoxical hypertension due to unopposed alpha-adrenergic activity;
- patients are on tricyclic antidepressants or abuse cocaine (increased risk of cardiac arrhythmias).

Problems with adrenaline self-injection devices:

Confusingly, Anapen® and Epipen are fired differently; they should not be interchanged because of this.

Epipen is triggered by pressure on the needle-containing black tip, once the safety cap has been removed from the other end. The white plastic under the safety cap looks like a button but isn't!

Anapen is fired by pressing the button under the safety cap.

Accidental injection into fingers occurs: there is a risk of ischaemia and patients should be advised to go to casualty.

ANAPHYLACTOID REACTIONS

These may be every bit as severe as IgE-mediated reactions. In most cases they are due to activation of mast cells directly or via other mechanisms that will indirectly activate mast cells.

Causes. The most common causes are:
- direct mast-cell stimulation: drugs (opiates, thiamine, vancomycin, radiocontrast media, some anaesthetic agents, especially those dissolved in cremophor, tubocurarine), foods (strawberries), physical stimuli (exercise, cold, trauma), venoms;
- immune complex reactions (types II and III), with release of anaphylotoxins C3a, C5a: reactions to IVIg, other blood products, heterologous antisera;
- cyclo-oxygenase inhibitors: nonsteroidal anti-inflammatory drugs (may also stimulate mast cells directly);
- massive histamine ingestion: eating mackerel and other related oily fish (scombrotoxin due . to breakdown of muscle histidine to histamine).

Immunological diagnosis
- History usually gives the clue. No tests are entirely specific. Challenge is very risky.
- Tryptase wilt be elevated.
- Specific IgE will not be detectable.

Management
- Acute management is the same as for anaphylaxis.

• For patients who require IV radiocontrast media and are known or suspected to react, then pretreatment with oral corticosteroids (50 mg prednisolone, 13, 7, and 1 hour prior to examination), together with an antihistamine (cetirizine 10-20 mg or fexofenadine 120-180 mg orally 1 hour before) and an H2-blocker (cimetidine, 400 mg orally 1 hour before) should be used. Low-osmolality dyes should be used as these have a lower incidence of reactions.

PREVENTION OF ANAPHYLAXIS

Prevention is the most important aspect of the management of anaphylaxis. Steps should be taken to limit exposure to agents known to precipitate and aggravate anaphylaxis (Box 4-2).

Box 4-2. Prevention of Anaphylaxis
1. Avoid exposure to agents known to cause anaphylaxis.
2. A careful history of previous reactions to suspected antigens is mandatory before administering any medication (especially parenterally). Attempts to identify specific allergens should utilize immediate type hypersensitivity skin tests or radioallergosorbent testing when available.
3. Use oral rather than parenteral medication.
4. Have patients wait in office 30 minutes after drug administration.
5. Have patients carry information on person concerning anaphylactic sensitivity.
6. Skin testing or conjunctival testing with various vaccines and antivenoms derived from animal serum is mandatory before administration of therapeutic doses.
7. Predisposed patients should be taught self-injection of epinephrine.
8. When antiserum is essential, use human serum preparations.
9. Avoid beta-adrenergic-blocking agents in anaphylaxis-prone patients.
10. Pretreat with steroids and antihistamines of patient requires procedure (radiocontrast media) or most have medications.
11. Great care must be taken with latex-allergic patients, as hospital staff with latex gloves and resuscitation with latex-containing equipment (masks, catheters, etc.) may make the reaction paradoxically worse during resuscitation.
12. Patients who have had severe reactions should be trained to self-administer adrenaline using a self-injection aid and should carry a Medic-Alert bracelet or equivalent. See below for indications.
13. Regular annual follow-up by a practice nurse should be undertaken to ensure that patients remain competent in using the adrenaline injector.
14. Latex-allergic patients need to be warned about possible reactions to foods (banana, avocado, kiwi fruit, chestnut, potato, and tomato) and be given advice on avoidance. It is important that they tell doctors and dentists as reactions may be triggered during operations by surgical gloves or anaesthetic equipment and by investigations such as barium enema (rubber cuff on tubing) and dental treatment.
15. Carrying a supply of antihistamines may also be helpful (used prophylactically if entering a situation of unknown risk, e.g. eating out).
16. Patients deemed to be at risk of further anaphylaxis should not receive treatment with β-blockers, as these agents will interfere with the action of adrenaline if required.
17. Patients should receive detailed counselling on how to avoid the triggering allergen; if a food is involved this should be undertaken by a dietician experienced in dealing with food allergy. Many foods may be 'hidden', so that the consumer is unaware of the contents. This applies particularly to pre-prepared foods and restaurant meals.
18. For bee/wasp anaphylaxis, patients should be warned to avoid wearing brightly coloured clothes and perfumes as these attract the insects. They should also stay away from fallen fruit and dustbins. Desensitization is possible. This is a process that requires considerable dedication on the part of the patient (and the hospital staff!). It should be reserved for those who have had a systemic reaction and where the risk of further stings is considered to be high.

5. ASTHMA

Asthma is one of the atopic diseases. Asthma, a lower airways disease characterized by enhanced responsiveness to a variety of stimuli and manifested by airways obstruction that changes spontaneously or therapeutically, is a common illness in both the pediatric and adult populations. The most widely accepted definition of asthma includes the following characteristics:

• Lower airway obstruction that is partially or fully reversible, either spontaneously or with bronchodilator or antiinflammatory treatments.

• The presence of chronic airway inflammation.

• Increased lower airway responsiveness to several stimuli, such as cold air or exercise in the natural environment and inhaled methacholine or histamine in a laboratory environment, with recurrent episodes of wheezing, coughing, and shortness of breath.

The cause is multifactorial, with a complex interaction of genetic background with environmental factors. There is also a complex interaction at the local level between changes in the airway (reactive airways disease), neurogenic components (particularly involving vasoactive intestinal polypeptide (VIP) and substance P), and the innate and specific immune system.

EPIDEMIOLOGY

The burden of asthma has been increasing worldwide, with regard to prevalence, cost, morbidity, and mortality. Approximately 26 million individuals in the United States have received a diagnosis of asthma sometime during their lifetime, 8.6 million of which were younger than 18 years. The onset of asthma in children is before the age of 2 years in 50% and before the age of 5 years in 80%. Asthma is now the most common chronic illness of childhood and is a leading cause of school absenteeism.

Asthma is considered a component of the atopic march, whereby genetically predisposed infants typically develop eczema (often with food allergies) shortly after birth, which often subsides as they develop inhalant allergen sensitivities and allergic rhinitis during the 2nd to 4th years of life and, very often, symptoms of asthma.

Viral infections that are clinically detectable only in the upper respiratory tract can be associated with bronchial hyperreactivity and small airway dysfunction. Viral infections account for as many as 80% of wheezing episodes in young children during the fall and winter seasons. Typically, respiratory syncytial virus predomintes in children younger than 2 years, whereas rhinovirus predominates in those older than 2 years. Respiratory syncytial virus is the main cause of infantile bronchiolitis, which generally manifests as wheezing in small babies and, at times, must be differentiated from asthma *Mycoplasma pneumoniae* may cause more than 50% of wheezing episodes in adolescents.

As many as 50% of children with asthma, especially those with milder levels of severity, have a clinical remission and become asymptomatic during the 10- to 20-year follow-up period. However, in these people, airway biopsy studies have documented ongoing airway inflammation and remodeling, and many experience a recrudescence of symptoms during years of follow-up.

PATHOPHYSIOLOGY
GENERAL PATHOPHYSIOLOGY

Although the underlying pathology in asthma is airway inflammation, clinical manifestations of asthma are related to the periodic development of airway obstruction (Fig. 5-1).

When evaluated, patients with mild intermittent or persistent asthma may have no detectable evidence of airflow obstruction on routine pulmonary function testing. However, those with moderate and severe persistent asthma may have abnormalities detectable both on physical examination and in pulmonary function testing (office-based spirometry or home-based peak expiratory flow measurements).
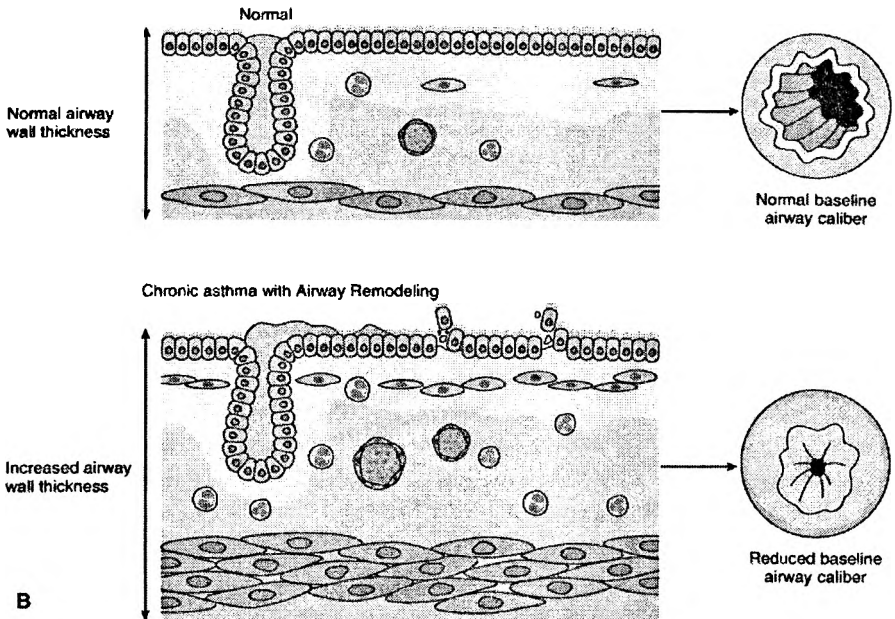
Figure 5-1. The airway remodeling process in asthma *(B)*.

The history usually reveals that asthma patients develop clinical symptoms (and thus, airflow limitation) after exposure to allergens, environmental irritants, viral infections, exercise, and cold air (Table 5-2).

Table 5-2. Asthma triggers

Infections	Viral
	Bacterial sinusitis
Allergens	Pollens
	Animal products
	Molds
	Dusts
	Cockroaches
Airway factors	Cold air
	Hyperventilation (e.g., crying, laughing)
	Exercise
Irritants	Noxious gases, odors
	Cigarette smoke
Pharmacologic	Aspirin
Psychosocial	Emotions

This propensity to develop airway obstruction in response to normally innocuous environmental agents is known is airway hyperreactivity. Its presence can be documented in the clinical pulmonary function laboratory using bronchoprovocation testing, in which pulmonary function is monitored while patients inhale increased concentrations of methacholine or histamine

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to establish the provocative concentration that causes a 20% fall in forced expiratory volume in 1 second (FEV_1).

Other stimuli that can be used to measure the degree of airway hyperreactivity include nonpharmacologic agents such as hyperventilation with cold, dry air, and with exercise. Indeed, the clinical severity of asthma - and thus, medication requirements - tends to parallel the degree of airway hyperreactivity.

One of the signs of airway hyperreactivity in patients with asthma is an exaggerated fluctuation in morning and evening peak expiratory flow rates. This assessment has been incorporated into the asthma guidelines in the classification of asthma severity. The normal diurnal variability in airflow in nonasthmatics is approximately 10% or less, but the variability may increase dramatically in patients with high degrees of airway hyperreactivity and severe asthma.

Postulated mechanisms for the development of airway hyperreactivity include airway inflammation, abnormalities in bronchial epithelial integrity, changes in intrinsic bronchial smooth muscle function, changes in autonomic neural control of airways (decreased beta-adrenergic and enhanced alpha-adrenergic and cholinergic responses), and the degree of baseline airflow obstruction.

One of the primary mechanisms responsible for the development of airway hyperreactivity is airway inflammation, which has now been documented directly using mucosal biopsies. The airway inflammation is complex and variable but is present in all persistent asthma severity levels and very early in the course of disease in adults and children. Th-2 lymphocytes, mast cells, and eosinophils appear to be the main orchestrators of the inflammatory process, but neutrophils may be involved in more severe cases. Eosinophils, whose tissue migration and activation may be directed by the secretory products of pulmonary mast cells, macrophages, and epithelial cells, have been linked to alterations in epithelial integrity, abnormalities in autonomic neural control of airway tone, and increased airway smooth muscle responsiveness. Another cell with a likely role in these events is the T-lymphocyte. Indeed, this cell, once activated by antigen, may orchestrate the development and maintenance of airway inflammation through the secretion of proinflammatory, soluble cytokines such as interleukin (IL)-4 and IL-5, which have the ability to influence the activation state of a variety of inflammatory cells in both autocrine and paracrine fashions.

Smoldering inflammation is also accompanied by a remodeling process, which includes epithelial disruption, edema, hypertrophied and hyperplastic smooth muscle bundles, increased vascularity, increased mucous secretion, and a remarkable thickening of the reticular basement membrane due to collagen deposition (see earlier figures). This remodeling may relate to the long-term decline in lung function and loss of reversibility observed in asthmatic patients.

Inflammatory mediators also play a major role in the pathogenesis of selected features of asthma, including the inflammation and remodeling processes (Fig. 5-2). These include the cysteinyl leukotrienes (Fig. 5-3).

Some of the cells that release these potent mediators, including eosinophils, basophils, and mast cells, have an inherent enhanced degree of mediator releasability in asthma, thus providing a possible explanation for the observed elevations of plasma mediator levels during laboratory-provoked and naturally acquired acute asthma.

Genetics and environment both participate in the pathogenesis of asthma. Family history very often reveals affected siblings, parents, or other first-degree relatives. No specific asthma gene has yet been identified, but recent advances in molecular biology promise to better define the genetic basis for asthma. Certain environmental factors may be prerequisite for its clinical presentation. For example, a propensity to develop airway hyperreactivity may be inherited, but appropriate exposure to certain allergens, respiratory viruses, chemicals, or psychosocial stimuli are associated as triggers for its clinical expression as asthma.
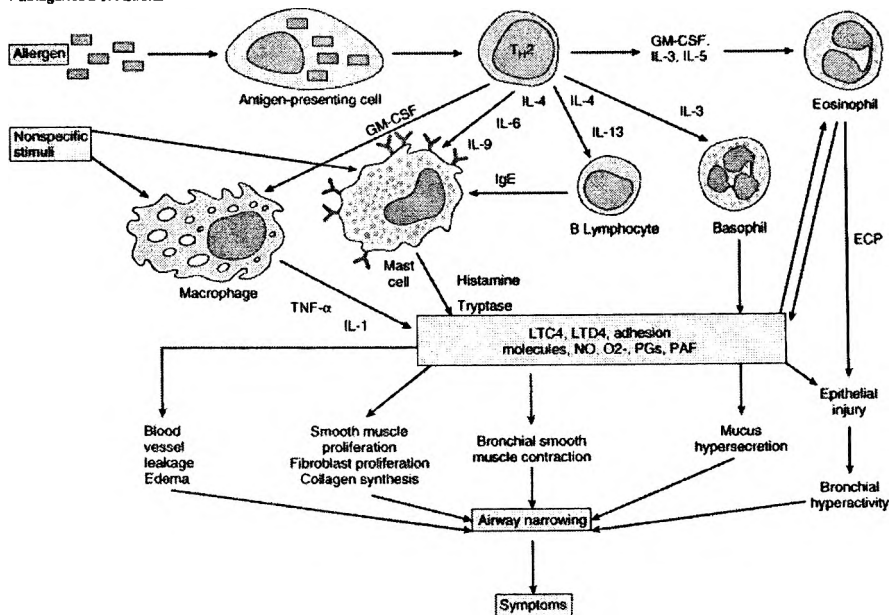
Figure 5-2. Cells and mediators interacting to result in asthma pathophysiology. ECP, eosinophil cationic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; LT, leukotriene; NO, nitric oxide; O_2-, superoxide; PAF, platelet-activating factor; PGs, prostaglandins; T_H, helper T cell; TNF, tumor necrosis factor.

Leukotriene Biosynthesis and Blockade
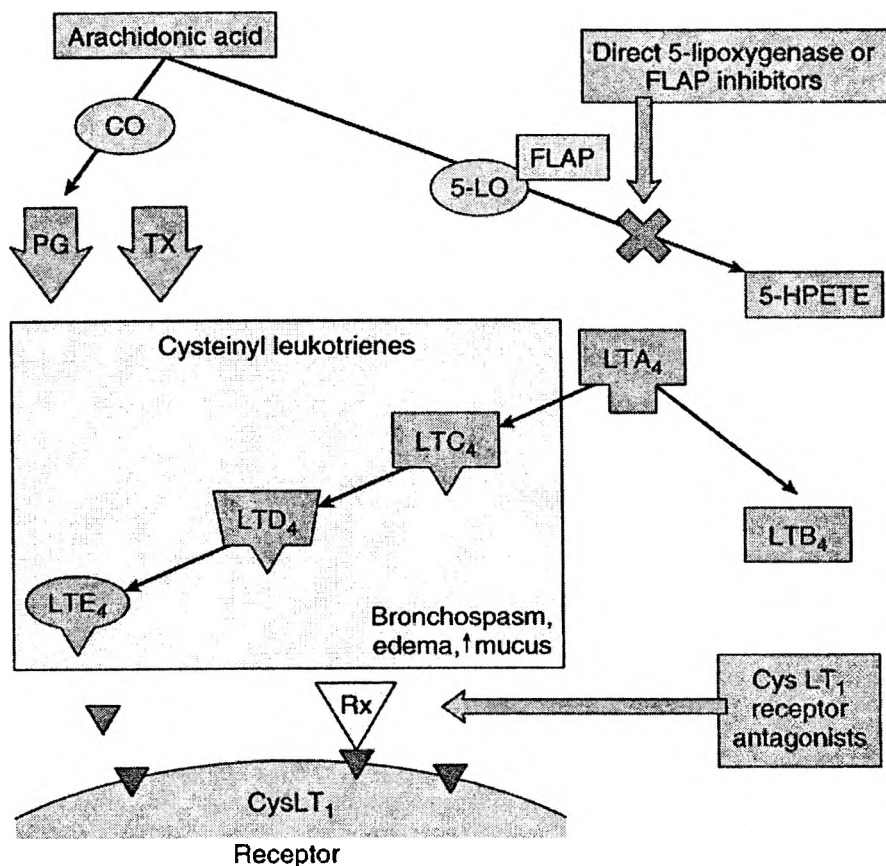
Figure 5-3. Leukotriene biosynthetic pathways and blockade. Note the interaction of the cysteinyl leukotrienes with the CysLT$_1$ (leukotriene) receptor and the role of receptor antagonists. Such a receptor is present on the surface of cells such as airway smooth muscle cells and eosinophils. H$_P$ETE, hydroperoxy eicosatetraenoic acid; PG, prostaglandin; Rx, treatment; TX, thromboxane.

Laboratory experiments have demonstrated that inhalation of a relevant allergen by an allergic asthmatic patient results in the development of an acute decrease in FEV$_1$ and the onset of asthma symptoms within 30 minutes of exposure (Fig. 5-4).
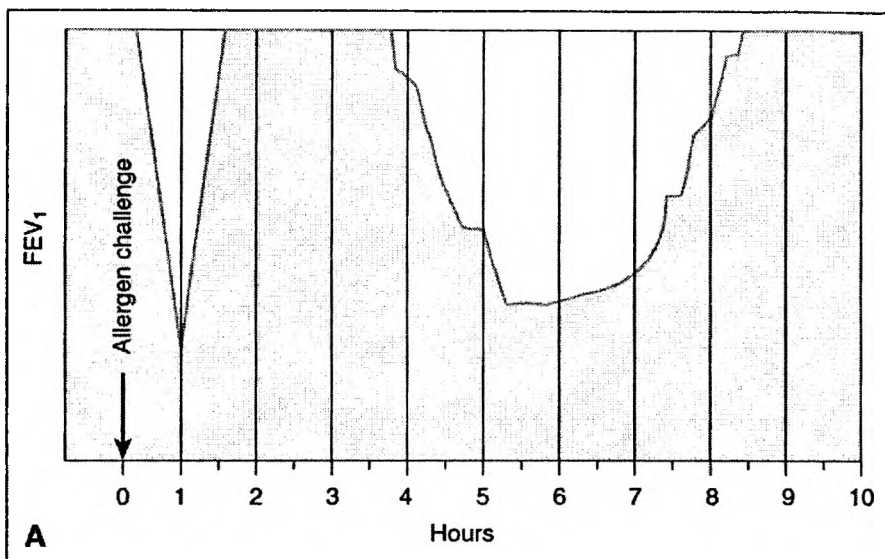
Figure 5-4. *A,* Early and late asthmatic responses in FEV₁ (forced expiratory volume in 1 second) to inhaled allergen challenge. *B,* Allergen-induced early- and late-phase airway tissue responses. Notably, airway hyperreactivity increases after late-phase asthmatic responses. ECP, eosinophil cationic protein; FcɛRI, Fcɛ receptor I; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; LT, leukotriene; MBP, major basic protein; PAF, platelet-activating factor; PG, prostaglandin; TGF, transforming growth factor; TNF, tumor necrosis factor.

Such a trigger may cause bronchial mast cells, macrophages, and epithelial cells to release inflammatory mediators, which then trigger the bronchospasm. Over the ensuing hours, airway function returns to baseline in most patients. If their progress is monitored, approximately 50% of these patients then experience a second decline in FEV₁ approximately 4 to 8 hours after exposure, termed a *late-phase allergic reaction* (see Fig. 5-4). Importantly, the degree of bronchial hyperreactivity to nonspecific stimuli is increased in patients experiencing late-phase allergic reaction. This is believed to be related to the intense airway inflammation that develops in these patients, manifested by increased numbers of eosinophils in the airways, along with other cells. The migration of eosinophils into the airways and their activation may be directed by inflammatory mediators released earlier during the immediate allergic reaction. Indeed, patients who experience sequential late-phase bronchial reactions could thus experience progressively heightened levels of airway hyperreactivity, as seen in asthma.

Viral respiratory infections also play a role in the pathophysiology of asthma with the development of increased levels of airway hyperreactivity and an increased frequency of late-phase asthmatic reactions to allergen during acute infections. Indeed, the increases in airway hyperreactivity that follow a respiratory viral infection may persist for weeks beyond the infection. Possible contributors to these phenomena include direct epithelial damage, the production of virus-specific IgE antibodies, enhancement of the production of IgE antibodies specific for other antigens, upregulation of neurogenic inflammatory pathways, and increases in the level of mediator release from inflammatory cells.

In addition to viruses and allergens, other environmental agents, including inhaled ozone, can induce airway inflammation and hyperreactivity. Once airway hyperreactivity is present, airway obstruction - and thus, the common asthma symptoms of wheezing and dyspnea - can be triggered

by subthreshold levels of exposure to nonspecific environmental irritants, such as cigarette smoke and sulfur dioxide.

PATHOPHYSIOLOGY OF ACUTE EXACERBATIONS OF ASTHMA

The development of the typical symptoms of acute asthma (progressive worsening of cough, breathlessness, wheezing, and chest tightness) is accompanied by decreases in expiratory airflow rates. Bronchial smooth-muscle contraction is one of the primary factors contributing to the airway obstruction. Other contributory factors include inflammation changes, such as mucosal edema and mucous plugging, which results in air trapping and hyperinflation. Physiologic changes that progress as the acute process worsens include both clinical and laboratory alterations. Clinically, patients with progressive airway obstruction use accessory muscles of respiration (sternocleidomastoid muscles) to maintain the state of hyperinflation. This, in turn, enables patients to maintain airway patency and thus, adequate gas exchange. Indeed, the use of accessory muscles to breathe correlates very well with the severity of an episode of acute asthma and is superior to dyspnea and wheezing as a sign of a severe episode.

The severity of acute asthma, however, is best assessed by pulmonary function testing. During acute asthma, progressive changes are noted in functional residual capacity (increased), FEV_1 (decreased), peak expiratory flow rate (decreased), and forced vital capacity (decreased or normal). The latter change correlates with the degree of hyperinflation. Blood gas assessment may reveal hypoxemia because of mismatching of ventilation and perfusion. Hypocapnia (reduced arterial carbon dioxide levels) and respiratory alkalosis (increased pH) are the usual manifestations of early acute asthma, because alveolar ventilation is maintained at this stage. However, with more severe obstruction, ventilation is compromised and arterial carbon dioxide levels rise (hypercapnia) with decreased pH and respiratory acidosis. The latter finding signals the development of acute respiratory insufficiency and the presence of an FEV_1 that is less than 25% of the predicted value.

Other physiologic changes that occur in acute asthma include increased pulmonary vascular resistance and an increased after-load on the left ventricle due to the high negative pleural pressures that result from lung hyperinflation. The clinical manifestation of these changes is the development of pulsus paradoxus, which is an exaggerated fall in systolic pressure during inspiration. Its presence correlates with an FEV_1 less than 50% of the predicted value for that patient.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The diagnosis of asthma requires the documentation of episodic airway obstruction and the reversibility of that obstruction, preferably using spirometry in children older than 5 years and repeated clinical examinations in younger children, as well as the exclusion of alternative diagnoses. These alternative diagnoses can include disorders such as vocal cord dysfunction in the older patient and vascular ring in the younger child (Tables 5-3 and 5-4). The presence of recurrent cough or wheezing triggered at nighttime or by exercise or cold air exposures, especially in the context of a positive family history, is a particularly helpful clue in establishing the diagnosis of asthma.

Some patients present with cough as the sole manifestation of asthma. These patients typically have normal pulmonary function tests, with some improvement with the bronchodilator, and manifest airway hyperreactivity to provocative stimuli, such as methacholine, exercise, or cold air.

During the history and physical examination, particular attention should be focused on the growth pattern of children. Severe asthma can suppress the growth of young children, but poor growth is a predominant feature of many of the masqueraders of asthma, such as cystic fibrosis. Also, the presence of upper respiratory findings compatible with allergic rhinitis (pale, boggy nasal turbinates, suborbital venous congestion -"shiners" - nasal crease, Denie's lines, and skin manifestations of atopic dermatitis should be noted. The examination should focus on the appearance of a hyperexpanded chest, presence of cyanosis, degree of respiratory distress, use of accessory muscles, wheezing, decreased inspiratory-to-expiratory ratio, rhonchi, and other findings on auscultation that might indicate pneumonia or atelectasis. The cardiac examination should be

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geared toward the identification of congenital heart disease in young children and congestive heart failure in adults.

Acute asthma symptoms usually consist of progressively increasing shortness of breath (dyspnea), cough and difficulty breathing with or without rhinorrhea, low-grade fever, and other manifestations of an upper respiratory infection. On auscultation, expiratory wheezing or a prolonged expiratory phase may be the only manifestation of mild asthma. However, as the obstructive process progresses, the expiratory phase becomes longer and the musical high-pitched rhonchi grow louder.

Tables 5-3. Differential diagnosis of wheezing (causes other than asthma)

Diagnostic Clues	Possible Cause
Sudden onset of wheezing, choking, or coughing; recurrent wheezing, persistent cough, or recurrent pneumonia	Foreign-body aspiration
Chronic wheezing that is not responsive to bronchodilators or corticosteroids; wheezing may increase with feeding, crying, positional changes, or flexion of the neck	Vascular rings
Persistent stridor and wheezing that have been present since birth	Laryngeal webs
Noisy breathing, especially on inspiration; noisy breathing and wheezing are intermittent and increase when the infant is supine; stridor present since birth; history of feeding difficulties	Laryngotracheobronchomalacia
Symptoms of upper respiratory tract infection (cough, fever, rhinitis); tachypnea, retractions, cyanosis	Branchiolitis
Failure to thrive, fever, diarrhea, recurrent pneumonia	Cystic fibrosis
History of prematurity and intubation; increased airway hyperreactivity, severe respiratory distress	Bronchopulmonary dysplasia
Frequent emesis; irritability during feedings; recurrent wheezing	Gastroesophageal reflux
Recurrent wheezing and pneumonia; episodes of cough or cyanosis associated with feeding	Tracheoesophageal fistula
Recurrent sinusitis, otitis media, and pneumonia	Primary immunodeficiency

Tables 5-4. Selected diagnostic tests for the evaluation of wheezing

Suspected Diagnosis	Selected Diagnostic Tests
Foreign body	Inspiratory and expiratory chest x-ray*, bronchoscopy
Vascular rings	Barium esophagraphy
Laryngeal web	Direct laryngoscopy
Laryngotracheobronchomalacia	Direct laryngoscopy, airway fluoroscopy
Enlarged lymph nodes/tumors	Chest x-ray, CT scan*, biopsy
Bronchiolitis	Nasal washing for presence of RSV*
Cystic fibrosis	Sweat test, genetic tests
Gastroesophageal reflux	pH probe, endoscopy
Tracheoesophageal fistula	Barium esophagraphy and fluoroscopy
Primary immunodeficiency	CBC with differential, quantitative Ig levels
Asthma	Trial of bronchodilators and corticosteroids
Congenital Heart Disease	CXR, EKG, ECHO*

* - CBC, complete blood count; CT, computed tomography; CXR, chest x-ray; ECHO, echocardiogram; EKG, electrocardiogram;

RSV, respiratory syncytial virus.

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Without appropriate treatment and reversal, signs of hyperinflation (air trapping) develop, with depressed diaphragms, decreased excursions of the chest wall with respiration, and hyperresonance to percussion. Subjectively, the patient experiences chest tightness and anxiety and works harder to breath. Accessory muscle use (visible contractions of the scalene and/or sternocleidomastoid muscles) and retractions (visible depressions in the chest wall during inspiration) develop with or without a marked degree of wheezing on auscultation. The patient usually assumes an upright posture to maximize air exchange. As respiratory muscles tire, the patient becomes lethargic and cyanotic, even with supplemental oxygen.

Maximal effort to breathe produces feeble air exchange, manifested by decreased intensity and duration or lack of inspiratory breath sounds as air exchange decreases. Consequently, a patient with severe obstruction and impending respiratory failure may not have audible wheezing because too little air is being ventilated to create the sound. With extreme fatigue, respiratory muscles fail, retractions decrease, and respiratory failure is imminent unless appropriate therapy is promptly initiated. Following the initial examination, serial assessment of the degree of respiratory distress, using a standardized clinical scoring system (Table 5-5), facilitates determination of response to therapy and ensures early detection of impending respiratory failure or other complications.

Table 5-5. Estimation of Severity of Acute Exacerbations of Asthma in Children[*]

Sign/Symptom	Mild	Moderate	Severe
PEFR**	70%-90% predicted or personal best	50%-70% predicted or personal best	<50% predicted or personal best
Respiratory rate, resting or sleeping	Normal to 30% increase above the mean	30%-50% increase above the mean	Increase over 50% above the mean
Alertness	Normal	Normal	May be decreased
Dyspnea***	Absent or mild; speaks in complete sentences	Moderate; speaks in phrases or partial sentences; infant's cry softer and shorter; infant has difficulty suckling and feeding	Severe; speaks only in single words or short phrases; infant's cry softer and shorter; infant stops suckling and feeding
Pulsus paradoxicus****	<10 mm Hg	10-20 mm Hg	20-40 mm Hg
Accessory muscle use	No intercostal to mild retractions	Moderate intercostal retraction with tracheosternal retractions; use of sternocleidomastoid muscles; chest hyperinflation	Severe intercostal retractions, tracheosternal retractions with nasal flaring during inspiration; chest hyperinflation
Color	Good	Pale	Possibly cyanotic
Auscultation	End expiratory wheeze only	Wheeze during entire expiration and inspiration	Breath sounds becoming inaudible
Oxygen saturation	>95%	90%-95%	<90%
PCO_2	<35	<40	>40

* - Within each category, the presence of several parameters, but not necessarily all, indicate the general classification of the exacerbation. ** - For children 5 yr or older. *** - Parents' or physicians' impression of degree of child's breath less ness. **** - Pulsus paradoxus does not correlate with phase of respiration in small children. PEFR, peak expiratory flow rate.

Between episodes of acute asthma, the physical findings vary with the chronicity of the disease process. In mild asthmatics, the examination is usually entirely normal, but wheezing may be elicited in children by gentle manual chest wall compression, which restricts chest expansion and increases the work of breathing. In contrast, severe asthmatics with a long history of airway obstruction that has not received appropriate therapy may have signs of chronic lung disease. These include a paucity of subcutaneous fatty tissue and a barrel-chest configuration. Adults with chronic asthma may produce copious amounts of sputum. Rales, wheezing, rhonchi, and decreased intensity and duration of the inspiratory phase of respiration are commonly found on auscultation. Chest radiography may show areas of atelectasis.

Asthma should be considered as part of the differential diagnosis in any patient with recurrent or chronic lower respiratory symptoms or signs of lower airway obstruction. Patients or their parents must be instructed that physician assessment is essential during suspected episodes of asthma so that wheezing or other signs of lower airway obstruction and reversibility, if present, can be documented.

Asthma is the most common cause of recurrent episodes of cough and wheezing in both adults and children. However, asthma is frequently misdiagnosed and underdiagnosed, especially in young children who wheeze only during respiratory infections and who are labeled as having bronchitis, bronchiolitis, or pneumonia.

Any patient with acute asthma who develops symptoms of pleuritic chest pain, severe dyspnea, cyanosis, and tachypnea, as well as physical findings of unilaterally decreased or absent breath sounds, should be evaluated radiographically for pneumothorax. With tension pneumothorax, the trachea, mediastinum, and cardiac landmarks may be shifted to the opposite side. Pneumomediastinum and subcutaneous emphysema, usually involving the neck and supraclavicular areas, are more common than pneumothorax. When mild, they may be asymptomatic and detected incidentally by radiography. With more extensive air dissection, the patient may complain of neck and chest pain, and the subcutaneous emphysema may be visibly evident as a soft tissue swelling of the neck and chest, which is crepitant (has a crunching sound) on palpation.

Cardiovascular manifestations can also be detected during acute asthma. Heart rate and blood pressure are frequently elevated. Pulsus paradoxus, an exaggerated decrease in systolic blood pressure during inspiration, can serve as an indicator of severity and a guide to therapy. Pulsus paradoxus and the patient's exaggerated use of accessory muscles both correlate highly with the degree of airway obstruction.

In patients who present with respiratory distress or wheezing for the first time, a complete differential diagnosis of all causes of upper and lower airway obstructive processes must be undertaken. In the older child or adult with mild, infrequent episodes of wheezing that respond to bronchodilator therapy, asthma is usually readily diagnosed. However, with daily wheezing, frequent exacerbations, lack of response to bronchodilators, or poor growth, other diagnoses must be considered. These include chronic obstructive pulmonary disease, cystic fibrosis, α_1-antitrypsin deficiency, carcinoid syndrome, and an associated immunologic deficiency.

Chronic obstructive pulmonary diseases, which include chronic bronchitis, emphysema, bronchiectasis, and bronchopulmonary dysplasia, are distinguished by their lack of significant reversibility with bronchodilator therapy. Cystic fibrosis, a multisystem disease, may present with chronic cough, wheezing, and recurrent infections, especially sinusitis. Additionally, malabsorption with bulky, foul-smelling stools, failure to thrive, and clubbing of the nail beds are common. Indeed, clubbing is a very rare sign of chronic asthma and, if present in a wheezing patient, suggests another chronic pulmonary disease, α_1-antitrypsin deficiency, an inherited autosomal-recessive disorder, is characterized by the onset of progressive emphysema in adults, especially those who smoke cigarettes, but may also manifest as hepatic disease in the neonate and young child.

In wheezing infants, the differential diagnosis includes disorders that are unique to that age group (see earlier tables), especially bronchiolitis. In many infants, bronchiolitis is the initial manifestation of asthma, and differentiation between the two is occasionally difficult. Even though

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these two diseases share common clinical manifestations, sequelae, and possible pathogeneses, the distinction between them remains clinically useful for the following reasons:

1. Many children with bronchiolitis do not develop asthma and may be inappropriately labeled as having asthma.

2. Children younger than 2 years frequently do not respond to inhaled or injected bronchodilators.

Status asthmaticus, a complication of asthma, is diagnosed by failure to improve significantly after appropriate bronchodilator therapy and indicates a need for hospitalization. This is manifested by post-therapy wheezing, elevations in respiratory rate, and abnormalities in the inspiratory-to-expiratory ratio. Progressive deterioration of respiratory function in the context of maximal medical therapy for status asthmaticus indicates impending respiratory failure, which progresses to respiratory failure if untreated. The diagnosis of impending respiratory failure is based on arterial blood gas findings of Pao_2 of less than 70 in 40% Fi_{O2}, and Pa_{CO2} greater than 45 (or an increasing Pa_{CO2} on serial blood gases) in the appropriate clinical setting.
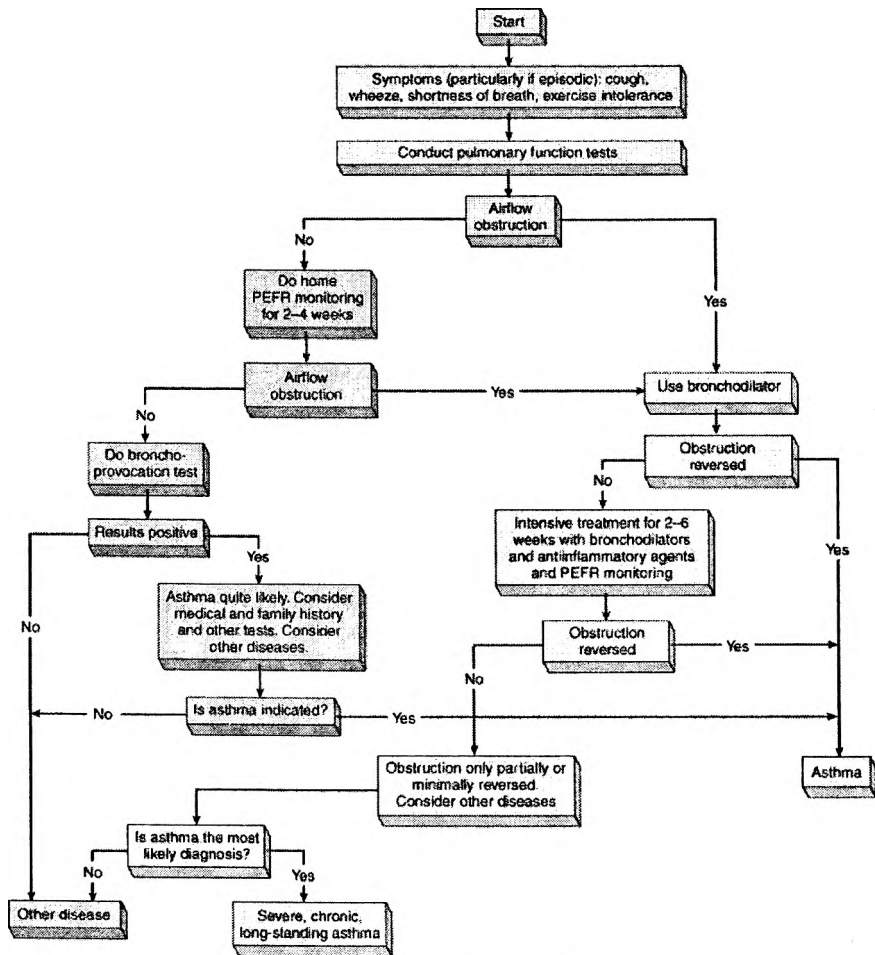
In children older than 5 years, specific laboratory studies should be performed to document asthma or rule out disorders that mimic it.

An algorithm for diagnosing asthma is shown in (Fig. 5-5).

Pulmonary function tests in asthma show airway obstruction at baseline or after methacholine challenge and, further, document reversibility of airway obstruction after administration of an aerosolized bronchodilator. In children younger than 5 years or people such as the elderly in whom testing is unreliable, the diagnosis must be made solely on the basis of historical and physical findings, in conjunction with clinical response to bronchodilators. Lack of a prompt response to broncho-dilators does not, however, eliminate asthma as a diagnostic consideration.

Patients who present with a history of isolated chronic cough or exercise-induced wheezing can be diagnosed by the reversibility of symptoms with a bronchodilator. When necessary, this impression can be confirmed by a positive pulmonary function or methacholine bronchoprovocation test. In patients who have sudden onset of wheezing and respiratory distress, the differential diagnosis for lower airway disorders includes respiratory infections, left ventricular failure, and foreign-body aspiration. Lower respiratory infections (pneumonia) generally produce fever and more localized findings of rales, decrease and change in quality of breath sounds, and egophony. A history of cardiac disease and auscultatory findings of diffuse crackles, basilar rales, and a third heart sound help to distinguish left ventricular failure with pulmonary edema from asthma.

In children, especially toddlers, aspiration of a foreign body that becomes lodged in a mainstem bronchus may produce wheezing that at times is partially responsive to bronchodilator therapy. The history of a choking episode and physical findings of unilateral wheezing and hyperresonance aid in distinguishing aspiration from asthma but do not confirm the diagnosis. Airway compression by anomalous vessels or mass lesions is often distinguishable from bronchiolitis by virtue of absence of signs of infection and from asthma by failure to respond to bronchodilators. Radiographic studies, such as barium swallow with fluoroscopy can be very helpful in distinguishing between these entities. Gastroesophageal reflux can be associated with asthma and is diagnosed by pH-probe testing or radiography. Cough secondary to drugs (e.g., angiotensin-converting enzyme [ACE] inhibitors) should be considered in patients presenting with cough as the primary manifestation. Patients in whom the diagnosis is unclear should be referred to an asthma care specialist.

Start

Symptoms (particularly if episodic): cough, wheeze, shortness of breath, exercise intolerance

Conduct pulmonary function tests

Airflow obstruction — No → Do home PEFR monitoring for 2–4 weeks

Airflow obstruction — Yes → Use bronchodilator

Airflow obstruction — No → Do broncho-provocation test

Use bronchodilator → Obstruction reversed — Yes → Asthma

Obstruction reversed — No → Intensive treatment for 2–6 weeks with bronchodilators and antiinflammatory agents and PEFR monitoring

Results positive — Yes → Asthma quite likely. Consider medical and family history and other tests. Consider other diseases.

Obstruction reversed — Yes → Asthma

Obstruction reversed — No → Obstruction only partially or minimally reversed. Consider other diseases

Is asthma indicated? — Yes → Asthma

Is asthma indicated? — No

Results positive — No

Obstruction only partially or minimally reversed. Consider other diseases → Is asthma the most likely diagnosis?

Is asthma the most likely diagnosis? — No → Other disease

Is asthma the most likely diagnosis? — Yes → Severe, chronic, long-standing asthma

Mosby items and derived items © 2006 by Mosby, Inc.

Figure 5-5. Algorithm for diagnosing asthma. PEFR, peak expiratory flow rates.

Pulmonary function tests are important in confirming suspected asthma. Between episodes of acute asthma, the findings depend on the chronicity and severity of the disease. Pulmonary function may be entirely normal in mild asthmatics, but acute airway obstruction can be induced by provocative methacholine inhalation. In contrast, marked reductions in expiratory flow rates may be present in severe asthmatics at baseline and are characteristically observed to a greater degree during acute asthma. However, a decreased expiratory flow rate due to asthma, an obstructive lung disease, must be differentiated from that due to restrictive lung diseases, such as cystic fibrosis.

Airway obstruction, when present, may or may not reverse with bronchodilators. If obstruction is detected, reversibility with bronchodilators should be determined and used to guide the formulation of a therapeutic regimen. Bronchodilator effectiveness may relate to the relative contribution of smooth muscle contraction versus inflammation as the cause of airway obstruction.

The clinician conducting an outpatient laboratory evaluation for asthma should always consider an immunologic cause and include the appropriate allergy testing so that potential inciting agents can be avoided. The most economic and reliable method is allergy skin testing, with serum-specific IgE antibody tests serving as an alternative method when skin testing is contraindicated. IgE levels may be a useful adjunct in suggesting an allergic cause. Additionally, sinus radiographs may be indicated in selected patients, because chronic sinusitis can exacerbate asthma.

Peripheral blood and sputum eosinophilia are usually present during recurrent and chronic asthma. Some clinicians, particularly those caring for adults, use the eosinophil count in sputum or blood as a guide to therapy, as decreased counts generally accompany clinical improvement. The radiographic features of uncomplicated acute asthma include hyperinflation, peribronchial cuffing, and atelectasis. Arterial blood (Table 5-6) usually shows hypoxemia, hypocarbia, and respiratory alkalosis, due to hyperventilation during the early stages of acute asthma. However, as the degree of airway obstruction increases or respiratory muscles tire, hypoxemia persists and carbon dioxide retention (hypercarbia) is detectable, resulting in a respiratory acidosis. This indicates impending respiratory failure.

Table 5-6. Arterial blood gas changes during acute asthma

Severity	PO2	PCO2	pH	Base excess
Mild	↓	↓	↑	Respiratory alkalosis
Moderate	↓↓	Normal	Normal	Normal
Severe	↓↓↓	↑	↓	Metabolic/respiratory acidosis

*- ↓, Low; ↑, high.

Identification of a viral cause using fluorescent antibody tests or enzyme-linked immunosorbent assays (ELISA) has little impact on acute therapy due to the paucity of available antiviral medications and should be limited to severely ill patients or the onset of an epidemic to document epidemiology.

Conclusions

• The diagnosis is dependent on history and examination. There is frequently an atopic background and a family history of atopic diseases. Wheeze is less common in children who tend to cough instead.

• Serial peak flow measurements may show the typical asthmatic pattern. Chronic disease may show loss of reversibility and be difficult to distinguish from chronic obstructive pulmonary disease (COPD). Reactive airways may be demonstrated with challenge tests.

• A high total IgE makes asthma more likely but does not correlate well with symptoms. A low IgE only excludes IgE-mediated bronchospasm. Skin-prick tests to common aeroallergens may pick up positives, but the history will indicate whether these are relevant clinically.

• There may be an eosinophilia on full blood count, although this is rarely marked and is only present in about 50% of asthmatics; sputum eosinophilia is much more common.

• Other serum markers have been proposed for assessing the severity of disease and adequacy of therapy. These include soluble CD23 (a cytokine involved in IgE production) and eosinophil cationic protein (ECP), which is said to correlate well with the underlying chronic eosinophilic inflammation. These tests are expensive and their role in monitoring remains to be determined.

TREATMENT
OUTPATIENT MANAGEMENT OF CHRONIC ASTHMA
The goals of effective outpatient asthma management are shown in (Box 5-1).

Box 5-1. Goals of Asthma Care?
- No chronic symptoms
- Normal or near-normal lung function
- Normal activity levels
- No recurrent exacerbations
- No missed school or work due to asthma
- No sleep disruption
- No (or minimal) need for emergency department visits or hospital izations
  - Optimal therapy with minimal adverse effects
  - Fulfillment of patient and family expectations and satisfaction

From NAEPP. Guidelines for the Diagnosis and Management of Asthma. NIH publication 97-4051A, May, 1997, National Heart, Lung, and Blood Institute: Global Initiative for Asthma. November, 1998, NIH publication 96-3659B. American Academy of Allergy, Asthma, and Immunology: Pediatric Asthma: Promoting Best Practice: Guide for Managing Asthma in Children. Rochester, NY, Academic Services Consortium.

Recent guidelines have focused on four major components of outpatient asthma management: 1) assessment and monitoring; 2) control of factors contributing to asthma severity; 3) patient education for a partnership; and 4) pharmacologic therapy. Asthma is considered a very "care-responsive" disease.

Assessment and Monitoring
The two main objective measures of lung function are officered spirometry and home-based peak expiratory flow-rate measurements. Office-based spirometry should be conducted in the initial evaluation of all patients with suspected asthma and during subsequent evaluations on a periodic basis.
To assess the response to therapy in the office, emergency department, or hospital, either spirometry or peak expiratory flow-rate measurement can be used. Measurement of peak expiratory flow rate (PEFR) with a peak flow meter should be used to monitor the course of persistent moderate to severe asthma at home and the response to therapy in patients 6 years of age or older. These values can provide valuable information to the managing clinician about asthma severity and the need to add or delete medications.
It is essential to provide teaching to patients for whom peak flow meters are prescribed, both on the proper use of the instrument and on the interpretation of values. For the latter, published predicted normal values for a given individual can be used. However, because the values for many patients are consistently higher or lower than predicted norms, establishing a "personal best" PEFR value is an acceptable alternative. The patient and clinician then use this value as a standard in evaluating subsequent measurements. Personal best PEFR values can be established by the performance of twice-daily PEFR measurements during a "well" period or during a period of maximal therapy. This value should be reestablished on a yearly basis. PEFR values should be recorded in the morning and evening, both before and after use of any inhaled medications. Highly stable asthmatics may not need to continuously monitor PEFR, although the ability to detect the early onset of obstruction may be compromised when not done daily during asymptomatic periods.
Through the use of predicted norm or personal best values, PEFR zones should be developed. Green zones (80% to 100% of predicted or personal best) indicate normal values. Yellow zones (50% to 80%) signal caution and a possible need for a temporary increase in medication. Alternatively, an increase in prophylactic therapy may be indicated. Finally, red zones (under 50%) indicate a medical emergency, whereby an inhaled bronchodilator should be used immediately and

the clinician should be notified if the values do not increase into the yellow or green zones (Fig.5-6).

Transport to an emergency facility may be indicated if the response is inadequate. This also signals the need for a temporary increase in medication (such as systemic corticosteroids).
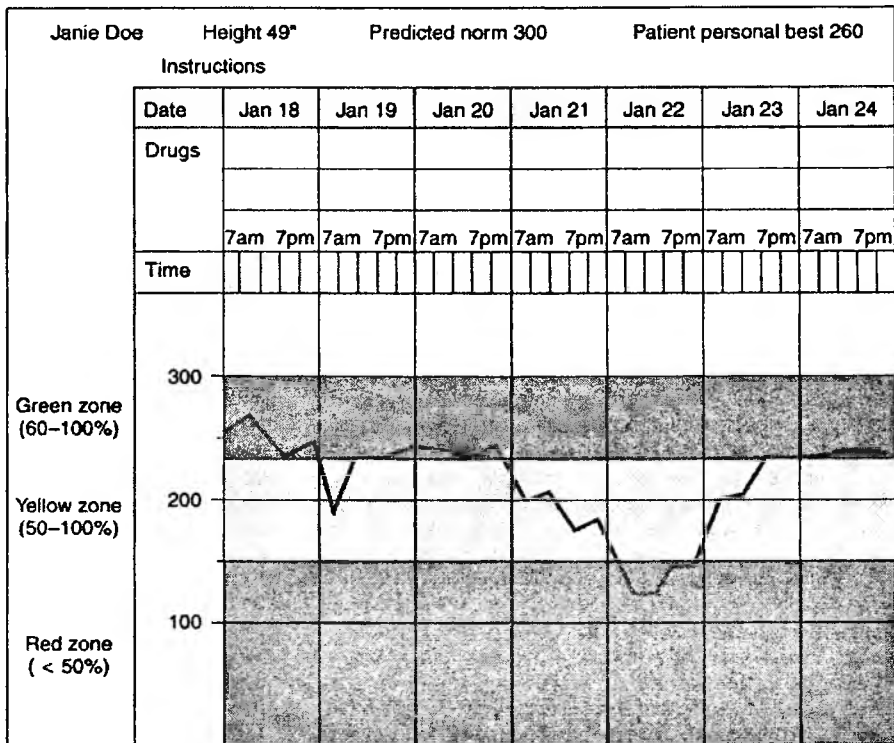
Janie Doe		Height 49"		Predicted norm 300		Patient personal best 260		
Instructions								
Date	Jan 18	Jan 19	Jan 20	Jan 21	Jan 22	Jan 23	Jan 24
Drugs							
	7am 7pm	7am 7pm	7am 7pm	7am 7pm	7am 7pm	7am 7pm	7am 7pm
Time							

Green zone (60–100%) — 300
Yellow zone (50–100%) — 200
Red zone (< 50%) — 100

(National Asthma Education and Prevention Program: Practical Guide for the diagnosis and management of asthma. Bethesda, MD. National Heart, Lung, and Blood Institute; National Institutes of Health, 1997.)

Figure 5-6. Typical peak flow meter diary. This patient dipped into the yellow zone on January 19th and recovered after use of a short-acting beta-2 agonist. The patient entered the red zone on January 22nd and gradually improved after beginning therapy with systemic corticosteroids. (National Asthma Education and Prevention Program: Practical Guide for the diagnosis and management of asthma. Bethesda, MD, National Heart, Lung, and Blood Institute; National Institutes of Health, 1997.)

Control of Factors Contributing to Asthma Severity

After identification of the offending allergens, thorough environmental control measures should be implemented in the patient's living and working environments. This may include:

■ measures to control outdoor allergen exposure, such as staying indoors with windows closed in an air-conditioned environment (especially during midday and afternoon, when pollen and mold counts may be high), and reduction of indoor allergen exposure to molds, dust mites, cockroaches, and pets. Indoor humidity levels should be maintained at 35% to 50%. Several other control measures may be particularly helpful, including air conditioning and the use of central indoor air-cleaning devices, such as mechanical filters (high-efficiency particulate air, or HEPA, filters) and electrical filters (electrostatic precipitator). Vacuum sweepers have a tendency to mobilize fine respirable allergens and provoke symptoms when used by dust-

allergic people, who should use a facemask, a central vacuum cleaner system with the collecting bag outside the home, or a cleaner fitted with a high-efficiency particulate air filter.

- additionally, nonallergen, indoor irritants, such as tobacco smoke, smoke from wood-burning heating stoves, strong odors and sprays, and chemical air pollutants, especially ozone and sulphur dioxide, may contribute to asthma exacerbations. Exposure to these irritants should also be reduced.

- attempts should be made to reduce house dust-mite exposure by reducing ambient temperature and avoiding high humidity (fewer house plants).

- avoid thick-pile carpets, heavy curtains, and other dust traps.

- mattress covers are desirable and all bedclothes should be washable (at high temperatures).

- de-miting mattresses is difficult: liquid nitrogen is effective but needs specialist services Acaricides such as benzylbenzoate may also be effective but may be irritant.

- if animal danders are a problem, the animal should go, although this news is rarely popular with patients! This is controversial as there is evidence that early exposure of children to pets in atopic families may reduce the chance of developing allergies.

- if allergen avoidance is not possible and the appropriate medications fail to control symptoms of allergic asthma, *allergy immunotherapy* may be considered. Allergy immunotherapy has been shown to reduce the symptoms of asthma associated with a variety of allergens, including house dust, cat dander, grass pollen, and alternaria. More recent studies have documented that children with monosensitization are less likely to develop new allergen sensitivities and that children with allergic rhinitis alone are less likely to develop new asthma when treated with allergen immunotherapy. Adverse reactions following allergen immunotherapy are higher in patients with asthma, so appropriate and additional vigilance and precautions are necessary to avoid asthma exacerbation.

- parents should also be queried about daycare attendance in infants and toddlers, since it may result in repeated exposure to respiratory viruses, which are a major trigger of wheezing in this age group. Reduction in the frequency of upper respiratory infections caused by such viruses may result in a significant clinical improvement.

Patient Education for a Partnership

Asthma education and the formulation of a partnership between the patient, family, and physician are of paramount importance in managing asthma. Educational topics should include a definition of asthma, asthma triggers and how to avoid or control them, key points about signs and symptoms of asthma, characteristic changes in the airways of patients with asthma, the role of the different types of medications (anti-inflammatory, bronchodilator), treatment, and patient fears about medications. This should also include education on the correct use of inhalers, criteria for pre-medicating to prevent symptoms, the optimal use of home PEFR monitoring, and the provision of written plans on recommended treatments for daily therapy (maintenance plan) and episodic acute asthma exacerbations (action plan). Specific, individualized guidelines for seeking advice from the clinician or emergency department care should also be provided. Such asthma education has been shown to reduce the morbidity associated with asthma and to improve asthma control.

Pharmacologic Therapy

General approach

Starting Initial Therapy—Reliever/Rescue Therapy Every patient with asthma of any severity requires uninterrupted access to the as-needed use of a short-acting bronchodilator. As indicated in the "Rules of Two™" (Box 5-2), refill of such a "quick-relief inhaler" more than two times a year can serve as a useful indicator of patients whose disease is poorly controlled. Also, use of more than one canister in 1 month indicates inadequate control and the need for more anti-inflammatory therapy. Regularly scheduled, daily use of short-acting beta-2 agonists is generally not recommended, as these agents have no long-term anti-inflammatory activity. Albuterol is generally the drug of choice for relief of bronchospasm, even though it is composed of a 50/50

racemic mixture of two stereoisomers of albuterol. Levalbulerol, the stereoisomer that provides the therapeutic benefit, is available for use when the albuterol response is poor or includes; side effects.

Box 5-2. Take control of your asthma "Rules of Two™ Can Help"*

- Do you take your quick-relief inhaler more than TWO TIMES A WEEK?
- Do you awaken at night with asthma more than TWO TIMES A MONTH?
- Do you refill your quick-relief inhaler more than TWO TIMES A YEAR?
- If you can answer yes to any of these questions, ask your doctor or pharmacist about a long-term controller antiinflammatory medication.
- A long-term controller medication can help to improve breathing and prevent asthma emergencies!

*Rules of Two™ is a registered trademark of Baylor Health System, Houston, TX.

Starting Initial Therapy—Controller Therapy

Define Severity Level: After diagnosing asthma but before beginning therapy the severity of a patient's asthma should be defined (Table 5-7).

Table 5-7. Clinical features of asthma—classification of severity

Classification	For Children >5 yr Who Can Use a Spirometer or Peak Flow Meter			
	Days with Symptoms	Nights with Symptoms	FEV, or PEF	PEF
Severe persistent	Continual	Frequent	<60%	>30%
Moderate persistent	Daily	>5/mo	>60%-<80%	>30%
Mild persistent	>2/week	3-4/mo	>80%	20%-30%
Mild intermittent	<2/week	<2/mo	>80%	<20%

Because pulmonary function testing is difficult in children younger than 6 years, only symptoms can be used to define severity in preschool asthma. Recently updated guidelines have made recommendations on the timing of initiation of controller therapy in preschool children with asthma (Box 5-3).

Box 5-3. When to Initiate Daily Asthma Therapy for Infants and Children Younger Than 5 yr

- Three or more episodes/yr of wheezing lasting more than 1 day affecting sleep in a child with Atopic dermatitis and/or parental asthma

Or two of the following - physician diagnosis of allergic rhinitis, peripheral eosinophils, wheezing apart from colds

- Symptomatic treatment more than two times a wk
- Two or more severe exacerbations less than 6 wk apart

Guidelines; for Diagnosis and Management of Asthma—Update on Selected Topics 2002. Bethesda, MD, National Institutes of Health, National Heart, Lung, and Blood Institute. June 2002, Publication No. 02-5075.

The general approach to therapy emphasizes early and aggressive use of controller medications with anti-inflammatory activity for persistent asthma. The severity level should decline after initiation of appropriate therapy. The patient's asthma can be reclassified after optimal therapy is attained according to the level of treatment required to maintain the control. These are as follows:

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(1) no daily controller needed for mild, intermittent; (2) one daily controller needed for mild, persistent; (3) inhaled corticosteroids (ICSs) with or without additional long-term control medications needed for moderate persistent; and (4) multiple, long-term control medications, including high-dose ICSs and possibly oral corticosteroids such as prednisone needed for severe persistent asthma.

There are several pitfalls to consider in assigning severity levels in patients with asthma. First, the severity of disease can change over time in either direction. Also, patients whose asthma is classified as "mild" - and indeed any patient with asthma - can have a severe exacerbation potentially resulting in death at any time. Finally, patients, particularly children, with viral-induced wheezing can have severe episodes with complete absence of symptoms for months in between the episodes.

Tailor Therapy to Severity: After assignment of a severity level, j therapeutic options can be selected based on the severity classification (Fig. 5-7).

Controller Therapy for Persistent Asthma in Children > 5 Years of Age

Mild	Moderate	Severe
Preferred: Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or SR theophylline	Preferred: Low- to medium-dose ICS + LABA Alternative: ↑ICS to med-dose or low-to med-dose ICS + either LTRA or theophylline	Preferred: High-dose ICS + LABA and if needed systemic corticosteroids

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA=Leukotriene Receptor Antagonist; SR = sustained release

(From Executive Summary of the NAEPP Expert Panel Report: Guidelines for the diagnosis and management of asthma—update on selected topics 2002. National Institutes of Health, National Heart, Lung, and Blood Institute. Bethesda, MD, Publication No. 02-5075, June 2002.)

Figure 5-7. Controller therapy for persistent asthma in children older than 5 years. ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LTRA, leukotriene receptor antagonist. (From Executive Summary of the NAEPP Expert Panel Report: Guidelines for the diagnosis and management of asthma—update on selected topics 2002. National Institutes of Health; National Heart, Lung, and Blood Institute. Bethesda, MD, Publication No. 02-5075, June 2002.)

For first-line therapy, the guidelines recommend no daily controller for intermittent asthma; daily inhaled corticosteroids (Table 5-8) for mild (low dose), moderate (medium dose), and severe (high dose) persistent asthma; and consideration of several non-ICS alternatives, including leukotriene receptor antagonists, in children with mild persistent asthma.

There are two general approaches to therapy: step-up (start low and intensify if needed) and step-down (start high and taper). Starting therapy with a non-ICS alternative and then stepping up to an ICS if needed in a patient with mild persistent asthma is one example of the step-up approach. Another example is starting ICS therapy using a low dose and then stepping up to a medium dose if needed in a patient with moderate persistent asthma. In general, a step-down approach using corticosteroids and designed to gain the quickest control of inflammation is recommended. An example of this approach is starting the patient with moderate persistent asthma on one of the following regimens and then tapering to the lowest possible dose: a high-dose ICS or medium-dose

ICS plus a short course of prednisone. Patient-specific factors such as age, ability to use inhalers, steroid phobia, and disease perception, as well as caregiver-specific factors, such as time available at the visit, should be considered. Proper inhaler use and airway delivery of the ICS depends on selection of the proper age-dependent delivery device and time spent educating the patient or parent.

Table 5-8. Estimate comparative daily dosages for inhaled corticosteroids

Drug	Low Daily Dose µg		Medium Daily Dose µg		High Daily Dose µg	
	Adult	*Child*	*Adult*	*Child*	*Adult*	*Child*
Beclomethasone CFC 42 or 84 µg/puff	168-504	84-336	504-840	336-672	>840	>672
Beclomethasone HFA 40 or 80 µg/puff	80-240	80-160	240-480	160-320	>480	>320
Budesonide DPI 200 µg/inhalation Inhalation suspension for nebulization (child dose)	200-600	200-400 0.5 mg	600-1200	400-800 1.0 mg	>1200	>800 2.0 mg
Flunisolide 250 µg/puff	500-1000	500-750	500-750	1000-2000	>2000	>1250
Fluticasone MDI: 44, 110, or 220 µg/putt DPI: 50, 100, or 250 µg/inhalation	88-264 100-300	88-176 100-200	264-660 300-600	176-440 200-400	>660 >600	>440 >400
Triamcinolone acetonide 100 µg/puff	400-1000	400-800	1000-2000	800-1200	>2000	>1200

DPI, dry powder inhaler; MDI, metered-dose inhaler.
National Heart Lung and Blood Institute: The NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topic; 2002.

Education should be provided to empower the patient or parent with sufficient knowledge to commit to and understand the needs as follows:
1. For the use of daily therapy (even if symptoms are minimal).
2. To continue using the drug even after symptoms improve.
3. To not expect immediate benefit from a controller drug (in contrast to their reliever drug). Although there is marked individual variability in responses, the onset of action of ICSs generally occurs over 7 to 10 days.
4. To maximize airway delivery of drug (if an inhaler or a nebulizer is chosen).
5. To understand possible medication side effects, expected benefits, and alternatives to treatment.

Reassessment After Starting Initial Therapy: Reassessment should generally occur within 3 months of the initial visit, at which time disease control should be assessed as evidenced by minimal or no nighttime awakening and cough, exertional symptoms, rescue beta-agonist use, and normal pulmonary function testing or peak flow meter values.
If this assessment reveals adequate disease control and the initial therapy was an ICS, then a 25% to 50% dose reduction is recommended if tolerated. If the first-line controller provided incomplete or no control, additional considerations are warranted.

Alternative diagnoses should be considered and eliminated either clinically or in the laboratory. These include cystic fibrosis, immune deficiency, and congenital airway anomalies. Likewise, concomitant conditions that increase asthma severity, such as sinusitis and gastroesophageal reflux disease, should be considered and treated if present. Adherence and administration technique should also be evaluated. It is possible that patients who report adherence may not truly be adherent, which could be revealed during an examination of pharmacy prescription refills. Also, an excellent drug may be providing no benefit because of inadequate airway delivery secondary to poor technique or an improper delivery device. Environmental exposures to allergen or smoke could be driving disease severity, such that no medication or combination of medications will be able to provide complete disease control. If these considerations provide no cause for the lack of drug response, then a referral to an asthma specialist (allergist or pulmonologist) should be considered and drug therapy adjusted. Possibilities include a doubling of the dose of the ICS, or the addition of a second controller (such as an LTRA or a long-acting beta-2 agonist if the initial choice was an ICS), or replacement of the initial controller with a new controller (such as replacement of an LTRA with an ICS).

Ongoing Reassessment: After disease control is established, regularly scheduled office visits should occur roughly every 12 months for mild intermittent, every 6 months for mild persistent, every 3 months for moderate persistent, and every month for severe persistent asthma. Drug doses and the number of drugs should be adjusted, with the goal of using the minimum effective dose and minimal number of drugs. However, even subtle signs of poor disease control, such as occasional exertional symptoms, should be viewed as evidence against a reduction or elimination of therapy.

Criteria for Possible Discontinuation of Controller Therapy:
Patients, especially children, who are on a low dose of a single drug, have been asymptomatic for at least 12 months (through all four major seasons of the year), and have a normal PEFR or FEV are the best candidates for discontinuation. Children in whom controller therapy is discontinued should be monitored carefully for evidence of recrudescence of disease activity, which has been reported within several months of discontinuation of long-term anti-inflammatory controller therapy.

Exercise-Induced Bronchoconstriction: Virtually every patient with typical, chronic asthma has exercise-induced bronchoconstriction (EIB) in varying degrees, but sometimes EIB can occur in isolation in the absence of any other evidence of chronic asthma. The treatment approach for the former type was summarized previously and includes daily controller therapy. However, even patients with well-controlled asthma may still have EIB. In general, most patients can prevent symptoms by use of a short-acting beta-2 agonist 15 minutes prior to exercise. However, albuterol is not always effective, and alternative medications should be considered. Inhaled cromolyn can prevent EIB and is free of the potential side effects of beta-2 agonists, such as tremor. For patients regularly active over an extended period, such as over 2 or more hours, a long-acting beta-2 agonist or LTRA can be considered because each has demonstrated a longer duration of effect and could be given at home. Finally, ICSs have been shown to reduce the severity of EIB and could be used daily to reduce the impact of EIB.

Individual Drug Considerations
Inhaled Corticosteroids
Inhaled corticosteroids are the gold standard for the long-term management of asthma in adults and children because they have been shown to reduce asthma symptoms, rescue medication use, the markers of airway inflammation, and, uniquely, the risk of asthma mortality. Early intervention with ICSs may preserve pulmonary function and prevent irreversible airway obstruction, remodeling, and hyperresponsiveness. The benefits of early intervention with ICSs in milder cases with recent onset were recently documented. These tremendous benefits must and can

be balanced against small, well-defined, and manageable risks of potential systemic adverse effects, including growth suppression in children. Local airway effects, such as thrush and dysphonia, are rare when spacing devices and mouth-rinsing are utilized.

Sources and Determinants of Systemic Bioavailability of Inhaled Corticosteroids: Even though ICSs were developed to replace more highly bioavailable oral corticosteroids, they can nonetheless be absorbed into the systemic circulation. Ordinarily, approximately 20% of the dose of an ICS enters the airways, and the remainder (about 80%) is swallowed (Fig. 5-8). ICSs can be absorbed from both the gastrointestinal system and the airway mucosa, but, especially for the newer ICSs, the majority of bioavailable drug originates from the airways. Thus, factors that increase the degree of airway delivery, while expected to enhance a drug's benefit, also generally increase the systemic bioavailability of a drug. Highly sensitive measurement techniques are required to detect the small effect that systemically bioavailable drugs can have on childhood growth.
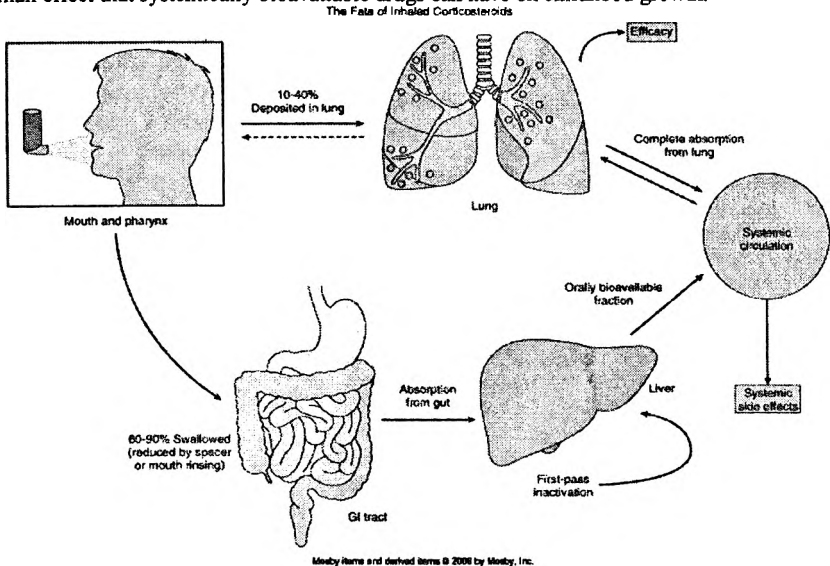
Figure 5-8. The fate of inhaled corticosteroids. Note that the major source of efficacy (lung delivery) is also the major source of systemic bioavailability and any safety concerns. GI, gastrointestinal.

Inhaled Corticosteroids and Their Delivery Devices: The swallowed fraction of the ICS dose is absorbed and metabolized "first-pass" in the liver. Fluticasone and mometasone are almost completely (approximately 99%) inactivated in the liver, and budesonide and triamcinolone, about 90% and about 80% to 90%, respectively, are also inactivated. Beclomethasone diproprionate, however, is largely metabolized to active metabolites and thus has the highest degree of gastrointestinal bioavailability. This difference likely provides the newer ICSs with a better safety profile compared with beclomethasone diproprionate.

Most of the drug in the blood, however, originates from the lower airways, where there is no local metabolism following absorption. Therefore, minimizing gastrointestinal bioavailability via the selection of newer ICSs or use of a spacing device will not necessarily eliminate the possibility of systemic bioavailability. Furthermore, factors that increase airway dose and delivery (i.e., increasing the microgram dose, use of spacers, formulation changes that result in smaller particle sizes [hydrofluroalkane-134a (HFA) versus chlorofluorocarbon (CFC) propellants], improved inhalation technique) may provide better benefit but may also increase the systemic bioavailability of the drug.

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Disease Severity Considerations: In patients with mild asthma, airways are more patent than in those with more severe asthma. As a result, drug deposition and absorption, and thus systemic side effect risk, may be higher. Several studies and indirect lines of evidence support that possibility, and the growth effects of ICS generally have been greatest in those with the mildest severity (see later). ICS-induced adrenal axis suppression was directly related to airway function in one study of asthmatic individuals. Nonetheless, the results argue for the approach most often taken: using low-dose ICS for the mildest cases or considering nonsteroid alternatives.

Growth Suppression: Prior to examining the potential effects of ICS on growth, it is important to recognize that poorly controlled asthma and systemic corticosteroid bursts can adversely affect growth. The Food and Drug Administration recently issued new guidelines for the class labeling of all corticosteroids, both inhaled and nasal, to reflect the possibility of a small degree of growth suppression. Many factors likely influence this risk, including total dose, drug delivery device and technique, genetic predisposition, age, adherence, and asthma severity.

Influence of Asthma Severity on Inhaled Corticosteroid-Induced Growth Suppression (Intermediate Term): Three 1-year trials compared the growth of children from 6 months to 8 years of age treated with budesonide nebulizing suspension or conventional asthma therapy. In these trials, the group of children with the mildest severity manifested a small degree of growth suppression, while the two groups with higher severity levels showed no such evidence. Most of the earlier studies examining the growth effects of ICSs also enrolled children with milder degrees of disease severity because poorly controlled asthma and frequent prednisone bursts (in the more severe patients) can also have an adverse impact on growth.

Long-Term Inhaled Corticosteroid Use: Linear growth was examined in children with asthma in the Childhood Asthma Management Program (CAMP). Compared with children re-ceiving placebo or nedocromil sodium, the budesonide treatment group had a small reduction in growth velocity during the last year that was not sustained for the remainder of the 4- to 5-year study. This study was reassuring and suggested that the effect of ICSs on growth was transient and restricted to the 1st year of a 4- to 5-year course of continuous therapy. A second study, with a different design, produced similarly reassuring results. In that study, children treated with budesonide for an average of 9.2 years reached their calculated target adult height, based on parental height, compared with 18 control, ICS-naive asthmatic patients and 51 healthy siblings. This study showed that, even if the ICSs do suppress growth during the 1st year of therapy, "catch-up" growth likely occurs later.

Risk Management: Strategies for Balancing Safety and Efficacy of Inhaled Corticosteroids: The most obvious method is the step-down approach to ICS therapy, whereby the patient is started on a high dose to achieve quick control of airway inflammation and then gradually tapered to the minimum effective dose that would be continued to maintain long-term control and less likely to have any impact on susceptible processes such as growth. Determining and maintaining a "low" minimum effective dose could depend on attention to other aspects of asthma care, including rigorous smoke and allergen environmental controls, vaccination for influenza virus, the diagnosis and treatment of concomitant conditions that could worsen asthma (i.e., rhinitis, sinusitis, gastroesophageal reflux disease), and the appropriate use of add-on therapy.

The safety of ICSs can be further managed and optimized through attention to several other aspects of care. The time of day of ICS administration - morning or evening for those who are stable on once-daily dosing - may modify the risk for growth suppression. A 4-week study of children with asthma examined the growth-suppressing effects of budesonide (800 µg) administered under two different dosing strategies. During one period, it was given as a single dose in the morning; during the other period, it was given as two divided doses - 400 µg in the morning and

400 μg in the evening. Lower leg growth rates were significantly lower in children receiving an evening dose than in children receiving only a morning dose. The results of this study suggest that for patients who are stable on once-daily dosing, the morning is the safest time for administration. Because that administration time may not maximize adherence or efficacy, other factors must be considered in designing an individualized therapeutic strategy.

When the ICS fails to provide sufficient control, options include doubling the ICS dose or adding on a second nonsteroidal controller medication. The latter possibility was supported by a recent study showing that, in children treated with ICS, halving the ICS dose and adding a second nonsteroidal drug was associated with faster short-term lower leg growth with no loss of asthma control, versus maintaining the original higher ICS dose alone. This result supports the widely held recommendations to use the lowest effective dose and, in poorly controlled patients, to add non-ICS therapy rather than double the ICS dose.

Safety management should also incorporate the monitoring of growth every 3 to 6 months and interpreting the resultant measurement and changes. The mouth should be rinsed after ICS administration to minimize the swallowed portion of drug. Also, careful attention should be given to potency differences when dosing ICS, especially when changing from a lower-potency to a higher-potency ICS. For example, a clinically equivalent dose of fluticasone and beclomethasone diproprionate may differ by twofold - about 400 μg of beclomethasone diproprionate are equivalent to about 200 μg of fluticasone.

Leukotriene Receptor Antagonists

Leukotrienes promote smooth muscle constriction and inflammatory events. Not surprisingly, leukotriene receptor antagonists (LTRAs) can reduce markers of inflammation and smooth muscle contraction. Thus, pediatric asthma guidelines state that LTRAs may be an alternative to low-dose ICS therapy in mild persistent asthma and may be an effective add-on to ICS therapy in moderate persistent asthma.

Zafirlukast, the first LTRA approved in the United States, was shown to be effective in the management of mild-to-moderate asthma. It improved pulmonary function and reduced the clinical symptoms of asthma as well as the need for ICSs. Zafirlukast is indicated for twice-daily oral treatment for the management of asthma in children as young as 7 years. Because it can inhibit the CYP450 isoenzyme CYP3A4, it can increase concentrations of certain concomitant medications such as theophylline. Food can also reduce zafirlukast's bioavailability; therefore, according to its package insert, it should be taken 1 hour before or 2 hours after a meal.

Controlled clinical trials have shown that montelukast, another approved LTRA, is effective in the management of adult and pediatric asthma. Montelukast is indicated as once-daily therapy for the treatment of mild-to-moderate asthma in children as young as 12 months and does not have known drug interactions or food restrictions. Efficacy was initially demonstrated in adults and 6- to 14-year-old children[24] and, more recently, in younger children. Interestingly, montelukast provided beneficial effects on (3-agonist use that were noted on the first day of use and provided the same improvement in pulmonary function, regardless of whether the patients were receiving ICS. A granule formulation of montelukast can be used to treat children as young as 1 year. Also, a recent controlled study showed that, in ICS-treated children with persistent asthma, the addition of montelukast improved pulmonary function and symptoms, with significant reduction in beta-2 agonist use.

Chromones

Cromolyn sodium has been used for more than 30 years as an inhaled mast cell stabilizer in the treatment of persistent asthma.

Efficacy has been demonstrated in adults and can be achieved in patients as young as 2 years using a nebulizer. Although patients taking cromolyn have experienced minor adverse effects such as cough, no serious adverse effects have been noted. The safety of this product has been the major driving force of usage over the years, even in the context of rather poor effectiveness. Controlled clinical trials in young children have shown that cromolyn is safe and efficacious as either monotherapy or in combination with beta-2 agonists. However, a randomized trial in more than 200

children to 4 years of age with moderate asthma showed that cromolyn was not more effective than a placebo. Also, cromolyn added little or no benefit to ICS therapy, supporting current pediatric guidelines that do not recommend cromolyn as add-on therapy to ICSs. These results, combined with a requirement for frequent three- or four-times-a-day dosing and the need for metered dose inhaler (MDI)/spacer or nebulizer, have led to an overall decline in cromolyn use and a recommendation that cromolyn not be used as first-line preventive therapy.

Inhaled nedocromil sodium appears to have a similar mechanism of action and a similar clinical profile to cromolyn, with the major advantage of safety and major disadvantage of minimal efficacy. In addition, bitter taste is a frequent complaint of regular nedocromil users. In the CAMP study, nedocromil significantly reduced the number of urgent-care visits $(P = 0.02)$ and courses of prednisone $(P = 0.01)$ but was similar to placebo in all other endpoints, including airway hyperresponsiveness, pre- and post-bronchodilator FEV_1, rate of hospitalization, daily symptom score, and rescue bronchodilator use. One difference from cromolyn is that, added to ICS therapy, nedocromil was modestly beneficial in asthmatic adults. Because this efficacy was not demonstrated in children, pediatric asthma guidelines do not recommend the use of nedocromil as add-on therapy to ICSs.

Methylxanthines

Theophylline has been used to treat asthma for more than 60 years. Theophylline is a phosphodiesterase inhibitor, relaxes airway smooth muscle (bronchodilation) - consequently improving airway function - and may have mild anti-inflammatory effects. However, its mechanism of action in asthma is not completely clear.

Theophylline was shown to be effective in treating mild-to-moderate asthma in children. Steroid-dependent children with asthma also demonstrated added benefit when theophylline was added to ICS therapy. These studies support the recommendation that theophylline can be used as add-on therapy to ICSs. Practically, it is usually the third drug added on after LTRAs and long-acting beta-agonists. Although it can be considered an alternative first-line therapy, it is not preferred for persistent asthma.

Theophylline use in children has been linked to changes in behavior and school performance. These adverse effects are more common when blood levels exceed the upper limits of the thera-peutic range (10 µg/L to 20 µg /L in adults, 5 µg /L to 15 µg /L in children) but also can be seen at therapeutic concentrations. Adverse effects, such as headache and other effects on the central nervous system, tremor, nausea, vomiting, and gastric irritation, also have been reported frequently in patients taking theophylline. Theophylline has numerous drug interactions that alter plasma levels. As a result of these safety issues, as well as the need for plasma concentration monitoring, theophylline use has dramatically decreased recently despite relatively low cost.

Long-Acting Beta-2 Agonists

Salmeterol is a long-acting inhaled beta-2 agonist indicated for long-term use and has been available as both an aerosol and a dry-powder inhaler. The latter is approved for children as young as 4 years. Salmeterol is not indicated for the treatment of acute j symptoms or exacerbations, due to a slow onset of action. Thus, patient education about the role of this medication is essential. Salmeterol was more efficacious than short-acting beta-2 agonists and placebo in treating mild-to-moderate asthmatic children, with effects (bronchodilation) lasting up to 12 hours. Although long-term benefits are well established in adults, a recent review article raised questions about whether treated children experienced the same degree of benefit and whether they shared the same disease processes as adults.

Tolerance can develop with prolonged salmeterol use, which can result in decreased bronchoprotection against methacholine challenge and exercise-induced bronchoconstriction. Although salmeterol has a protective effect against exercise-induced asthma, the duration of this effect may wane even during regular once-daily salmeterol treatment, despite the reduced frequency of dosing and concomitant use of ICSs in children.

Current asthma guidelines recommend that long-acting beta-2 agonists should not replace anti-inflammatory therapy but should be considered as possible add-ons. For children with

moderate-to- severe asthma, combining salmeterol with budesonide improved morning and evening PEFR and symptom-free days and reduced the use of rescue medications. Patients should be instructed not to stop anti-inflammatory therapy while taking salmeterol even though their symptoms may significantly improve. Also, salmeterol was recently reformulated to include fluticasone in a single inhaler. As such, the fluticasone/salmeterol dry-power inhaler may be a useful option for nonadherent patients or for those who require combination therapy, since it reduces the number of inhalations per day.

A second agent, formoterol, has been approved in the United States for use by adults and children older than 12 years. Formoterol has a quicker onset of action than salmeterol. The advantages and limitations of long-term asthma controllers, including long-acting beta-2 agonists, are summarized in Table 5-9.

Oral Corticosteroids

Orally administered or injected corticosteroids are indicated for the acute, short-term therapy of severe asthma exacerbations. Systemic corticosteroid therapy is indicated in the management of acute asthma and is mandatory in the therapy of status asthmaticus. By appropriately timing the intervention with corticosteroids, the clinician may benefit the patient and reduce hospitalizations. Since the action of corticosteroids is dependent on cellular internalization, therapy should be instituted promptly once an indication for use is established.

Typically, patients begin oral prednisone (2 mg/kg/day or max. 60 mg/day) at the onset of an acute exacerbation and continue I the treatment for 3 to 10 days. Oral preparations also can be used as alternate-day maintenance therapy for severe persistent asthma. Although high-dose, short-term corticosteroid therapy is relatively safe in severe life-threatening disorders, chronic systemic administration in patients with severe asthma carries a significant risk for adverse effects, including growth suppression, adrenal suppression, osteoporosis, fractures, cataracts and glaucoma, weight gain, and hypertension. Complications detectable on physical examination include weight gain, "moon-type" fades, hirsutism, polycythemia (red, ruddy complexion), and short stature. Such side effects of excessive steroid therapy for chronic asthma should be avoidable complications, and oral corticosteroid exposure can be reduced by the use of inhaled corticosteroids.

Table 5-9. Advantages and limitations of long-term asthma controllers

Drug Class	Advantages	Limitations
Inhaled corticosteroids	Reduce exacerbations Improve pulmonary function Reduce airway responsiveness Reduce airway inflammation	Increased risk of systemic side effects with prolonged, high-dose therapy Limited information on long-term use in children Limited information on use in young children
Leukotriene antagonists	Reduce symptoms improve pulmonary function Reduce exercise-induced bronchospasm Prevent allergen-induced inflammation	Limited information on reduction of airway inflammation No apparent effect on airway responsiveness No information about impact on natural history of asthma
Long-acting beta-2 agonists	Reduce exacerbations Improve pulmonary function Reduce airway responsiveness Attenuate exercise-induced bronchospasm	Reduced effect with long-term treatment No apparent effect on inflammation No information on use in young children

National Heart, Lung, and Blood Institute: The NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002.

Anticholinergic Agents

In the outpatient setting, anticholinergic agents such as ipratropium bromide can have possible additive benefit to inhaled beta-2 agonists for severe exacerbations and can be used as a possible alternative bronchodilator for children who do not tolerate inhaled beta-2 agonists.

Anti-Immunoglobulin E Antibody

Efficacy of a humanized monoclonal antibody against human IgE (Omalizumab) was recently demonstrated in patients with allergic asthma. This antibody is administered by subcutaneous injection and dramatically reduces serum IgE levels. The drug improved a number of asthma outcomes but did not induce remission and also benefited patients with allergic rhinitis. Effects disappeared when the drug was discontinued. Likely positioning in the future will be in severe asthmatics who are using high-dose ICSs or maintenance oral corticosteroids and possibly in those who are nonadherent with daily controller therapy (because anti-IgE is given every several weeks). Cost will be an important consideration in its use.

Allergen Immunotherapy

Allergen immunotherapy has demonstrated efficacy in and is widely used to treat allergic rhinitis, even in patients with asthma. The role of allergen immunotherapy is less well defined in patients with asthma, and some studies have raised doubt about beneficial effects in such cases. Safety concerns are also slightly higher in patients with asthma than in those with uncomplicated allergic rhinitis. When used properly by an asthma specialist, allergen immunotherapy may be a viable option for patients whose asthma is triggered by allergic triggers and whose condition cannot be controlled with pharmacologic therapy. The next decades are virtually certain to improve both the efficacy and safety of this therapeutic approach.

Other Therapies

Other therapies are available for patients who fail to respond adequately to the medications discussed here but will generally be used by asthma specialists due to issues regarding efficacy or safety. Most patients who are viable candidates for these therapies already failed therapy with high-dose ICSs and maintenance oral corticosteroids. These agents have immunosuppressive or anti-inflammatory effects and include methotrexate (an antimetabolite), cyclosporin A (an immunosuppressive fungal metabofite), gold, troleandomycin (a macrolide antibiotic), and cytokine-directed therapies. Annual influenza virus vaccination is recommended for adults and children with asthma severe enough to require regular medical follow-up or hospitalization.

Home/Emergency Department Management of Asthma Exacerbation

The guidelines for the management of asthma exacerbations at home, in the emergency department, and in the hospital are summarized in Figures 5-9 and 5-10. Status asthmaticus (poor response to emergency department treatment protocol) is treated with IV corticosteroids, oxygen, and a nebulized beta-agonist on a regular, frequent (every 1 to 2 hours), or even continuous basis. Patients are weaned from it as they improve. If the patient has been on chronic maintenance theophylline therapy as an outpatient, then parenteral theophylline therapy also should be instituted. Most pediatric patients improve on this therapeutic regimen and are discharged within 3 days, but adults frequently respond less rapidly and require longer periods of hospitalization. In general, beta-adrenergic dosing intervals of less than 2 hours require observation and monitoring in an intensive care facility. A patient with status asthmaticus must be monitored closely during the first 6 to 12 hours of hospitalization for impending respiratory failure so that therapy to prevent progression to respiratory failure can be instituted.

Therapy for impending respiratory failure consists of the correction of acid-base imbalances in the setting of an intensive care unit, where cardiac and respiratory function can be closely monitored. If respiratory failure supervenes despite intense I medical management, artificial mechanical ventilation is indicated.
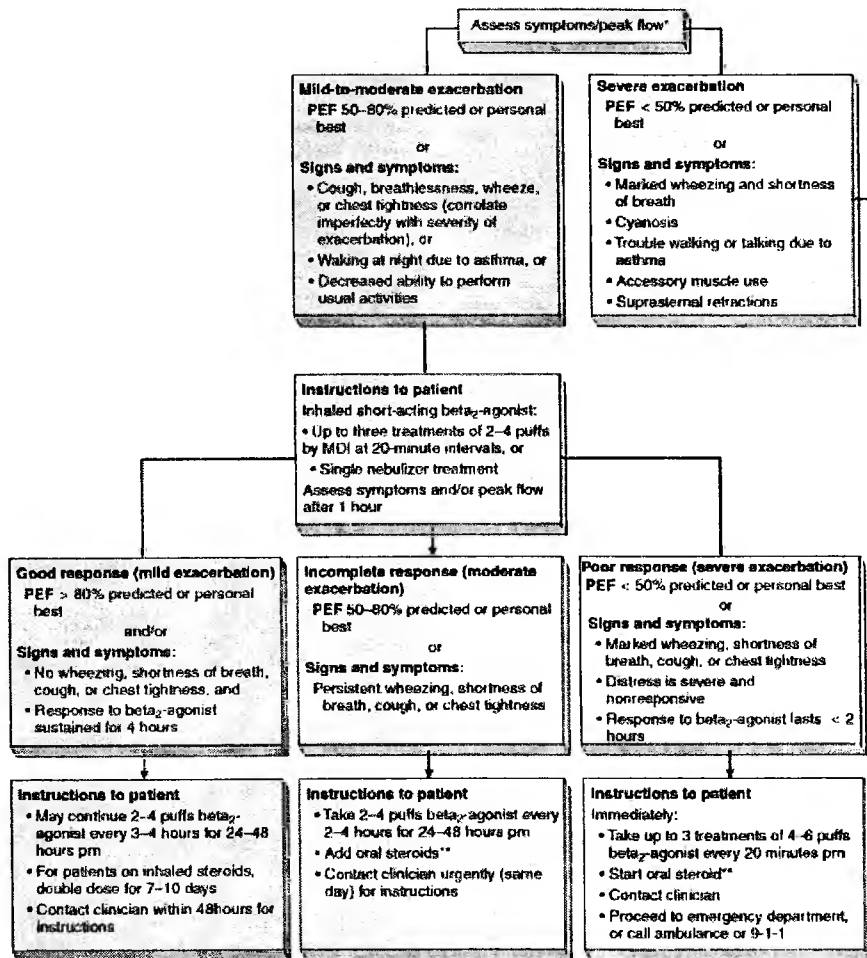
Figure 5-9. Home management of asthma exacerbations. MDI, metered dose inhaler; PEF, peak expiratory flow. (From National Asthma Education and Prevention Program: Practical Guide for the diagnosis and management of asthma. Bethesda, MD, NIH Publication Number 97-4053, October 1997, page 27; National Heart, Lung, and Blood Institute; National Institutes of Health, 1997.)

Figure 5-10. Emergency department– and hospital-based management of asthma exacerbations. FEV_1, forced expiratory volume in 1 second; O_2, oxygen; PEF, peak expiratory flow. (From National Asthma Education and Prevention Program: Practical Guide for the diagnosis and management of asthma. NIH Publication Number 97-4053. Bethesda, MD, National Heart, Lung, and Blood Institute of Health, 1997.

Management of Asthma During Pregnancy

It is essential that sufficient lung function and blood oxygenation be maintained during pregnancy so that an adequate oxygen supply to the fetus is provided. Increased perinatal mortality, increased prematurity, and low birth weight can all result from poorly controlled asthma. For most drugs used to treat asthma, there is little evidence to suggest an increased risk to the fetus.

Exceptions include corticosteroids and epinephrine. Therapy with the lowest possible doses of the fewest possible medications should be the goal of treatment of asthma during pregnancy.

Identification of Patients at Risk for Asthma-Related Death

Care of asthmatic patients should include the identification of patients at risk for asthma-related death (Box 5-4).

Box 5-4. Risk Factors for Death from Asthma

History of Severe Exacerbations
- History of sudden severe exacerbations
- Prior intubation for asthma
- Prior admission for asthma to an intensive care unit

Asthma Hospitalizations and Emergency Visits
- Two of more hospitalizations in the past year
- Three or more emergency care visits in the past year
- Hospitalization or emergency visit in past month

Beta-2 Agonist and Oral Steroid Usage
- Use of more than two canisters per month of short- acting inhaled beta-2 agonist
- Current use of oral steroids or recent withdrawal from oral steroids

Complicating Health Problems
- Comorbidity (e.g., cardiovascular diseases or chronic obstructive pulmonary disease-COPD)
- Serious psychiatric disease, including depression, or psychosocial problems
- Illicit drug use

Other Factors
- Poor perception of airflow obstruction or its severity
- Sensitivity to Atternaria (an outdoor mold)
- Low socioeconomic status and urban residence

Clues include the presence of previous life-threatening exacerbations of asthma, the lack of adequate and ongoing medical care that provides appropriate follow-up and prophylactic therapy, and significant depression or psychosocial behavioral problems.

Asthma as a Component of a Whole-Airway Disease

There is a strong relationship between events in the upper and lower airways, which are linked epidemiologically and pathophysiologically. The evolving concept is "one airway, one disease." This has led to the development of a set of guidelines termed *ARIA*, for Allergic Rhinitis and its Impact on Asthma. These guidelines strongly recommend that persistent asthmatics be evaluated for nasal disease (allergic rhinitis) and vice versa. Moreover, a combined approach to therapy, considering both safety and efficacy, is recommended.

Sulphite sensitivity

Some individuals are unusually sensitive to sulphites. These agents include sulphur dioxide, sodium and potassium metabisulphite, and sulphite. These agents are used widely in foods and drinks as antioxidants and preservatives.

Presentation Reactions include severe wheeze accompanied by flushing, tachycardia and, if severe, may mimic anaphylaxis. Urticaria and angioedema are not usually features.

Cause Mechanism is unclear but probably involves direct mast-cell stimulation and cholinergic stimulation. IgE antibodies have occasionally been detected. There does not appear to be any cross-reactivity with other agents.

Diagnosis
• The history is usually diagnostic, with reactions typically to white wine or beer, soft drinks, pickles, salami and preserved meats, dried fruits, shrimps/prawns, and prepared salads.
• Certain drugs for injection contain sulphites, particularly adrenaline-containing local anaesthetics used by dentists.
• No tests are of particular value except for exclusion followed by re-challenge under controlled conditions (with facilities for resuscitation).

Treatment Management is by avoidance and proper dietary advice is required. Care must be taken with the prescription of drugs. Severe reactors may need to carry adrenaline (without sulphites).

Aspirin sensitivity

Presentation In addition to its propensity to cause angioedema, aspirin is also associated with a triad of asthma, nasal polyposis, and hyperplastic sinusitis (Samter's triad). Each feature can occur without the others.

Cause
• Effect is due to a sensitivity to cyclo-oxygenase inhibition, and therefore occurs with other NSAIDs but not usually with choline or sodium salicylate or paracetamol.
• There is a loss of bronchodilating prostaglandins and a shunting of substrate to the lipooxygenase pathway with the production of bronchoconstrictor leukotrienes.
• Some patients with aspirin intolerance also react to tartrazine and related azo-dyes.

Diagnosis
• Specific IgE tests are of uncertain value. Flow-CAST assay may show positives in some patients.
• Aspirin challenge is not recommended unless there is doubt about the diagnosis, as reactions may be severe.

Treatment
• Exclusion of natural salicylate from the diet may be helpful if asthmatic symptoms and nasal polyps are troublesome.
• Obstructing polyps need to be removed surgically; oral or topical corticosteroids will lead to shrinkage. Regrowth after surgery may be prevented by diet and drug therapy with topical nasal steroids and oral agents.
• Large polyps may need treatment for short periods with betnesol drops, before nasal steroid sprays will be effective. Intransal frusemide spray may be an alternative (50 μg/puff).
• The combination of oral antihistamines and monteleukast can be helpful.
• Aspirin desensitization can be undertaken: incremental doses of aspirin are administered over 2 days; tolerance persists only while aspirin is administered regularly. Risks of triggering severe acute asthma are high, and the treatment should be undertaken with intensive care unit back-up.

6. ALLERGIC RHINITIS

Allergic rhinitis is the most common allergic disease. Although not life threatening, this frequent illness causes considerable morbidity and results in the expenditure of billions of dollars in direct and indirect health care and the loss of millions of work and school days.

Allergic rhinitis is provoked by exposure to antigenic environmental factors referred to as allergens, with resultant sneezing, nasal pruritus, rhinorrhea, nasal mucosal edema, and subsequent nasal obstruction induced by an immunoglobulin (Ig) E-mediated response. Symptoms can be episodic or perennial; because symptoms recur annually during certain months, the syndrome is sometimes called *seasonal* allergic rhinitis. The predominate allergens causing seasonal allergic rhinitis are outdoor pollens, such as tree, grass, or ragweed pollen. Typically, seasonal allergic rhinitis does not develop until after the patient has been sensitized by two or more seasons. Seasonal allergic rhinitis is frequently referred to as *hay fever* or *summer cold,* but these descriptive terms are misleading and should be discarded because fever is not a symptom of allergic rhinitis, and the common cold virus is not the etiology. Perennial allergic rhinitis can be constant or recurrent and occurs year-round. It can also be associated with seasonal exacerbations.

Recent guidelines for the management of allergic rhinitis have redefined the illness as intermittent or persistent rather than seasonal and perennial (see Box 6-1). Intermittent rhinitis is defined on the basis of symptoms that are present for less than 4 days per week and for less than 4 weeks. If symptoms are present for more than 4 days per week or have lasted for more than 4 weeks regardless of the number of days per week, the illness is classified as *persistent* allergic rhinitis. In addition, the severity of symptoms should be designated as mild or moderate to severe.

Box 6-1. Clinical classification of allergic rhinitis
1. Duration
a. *Intermittent* (seasonal): Symptoms present
- Less than 4 days/wk or
- Less than 4-6 wk/yr
b. *Persistent* (perennial): Symptoms present
- More than 4 days/wk and
- More than 6 wk
2. Severity
a. *Mild*: Symptoms do not affect lifestyle
b. *Moderate-severe*: Symptoms affect lifestyle
- Sleep disturbance
- Impair leisure or sport activities
- Impair school or work

CAUSES OF RHINITIS
Allergic.

Vasomotor.

Non-allergic rhinitis with eosinophilia (NARES).

Drug-induced: a-agonist nasal sprays, cocaine abuse (direct); antihypertensives, chlormethiazole (indirect).

Irritant: fumes, solvents.

Infectious: viral, bacterial, leprosy, cilial dyskinesia.

Vasculitis: Wegener's granulomatosis.

Mechanical: nasal polyps, septal deviation, foreign bodies, tumours, sarcoidosis.

Pregnancy: last trimester (related to oestrogen levels).

IMMUNOLOGICAL MECHANISMS

• Mechanisms in allergic rhinitis are very similar to those described above for asthma, although histamine release plays a more significant role and the role of neurogenic mechanisms is less well established.

• Histamine and leukotrienes are though to be responsible for the itch, sneezing, rhinorrhoea, and nasal obstruction, through swelling and hyperaemia.

• There is a predominant eosinophilia in tissue and secretions.

• Perennial rhinitis may be a manifestation of chronic antigen exposure and, like chronic asthma, may lead, via type IV mechanisms, to chronic tissue damage with connective tissue proliferation.

• Allergens involved are similar to those involved in asthma, i.e. aero-allergens, although larger allergens will tend to be trapped preferentially in the nose.

• Nasal polyps may occur as a result of chronic allergic stimulation.

PATHOPHYSIOLOGY

Allergic rhinitis adversely affects normal nasal function which, besides its role as an airway (Fig. 6-1A and B) includes filtration of particulate matter from inspired air, humidification of air, olfaction, and phonation.
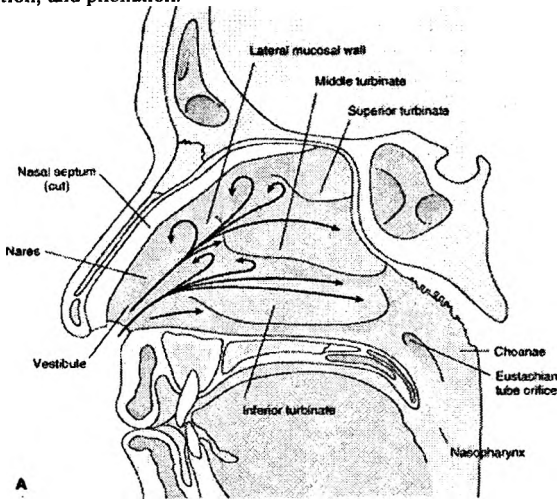
NASAL FUNCTION: IMPORTANT ASPECTS

1. Passage of air
2. Humidification
3. Warming of air
4. Filtering of air
5. Mucociliary action
6. Olfaction
7. Phonation

Figure 6-1. A, The inside of the nose, illustrating how the inspired air, after entering the nose, circulates over, under, and around the inferior, middle, and superior nasal turbinates. This pattern of circulation enables the nasal mucosa to more effectively filter, humidify, and warm the air. B, Major aspects of the nasal function.

The patient with allergic rhinitis has compromise not only of nasal function but also of other portions of the contiguous respiratory tract, including the eustachian tube, sinuses, and bronchi, which can be affected. Allergen-provoked eustachian tube obstruction has been detected not only after intranasal provocation but also during seasonal, natural pollen exposure. Allergen, methacholine, or histamine bronchial challenge provokes lower airway obstruction (i.e., asthma) in 30% or patients with allergic rhinitis. That allergic rhinitis contributes to the pathogenesis of sinusitis has also been suggested.

CLINICAL PRESENTATION

Seasonal (intermittent) allergic rhinitis begins with frequent sneezing, nasal pruritus, and clear rhinorrhea and then progresses to nasal obstruction (Table 6-1).

Table 6-1. Allergic rhinitis: symptoms, pathophysiology, and effector mediators

Symptoms	Pathophysiology	Effector mediators
Tickling, itchiness, nose rubbing, allergic "salute"	Pruritus	Histamine, prostaglandins
Sneezing	Sneezing	Histamine, leukotrienes
Nasal congestion, stuffy nose, mouth breathing, snoring	Mucosal edema, increased vascular permeability	Histamine, leukotrienes, bradykinin, platelet-activating factor
Runny nose, postnasal drip, throat clearing	Rhinorrhea, mucous secretion	Histamine leukotrienes

Perennial (persistent) allergic rhinitis tends to manifest more stuffiness. Patients emphasize early morning and late evening symptoms, and nasal obstruction may interrupt sleep. They also complain of itching of the eyes, throat, ears, and nose. To relieve the nasal itch, some children may press the palm or arm upward against the nose in an "allergic salute". Constant rubbing of the itchy nose may produce a transverse nasal crease, a horizontal groove across the lower third of the nose. With nasal obstruction, the patient becomes a mouth breather, so snoring is a nighttime symptom. Mouth breathing may contribute to orofacial dental abnormalities that require orthodontic procedures, but this has not been established definitely.

Seasonal (intermittent) allergic rhinitis is frequently accompanied by allergic conjunctivitis. When symptoms of nasal obstructin are severe, adjacent sinuses may be involved, causing facial discomfort or headaches. Patients with eustachian tube dysfunction complain of fullness or popping sounds in the ears. Hearing loss in a child with perennial (persistent) allergic rhinitis suggests a conductive hearing deficit associated with otitis media with effusion. Loss of sense of smell and taste is also described. A few patients may complain of generalized malaise, irritability, and fatigue, which may be related to interrupted sleep.

Patients with seasonal (intermittent) pollinosis describe increased symptoms as the season progresses, especially on dry, windy days; symptoms may continue well beyond the season. Repeated exposure to allergens increases nasal reactivity and "primes" nasal mucosa, so that ordinarily innocuous concentrations of allergens and other environmental factors provoke symptoms. The pattern of symptoms helps distinguish seasonal (intermittent) from perennial (persistent) allergic rhinitis. In subtropical climates, a seasonal aeroallergen exposure pattern may not be obvious, as pollen seasons extend for many months and fungi can be airborne year-round. In much of the United States, as well as other temperate climates, trees pollinate in spring, grasses in late spring and summer, and weeds during late summer and early fall. Increased pollen concentrations - and thus, frequent complaints of more symptoms - are noted in areas of high plant density. Yet, windblown, airborne pollens can spread for miles and cause symptoms. If they have direct contact with considerable amounts of pollen, patients can have angioedema, especially of the eyes and throat.

Patients with perennial (persistent) symptoms are more of a diagnostic challenge. Continuous exposure to home or occupational factors induces persistent symptoms, because congestion of the mucosal tissues does not return to normal during the few hours free of allergen exposure. In these patients, nonallergenic aerosolized irritants, such as cigarette smoke, fumes, industrial pollutants, and cosmetics, provoke increased symptoms. Additional nonallergenic factors include changes in barometric pressure, temperature, and humidity.

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Examination of nasal mucosa requires the use of a nasal speculum with an appropriate light source. Although fiberoptic rhinoscopy is not needed for most cases, it can be a valuable adjunct in a more thorough inspection of the nose and nasopharynx. With development of nasal allergy, clear nasal secretions are evident. The mucosa appear pale, boggy, blue-gray, and edematous without much erythema. The turbinates become swollen and obstruct the nasal airway. When this occurs, it may be necessary to shrink the mucosa and to use a vasoconstrictor to document nasal polyps, which occur in 10% to 15% of adult patients. Conjunctival edema and hyperemia, along with Dennie's lines, are frequent findings. Allergic rhinitis patients with considerable nasal obstruction and venous congestion, particularly children, demonstrate edema and darkening of the tissues beneath the eyes. These so-called "allergic shiners" are not pathognomonic for allergic rhinitis; they can also be seen in patients with recurrent nasal and sinus congestion of any cause.

DIAGNOSIS

• Diagnosis relies heavily on the history and on examination of the nose. Rhinoscopy may be necessary to obtain a good view; use of an otoscope is adequate for most purposes.

• Eosinophil count in blood is rarely elevated.

• Elevated total IgE may indicate an allergic basis, but a normal IgE does not exclude allergy.

• Skin-prick tests (SPTs) demonstrate sensitization to aeroallergens, but the clinical relevance can be determined only from the history. The most useful allergens in study of allergic rhinitis are the inhalants, especially the pollens, the molds (fungi), house dust, and animal product (Box 6-2.)

• Specific IgE (RASTs) should be limited only to confirming equivocal SPTs, or when drugs such as antihistamines cannot be discontinued. Both RASTs and SPTs may be negative even in the presence of significant local allergy if no specific IgE is free to spill over into the bloodstream.

• Examination of nasal secretions for excess eosinophils may be helpful, although there is a condition of non-allergic rhinitis with eosinophilia (NARES). This is often associated with aspirin sensitivity and asthma; sinusitis is also common. Peripheral blood eosinophilia is variable and is a poor diagnostic marker.

• If the suspect allergen is available, then nasal provocation tests may be possible.

Box 6-2. Selected inhalant allergens useful in evaluation and testing for allergic rhinitis pollens (vary with geographic area)
     Weeds (ragweed, plantain, etc.)
     Grasses (timothy, rye, etc.)
     Trees (oak, maple, etc.)
Fungi (molds)
     • Seasonal *(Alternaria,* etc.)
     • Storage *(Aspergillus,* etc.)
Animal products
House dust mites (cuticle, feces)
Dogs, casts (dander, saliva)
Birds (feathers, droppings)

DIFFERENTIAL DIAGNOSIS

Allergic rhinitis needs to be distinguished from non-allergic causes, such as vasomotor rhinitis, rhinitis medicamentosa, and infectious cause and other condicions (Box 6-3).

Box 6-3. Differential Diagnosis of Chronic Rhinitis and Nasal Obstruction
Rhinitis
     • Allergic rhinitis: Seasonal or perennial
     • Infectious rhinitis: Chronic or acute (frequent recurrences)
     • Obstructive foreign body
     • Rhinitis secondary to topical decongestants, rhinitis medicamentosa

- Nonallergic rhinitis with eosinophilia (NARES)
- Nonallergic vasomotor rhinitis (cholinergic)
- Hormonal rhinitis: Pregnancy or hypothyroidism
- Atrophic rhinitis

Other Causes of Nasal Obstruction

Rhinosinusitis

Anatomical abnormality (e.g., deviated septum, enlarged adenoids)

Nasal polyps

Tumor (e.g., angiofibroma)

Cerebrospinal fluid leakage secondary to perforation of the cribriform plate by fracture or tumor Granulomatous disorders (e.g., Wegener's granulomatosis, sarcoidosis)

A comparison of allergic and nonallergic rhinitis (persistent) is made Table 6-2.

Table 6-2. Comparison of allergic and nonallergic rhinitis

Allergic		Nonallergic	
		NARES*	Vasomotor
History			
Occurrence	Seasonal, perennial	Perennial	Perennial
Age	Children, adults	Mostly adults	Mostly adults
Sex	Male, female	Male, female	Mostly female
Physical examination			
Edema	Moderate, marked	Moderate	Moderate
Secretions	Watery	Watery	Mucoid, watery
Laboratory tests			
Nasal eosinophils	Common	Common	Coincidental
Allergen tests	Positive	Coincidental	Coincidental
Therapy			
Antihistamines	Beneficial	Rarely help	Rarely help
Decongestants	Helpful	Sometimes help	Sometimes help
Steroids	Beneficial	Helpful	Rarely help
Cromoryn	Beneficial	Not helpful	Not helpful
Ipratropium	Not helpful	Not studied	Helpful
Immunotherapy	Beneficial	Not indicated	Not indicated

* - NARES, nonallergic rhinitis with eosinophilia.

TREATMENT

• Topical or systemic antihistamines provide relief in mild cases.

• More severe cases may require topical steroids or mast-cell blocking agents such as disodium cromoglycate or nedocromil sodium.

• Ipratropium bromide is particularly helpful in vasomotor rhinitis.

• Ensure patient understands optimum head position for use of nasal sprays: head forward looking at feet, with nozzle pointed away from the nasal septum. Most therapeutic failures are due to incorrect use of sprays.

• Decongestants should be used with caution (or not at all) because of a rebound increase in symptoms.

• Very severe cases may require courses of oral corticosteroids. Depot injections of long-acting steroid have been used in the past in seasonal rhinitis: these are not recommended (risk of avascular necrosis of joints).

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• If drug therapy fails at maximal levels, then immunotherapy may be appropriate if a single allergen is responsible and there are no contraindications such as severe asthma, pregnancy, β-blockers, or ischaemic heart disease. This should only be undertaken in hospital. Results for seasonal allergens are excellent.

• Surgery may be required for sinus involvement and for polyps, if topical steroid therapy fails to reduce them.

• Environmental control may be important as adjunctive measures. Avoidance of allergens where possible should be tried. In the grass-pollen season avoid opening windows more than necessary during the day (especially in the afternoon and evening when pollen count is high). Air filtration systems able to trap pollens are available for cars and for houses, although the latter are expensive to install. Masks are likely to be of little value.

• Cold air and spicy foods may exacerbate symptoms in vasomotor rhinitis.

The Algorithm for Management of Allergic Rhinitis, Formulations and Dosages of Selected H_1-Antagonist, Formulations and Dosages Intranasal Corticosteroids are outlined in Table 6-3, Table 6-4, Table 6-5.

Studies comparing intranasal steroids versus placebo showed decreased histamine levels in nasal lavages of those treated with the steroids, which was associated with significant improvements in nasal symptom scores, use of rescue medications, and number of symptom-free days. These agents have been shown to be effective in adults, adolescents, and children. A 3- to 5-day course of a topical decongestant such as oxymetazalone may be used when starting intranasal corticosteroid therapy in patients with severe allergic rhinitis to optimize intranasal corticosteroid delivery to the nasal mucosa.

Table 6-3. Stepwise algorithm for management of allergic rhinitis

Intermittent (Seasonal)		Persistent (Perennial)	
Mild	*Moderate-Severe*	*Mild*	*Moderate-Severe*
Environmental control	Environmental control	Environmental control	Environmental control
plus	plus	plus	plus
Antihistamine	Antihistamine	Antihistamine	Antihistamine
± decongestant	± decongestant	± decongestant	± decongestant
or	plus	or	plus
Nasal corticosteroid	Nasal corticosteroid	Nasal corticosteroid	Nasal corticosteroid
or	or	or	or
Nasal cromolyn	LT receptor antagonist	LT receptor antagonist	LT receptor antagonist
or	plus	consider	plus
LT* receptor antagonist	Specialist referral consider Allergen immunotherapy	Specialist referral	Specialist referral consider Allergen immunotherapy

* - leucotriene

Table 6-4. Formulations and dosages of selected H₁ antagonists

H1-Receptor antagonist	Formulation	Recommended dose
First Generation (Selected)		
Chlorpheniramine (Chlor-Trimeton)	Tablets: 4 mg, 8 mg, 12 mg Syrup: 10 mg/5 mL Parenteral solution: 10 mg/mL	Adult: 8-12 mg 2x/day Child: 0-0.35 mg/kg/24 hr
Hydroxyzine Atarax	Capsules: 25 mg, 50 mg Syrup: 10 mg/5 mL	Adult: 25-50 mg 2x/day Child: 2 mg/kg/24 hr
Diphenhydramine (Benadryl)	Capsules: 25 mg, 50 mg Elixir: 12.5 mg/5 mL Syrup: 6.25 mg/5 mL Parenteral solution: 50 mg/mL	Adult: 25-50 mg 3x/day Child: 5 mg/kg/24 hr
Second Generation		
Cetirizine (Zyrtec)	Tablet: 10 mg Syrup: 5 mg/5 mL	Adult: 10 mg/day Child 2-6 yr old: 2.5-5 mg/day >6 yr old: 5-10 mg/day
Fexofenadine (Allegra)	Tablets: 30 mg, 60 mg, 180 mg	Adult: 60 mg 2 x/day or 180 mg/day Child 6-11 yr old: 30 mg 2 x/day >12 yr old: 60 mg 2 x/day or 180 mg/day
Loratadine (Claritin)	Tablets: 10 mg SL Tablets: 10 mg Syrup: 1 mg/1 mL	Adult: 10 mg/day Child >3 yr old, >30 kg: 5 mg/day >3 yr old, >30 kg: 10 mg/day
Desloratadine (Clarinex)	Tablets: 5 mg	Adult: 5 mg/day Child: >12 yr old: 5 mg/day

Concerns about steroid systemic side effects in children have led to numerous growth studies using intranasal steroids. In a year-long study of prepubertal children 6 to 9 years old with perennial allergic rhinitis treated with beclomethasone dipropionate 168 mg twice daily, overall growth rate was significantly slower, by 1 cm, than in the placebo-treated group. The difference in growth rate was evident as early as 1 month into treatment. No significant between-group difference was found in the hypothalamic-pituitary-adrenal axis assessment. In a similar 1-year study, prepubertal patients between 3 and 9 years of age with perennial allergic rhinitis were treated with mometasone furoate agueous nasal spray 100 pg once a day. After 1 year, no suppression of growth was seen in subjects treated with mometasone furoate agueous nasal spray, and mean standing heights were actually higher in the mometasone furoate agueous nasal spray group than in the placebo group at all time points.

Local adverse events associated with Intranasal Corticosteroids include rare nasal-septal perforation, usually related to improper administration directed toward the septum instead of to the lateral area of the nasal cavity. More commonly, there is dissatisfaction with smell, taste, and a drip sensation.

Table 6-5. Formulations and dosages of intranasal corticosteroids

Generic name	Brand name	Formulation	Pediatric dose	Adult dose
Beclomethasone	Beconase AQ	Spray 42 µg	6-12 yr old 1 spray bid	>12 yrold 1-2 sprays bid
Dipropionate, monohydrate	Vancenase AQ	84 µg	>6 yr old 1-2 sprays qd	1 -2 sprays qd
Beclomethasone Dipropionate	Beconase	Inhalation Aerosol 42 µg	6-12 yr old 1 spray bid	>12 yr old 1 spray bid-qid
Budesonide	Rhinocort AQ	Spray 32 µg	>6 yr old 1 spray qd	1 spray qd
Flunisolide	Nasarel	Solution 0.025%	6-14 yr old 2 sprays bid	>14 yrold 2 sprays bid
Fluticasone Propionate	Flonase	Spray 50 µg	>4 yr old 1 spray qd	1-2 sprays qd
Mometasone Furoate, monohydrate	Nasonex	Spray 50 µg	3-11 yrold 1 spray qd	>12 yr old 2 sprays qd
Triamcinolone	Nasacort	Spray 55 µg	6-12 yr old 1 spray qd	>12 yrold 2 sprays qd
Acetonide	Tri-Nasal	50 µg	>12 yr old 2 sprays qd	2 sprays qd

DECONGESTANTS

Decongestants contain sympathomimetic agents that activate alpha-adrenergic receptors and cause vasoconstriction, thus reducing nasal congestion. Available oral formulations include pseudophedrine and phenylephrine. Based on a recent report regarding the risk of hemorrhage stroke in patients receiving phenylpropanolamine, the U.S. Food and Drug Administration has removed it from the market. The effective dose for pseudophedrine is 1 mg/kg four times a day in children younge than 6 years; 30 mg four times a day in children 6 to 12 years old and 60 mg four times a day or 120 mg extended release twice a day in patients older than 12 years. Unfortunately, some patients experience side effects with pseudophedrine, including nervousness, irritability, tachycardia, palpitations, headache, and insomnia. These drugs should be used with caution, as they may cause urinary retention and increased blood pressure in older individual and prostate hypertrophy in men. Prolonged use of oral decongestants may lead to withdrawal symptoms of headache and fatigue when the drug is discontinued. They have limited action on the other symptoms of rhinitis, including rhinorrhea, sneezine and itching. Combinations of antihistamines and decongestant provide patient convenience and additional relief of symptoms of allergic rhinitis. Pseudophedrine combined with fexofenadine (Allegra D), ceterizine (Zyrtec D), and lortradine (Claritin D) are examples, of these products.

MAST CELL STABILIZERS

Intranasal cromolyn sodium is a nonsteroid mast cell stabilizer agent that is available without a prescription. Although the mechanism of action remains uncertain, it has anti-inflammatory properties and clearly blocks the early- and late-phase responses in a laboratory setting. It has been shown clinically to relieve sneezing, rhinorrhea, nasal congestion, and pruritis. Yet in head-to-head clinical trials, intranasal corticosteroids are more effective than cromolyn. Cromolyn has an excellent safety profile, may be used immediately prior to an anticipated exposure to prevent

symptoms, and is recommended to be administered four times a day. Intranasal cromolyn is considered first-line treatment for the pregnant patient with allergic rhinitis.

LEUKOTRIENE RECEPTOR ANTAGONISTS

Several studies have identified clear increments in leukotriene levels in nasal lavage fluid in association with the immediate nasal response to allergen. Nasal insufflations provocation studies show that both LTC_4 and LTD_4 induce an increase in nasal airway resistance, as measured by rhinometry. The leukotriene receptor antagonist montelukast is currently approved for the therapy of allergic rhinitis. Montelukast selectively blocks the receptor that mediates the function of the various leukotrienes. Several clinical trials have documented the efficacy of montelukast in the management of allergic rhinitis versus placebo, and its efficacy is comparable to that of the antihistamines.

ORAL CORTICOSTEROIDS

A short burst (3 to 5 days) of oral steroids may be appropriate for some patients with very severe symptoms or to gain control of symptoms during acute exacerbations. Generally, the Prednisone dosage is 1 mg/kg/day for pediatric patients to a maximum of 60 mg/day. Adults may be treated with 40 to 60 mg/day in divided doses for 3 to 5 days. Long-term daily treatment with oral steroids is contraindicated, and instead, maintenance control of symptoms with intranasal steroids is recommended to gain control of symptoms. The intranasal steroids should be started at the same time as the short oral steroid burst.

IMMUNOTHERAPY

When symptomatic drug therapy and avoidance cannot control symptoms, immunotherapy (hyposensitization) should be considered. Several double-blind controlled studies have shown immunotherapy to be 80% effective in reducing the symptoms of seasonal as well as perennial allergic rhinitis. The patient's symptoms should closely correlate with the presence of specific IgE antibodies. Positive allergy tests that do not confirm Immunotherapy may be expected to provide significant clinical improvement in more than 80% of patients with pollen-induced allergic rhinitis. If improvement is not obtained after a 2-year trial, the patient should be reevaluated and discontinuation of immunotherapy should be considered. The duration of immunotherapy injections in patients who achieve clinical benefits is dependent on the patient's overall clinical response. In response to clinical improvements, the patient should be given the opportunity to stop treatment after approximately 3 to 5 years of injections. Many children with allergic rhinitis tend to improve with age and time. They are not "growing out" of the allergy, because improvement is related not to physical growth but to an as-yet-undefined age-related phenomenon.

7. ALLERGIC CONJUNCTIVITIS

Allergic conjunctivitis often accompanies rhinitis (the two areas are connected by the lacrimal ducts). The mechanisms are identical.

Presentation
• Typical features include itching and watering of the eye, with redness and swelling.
• More extreme forms include vernal conjunctivitis, in which giant papillae are seen on the tarsal surface of the eyelid. In this condition the allergic component is a trigger. This disease is difficult to treat but may burn out after 5-10 years.

Diagnosis
• As for rhinitis.
• Specific IgE may be detected in tears but it is rarely of value as a diagnostic test.
• Challenge tests may be helpful in very rare circumstances.

Treatment
•   Topical antihistamines and mast-cell stabilizing agents (disodium cromoglycate and nedocromil) may help to relieve symptoms. Lodoxamide is another mast-cell stabilizer specifically available for allergic eye problems.
•   Oral antihistamines are valuable for more severe symptoms.
•   Topical steroids may be very valuable but should only be prescribed under ophthalmological supervision, as long-term use may lead to glaucoma and cataract.
•   Short-course oral steroids may be used for severe symptoms unresponsive to topical treatment, and may be used to cover periods of exams, etc.
•   Topical cyclosporin and NSAIDs (flurbiprofen and diclofenac) have also been used successfully in vernal conjunctivitis.
•   Immunotherapy (either injected or sublingual) is often valuable; vernal conjunctivitis however responds less well.

8. SINUSITIS

Causes
• Allergy, with secondary infection due to allergic swelling closing off the drainage ostia. Usually associated with other allergic features.
• Primary infective: due to mechanical drainage problem; secondary to humoral immune deficiency.
• Aspirin intolerance.
• Ethmoiditis in children may mimic conjunctivitis.
• Inflammatory disease such as Wegener's granulomatosis and midline granuloma.

Presentation
• Usually obvious with pain over sinuses.
• Maxillary sinusitis may also present as dental pain in upper molars.

Diagnosis
• Plain radiographs not recommended; CT scanning is most sensitive.
• Nasal smears will demonstrate eosinophilia if there is an allergic cause, but neutrophilia will be present in infective cases.
• Measurement of humoral immune function (immunoglobulins, IgG subclasses, and specific antibodies) and antineutrophil cytoplasmic antibodies (ANCA) should be considered in chronic sinusitis.

Treatment
• Treat underlying cause
• Obstructed sinuses can be washed out. This can be done by an endoscopic procedure that allows the sinuses to be inspected.
• Nasal decongestants and topical steroids assist in reducing oedema and promoting free drainage.
• Antibiotics are required for infective problems. *Haemophilus influenzae* and pneumococcus are the most common organisms. Ciprofloxacin, clarithromycin, and azithromycin are appropriate as they penetrate well into sinus fluids.

SECRETORY OTITIS MEDIA (GLUE EAR)
It has been suggested that this is related to underlying allergy but there is little evidence for this in children, unless there is allergic disease elsewhere in the respiratory tract. Rarely, it may be related to specific antibody deficiency or a more widespread antibody deficiency. The history will reveal if there are other infective problems that would suggest such a diagnosis.

9. FOOD ALLERGY

Food hypersensitivity is a common clinical allergic problem. Adverse reactions to foods are classified as either food allergies or food intolerance. The utilization of these terms has allowed better communication regarding various reactions to food components. *Adverse food reaction* is a general term that can be applied to a clinically abnormal response to an ingested food or food additive. Adverse food reactions may be secondary to *food hypersensitivity (allergy)* or *food intolerance*.

Food hypersensitivity (allergy) (Box 9-1) is an immunologic reaction resulting from the ingestion of a food or food additive. This reaction occurs only in some patients, may occur after only a small amount of the substance is ingested, and is unrelated to any physiologic effect of the food or food additive. To most physicians, the term is synonymous with reactions that involve the immunoglobulin E (IgE) mechanism, of which anaphylaxis is the classic example.

Box 9-1. Food Hypersensitivity (Allergy): Immunologic Spectrum
IgE mediated ------------------→Non-IgE mediated
    Oral allergy syndrome
    Anaphylaxis
    Urticaria
        Eosinophilic esophagitis
        Eosinophilic gastritis
        Eosinophilic gastroenteritis
        Atopic dermatitis
                Protein-induced enterocolitis
                Protein-induced enteropathy
                Eosinophilic proctitis
                Dermatitis herpetiformis

Food intolerance (Box 9-2) is a general term describing an abnormal physiologic response to an ingested food or food additive.

Box 9-2. Food Intolerance: Non-Immunologic Adverse Reactions
Toxic/Pharmacologic
- o   Bacterial food poisoning
- o   Heavy metal poisoning
- o   Scromboid fish poisoning
- o   Tyramine
- o   Histamine
- o   Caffeine

Nontoxic/Intolerance
- o   Lactase deficiency
- o   Galactosemia
- o   Pancreatic insufficiency
- o   Gallbladder/liver disease
- o   Hiatal hernia
- o   Gustatory rhinitis
- o   Anorexia nervosa

This reaction has not been proven to be immunologic in nature and may be caused by many factors, including toxic contaminants (e.g., histamine in scromboid fish poisoning, toxins secreted by *Salmonella, Shigella,* and *Campylobacter* spp.), pharmacologic properties of the food (e.g., caffeine in coffee, tyramine in aged cheeses), characteristics of the host such as metabolic disorders (e.g., lactase deficiency), and idiosyncratic responses.

The term *food intolerance* has often been overused and, like the term *food allergy,* has been applied incorrectly to all adverse reactions to foods. IgE-mediated (type I) hypersensitivity accounts for the majority of well-characterized food allergic reactions, although non-IgE -mediated immune mechanisms are believed to be responsible for a variety of hypersensitivity disorders. In this chapter, we examine adverse food reactions that are IgE mediated, non-IgE mediated, or have characteristics of both.

PREVALENCE

The true prevalence of adverse food reactions is still unknown. As many as 25% of people believe that they may be allergic to some food. However, the best available studies suggest that the actual prevalence of food allergy is 1.5% to 2% of the adult population. The prevalence of adverse food reactions in young children is estimated at between 6% and 8%. Several well-controlled studies have revealed that the vast majority of food allergic reactions present in the 1st year of life.

Causes true food allergy

• True food allergy is very real and may be severe. It is most common in children (up to 0.5% may be allergic to cows' milk). Almost any food can cause true allergy mediated via IgE.

• Most allergens involved in food allergy are heat stable (resisting cooking) and acid stable (resisting stomach acid). There are exceptions to this, so that a food will be allergenic cooked but not raw or vice versa: these foods are typically fruit and vegetables.

• Cows' milk allergy is common, especially in children under 5. The proteins responsible for the allergic response include β-lactoglobulin, α-lactalbumin, casein, bovine serum albumin, and bovine immunoglobulins. Often the response is against more than one antigen. This allergy usually disappears by the age of 5 years. Rarely, gastrointestinal haemorrhage may result (Heiner's syndrome is this complex accompanied by iron-deficiency anaemia and pulmonary haemosiderosis).

• Egg, milk, and wheat allergy are common in the under-fives, and often disappears with age, although anaphylactic responses may occur. The major antigens are ovomucoid and ovalbumin. Cross-reaction with chicken meat is unusual.

• Fish allergy may be severe, such that inhalation of allergens in the vapour from cooking fish or second-hand contact (e.g. kissing someone who has eaten fish) may be enough to trigger reactions. The allergens are species-specific in 50% and cross-reactive with all fish in the remainder. Fish allergy is usually permanent. Similar constraints apply to shellfish, both crustacea (prawns, crabs, and lobster) and molluscs (mussels, scallops, and oysters).

• The legumes, peanuts and soya, are major causes of severe allergic reactions. These agents cause major problems because they are widely used as food 'fillers' and may not be declared on labels. Avoidance may be difficult. Sensitization is often extreme, such that small amounts of residual protein in peanut (groundnut) oil may be enough to trigger reactions. Sensitization may occur through the use of groundnut oil in formula milks. Arachis oil (groundnut oil) is used as a carrier in certain intramuscular injections. True nuts may be equally troublesome. These reactions are usually lifelong, although a proportion of children who develop peanut allergy early in life may grow out of it (oral challenge required).

• Cereals may cause direct allergic responses if ingested or cause symptoms via gluten intolerance (coeliac disease). Flour also causes baker's asthma as an occupational disease. Wheat, barley, and rye are all closely related. Symptoms are less extreme and this is hypothesized to be due to proteolysis reducing the allergenicity, although why this does not apply to other foods is unclear. Rice and maize allergies are rare.

• Oral allergy syndromes, where there is allergy to pollens and cross-reactive food allergies (usually non-anaphylactic). Allergens tend to be heat-labile.

- birch pollen allergy with allergy to hazelnut, apple, pear, and carrot;
- birch pollen allergy with stone fruits (plums, peaches, cherries, almonds);
- ragweed allergy with melon, banana;
- grass pollen allergy with tomato, melon;
- mugwort pollen allergy with celery, carrots, spices (includes vermouth!).

• Other described associations include latex with banana, avocado, kiwi fruit, chestnut, lettuce, pineapple, and papaya.

• Occasionally trace contaminants may be responsible for allergy, as in the case of antibiotics in meat (used by farmers to improve the animals' weight gain), which may lead to reactions to meat and to therapeutic drugs.

Causes food intolerance. True food allergy must be distinguished from food intolerance, which takes many forms.

• Pharmacological: caffeine and theobromine (tachycardias in heavy tea/coffee drinkers), tyramine (headache, hypertension in patients on MAOIs), alcohol (obvious symptoms, plus beer drinkers' diarrhoea), NSAIDs (may include natural salicylates), figs (laxatives).

• Toxic: scombrotoxin (histamine from spoiled mackerel), green potatoes, flatoxins (peanuts), lectins (PHA in undercooked kidney beans), food poisoning (*Bacillus cereus* (fried rice), staphylococcal toxins), monosodium glutamate (headaches, nausea, and sweating— Chinese restaurant syndrome).

• Enzyme deficiencies: lactase deficiency (common in Asians; diarrhoea due to laxative effect of lactose), also sucrase and maltase deficiency (excess undigested fructose causes diarrhoea, abdominal cramp, and bloating; high levels in onions, peppers, and fruit juices).

• Other bowel disease: Crohn's disease, coeliac disease, infections *(Gardia, Yersinia)*, bacterial overgrowth (in association with reduced motility, e.g. systemic sclerosis), 'irritable bowel syndrome' (other causes must be excluded).

• Pancreatic insufficiency: cystic fibrosis, Schwachman's syndrome

• Psychogenic: 'smells', somatization disorder.

Immunological mechanisms

For true allergic reactions pre-sensitization is required. The bowel contains a specific subset of mast cells, which are capable of being armed by IgE. Activated T cells are also present. The pattern of reactions is probably very similar to that in mechanisms involving mast cells in other sites, although it is less well studied because of inaccessibility.

Abnormalities of mucosal immunity may contribute to the generation of IgE antibodies to foods. IgA deficiency may be a predisposing factor to allergic disease in general and also to coeliac disease, although cause-and-effect has not been proven beyond reasonable doubt. Exposure of an immature mucosal immune system may also be a factor, hence the lower rates of food allergy in babies breastfed and weaned late.

It has been suggested that some of the slower-onset food reactions may involve type III (immune complex reactions): this is difficult to prove as IgG anti-food antibodies are not uncommon in healthy individuals. Recent publications indicating that irritable bowel disease is associated with IgG anti-food antibodies need to be viewed with caution.

Type IV (cell-mediated) hypersensitivity has been discussed in several disorders where the clinical symptoms do not appear until several hours after ingestion of the suspected food. This type of immune response may contribute to some adverse food reactions, but significant supporting evidence of a specific cell-mediated hypersensitivity disorder is lacking.

Clinical manifestation of food hypersensitivity

Symptoms of true food allergy are invariably limited to the gut, the skin, and the respiratory tract. Symptoms outside these systems are much less likely to be due to true allergy.

There is no convincing association with arthritis. There is no evidence that food allergy is a cause of chronic fatigue syndromes, and thus 'desensitization' therapies have nothing to offer;

equally there is no evidence to support *Candida* overgrowth as a cause of chronic fatigue syndromes.

IMMUNOGLOBULIN E MEDIATED HYPERSENSITIVITY
Gastrointestinal Food Hypersensitivity Reactions

The signs and symptoms of food-induced IgE-mediated gastrointestinal allergy in human may be secondary to a variety of syndromes, including the oral allergy syndrome (Box 9-3), immediate gastrointestinal hypersensitivity (Box 9-4), and a small subgroup of allergic eosinophilic gastroenterocolitis (Box 9-5).

Box 9-3. Oral Allergy Syndrome (Pollen-Associated Food Allergy)
Oral Manifestations
> Burning
> Swelling
> Itching
> Erythema
> Immediate onset of symptoms

Age of Onset
> Beyond Infancy
> Typical <5 yr

Proteins Implicated
> Heat-labile fresh fruit and vegetable allergens
> Pollen and latex cross-reactivity

Pathology
> Immunoglobulin E antibodies

Treatment
> Avoidance
> Cooking the food

Natural History
> Unknown

Box 9-4. Immediate Gastrointestinal Hypersensitivity
Manifestations
> Nausea, abdominal pain, and vomiting with 1-2 hr
> Diarrhea within 2-6 hr
> Frequently associated with atopic disease
> Food-specific immunoglobulin antibodies
> Radiographic: Gastric hypotonia and pylorospasm

Age of Onset
> Infancy, childhood

Proteins Implicated
> Milk, egg, peanut, soy, cereal, fish

Pathology
> Immunoglobulin E-mediated

Treatment
> Protein elimination

Natural History
80% of cases resolve after protein elimination diet (except in the case of peanut and fish allergy

The diagnosis of these symptoms is made by a suggestive clinical history, positive prick skin tests, complete elimination of the suspected food allergen for up to 2 weeks with resolution of symptoms, and oral food challenges. After avoidance of a particular food for 10 to 14 days, it is not

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unusual for symptoms of vomiting to occur during a challenge even when the patient had previously ingested that food without vomiting.

Respiratory and Skin Food Hypersensitivity Reactions

Respiratory and *ocular* symptoms are common concurrent manifestations of IgE-mediated reactions to foods. Symptoms may include periocular erythema, pruritus, and tearing; nasal congestion, pruritus, sneezing, and rhinorrhea; and coughing, voice changes, and wheezing. Isolated naso-ocular symptoms are an uncommon manifestation of food hypersensitivity reactions.

The *skin* is a frequent target organ in IgE-mediated food hypersensitivity reactions. The ingestion of food allergens can either lead to immediate cutaneous symptoms or aggravate more chronic symptoms. Acute *urticaria* and *angioedema* are probably the most common cutaneous manifestation of food hypersensitivity reactions, generally appearing within minutes of ingestion of the food allergen. The foods commonly causing these reactions in children include eggs, milk, peanuts, and tree nuts. In adults, this list includes fish, shellfish, tree nuts, and peanuts.

Atopic dermatitis is a chronic skin disorder that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, chronically relapsing course, and association with asthma and allergic rhinitis. As many as one third of children with atopic dermatitis have at least one food allergic reaction. Foods to which they typically react include milk, egg, peanut, soy, wheat, fish, and tree nuts. Food challenges may be needed to help with the diagnosis of food allergy in these children.

MIXED IMMUNOGLOBULIN E MEDIATED AND NON-IMMUNOGLOBULIN E MEDIATED

Allergic eosinophilic gastroenteropathy (Box 9-5) is a disorder characterized by infiltration of the gastric or intestinal walls with eosinophils, absence of vasculitis, and, frequently, peripheral eosinophils. Patients presenting with this syndrome frequently have postprandial nausea and vomiting, abdominal pain, diarrhea, occasional steatorrhea, and failure to thrive (young infants) or weight loss (adults). There appears to be a subset of patients with allergic eosinophilic gastroenteritis who have symptoms secondary to food. These patients generally have the mucosal form of this disease with IgE-staining cells in jejunal tissue, elevated IgE in duodenal fluids, atopic disease, elevated serum IgE concentrations, positive prick skin tests to a variety of foods and inhalants, peripheral blood eosinophils, iron deficiency anemia, and hypo-albuminemia.

Box 9-5. Allergic Eosinophilic Gastroenterocolitis

Manifestations

    Abdominal pain

    Anorexia

    Early satiety

    Failure to thrive

    Gastric outlet obstruction

    Gastric or colonic bleeding

    ±70% of cases atopic

    Elevated immunoglobulin E

    ±Food-specific immunoglobulin E

    50% of cases with peripheral eosinophilia

    Radiographic: Antral obstruction, Menetrier's disease, gastroesophageal reflux, bowel wall edema, vomiting, diarrhea, protein-losing enteropathy, decreased albumin

Age at Onset

    Neonate to adolescent

Proteins Implicated

    Cow's milk, egg, fish, soy, cereals

    <50% skin test specificity

Pathology

    Marked eosinophilic infiltration of mucosa and submucosal gastric antrum, esophagus, duodenum, and colon

Treatment
- 50% of patients respond to dietary elimination of documented allergen
- Excellent response to hydrolyzed protein formula in patients<2 yr
- Excellent response to L-amino acid formula
- Responsive to steroids

Natural History

Disorder is typically prolonged

The diagnosis of this entity is based on an appropriate history and a gastrointestinal biopsy demonstrating a characteristic eosinophilic infiltration. Multiple sites (up to eight) may need to be biopsied to effectively exclude eosinophilic gastroenteritis, because the eosinophilic infiltrates may be quite patchy. Patients with the mucosal form of the disease may have atopic symptoms, including food allergy, elevated serum IgE concentrations, positive skin tests or radioallergosorbent tests (RASTs), and peripheral eosinophilia. Other laboratory studies consistent with this disease include Charcot-Leyden crystals in the stool, anemia, hypoalbuminemia, and abnormal D-xylose tests. An elimination diet for as long as 12 weeks may be necessary before complete resolution of symptoms and normalization of intestinal histology.

NON-IMMUNOGLOBULIN E-MEDIATED FOOD HYPERSENSITIVITY

Dietary protein enterocolitis (also known as protein intolerance) (Box 9-6) is a disorder that presents most commonly in children between 1 day and 1 year of age.

Box 9-6. Dietary Protein Enterocolitis (Protein Intolerance)

Manifestations

Diarrhea with bleeding
Anemia
Emesis
Abdominal distention
Failure to thrive
Hypotension
Fecal leukocytes
Normal immunoglobulin E
Food challenge: Vomiting in 3-4 hr; diarrhea in 5-8 hr

Age at Onset

1 day to 1 yr

Implicated Proteins

- Cow's milk, soy, rice, poultry, fish

Pathology

Patchy villous injury and colitis

Treatment

- 80% or more of cases respond to hydrolyzed casein formula, and symptoms clear in 3-10 days
- Up to 20% of cases require L-amino acid formula or temporary intravenous therapy

Natural History

- In general: With treatment, 50% of cases resolve by 18 mo; 90% of cases resolve by 36 mo
- Cow's milk: With treatment, 50% of cases resolve by 18 mo; 90% of cases resolve by 36 mo
- Soy: Illness is often more persistent

The typical symptoms are isolated to the gastrointestinal tract and consist of typically recurrent vomiting and/or diarrhea. The symptoms can be severe enough to cause dehydration. Cow's milk or soy protein (particularly in infant formulas) are most often responsible for this

syndrome, although egg sensitivity has been reported in older patients. The children will often have stools that contain occult blood, polymorphonuclear neutrophils, and eosinophils and are frequently positive for reducing substances (indicating malabsorbed sugars). Prick skin tests for the putative food protein are characteristically negative. Jejunal biopsies classically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. A food challenge with the responsible protein generally results in vomiting or diarrhea within minutes to several hours, occasionally leading to shock. It is not uncommon to find children who are intolerant to both cow's milk and soy protein. This disorder tends to subside by 18 to 24 months of age. Elimination of the offending allergen generally results in improvement or resolution of the symptoms within 72 hours, although secondary disaccharidase deficiency may persist longer. Oral food challenges, which should be done in a medical setting because they can induce severe vomiting, diarrhea, dehydration, or hypotension, consist of administering 0.6 g/kg body weight of the suspected food allergen.

Dietary protein proctitis generally presents in the first few months of life and is often secondary to cow's milk or soy protein hypersensitivity. Infants with this disorder often do not appear ill and have normally formed stools. Generally, this problem is discovered because of the presence of blood (gross or occult) in the stools. Gastrointestinal lesions are confined to the small bowel and consist of mucosal edema, with eosinophils in the epithelium and lumina propria. If lesions are severe with crypt destruction, polymorphonuclear neutrophils are also prominent. It is thought, but without proof from well-controlled studies, that cow's milk and soy protein-induced colitis resolves after 6 months to 2 years of allergen avoidance. Elimination of the offending food allergen leads to resolution of hematochezia within 72 hours, but the mucosal lesions may take up to 1 month to disappear and range from patchy mucosal injection to severe friability with small aphthoid ulcerations and bleeding.

Celiac disease is an extensive enteropathy leading to malabsorption. Total villous atrophy and an extensive cellular infiltrate are associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat oat, rye, and barley. The general incidence is thought to be 1 in 4000 but has been reported as high as 1 in 500 in Ireland. Patient have genetic predisposition to this disease-approximately 90% of patients are HLA-B8 positive, and nearly 80% have the HLA-DW3 antigen. Patients often have presenting symptoms of diarrhea or frank steatorrhea; abdominal distention and flatulence; weight loss; and, occasionally, nausea and vomiting.

Diagnosis
The history may give good clues about particular foods that cause problems.

Skin-prick tests are helpful for foods causing severe reactions (milk, egg, fish, peanuts, true nuts), while being less useful for other food groups. There are some minor exceptions to the general statement: children younger than 1 year may have IgE-mediated food allergy without a positive skin test; and children younger than 2 years may have smaller wheals, possibly due to the lack of skin reactivity. Conversely, a positive skin test to a food ingested in isolation that provokes a serious systemic anaphylactic reaction may be considered diagnostic. If commercial reagents do not work, then the fresh food should be tried (stab lancet into food then into patient). However, SPT may be dangerous in those who have had severe anaphylactic reactions. Dose is unstandardized.

An intradermal skin test is a more sensitive tool than the prick skin test but is much less specific when compared with a double-blind placebo-controlled food challenge (DBPCFC). Intradermal skin testing increases the risk of inducing a systemic reaction compared with prick skin testing.

RAST tests are less sensitive. Total IgE is not especially helpful. The newest generation of in vitro studies for specific IgE deludes the CAP-RAST (CAP-FEIA®). For patients with suspected food allergy, there are now accepted levels of specific IgE that are more than 95% predictive of a patient being allergic to that food. This test is best used for patients with possible allergic reactions to milk, eggs, and peanuts (and possibly wheat, soy, and fish).

The allergy practitioner will need to have a good understanding of the biological families in which plants are grouped, as this often helps explain patterns of reactivity: members of the same biological family often share common antigens.

Dietary manipulation plays an important role in diagnosis, but is time-consuming and should be undertaken only in collaboration with a dietician. Elimination diets (oligoallergenic diets), with gradual reintroduction of foods in an open but controlled manner, may be helpful in identifying troublesome foods. Formal confirmation requires a DBPCFC, in which the suspect food is disguised in opaque gelatine capsules. A DBPCFC is the best means of controlling for the variability of chronic disorders (e.g., chronic urticaria, atopic dermatitis), any potential temporal effects, and acute exacerbations secondary to reducing or discontinuing medications. Particularly, psychogenic factors and observer bias are eliminated. False-negative challenges are rare in a DBPCFC but may occur when a patient receives insufficient material during the challenge to provoke the reaction or the lyophilization of the food antigen has altered the relevant allergenic epitopes (e.g., fish). Overall, the DBPCFC has proven to be the most accurate means of diagnosing food allergy at the present time.

Open food challenges (or single-blind challenges) may be utilized in many cases to diagnosis patients with food allergy. There are many different schemes available for the administration of food for an oral challenge.

Differentiation of food intolerance requires careful history-taking. Patients should be investigated for evidence of malabsorption (iron, B12, folate, clotting, calcium, and alkaline phosphatase) and for coeliac disease (endomysial or tissue transglutaminase antibodies); if there is diarrhoea, do stool microscopy and culture. Acute-phase proteins will indicate likely inflammatory bowel disease.

Bacterial overgrowth, lactose intolerance, and pancreatic insufficiency can be diagnosed on appropriate radioisotopic tests or by measuring breath hydrogen production.

Radiology of the bowel may be revealing and biopsy should always be considered: enzyme levels can be measured and coeliac disease confirmed rapidly. In early coeliac disease, histology may show only a lymphocytic infiltrate without complete villous atrophy.

The diagnosis of food allergy remains a clinical exercise that utilizes a careful history, selective prick skin tests or RASTs (if an IgE-mediated), appropriate exclusion diet, and blinded provocation (Boxes 9-7, 9-8, 9-9).

Box 9-7. Diagnostic Approach: Non-IgE-Mediated Disease
Includes disease with unknown mechanisms
Food additive allergy
Elimination diets (may need elemental diet)
Oral challenges
Timing/dose/approach individualized for disorder
Enterocolitis syndrome can elicit shock
Enteropathy/eosinophilic gastroenteritis-prolonged feedings to develop symptoms
DBPCFCs preferred
May require ancillary testing (endoscopy/biopsy)

Box 9-8. Diagnostic Approach: IgE-Mediated Food Allergy
Test for specific IgE antibody
Negative: Reintroduce food*
Positive: Start elimination diet
Elimination diet
• No resolution: Reintroduce food*
• Resolution
  ▪ Open/single-blind challenges to "screen"
  ▪ DBPCFC for equivocal open challenges

Box 9-9. Food Allergy Prevention
Aimed at "high-risk" newborn
Positive family history: Biparental or parent/sibling

Breastfeeding generally protective of allergy
Wean/supplement with extensively hydrolyzed hypoallergenic protein hydrolysate
Delay introduction of solid foods >6 mo
Cow milk/dairy: 6-12 mo
Egg: 12-24 mo
Peanut, tree nut, seafood: >24-48 mo

Treatment

• Distinguish food allergy from intolerance and non-food related symptoms.

• Education of the patient about their symptoms and the cause. This may be hard if the patient already has a well-established preconception that he/she has a 'food allergy. When eating away from home, food-sensitive individuals should feel comfortable to request information about the contents of prepared foods. Children older than 7 years usually can be taught to inject themselves with epinephrine. The physician must be willing to explain and, with the parents, help instruct school personnel about these issues. In the home, consider the need to eliminate the incriminated allergen, or if this is not practical, place warning stickers on foods with the offending antigens.

• Management of food allergy is mainly avoidance, while maintaining a nutritious diet: specialist dietetic support is required. Elimination diets may lead to malnutrition or eating disorders, especially if these diets exclude a large number of foods or are utilized for extended periods. Studies have shown that symptomatic food sensitivity generally is lost over time, except for sensitivity to peanuts, tree nuts, and seafood. Symptomatic food sensitivity is usually very specific, so patients rarely react to more than one member of a botanical family or animal species. Certain factors place some individuals at increased risk for more severe anaphylactic reactions: (1) history of a previous anaphylactic reaction; (2) history of asthma, especially if poorly controlled; (3) allergy to peanuts, nuts, fish, and shellfish; (4) the need for beta-blockers or angiotensin-converting enzyme (ACE) inhibitors; and (5) possibly being female.

• Antihistamines (H1 and H2) may be of value taken prophylactically when patients with true food allergy are eating in unfamiliar surrounding; routine use is unnecessary.

• Patients who have had anaphylaxis need to have adrenaline for self-injection.

• Oral disodium cromoglycate may help occasional patients.

• Short course of steroids may be necessary for severe disease (eosinophilic gastropathy, enteritis).

• Immunotherapy

• Recent blinded, placebo-controlled studies of rush immunotherapy for the treatment of peanut hypersensitivity demonstrated efficacy in a small number of patients. Birch pollen immunotherapy in birch pollen allergic patients with oral allergy syndrome may lead to reduced food reactions. Newer types of vaccines for immunotherapy specifically for food-induced anaphylaxis are being developed and include humanized anti-IgE monoclonal antibody therapy, plasmid-DNA immunotherapy, peptide fragments ("overlapping" peptides), cytokine-modulated immunotherapy, immunostimulatory sequence-modulated immunotherapy, bacteria-encapsulated allergen immunotherapy, and "engineered" recombinant protein immunotherapy. Additionally, recent studies with humanized, monoclonal antibody anti-IgE have been utilized in phase I trials for patients with peanut allergy. This type of therapy appears to be a promising option for patients with a history of food-induced anaphylaxis or with a food allergy that puts them at risk for a future systemic anaphylactic reaction.

• Enzyme-potentiated desensitization (EPD) is not of proven value despite claims by some practitioners to the contrary.

• Management of food intolerance depends on the underlying cause.

10. ATOPIC DERMATITIS

Atopic dermatitis (AD) eczema is the most common manifestation of atopic disease. Among the descriptive labels assigned to this itchy, chronic, inflammatory skin condition (including atopic eczema, infantile eczema, and neurodermatitis) is *"asthma of skin"*, implying its link to the pulmonare entity. It is usually worst in childhood, improving with age in 80%. It affects particularly the cheeks and flexures and is a risk factor for the development of contact dermatitis in later life. Asthma or rhinitis will develop in 50-75% of patients. It is on the increase. Eye involvement may occur, with an atopic keratoconjunctivitis, and in severe cases subcapsular cataract may form. Viral infections such as eczema herpeticum, molluscum contagiosum, and warts are common in atopic eczema and do not indicate a significant generalized immunodeficiency but are a manifestation of disturbed local immunity.

Risk factors that influence the incidence of atopic dermatitis are listed in Box 10-1.

Box 10-1. Risk Factors That Increase the Incidence of Atopic Dermatitis

Parental history of atopy or AD: The strongest risk factor. Maternal atopy>>>paternal atopy.

Female-to-Male: 1.13:1.

Social class: Upper (35%) >> lower (14%).

Family structure: Prevalence of AD is inversely related to sib-ship size. Strongest predictors of AD were lower number of older sibs.

Hygiene hypothesis: The relative freedom from infections caused by viruses, bacteria, and helminths during infancy.

Migration: Moving to an urban setting increases the risk of developing atopy.

Maternal smoking: Smoking during pregnancy and lactation increases risk of atopy.

Questionable factors: Prolonged gestational age, increased intake of polyunsaturated fat, hard water, and month of birth.

Causes

• There is a genetic basis, as demonstrated by twin studies, although whether the background is the same as for asthma (chromosome 11 or 5) has not yet been demonstrated.

• In addition to the immunological factors, there are abnormalities of the lipids of the skin and evidence for autonomic nervous abnormalities (white dermographism). There is a reduced threshold for itch, which leads to a vicious cycle of itch and scratch, leading to the lichenification of chronic eczema.

• Non-specific irritants make the disease worse, such as wool, heat, and stress.

• Staphylococcal infection is common, and may play a role in exacerbating the disease: IgE against the bacterium may be detected, although the role is unclear. Staphylococcal superantigens have also been suggested to play a role. Cutaneous fungi may also exacerbate the disease.

• Role of diet is controversial. It has been suggested that maternal diet during pregnancy may contribute, as may a lack of breastfeeding. The contribution of diet to established symptoms is even more controversial, although some children are helped by exclusion diets. It is rare that adults are helped by dietary manoeuvres.

Immunological features

In atopic individuals, the combination of the genetic predisposition and environmental exposures results in the spectrum of immunologic aberrations (Box 10-2).

Box 10-2. Some immunologic aberrations noted in atopic dermatitis

Increased number of (IL-4- and IL-5-secreting) Th2-lymphocytes resulting in increased IgE levels with specific IgE antibodies

Eosinophilia with its associated

Increased eosinophilic cationic protein

Increased eosinophilic major basic protein
Increased eosinophil-derived neurotoxin levels
Increased urinary eosinophil protein X
Decreased number of (IFN-γ-secreting) Th1-lymphocytes
Increased basophil (and mast cell) spontaneous histamine release
Increased expression of CD23 on mononuclear cells
Chronic macrophage activation with
  Increased secretion of GM-CSF
  Increased secretion of PGE_2
  Increased secretion of IL-10
Increased serum sIL-2 receptor levels
T-cell skin homing receptors (cutaneous lymphocyte associated antigen) rather than lung-homing receptors
Increased number of high-affinity IgE-bearing Langerhans' cells

• Precise role of type I responses is unclear. IgE levels are often very high, and specific IgE may be detected against a variety of aero- and food allergens, although most of the IgE is 'junk', with no recognizable specificity.

• Langerhan's cells in the skin do have IgE receptors, although their role in atopic eczema is speculative. Keratinocytes release cytokines when damaged, which will excite the immune response (TNFα, IL-1, IL-6, IL-8).

• There is more evidence for a type IV reaction with an infiltrate of $CD4^+$ T cells into the epidermis and dermis; most of these cells are of the Th2 phenotype which will support IgE production. As part of the inflammatory response, eosinophils, mast cells, and basophils are all increased in the affected skin, and mechanisms similar to those found in the chronic phase of asthma probably predominate.

Diagnosis

The diagnosis of AD can be made by the clinical recognition of three essential criteria: atopy, pruritus, eczema. It would indeed be difficult to make the diagnosis of AD without atopy!

Atopy

The simple definition of *atopy* is a personal or familial history of AD, asthma, or allergic rhinitis. The presence of an elevated IgE level or positive skin prick or radioallergosorbent test (RAST) adds some objective evidence of atopy. However, these criteria are but epiphenomena of what atopy really is.

• Th1/Th2 lymphocyte transient reversal, with its specific, resultant cytokinal profiles, that is unique in the patient with AD (Fig. 10-1).

• 80% of cases will have a high IgE, often > 1000 kU/l. Specific IgE may be detected by SPT or RAST, but this rarely helps in management.

• Blood eosinophilia is common.

• Atypical patterns of eczema with other infections should raise the possibility of the hyper-IgE syndrome. Here the IgE is even higher, usually > 50 000 kU/l, and there may be evidence of other humoral abnormalities such as low IgG2, so a full investigation of humoral immunity is warranted.

T-CELL CYTOKINE PATTERNS
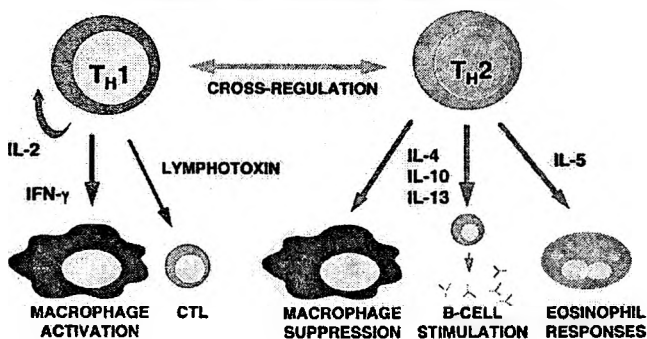
Figure 10-1. T-helper (Th) cell paradigm. CTL, cytotoxic T-lymphocyte; IFN, interferon; IL, interleukin.

Pruritus

Pruritus could be considered the 'primary lesion' of AD, and the diagnosis of AD should not be made if there is no history of itching. The pruritus is variable, fluctuating from mild to extremely intense.

Box 10-3. The Full Spectrum of "Triggers" of Itch in Atopic Dermatitis
Scratching
Xerosis
Irritants
Lipid solvents (e.g., soaps, detergents)
Disinfectants (e.g., bleaches, cleaning chemicals)
Coarse bedding
Occupational and/or hobby irritants
Household fluids (e.g., juices from fresh fruits, vegetables,meats)
Wool
Perfumes
Contact allergens
Furry animals (cat more than dog)
House dust mites
Pollens (seasonal)
Molds
Human dander ("dandruff")
Microbial agents
Viral (including upper respiratory infections)
Staphyloccocus aureus (as pathogen, or "super-antigen")
Pityrosporon yeast
Candida (rarely)
Dermatophytes (rarely)
Foods
Vasodilatory (alcohol, spicey)>> Contactants > allergens
Psyche
Stress

Anxiety
Chronic disease
Sleep deprivation
Other
Climate
Especially heat and sweating
Cold, dry weather
Extremes or sudden changes of temperature and humidity
Hormones
Puberty
Menstrual cycle

Eczema

Eczema is a clinical symptom. Histologically, all eczemas are spongiotic dermatitis, but not all spongiotic dermatoses are clinically eczematous (Fig. 10-2).

Atopic Dermatitis: Histology

Progression of Atopic Dermatitis
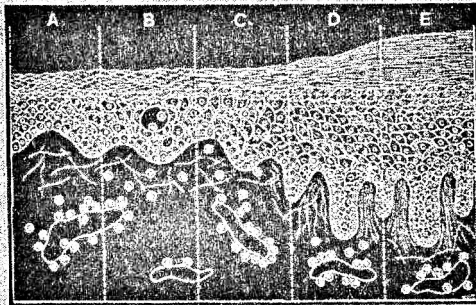
Acute ➤ Subacute ➤ Chronic

A. Initial perivascular infiltration. B. Papillary dermal edema. C. Abnormal scale, D. Hyperplasia. E. Hyperkeratosis.

From Murphy GF. *Dermatopathology*. Philadelphia, Pa: WB Saunders Company; 1995:53.

Figure 10-2. The histology of eczema.

Spongiosis is the result of T-lymphocyte activation and the proinflammatory mediators released from the diverse T cells, and the varied inciting secretagogues produce the spectrum of clinical presentations. The bulla and vesiculobullous lesions of the Th1-driven acute allergic contact dermatitis are never seen in the papulovesicular Th2-driven lesions of AD. The eczema of AD is almost exclusively isomorphic: It is not an itch that erupts on its own but an itch that erupts when scratched (or rubbed).

The characteristic clinical features of the eczema of AD are as follow:

1. It occurs predominantly at an early age (usually between 2 and 5 months of age). There is a correlation between the age of onset of AD and its severity. The earlier the onset, the more severe the course.

2. The age-related distribution demonstrates the condition's isomorphic feature (Fig. 10-3).

3. AD is a chronic and relapsing eczema.
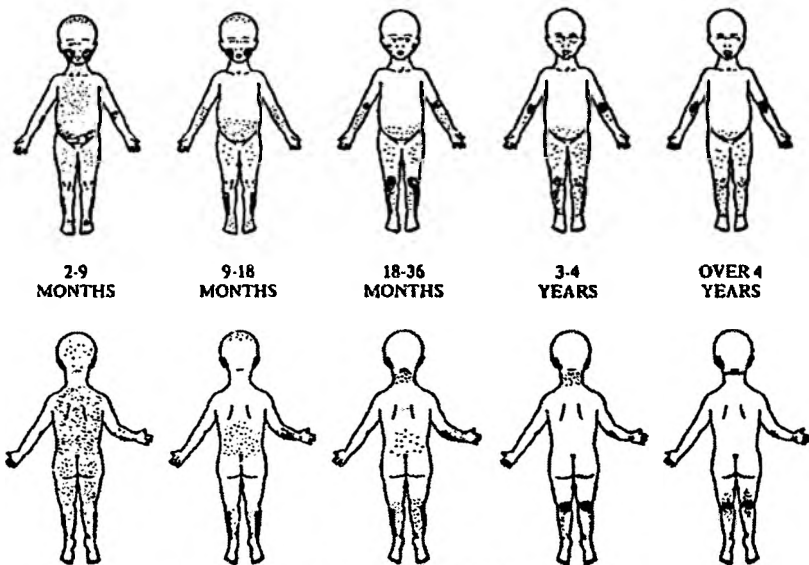
Figure 10-3. Distribution of atopic dermatitis in relation to age.

There are other noneczematous finding that are frequency seen in patients with AD. These noneczematous finding have been called "minor" or nonessential factors for the diagnosis of AD (Box 10-4).

Box 10-4. "Minor" or Unessential Features of Atopic Dermatitis
Xerosis ("dry skin")
Keratosis pilaris ("chicken" skin)
Perifollicular accentuation
Allergic "shiners"
Dennie-Morgan lines
Pityriasis alba
Anterior neck fold
Palmar and/or plantar hyperlinearity
Periocular milia
Anterior capsular cataracts
Keratoconus

Differential Diagnosis of AD are listed in Table 10-1.

Treatment
• Reduce itch by the use of emollients and antihistamines, inflammation by the use of topical steroids, and staphylococcal superinfection by the use of appropriate oral antibiotics.
• Ciclosporin is helpful in severe disease as a temporary measure but the disease relapses as soon as the drug is withdrawn. Topical agents, tacrolimus and pimecrolimus, may be effective and do not have the same adverse effects as steroids.
• PUVA.
• High dose IVIg has also been shown to be beneficial in resistant cases.

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• Theoretically, γ-interferon should be helpful, by reducing the Th2 predominance, and this has been borne out in several small trials.

• Where babies, by virtue of a strong family history, are at risk of developing atopic eczema, avoidance of cows' milk for the first 6 months of life and late weaning may be helpful.

The addition of γ-linoleic acid and fish oil have been suggested to be helpful; the evidence from controlled trials is less supportive.

• Avoidance of egg, milk, or wheat may help some children. In adults if there is concern over the contribution of food, then a 2 week trial of an elimination diet will identify whether food is contributing.

Table 10-1. Differential Diagnosis of AD

Differential Diagnosis of Pediatric Eczemas	Differential Diagnosis of Adult Eczemas
Atopic dermatitis	Allergic contact dermatitis
Acrodermatitis enteropathica	Cutaneous T-cell lymphoma
Agammaglobulinemia	Glucagonoma syndrome
Ataxia-telangiectasia	Irritant contact dermatitis
Hartnup's disease	Pellagra
Hyper-IgE syndrome	Pityriasis rubra pilaris
Netherton's syndrome	Psoriasiform eruptions
Phenylketonurea	Scabies
Scabies	Seborrheic dermatitis
Seborrheic dermatitis	
Wiskott-Aldrich syndrome	

A recommended algorithm for the management of AD can be found in Figure 10-4.
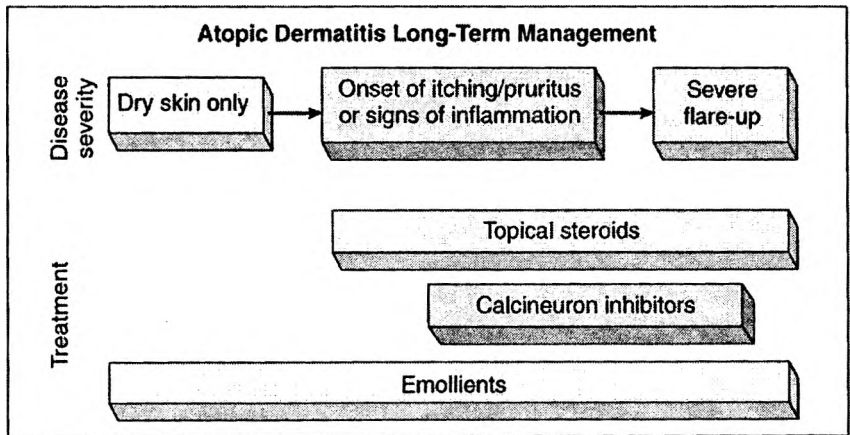
Figure 10-4. An algorithm for the management of atopic dermatitis.

Emollients. The intent of emollients and moisturizers is to hydrate the skin, which enhances medication penetration and the barrier function (see previous section). Vaseline remains the standard to accomplish those goals; unfortunately, it is not very acceptable cosmetically. There is little evidence that the addition of other ingredients (e.g., aloe, vitamins) have any beneficial effect. Preparations with fragrances should be avoided. An 8% ceramide-containing cream (e.g. Triceram

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cream) has been shown to repair the damaged barrier function and enhance the water-holding function in addition to providing a significant clinical improvement of xerosis.

TOPICAL CORTICOSTEROIDS

Topical corticosteroids have been the cornerstone of treatment for AD for decades. However, monotherapy with topical corticosteroids is not likely to control AD. Adjuvant skin care in combination with patient/parent education is also very important. Based on the best evidence-based data, once- or twice-daily topical corticosteroids are justified as first-line therapy in all patients with AD. The younger the patient, the milder the choice of therapy. Facial, genital, and intertriginous areas should be treated with very mild corticosteroids (1% or 2.5% hydrocortisone). Hands and feet require higher-potency topical corticosteroids (0.1% triamcinalone ointment). Similarly, lichenified plaques warrant higher-potency preparations. Box 10-5 ranks selected topical steroids from superpotent (Group I) to less potent (Group IV). Potency of corticosteroids used to treat the acute dermatitis may not be the same as the preparations required for maintenance.

Box 10-5. Ranking of Selected Brand-Name Topical Steroids*

Croup I: Superpotent (anti-inflammatory activity > 1500)
> Temovate 0.05%
> Diprolene 0.05%
> Ultravate 0.05%
> Psorocon 0.05%

Group II: High potency (anti-inflammatory activity = 100-500)
> • Lidex 0.05%
> • Halog 0.05%
> • Cyclocort 0.05%
> • Topicort 0.25%
> • Diprosone 0.05%
> • Elocon 0.1%
> • Florone 0.05%
> • Maxiflor 0.05%
> • Lotrisone 0.05%

Group III: Midpotency (anti-inflammatory activity = 10-100)
> • Synalar 0.025%
> • Kenalog 0.1%
> • Aristocort 0.1%
> • Cord ran 0.05%
> • Locoid 0.1%
> • Cutivate 0.05%
> • Westcort 0.2%
> • Cloderm 0.1 %
> • Valisone 0.1%
> • Benisone 0.028%

Group IV: Low potency (anti-inflammatory activity = 1-10)
> Hydrocortisone (1 % is OTC; >1 % is prescription)
> Tridesilon 0.05%
> DesOwen 0.05%
> Aclovate 0.05%
> Decadron 0.1 %
> Medrol 1 %
> Metiderm 0.5%

Research of medication compliance in several chronic conditions suggests that between 30% and 40% of medication is not used as prescribed. The successful management of dermatologic conditions is often hindered by intentional or subconscious noncompliance. Aesthetic appeal of a

product is probably the most important aspect of a topical therapy to a patient. No matter how effective a formulation, if patients find it irritating, disagreeable, or difficult to use, the efficacy of that product is compromised. In AD, ointments are usually more effective than creams, lotions, or gels; however, always take aesthetic appeal into consideration.

Patients who have chronically used topical corticosteroids without success will not be good candidates of their continued use. Many of these patients will benefit from corticosteroids in conjunction with the newer immunomodulators.

TOPICAL IMMUNOMODULATORS

Since the year 2000, topical immunomodulators (caclineuron inhibitors) have been gaining a firm footing in the management algorithm of AD and offer an additional treatment option, either as monotherapy or in combination with topical corticosteroids. Their safety profile and enhanced efficacy; particularly for eczema involving the head and neck, and the fact that they suppress inflammation through pathways independent of those utilized by glucocorticoids is most appealing. There is some concern based on animal studies that there may be increased risk of neoplasias with prolonged use of these medications.

Tacrolimus (Protopic) ointment in concentrations of 0.03% and 0.1%, Pimecrolimus (Elidel) cream 1%. Both are calcineuron inhibitors that have been shown to be efficacious for mild to moderately severe AD for both short-term and long-term therapy (up to 3 years of use), with no increased infections. The most common adverse effects (with tacrolimus slightly more often than with pimecrolimus) were local application site events, included skin burning (up to 23%), pruritus (22%), and erythema (8%).

Patients using the immunomodulators experienced fewer flare-ups and reduced the need for topical corticosteroids by more than 50%. At present, some clinicians use topical immunomodulators initially, and most continue to use topical corticosteroids. However, as soon as the case is refractory and requires long-term treatment, the trend is to introduce topical modulators.

ANTIMICROBIALS

The relationship between skin colonization and secondary infection with *S. aureus* and AD activity remains unclear. It is well known that *S. aureus* is abundant in AD, both in clinically involved and uninvolved areas, and the density increases with the severity of the lesion. Few doubt the need for antibiotic therapy for the obviously infected lesion, but management of nonclinically infected skin is less certain.

For localized infection, topical mupirocin (Bactroban) usually suffices. Systemic antibiotics are necessary for patients with multifocal infections or impetigo. Oral cefuroxime 15 mg/kg twice a day for 10 days is the preferred systemic antibiotic. If there is no clinical improvement in patients after 2 weeks of antibiotic therapy, a culture for bacterial sensitivities should be taken.

ANTIHISTAMINES

Antihistamines have long been prescribed for AD because it is believed that they will block histamine receptor type 1 (H_1)-induced pruritus; however, as noted previously, histamine is but one of many mediators that can induce pruritus in AD. Sedating antihistamines may offer some relief by their sedative effect; however, this author prefers using more effective sedatives (e.g., chloral hydrate, Zolpidem) for more effective sedation for adult patients. Studies comparing sedative and nonsedative antihistamines with placebo for the itch of AD do not show a clear benefit for the active drugs.

Topical doxepin (Zonalon) has been effective in relieving some of the pruritus of AD; however, it was most effective in those patients who experienced sedation, and there was a 13% incidence of allergic contact dermatitis in those using the drug.

SYSTEMIC THERAPEUTIC OPTIONS

For severe AD, especially when other treatments fail, systemic corticosteroids (e.g., prednisone 0.05 to 1.0 mg/kg/day to a maximum of 60 mg per day; methylprednisolone 0.04 to 0.08 mg/kg/ day) are recommended for short-term management of disease activity. Long-term administration of systemic corticosteroids for AD should be avoided. Cyclosporine (0.3 to 0.5 mg/kg/day) is an excellent alternative for the short-term treatment of refractory disease, especially if repeated courses of prednisone are considered.

PHOTOTHERAPY

When topical agents fail in the treatment of moderately severe and severe AD, phototherapy can be a useful modality. The preferred form of phototherapy is narrowband ultraviolet B (available in selected medical centers). Photochemotherapy, which combines methoxsalen with ultraviolet A light, has proven efficacious in the treatment of AD. The administration of phototherapy should be restricted to specialists. Remember, the more complex the intervention, the more precarious the risk-to-benefit ratio.

11. CONTACT DERMATITIS (HYPERSENSITIVITY)

Presentation
- Contact dermatitis (CD) is a localized type IV reaction due to contact with a triggering allergen. Reaction is eczematous, often with blistering and weeping. The pattern of rash together with a careful exposure history usually identifies possible allergens.
- It needs to be distinguished from straightforward irritant dermatitis due to a localized toxic effect that does not involve the immune system. Typical irritants are solvents, acids, alkalis, and other chemicals. The skin has a limited number of ways in which it can respond, and the appearance of irritant and allergic dermatitis can be clinically similar.

Causes
- Many topically applied compounds can cause delayed-type hypersensitivity reactions.
  - nickel allergy often leads to dermatitis affecting the ear lobes, under the back of watches, and where jean studs press on the skin. Those regularly handling coins will get hand eczema. This is the commonest contact dermatitis.
  - aniline dyes in leather cause dermatitis affecting the feet and where leather belts come in contact with skin.
  - chromium: hand eczema, usually in those handling cement.
  - cobalt: used as a stabilizer for the head on beer!
  - latex and synthetic rubbers: related to chemical accelerators and hardeners (thiurams, mercapto compounds, carbamates); there is no evidence that latex proteins themselves cause type IV reactions.
  - hair dyes, formaldehyde (perming lotions).
  - fragrances and cosmetics (biocides, phenylenediamine, parabens).
  - topical antibiotics (gentamicin, neomycin, bacitracin, benzocaines).
  - colophony (rosin) and other resins (adhesives in plasters).
  - ivy, sumac tree, chrysanthemum, feverfew, primula.
- Some allergens require concomitant exposure to sunlight for the effect to develop; rash only develops on sun-exposed areas of contact:
  - plants: limes, lemons, figs, giant hogweed, pine wood;
  - drugs, including sulphonamides, tetracylines, and phenothiazines; and sunscreens (p-aminobenzoic acid, oil of bergamot).

Immunology
Types I and IV hypersensitivity may coexist. In most cases the allergens are low molecular weight substances that penetrate the skin readily and lead to neoantigen formation. As with all T-lymphocyte-mediated responses, sensitization precedes reactivity. Active lesions show a sparse $CD4^+$ T-lymphocytic infiltrate but few eosinophils.

Diagnosis
The careful history and physical examination give the most important information. This should be supplemented by patch testing. SPT and measurement of total IgE are of little value.

Standard panel by patch testing will include metals (nickel, chromium), preservatives, fragrances, rubber mix, lanolin, formaldehyde, balsam of Peru, and colophony (Table 11-1).

Contact dermatitis should be included in the differencial diagnisis of every eczematous eruption (Box 11-1), especially eczematous lesions that do not respond to appropriate therapy or any skin lesion that exacerbates following topical therapy.

Unfortunately, the histology (i.e., spongiotic dermatitis) of all eczemas is the same. Thus, whereas a biopsy can confirm spongiosis, it is the history that suggests CD and patch testing that confirms allergic CD.

Table 11-1. Thin-layer rapid-use epicutaneous test panel of standard antigens

Substance	Source
Nickel sulfate	Metal objects
Wool alcohols (lanolin)	Ointments, creams, lotions, soaps
Neomycin sulfate	Antibiotic creams, lotions, ointments
Potassium dichromate	Cement, industrial chemicals
Caine mix (benzocaine, tetracaine hydrochloride, dibucaine hydrochloride)	Topical anesthetic medications
Fragrance mix	Toiletries, perfumes, flavorings
Colophony	Adhesives, sealants, pine oil cleaners
Paraben mix	Cosmetics, skin creams, paste bandages
Negative control	
Balsam of Peru	Resin used in cosmetics, perfumes, flavoring agent in cough syrups, lozenges, chewing gum, and candles
Ethylenediamine dihydrochloride	Stabilizer, emulsifier, and preservative in topical fungicides, topical antibiotics, eye drops, and nose drops
Cobalt dichloride	Metal-plated objects and costume jewelry
p-tert-Butylphenol formaldehyde resin	Waterproof glues, leather goods
Epoxy resin	Adhesives, surface coatings, paints
Carba mix	Stabilizer in rubber products, pesticides, glues
Black rubber mix	Antioxidant and antiozonate in almost all black rubber products (e.g., tires, hoses)
Cl+ Me-isothiazolinone	Antibacterial preservative in shampoos, creams, lotions, and other skin care products
Quaternium-15	Preservative in shampoos, lotions, soaps, and other skin care products
Mercaptobenzothiazole	Vulcanization accelerator used in most rubber products and some adhesives
p-Phenylenediamine	Permanent and semipermanent hair dyes
Formaldehyde	Building materials and plastics industry
Mercapto mix	Accelerators found in rubber products
Thimerosal	Mercury-containing preservative in cosmetics, nose drops, and eardrops
Thiuram	Antimicrobials and antioxidants found in rubber products

Box 11-1. Differential Diagnosis of "Eczema"

Contact dermatitis (allergic or irritant)
Seborrheic dermatitis
Atopic dermatitis
Nummular eczema
Stasis dermatitis
Dyshidrotic eczema
Asteatotic eczema
Lichen simplex chronicus
Autosensitization or "id" reaction
Dermatophytosis
Pityriasis rosea

Photoallergy dermatitis
Photocontact dermatitis
Polymorphous light eruption
Drug-induced eczema
Wiskott-Aldrich disease
Acrodermatitis enteropathica
Vitamin deficiencies
   Pellagra
   Riboflavin deficiency
Hartnup's disease
Hyper-IgE syndrome

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Autosensitization or "id" reaction
Dermatophytosis
Pityriasis rosea

Photoallergy dermatitis
Photocontact dermatitis
Polymorphous light eruption
Drug-induced eczema
Wiskott-Aldrich disease
Acrodermatitis enteropathica
Vitamin deficiencies
   Pellagra
   Riboflavin deficiency
Hartnup's disease
Hyper-IgE syndrome

TREATMENT

The identification of the offending agents is the key to success in managing patients with CD. All other measures are directed toward symptom relief with the suppression of the resulting inflammatory reaction.

The aggressiveness of the prescribed treatment should be determined by the limitations on the quality of life caused by the CD. Localized acute CD warrants different treatment than other special circumstances, that is, occupational dermatitis, chronic contact dermatitis (Box 11-2).

Box 11-2. Treatment of Contact Dermatitis
1. Avoidance
2. Topical antipruritics
3. Topical anti-inflammatory agents
4. Systemic anti-inflammatory agents
5. Instructions to prevent recurrences

AVOIDANCE

Only after the putative agent is identified can avoidance be instituted. Unless the causative agent is removed, all other modalities of treatment are palliative.

TOPICAL ANTIPRURITICS

In the acute phase, when itching, edema, and oozing are features, compresses with cold water to which crushed ice has been added are valuable. Cold is usually an effectively antipruritic, whereas the addition of calamine, colloidal oatmeal, or other soothing substances is of questionable value; topical diphenhydramine (Benadryl) should be strictly avoided because of the risk of cutaneous sensitization.

TOPICAL ANTI-INFLAMMATORY AGENTS

Two classes of effective, topical anti-inflammatory agents are available. Topical corticosteroids have a long track record of effectiveness and safety (when used appropriately), and the newer calcineuron inhibitors (tacrolimus [Protopic], pimecrolimus [Elidel]), which are at least as effective as the low to moderately potent corticosteroids. These topical agents can manage cases of CD localized to less than 10% of the patient's body surface area. Low-potency, nonfluorinated corticosteroids or calcineuron inhibitors are recommended for the thinner skin (i.e., face, eyelids, genital areas), and the higher-potency corticosteroids are indicated for other skin, especially if the lesions are lichenified and the condition is "chronic" (see chapter "Atopic dermatitis" Box 10-5).

The amount of medication to apply remains a most perplexing issue in the management of skin disease. A guide for proper application of creams is noted in Figure 11-1.

Another guide is referred to as the "Kleenex test": When a treated site is lightly dabbed with tissue paper, it should not reveal any "grease." If there is any on the tissue, too much medication has been applied.

SYSTEMIC ANTI-INFLAMMATORY AGENTS

Systemic anti-inflammatory agents are indicated for those more uncomfortable patients. Immunosuppression is usually most appropriate during the acute eruptive stages. Prednisone (0.5 to 1.0 mg/kg/day) is the treatment of choice. Generally, this dosage should be tapered (by half, and then discontinued) after the acute phase has resolved. The total treatment time is usually 10 to 14 days. Tapering the treatment too soon often results in a rebound of the initial dermatitis. More gradual tapering is not necessary, and steroid side effects, although possible, are very rare with this duration of treatment.

Oral cyclosporine at a dose of 3 mg/kg/day should be considered for patients with more chronic (6 weeks or longer) allergic CD and for diabetics. Oral antihistamines, while very effective for contact urticaria, offer minimal relief from the pruritus of allergic CD.

The patient must be instructed to avoid the cause of the CD once it is identified. Cross-reacting agents should be included in the list of avoidances.

Figure 11-1. A parent's guide to the use of topical treatment. (From Long CC, Millis CM, Finlay AY: A practical guide to topical therapy in children. Br J Dermatol 1998;138(2):293–296.)

12. DRUG ALLERGY

Immunologically mediated adverse drug reaction or drug allergy and/or hypersensitivity account for 6% to 10% of adverse drug effect. Table 12-1 provides a general overview of adverse drug reaction.

Table 12-1. Classification of Adverse Drug Reactions

Predictable Adverse Reactions Occurring in Normal Patients

Reaction	Example
Overdosage or toxicity	Hepatic failure with acetaminophen
Side effects	Urinary retention with anticholinergic medications
Secondary or indirect effects	Clostridium difficile colitis with use of ampicillin
Drug-drug interaction	Erythromycin increasing theophylline blood levels
Unpredictable Adverse Reactions	
Allergy and hypersensitivity reactions (IgE-mediated)	Anaphylaxis from β-lactam antibiotic
Pseudoallergic reactions (non-IgE-mediated events that mimic IgE-mediated events)	Anaphylaxis with radiocontrast dye
Intolerance	Tinnitis after a single aspirin
Idiosyncratic reactions	Hemolytic anemia in patients with G6PD deficiency exposed to primaquine

There are a number of specific characteristics that are generally helpful in distinguishing drug allergy from other adverse drug reaction.

Chief Characteristics of Drug Allergy and Hypersensitivity:
- Occurs in only a small fraction of patients after prior sanitization
- Can be reproduced by very small dose of the drug
- Will subside within several days to weeks following discontinuation of the drug
- Produces manifestations that differ from any known pharmacologic actions of the medication
- Can mimic other known allergic reactions, such as serum sickness and/or anaphylaxis
- Hypersensitivity, which can manifest as pulmonary infiltrates with eosinophilia, drug fever, and/or lupus syndrome
- Onset usually prompt (hours or days) but can occur within several months of administration of a drug
- Immunologic mechanism that is demonstrable or the putative mechanism

Many drug hypersensitivity reaction can be classified according to the revised Gell and Coombs schema. Table 12-2 is a synopsis of the clinical manifestation and mechanism of each reaction type.

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Table 12-2. Examples of Drug Allergy Categorized According to the Revised Gell and Coombs Reaction Classification

Reaction Type Clinical Presentation	Revised Cell and Coombs Reaction Type	Mechanism
Anaphylaxis, bronchospasm, urticaria, angioedema	Type I: Anaphylactic	Antigen cross-links IgE on cell surface, resulting in mediator release
Hemolytic anemia due to binding of drug to red cells, thrombocytopenia, interstitial nephritis	Type IIa: Cytotoxic	Cell-bound antigen reacts with IgG or IgM antibody, thus activating complement and producing cell injury
	Type IIb: Cell stimulating	IgG cell-stimulating antibody interacts with cell surface receptors involved in cell signaling
Serum sickness, drug fever	Type III Immune complex	Formation of antigen-antibody complexes that activate complement, resulting in recruitment of macrophages and leukocytes that cause tissue damage
Contact dermatitis with topical application	Type IVa1: Cell mediation hypersensitivity	Antigen is presented to sensitized CD4+ T-lymphocytes (Th1 cells) that release cytokines that attract other cells, which cause tissue inflammation
Delayed allergic reactions	Type IVa2: Cell mediated hypersensitivity	Antigen is primarily presented to sensitized CD4+ T-lymphocytes (Th2 cells); sensitized CD8+ T-lymphocytes (Th2 cells) also may be involved
Toxic epidermal necrolysis (TEN)	Type IVb: Tissue injury by cytotoxic T-lymphocytes	Cytotoxic CD8+ T-lymphocytes recognize fragments of antigen on the surface of target cells

Epidemiology

The frequency of adverse drug reaction is not precisely known. In study of hospitalized patients on medical floors, the estimates of prevalence of adverse drug reaction range from 15% to 30%. Of all adverse reaction, approximately 6% to 10% are believed to represent drug hypersensitivity. Drugs that have been implicated frequently in allergic drug reactions are listed in Box 12-1.

Box 12-1. Listing of Drug Groups Most Frequently Implicated in Allergic and Pseudoallele Drug Reactions

Allopurinol
Anesthetic agents (muscle relaxants, thiopental)
Antiarrythmic agents (quinidine, procainamide)
Anticonvulsants (hydantoin, tegretol)
Antihypertensive agents (hydralazine, methyldopa, angiotensin-converting enzyme inhibitors)

Antimalarials
Antipsychotic tranquilizers (phenothiazines, tricyclics)
Antisera and vaccines (antitoxins, monoclonal antibodies)
Antituberculosis drugs (isoniazide, rifampin)
Aspirin and nonsteroidal anti-inflammatory drugs
Cisplatin
Enzymes (chymopapin, L-asparaginase, streptokinase)
Grisefulvin Heavy metals (gold)
Narcotics (codiene, morphine)
Nitrofurans
Organ extracts (adrenocorticotropic hormone, insulin)
Penicillamine
Penicillins and cephalosporins
Phenolphthalein
Radiocontrast media
Sedative-hypnotics (barbiturates)
Sulfonamides

In recent years, several new classes of drugs have come into wide-spread use special consideration. There classes include monoclonal antibodies, cytokines, cyclo-oxygenase-2 (COX-2) inhibitors, and angiotensin-converting enzyme inhibitors (ACEs).

Monoclonal antibodies are used to treat many disorders, including lymphoma, breast cancer, inflammatory bowel disease, and rheumatoid arthritis. Many monoclonal antibodies are chimerized with murine proteins and lead to hypersensitivity reactions. For example, rituximab (Rituxan) is a chimeric antibody with a small murine component that binds CD20 on B-lymphocytes and is used in the treatment non-Hodgkin's lymphoma. Frequently, there are reactions during infusions, including fever, rigors, diaphoresis, flushing hypotension, bronchospasm, dyspnea, and a sensation of tongue and throat swelling. These infusion reactions are common with other monoclonal antibodies and are easily treated by reducing the infusion rate and, in some patients, pre-treatment with antihistamines, acetaminophen, and corticosteroids. There are also rare reports of allergic reactions including anaphylaxis, angioedema, serum sickness, immune-mediated thrombocytopenia, and anemia. Cytokine-release syndrome (or cytokine storm) occurs when binding of the monocolonal antibody-target cell complex via the Fc receptor activates macrophages in the liver, spleen, or lung. This activation leads to increasing concentrations of tumor necrosis factor alpha and interleukin-6 proportional to the number of malignant lymphocytes.

Treatment with cytokines such as interferon (INF)-β for multiple sclerosis, and INF-α for hepatitis C has become widespread in recent years. INF- β for the treatment of multiple sclerosis is commonly associated with flulike symptoms and local injection site reactions. There are case reports of capillary leak syndrome, anaphylaxis, and a thrombotic thrombocytopenic purpura-like syndrome in patients receiving INF- β. INF- β -neutralizing antibodies can develop and decrease the effectiveness of treatment. Reports of the prevalence of neutralizing antibodies in patients receiving INF-α for the treatment of hepatitis C vary from 1.2% to 20.2%.

Aspirin (ASA) and nonselective NSAIDs are inhibitors of cyclo-oxygenase-1 capable of producing nonimmunologic-mediated bronchoconstriction, urticaria, and anaphylaxis. The selective cyclo-oxygenase-2 inhibitors celoecoxib (Celebrex) and refecoxib (Vioxx) have been tolerated in aspirin-intolerant asthma patients, patients with history of angioedema with aspirin, and patients with adverse respiratory and cutaneous reactions to NSAIDs. There have been reports of patients with NSAID-triggered urticari developing urticaria following COX-2 exposure.

Angiotensin-converting enzyme inhibitors are associated with angioedema in 0,1% to 0,5% of patients who use them, and symptoms occur within 1 month of therapy in the majority of patients. Because there appears to be cross-reactivity among ACE inhibitors, the entire class is contraindicated in a patient who has developed angioedema. Angiotensin II antagonists (ARB) are used as alternatives to ACE inhibitors and are not contraindicated in those with ACE inhibitor-

induced angioedema. However, there are reports of patients with angioedema secondary to ACE inhibitors who subsequently developed angioedema while taking an angiotensin II antagonist. Thus, caution must be exercised when giving angiotensin II antagonists to patients with a history of angioedema from ACE inhibitors.

IMMUNOGENICITY OF DRUGS

Molecular weight of at least 3 to 5 kDa and multivalency are generally required for a compound to be immunogenic. Therefore, with the exception of a few protein drugs, such as insulin or streptokinase, very few drugs are complete antigens. The vast majority of drugs are organic chemicals with molecular weights less than 1 kDa that function as univalent ligands. Based on the classic reports of Landsteiner in the 1920s, it is generally acknowledged that low-molecular-weight drugs (haptens) are not immunogenic unless they are bound to a high-molecular-weight (>5 kDa) substance, usually a protein (carrier).

β-Lactam antibiotics are reactive with proteins and can directly haptenize carrier proteins. Most drugs, however, are not chemically reactive with proteins. It is probable that the haptens from most drugs are reactive metabolites of the parent compound that then bind to carrier proteins; certainly, this is the case with metabolites of penicillin. Studies of human IgE to sulfonamides have demonstrated the N4-sulfonamidoyl determinant to be the major sulfonamide haptenic determinant. For most other allergenic drugs, the formation of reactive metabolites and their conjugation with carrier proteins is somewhat speculative. In the absence of the relevant drug haptens, immunologic assessment is, of course, impossible.

CLINICAL PRESENTATION

The clinical presentations of drug allergy can take many different forms, and they are generally not pathognomonic for drug hypersensitivity. That is, similar clinical presentations can be the result of exposure to other allergens, or they can be associated with other nonimmunologic diseases. Dermatologic manifestations are the most common manifestation of drug allergy. However, many other organ systems can be involved, either alone or in combination, in a patient with drug allergy. It should be appreciated that in many reactions that are believed to be drug allergy, a definitive immunologic mechanism has not been established. A list of the clinical presentations of drug allergy is given in Box 12-2.

Anaphylaxis, a potentially life-threatening condition, can include any or all of the following: hypotension, bronchospasm, laryngeal edema, angioedema, and generalized urticaria. If the antigen has been ingested, gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or cramping, may be prominent. Symptoms ussualy begin within 30 minutes of drug and generally subside within 24 hours.

Serum sickness-like reactions occur 1 to 3 weeks after drug exposure. Other multisystemic clinical presentations of drug allergy include drug fever, drug-induced lupus erythematosus, and vasculitis.

Box 12-2. Listing of Various Single-Organ and Multisystem Manifestations of Drug Allergy

Single-organ system involvement
Dermatologic manifestations (see Box 12-3)
Respiratory or pulmonary manifestations
      Asthma
      Acute infiltrative reactions (probably allergic)
      Hypersensitivity pneumonia
      Pulmonary infiltrates with eosinophilia
      Nitrofurantoin reactions
      Noncardiac pulmonary edema
Hematologic manifestations
Eosinophilia

Drug-induced immune cytopenias
    Thrombocytopenia
    Hemolytic anemia
    Agranulocytosis
Hepatic manifestation
    Cholestasis
    Hepatocellular damage
    Mixed pattern
Renal manifestations
    Glomerulonephritis
    Nephrotic syndrome
    Acute interstitial nephritis
Lymphoid system manifestations
    Pseudolymphoma
    Infectious mononucleosis-like syndrome
Multisystem involvement
Immediate generalized reactions
    Anaphylaxis
    Anaphylactoid reactions
Serum sickness
Drug fever
Drug-induced autoimmunity (lupus erythematosus)
Vasculitis

Of all the organ system affected by drug allergies, the most frequently involved is the skin (Box 12-3).

Box 12-3. Dermatologic Manifestations Are the Most Common Symptoms of Allergic Drug Reactions
Most Common
Exanthematous eruptions or morbilliform eruptions
Urticaria
Angioedema
Contact dermatitis
Less Common
Fixed drug eruptions
Erythema multiforme
Sevens-Johnson syndrome
Generalized exfoliative dermatitis
Photosensitivity
Uncommon
Purpura
Toxic epidermal necrolysis (Lyell's syndrome)
Erythema nodosum

DIAGNOSIS OF DRUG ALLERGIES
Occasionally, diagnosis of drug allergy is fairly straightforward, but this is not usually the case. As indicated in Box 12-4, the most important diagnostic tool is the history.

Box 12-4. Guidelines for Diagnosis of Drug Allergy
History
Careful, complete drug history

Clinical manifestations consistent with drug allergy; a temporal relationship between drug exposure and onset of clinical manifestations consistent with drug allergy.

In vitro Testing (Table 12-3)
Research tool
Generally no clinical value
In vivo Testing
Clinically indicated in selected cases
Cutaneous testing
Provocative test dosing

Table 12-3. Testing for drug allergy

Immediate tests	*Later tests*
• Mast cell tryptase, C3, C4, as soon after the reaction as possible and at 24 hours	• Refer to immunologist/allergist for investigation
• Serum albumin	• Specific IgE, SPT and intradermal testing: Flow-CAST; drug challenge (DBPC)

First, it is imperative to have a complete and accurate list of all the drugs taken by the patient over the previous month. If a physician does not specifically ask about such nonprescription drugs as aspirin, the patient may not volunteer this information. Second, it is necessary to study the patient's manifestations to see if they are consistent with known drug allergies. As discussed above, it is important to recognize the protean nature of drug allergy and that it is not confined to rashes. Finally, it is important to consider the temporal relationship between exposure(s) to the drug and onset of clinical manifestations. If a patient is receiving a drug for the first time allergy generally does not occur until several days have passed. However, it usually occurs within several months. That is, if patient has been receiving a drug on a daily basis for over a year, that drug is not likely to be the cause of drug allergy. If a patient has received a drug in the past, sensitization may already have occurred, and drugs allergy may appear immediately upon readministration.

There are numerous in vitro tests that have been utilized in the investigation of drug allergy. Among these are histamine release, drug-specific IgE radioallergosorbent tests (RASTs), immunoassays for specific IgG or IgM, lymphocyte reactivity as measured by lymphokine production or lymphocyte transformation, and agglutination and lysis of blood cells in the presence of the suspected drug and the patient's serum. With the exception of the last, which may be clinically useful in the evaluation of immunologically mediated cytopenias, in vitro tests are rarely of clinical value, even though they may be valuable research tools. Studies indicate that elevated levels of perform, granzyme B, tumor necrosis factor-α, and Fas-L are found with delayed cutaneous reactions to drugs. It is possible that these markers may be used in the future to monitor cytotoxic T-cell response in delayed drug reactions.

In vivo testing for drug allergy—that is, cutaneous testing or provocative test dosing—may be clinically indicated in selected cases. It must be recognized that a serious limitation of cutaneous testing is the dearth of appropriate multivalent test reagents or drug metabolites. This is primarily because the antigenic determinants responsible for drug allergy are unknown for most drugs. If a patient has a history compatible with drug allergy, cutaneous tests are negative, and there is a clear indication for a drug reaction, provocative test dosing may be considered. In this method of testing, the initial dose is one that would not cause a serious reaction. Subsequent doses represent incremental increases. An example is given in Table 12-4. At each dose increment, it is imperative to ascertain whether or not any symptoms have occurred before proceeding to the subsequent dose.

Table 12-4. Typical protocol for provocative test dosing in a patient with history of penicillin allergy*

If a patient has negative prick and intradermal tests to Penicilloyl-polylysine (Pre-Pen), the major determinant, and to the minor determinant mixture (if available) or to penicillin G potassium, you may test dose as follows:	
Route	**Amount**
IV	1/1000 of full dose
IV	1/100 of full dose
IV	1/10 of full dose
IV	full dose

* - Following each dose increment, it is necessary to assess the patient and determine whether any symptoms of allergy have developed.

It is important to appreciate the difference between provocative test dosing and desensitization. The former describes the incremental administration of a drug to which a patient probably does not have an IgE-mediated allergy, even though the history is somewhat suggestive of an allergic reaction. On the other hand, if true IgE-mediated allergy exists, the incremental administration of the drug is termed desensitization, as it converts the patient from a stale of sensitivity to that of nonsensitivity to the drug. The mechanism is not entirely clear, but it may be the result of graded antigen binding of specific IgE or of controlled mediator release. Box 12-5 indicates agents for which desensitization can be carried out.

Box 12-5. Agents for which drug desensitization protocols are published
Allopurinol
Aminoglycosides
Aspirin
Dapsone
Furosemide
Heterologous antisera
Insulin
Measles mumps rubella vaccine
Penicillin
Sulfa
Tetanus toxoid
Vancomycin

Conclusion
• Diagnosis of drug reactions requires a good history.
• Investigation of an acute reaction requires confirmation of the nature of the reaction.
• Ideally, it should be possible to measure complement breakdown products (C3d, C3a, C5a) and urinary methylhistamine but, due to the withdrawal of appropriate commercial assays and the need for usually unobtainable stabilizers in blood tubes (Futhan-EDTA), these additional tests are not usually done.
• Reliable specific IgE tests are available to only a few drugs (thiopentone, suxamthonium, major determinants of penicillin).
• Skin prick testing followed by intradermal testing is required
• Challenge tests are of more value but are time-consuming and potentially dangerous.

Treatment of drug allergies
• Treatment of all drug reactions involves immediate cessation of the drug and, if the reaction is severe, resuscitation as for anaphylaxis (Chapter 4).
Prevention of drug allergy is obviously a desirable goal (Box 12-6).

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Box 12-6. Key Measures for the Prevention of Drug Allergy

Prescribe drugs only if essential.

Prior to prescribing drugs, obtain a thorough, careful drug history; drugs to which patients have had reactions or cross-reacting drugs should not be prescribed.

Perform cutaneous tests prior to administration of foreign antisera.

If an allergic drug reaction occurs, fully inform the patient; medical records should reflect the incident.

Report adverse drug reactions, such as drug allergy, to the Food and Drug Administration; this is especially important for newly introduced drugs.

Penicillin allergy

• Penicillin allergy is very common, perhaps occurring in up to 8% of treatment courses. Most of the reactions are trivial. Severe reactions are rare and occur mainly after parenteral administration.

• Occasional patients react on apparent first exposure and it has been suggested that sensitization may occur through antibiotics occurring in food.

• All four types of Cell and Coombs' hypersensitivity reactions may occur with penicillin, together with reactions of uncertain significance such as Stevens-Johnson syndrome.

• There are major antigenic determinants (benzylpenicilloyl nucleus) and minor determinants (benzylpenicillin, benzylpenicilloate, and others), although both are capable of causing severe immediate reactions.

> • Currently available tests (RAST and SPT/IDT) detect only major determinants, although benzylpenicillin may detect some minor-determinant-only reactions if suitably diluted and used for SPT.

• Tests for IgE (i.e. RAST and SPT) have no predictive value for other types of reactions. Up to 3% of SPT-negative patients may subsequently have reactions, although the reaction rate falls if both major and all minor antigens are used for testing. Some recent studies have claimed very few false-negative results with SPT. Conversely, not all SPT-positive patients will react when subsequently challenged.

• There have been difficulties in obtaining skin test reagents containing minor determinants, which makes accurate testing difficult.

• Up to 75% of patients who have had a reaction to penicillin will tolerate the drug subsequently. This probably applies to patients with non-specific reactions of dubious allergic aetiology (nausea, vomiting, diarrhoea) but more care should be taken in patients with a history of angioedema, Stevens-Johnson syndrome, etc.

• There is a high level of cross-reactivity with other semisynthetic penicillins with a β-lactam ring, such as the carbapenems and the monobactams (up to 50% in the case of imipenem), for IgE-mediated reactions.

• Cephalosporins and cephacarbams also cross-react, but at a lower level: up to 5.6% of penicillin-allergic (SPT positive) patients may also react to cephalosporins. Older figures are higher, but may relate to first-generation cephalosporins. Anaphytaxis to cephalosporins is said to be very unlikely if there are no responses to major or minor determinants of penicillin. In some cases the IgE is directed not at the nucleus but at the side-chain, which may be shared between a penicillin and a cephalosporin (e.g. aztreonam and ceftazidime).

• The specific morbilliform rash associated with the administration of amoxycillin to patients with acute EBV infection does not indicate a likelihood of subsequent true penicillin allergy.

Management

• The management of the penicillin-allergic patient depends on obtaining a clear history from the patient

• For patients with severe reactions, avoidance is the best course, including other semisynthetic β-lactam antibiotics.

• If penicillin or equivalent is essential, rush desensitization schedules may be used, although there is a high risk of reactions, for which supportive therapy will be required. The desensitization must be followed by the treatment course and there is no lasting tolerance. Desensitization should not be attempted in those who have had a Stevens-Johnson reaction.

Other antibiotics
• Little is written about true allergy to other antibiotics.
• Patients with AIDS have a very high reaction rate to trimethoprim-sulphamethoxazole. This has been associated with IgE to a derivative of the sulphamethoxazole.
• Abnormal metabolism with generation of toxic intermediates has been proposed as a mechanism for the generation of erythema multiforme and Stevens-Johnson syndrome. Cross-reactivity to sulphonamides may also affect other drugs that are closely related such as furusemide, hydrochlorothiazide, and captopril.
• Skin prick and intradermal testing can be carried out where reactions are not suggestive of a type I reaction (but not if the reaction is Stevens-Johnson).

Insulin allergy
• Insulin allergy may occur due to changes in the tertiary structure of insulin engendered in the manufacturing process for human insulin, or previously due to the sequence differences in bovine and porcine insulin, with the production of IgE antibodies. These do not recognize natural human insulin.
• Other components such as protamine and zinc may also cause allergic reactions.
• There is urticaria at the site of injections and frequently induration. Rarely, systemic reactions occur.
• Treatment is difficult: local reaction may be amenable to the prophylactic use of antihistamines or the inclusion of a tiny dose of hydrocortisone (1-5 mg) with the insulin.
• 'Desensitization' regimes have been used where there are major problems and diabetic control has failed.

Anaesthetic allergy
• The major difficulty of the investigation of anaesthetic reactions is that multiple drugs are administered nearly simultaneously.
• Patients suffering an acute reaction to anaesthetics should be referred to a specialist centre for investigation (the Royal College of Anaesthetists has produced guidelines on management for anaesthetists).
• Confirmation of the reaction at the time requires a blood sample for mast cell tryptase, complement C3 and C4, and albumin (calculation of dilutional effects).
• Complex regimes of serial blood sampling have been recommended: these are impractical and add nothing to the subsequent investigation.
• Measurement of specific IgE at the time of the reaction is unhelpful, as a negative result may be due to consumption.
• Detailed anaesthetic records must be forwarded to the drug allergy testing unit.
• Some of the drugs used (opiate derivatives) are capable of inducing mast-cell degranulation, while solvents such as cremophor, used to dissolve lipophilic drugs, may activate the complement system.
• Problems of severe reactions peroperatively may also arise from synthetic plasma expanders and blood products and in patients with unrecognized (or ignored) sensitivity to latex.
• There is extensive cross-reactivity between the neuromuscular blocking agents; prior exposure is not necessary (possibly cross-reaction with microbial products).
• RAST tests for specific IgE are currently limited commercially to suxamethonium and thiopentone, although research centres may have tests for IgE to other agents.

• SPT and intradermal testing are necessary to identify causative agents and identify safe alternatives.

• Challenge testing should only be carried out with full resuscitation facilities to hand.

• Guidance on testing is detailed in Chapter 3.

Local anaesthetics

• Local anaesthetics may cause both type I and type IV reactions, so a careful history is required to identify the nature of the reaction and guide subsequent testing.

• Overdose of local anaesthetic may cause significant adverse reactions; it is essential to exclude this possibility.

• Local anaesthetics divide into two groups: group I are the benzoic acid esters, including benzocaine and procaine; group II are the amides, including lignocaine, bupivacaine, and prilocaine. There is little cross-reactivity between the two groups, but there is often cross-reactivity within the groups.

• Local anaesthetics may contain sulphites (particularly if adrenaline is present) and other preservatives such as parabens, which may cause adverse reactions in their own right

• Articaine appears to be the local anaesthetic least likely to cause reactions and is the drug of choice where there is doubt about previous reaction history.

Drug-induced Stevens-Johnson syndrome. Drugs, particularly sulphonamides and penicillins, may cause the Stevens-Johnson syndrome. The immunological mechanism is uncertain.

!Stevens-Johnson syndrome is, however, a contraindication to any form of cutaneous challenge testing or further administration of the drug.

13. LATEX ALLERGY

Latex allergy is an increasing problem in hospitals, mainly triggered by the massive increase in latex glove usage during the 1980s when AIDS was identified. Up to 20% of staff in high glove usage areas may become sensitized to latex.

PRESENTATION

Type I reactions occur with anaphylaxis, asthma, angioedema, rhinoconjunctivitis, and contact urticaria.

Typical reactions occur with gloves, condoms, and new elasticated clothing. Cause Type I reactions develop against a range of proteins present in the latex.

Range of latex-containing domestic and medical products is very large.

Cross-reaction to foods is frequent bananas, avocado, kiwi fruit, potato, tomato, chestnut, lettuce, pineapple, papaya.

Type IV reactions occur due to plasticizers used in the manufacture (not latex), and cause a localized dermatitis.

The medical history in latex allergy requires knowledge of personal risk factors for the development of the disease. Certain medical conditions predispose these subjects to development of latex allergy through a combination of genetic (atopy), medical condition (spina bifida), and environmental (occupation and personal exposure) situations. In addition, the clinician must be aware that allergic reactions in certain clinical settings often indicate the possibility of latex allergy as the cause. Anaphylaxis during or shortly after administration of barium by a latex balloon-tipped catheter or placement of a bladder catheter or unexplained anaphylaxis during surgical operations should raise the physician's suspicions that latex allergy may be implicated. Other situations where latex material comes in contact with mucous membranes (dental work) or vascular systems and results in angioedema or other allergic manifestations are compelling and raise questions of the possibility of latex allergy.

In situations where latex materials are not constantly in contact with the skin, it seems that dermatitis is not a prominent problem. However, when the patient frequently wears latex materials, dermatitis is often found. The majority of health care worker with latex allergy report dermatitis at the site of latex glove contact. This dermatitis is often irritant in nature, which breaks down the skin barrier and may allow access of proteins to the immune system. This in turn may lead to the development of IgE-mediated latex allergy. Because 30% of health care workers without latex allergy may have irritant dermatitis, its presence is not diagnostic. Frequent hand washing, multiple glove changes, glove powder, and failure to completely dry the skin may contribute to this common dermatitis. Irritant dermatitis can be easily recognized by the findings of dry, cracked skin surface; itching; and erythema that is *not* accompanied by vesicles, blistering, or weeping of the skin. This dermatitis may respond to cotton glove liners, reduction of powder use, thorough hand drying, non-petroleum-based barrier creams that cause latex to degrade, as well as moisturizers.

Others may develop contact dermatitis; a type IV cell-mediated immune response. This dermatitis is distinguished from irritant dermatitis because of its vesicular, weeping appearance coupled with dermatitis extending away from the site of direct contact with latex materials. This is due to the fact that lymphocytes and Langerhans cells may home to remote sites away from the site of contact but are activated on contact with the offending allergen. Contact dermatitis from latex additive chemicals is most commonly induced by thiuram and mercapto-benzothiazole derivatives. This may be diagnosed by the use of standard patch testing. Recently, reports of contact dermatitis from latex protein have been described. No standardized reagent for the patch testing of latex proteins is available that would allow a systematic and safe evaluation of a patient. It is critical that the physician understand that dermatitis may or may not be present in a patient with latex allergy. Neither the presence nor absence of dermatitis is diagnostic of type I IgE-mediated allergy to latex but often may accompany it.

A number of other factors enhance the risk of developing latex allergy. These include the need for multiple surgeries or chronic mechanical ventilation, ventriculoperitoneal shunts in children, and

hospitalization of premature infants. They all have remarkably similar profiles of exposure to latex, especially latex examination gloves.
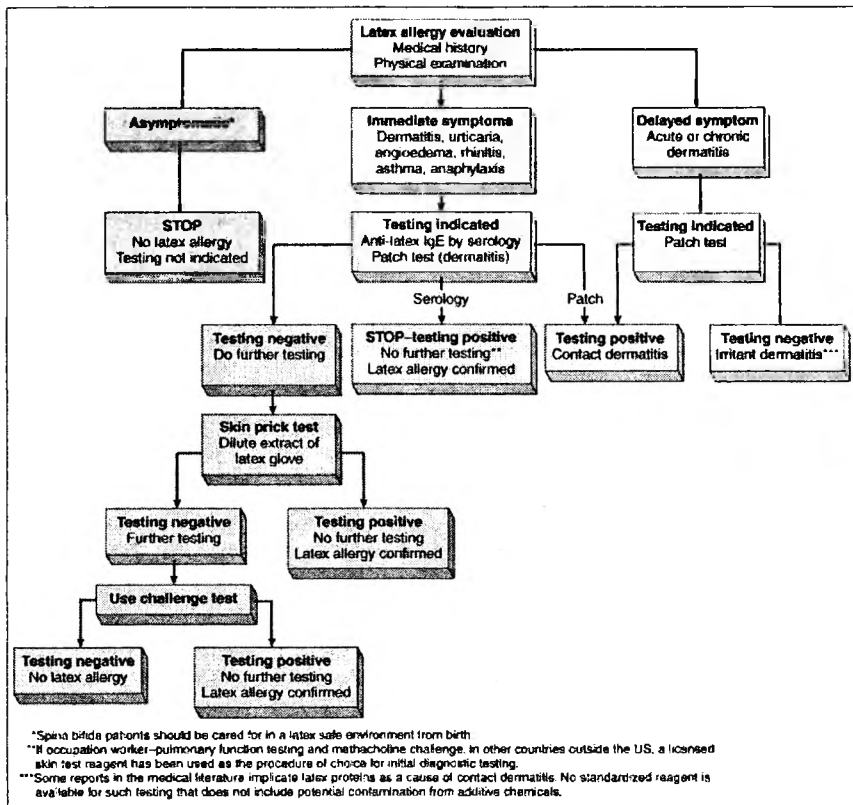
DIAGNOSIS OF LATEX ALLERGY

Figure 13-1. An algorithm for the diagnosis of latex allergy in the United States, where no diagnostic skin test reagent is cleared for use by the Food and Drug Administration.

SPT with graded concentrations (1 HEP, 10 HEP, 100 HEP; HEP = histamine equivalent potency) identifies 96%; pure latex solutions may also be used.

Challenge tests may be required: blind glove challenge (in a box); open glove challenge, and SPT with prick through a glove have all been used.

Type IV reactions are identified by patch testing.

Current specific IgE tests (RAST) identify only 85% of allergic patients.

The latex reagents for testing are ammoniated latex extracts or finished product (high-allergen latex glove). Unfortunately, a standardized finished product for such testing is not available to the clinician. Attempts to use finished materials in an office practice of allergy may result in false-negative reactions because the source product is low in allergen or even leads to adverse reactions because of excessively high allergen content. To combat the latter problem, most practicing

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allergists have used sequential multiple dilutions to avoid the risk of systemic reactions. This risk should not deter the release and use of latex skin test reagents. Inability to confirm a diagnosis of latex allergy because of unavailability of skin testing reagents may present more risk to a patient who would continue latex exposures (e.g., health care work) that result in life-threatening reactions or asthma.

The second available method to detect latex-specific IgE is serologic testing. The three commercially available tests include the CAP radioallergosorbet test fluorescent enzyme linked immunoassay (FEIA) from Pharmacia, Uppsala, Sweden; AlaSTAT from Diagnostics Products Corporation (DPC) Los Angeles, California; and HY-TEC-EIA from Hycor Biomedical, Irvine, California. The sensitivity of the CAP and AlaSTAT is similar, with approximately 25% false-negative tests. The HY-TEC has a 27% false-positive result. These tests are very useful when coupled with a medical history but do not demonstrate complete diagnostic reliability. Serologic testing in some research centers has shown high sensitivity and specificity as well.

The presence of circulating IgE in the serum alone is not sufficient to make a diagnosis of latex allergy. Medical history and physical examination coupled with laboratory confirmation are necessary to confirm a diagnosis, when possible. Insufficiently sensitive and specific diagnostic reagents have hindered this endeavor. This may lead to some subjects who have latex hypersensitivity remaining undiagnosed while some without this allergy may be overdiagnosed. The clinician must use clinical judgment when the tests are asynchronous to the history and exam.

Research findings indicate that specific challenges by glove provocation, hooded exposure chamber, and nasal provocation may result in improved diagnostic sensitivity. Currently, these are impractical, given the lack of standard reagents or gloves for such challenges. The clinician must use judgment in discerning the proper diagnosis and therapy of a patient with a positive history and negative serologic test, because 25% of subjects with latex allergy have a negative serum test. Other tests, including flow cytometry, cell proliferation, and patch testing, have been helpful but not always available to the practicing clinician.

MANAGEMENT OF THE NRL ALLERGIC PATIENT

• For type I reactions avoidance is required. This requires education of patient and employers.

• Occupational issues are difficult, especially in the Health Service.

• Latex is a substance identified in COSHH regulations as hazardous to health. Employers are therefore required by law to minimize exposure and carry out risk assessments where latex is used.

• Consideration of management of anaphylaxis away from hospital, including self-administration of hydrocortisone may be desirable.

• Pharmacy will advise on latex content of drugs: latex is used in bungs in drug vials.

• Hospitals should keep identified boxes of latex-free equipment in key areas.

• A safe environment is one where there is no NRL direct skin, mucous membrane, or aeroallergen contact by a Person with NRL allergy. Currently, NRL products made by a dipping method with a powder donning lubricant are the most likely to result in serious reactions from either direct contact or aeroallergen inhalation. An NRL product heat vulcanized at 600°C for 1 hour will have considerably less allergen content than a product heat vulcanized at 100°C for a few minutes.

• NRL-"safe" precautions in the operating room have allowed for uncomplicated anesthesia for the majority of patients with NRL allergy. Premedication with antihistamines and corticosteroids may be used, but there is no documentation that this improves patient outcome. Occasionally, NRL-safe precautions have failed to prevent an allergic reaction in some individuals. Because the level of aeroallergen in operating rooms declines when there is no activity, it has been suggested that operating on latex-allergic patients as the first case of the day to avoid aeroallergen exposure is safe.

• In addition to the operating room, safe care for NRL patients in an ambulance, emergency room, laboratory, radiology, general ward, intensive care unit, post anesthesia care unit, and clinic is required. Medical literature repeatedly demonstrates that powdered NRL gloves are the major contributor of transferable allergen. Strict avoidance of the use of powdered NRL gloves is necessary in all these areas, as it is impossible to predict when an NRL-allergic patient may present for care. Not only should the patient wear proper identification about the NRL allergy, but the room or area in which they receive care should be clearly marked to prevent accidental exposure (e.g., by bringing a powdered NRL balloon into the room). Policies and procedures for caring for such patients are necessary. Central purchasing should control ordering practices and maintain lists of alternative products.

• Successful management of the natural rubber latex (NRL)-allergic patient is critical to avoid untoward allergic reactions and occupational asthma. Avoiding contact with NRL products has remained the mainstay of therapy (Box 13-1).

Box 13-1. Latex-Safe Precautions in Hospital and Clinical Settings in Documented or Suspected Latex Allergy

• Only non latex glove use

• Allergy alert band for the patient

• "Latex-safe precautions" on door to patient room

• Check all medical devices for latex content

• No latex contact to skin or mucosal surfaces of patient (no source for inhalation)

• No intravenous valves inline Inject medication via stopcock devices instead of injector ports on tubing

• Operating room - Schedule as the first case of the day if powdered gloves in prior use in operating room

• Multiple-dose vials - Take top off or change needle after drawing up medication

• Premedication - Not necessary when strict latex-Safe precautions used

• Ideal - Latex gloves used should be powder free and low in allergen for nonlatex allergic patients

• Ban powdered latex products manufactured by dipping process from building (e.g., balloons).

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14. ANGIOEDEMA

Angioedema is a deep-tissue swelling that must be distinguished from urticaria. It is rarely itchy, and tends to give discomfort from pressure. In hereditary angioedema and sometimes in idiopathic angioedema, there is often a premonitory tingling before the swelling occurs. Any part of the body (including gut) may be involved.

Causes

• Allergic (accompanied by other features such as urticaria, anaphylaxis, etc.).

• Hereditary C1 -esterase inhibitor or C4BP deficiency.

• ACE deficiency.

• Acquired C1-esterase inhibitor deficiency (autoantibody-mediated, SLE, lymphoma). Lymphoma associated acquired C1-esterase inhibitor deficiency is usually due to splenic villous lymphomas.

• Physical (pressure, vibration, water - often with urticaria).

• Drugs (angiotensin-converting enzyme (ACE) inhibitors; NSAIDs, statins, proton-pump inhibitors are the commonest drugs).

• Idiopathic (rarely involves larynx) - other causes excluded.

Immunological features

• Mechanism is thought to involve activation of the kinin system with bradykinin production, leading to tissue oedema. ACE inhibitors inhibit bradykinin breakdown (also cause cough due to excess bradykinin).

• Histamine is not involved (unless there is accompanying urticaria).

• C1 -esterase inhibitor is known to be a control protein for the kinin cascade in addition to its role in the complement and clotting systems.

• There are polymorphisms of this enzyme but it is not known whether they correlate with the tendency to develop angioedema.

• Congenital ACE deficiency has also been associated with angioedema.

Diagnosis (see Fig 14-1)

• History will give useful clues: family history, connective tissue disease, lymphoma (may be occult), drug exposure, association with physical stimuli.

• Angioedema with urticaria will not be due to hereditary angioedema.

• In angioedema without urticaria, C1-esterase inhibitor deficiency should be excluded. C4 will be low, even between attacks, C1 -inhibitor will be low in type I but high in type II (Chapter 1). Levels of C2 are said to distinguish acquired from inherited C1-esterase inhibitor deficiency (low in inherited deficiency) but this test is not reliable.

• If acquired C1 esterase inhibitor deficiency is suspected, check serum immunoglobulins, serum and urine electrophoresis, and β_2-microglobulin. Examine for lymphadenopathy and splenomegaly and consider chest/abdominal CT scan.

•Connective tissue disease will usually be obvious, but detection of autoantibodies (antinuclear antibody (ANA), dsDNA, and extractable nuclear antigen (ENA) antibodies) may be necessary.

• Laboratory testing for angioedema see in Table 14-1.

Table 14-1. Testing for angioedema

Immediate tests	Later tests
C3, C4, C1 esterase inhibitor	Consider immunoglobulins, electrophoresis (serum, urine), β2-microglobulin (immunochemical and functional) - urticaria not present
Tryptase (if urticaria present)	ANA ds-DNA, ENA (suspected CTD) CT scan chest/abdoment if lymphoma suspected

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Hereditary angioedema

In patients with recurrent angioedema, several disorders should be considered in the differential diagnosis, including hereditary angioedema (HAE), acquired deficiency of the inhibitor of complement (C)1 esterase, and angioedema-eosinophilia syndrome. Hereditary angioedema is an autosomal disorder characterized by episodic, nonpruritic, and painless subcutaneous swellings lasting for several hours to days. The lesions are often triggered by local trauma or emotional stress and are usually asymmetrical. Unlike acquired angioedema, an urticarial reaction pattern is not present in patients with this disorder. Also, a history of recurrent nausea, vomiting, and abdominal colicky pain resulting from localized intestinal edema is common in ihis patient population.

The onset of HAE usually begins in childhood or young adulthood. There is often a positive history of other family members with similar complaints. It is important to differentiate HAE from other causes of angioedema, because patients with this disorder may be at greater risk for laryngeal edema leading to sudden death. The underlying mechanism for HAE is a genetically determined partial deficiency of an alpha2-glycoprotein, termed Cl esterase inhibitor (C1 INH). This serum protein normally inactivates the first component of complement. The absence of Cl INH results in excessive consumption of the complement component, C4. Thus, patients with HAE have chronically depressed serum levels of C4, and during acute attacks, both C4 and C2 levels are depressed. In approximately 85% of the patients, Cl INH levels are low, whereas in the remaining 15%, the protein is present in normal amounts. In this latter group, the inhibitory activity of Cl INH is abnormal; a functional Cl INH assay is necessary to correctly identify this of HAE.

Pathogenesis of hereditary angioedema see Fig 14-2.

Diagnosis

• Typically C4 and C2 are undetectable during an acute attack and low/absent in between.

• In type I, there will be a low C1-inhibitor level immunochemically and this will become undetectable in an acute attack.

• In type II, there will be a normal or high level of inhibitor measured immunochemically, but function will be low or absent.

• Angioedema may be acquired secondary to SLE or lymphoma and these may be distinguished from HAE by the reduction in C1q, although this is not always reliable.

Treatment

• Treat major attacks with purified (steam-treated) inhibitor (1000-1500 IU, i.e. 2-3 ampoules) by slow intravenous injection.

• FFP may be an emergency alternative but there are the usual risks of transmitted infection and it is also possible for FFP to exacerbate attacks by providing more substrate.

• Tracheostomy may be required if there is significant laryngeal oedema.

• Prophylaxis may be obtained with modified androgens (danazol, 200-600 mg/day; or stanozolol, 2.5-10 mg/day) or anti-fibrinolytics (tranexamic acid 2-4 g/day). Regular liver function tests and liver ultrasounds are required for monitoring therapy with all these agents.

• Prophylactic purified inhibitor should be used before high-risk surgical procedures, although tranexamic acid may be adequate for minor procedures.

• Dental work should always be carried out in hospital in view of the risk of developing oral oedema and airway obstruction.

• Abdominal attacks respond poorly to purified inhibitor - treatment should be conservative: analgesia (NSAIDs), IV fluids, and avoidance of unnecessary laparotomies (unless there is good evidence for other pathology).

Episodic angioedema with eosinophilia

• Angioedema associated with cyclic weight gain (up to 15%), fever, urticaria, and eosinophilia.

• Cause unknown.

• Said to be benign.

Box 14-1. Differencial diagnosis of angioedema
- Hereditary angioedema
- Acquired C1 inhibitor deficiency
- Angioedema-eosinophilia syndrome
- Panniculitus, cellulites
- Thrombophlebitis, lymphangitis
- Cellulites granulomatosa

Treatment of angioedema (see Fig 14-1)
• Treatment is dependent on the cause.

• Acquired C1-esterase inhibitor deficiency due to lymphoma will be improved by effective treatment of the underlying disease, as will the autoimmune-associated angioedema.

• Purified C1-esterase inhibitor may be required in acquired C1-esterase inhibitor deficiency. Frequent doses may be required, due to the presence of inhibitory antibodies: in severe cases, plasmapheresis and immunosuppression may be required. FFP is less effective and may actually make the angioedema worse by providing extra substrate.

• There is no role for C1-esterase inhibitor concentrate in idiopathic angioedema without evidence of deficiency.

• Control may be helped with antifibrinolytics (tranexamic acid, 2-4 g/day), or modified androgens (stanozolol, 2.5-10 mg/day; danazol, 200-800 mg/day). Monitor LFTs every 4-6 months and consider annual ultrasound liver.

• Idiopathic form (other causes excluded) responds best to tranexamic acid and less well to modified androgens.

•In acute attacks, adrenaline, antihistamines, and steroids are less effective than in anaphylaxis. Laryngeal involvement is less common in the non-hereditary forms.

• Patients with a history of angioedema for any reason should never be given ACE inhibitors, as these drugs may precipitate life-threatening events.
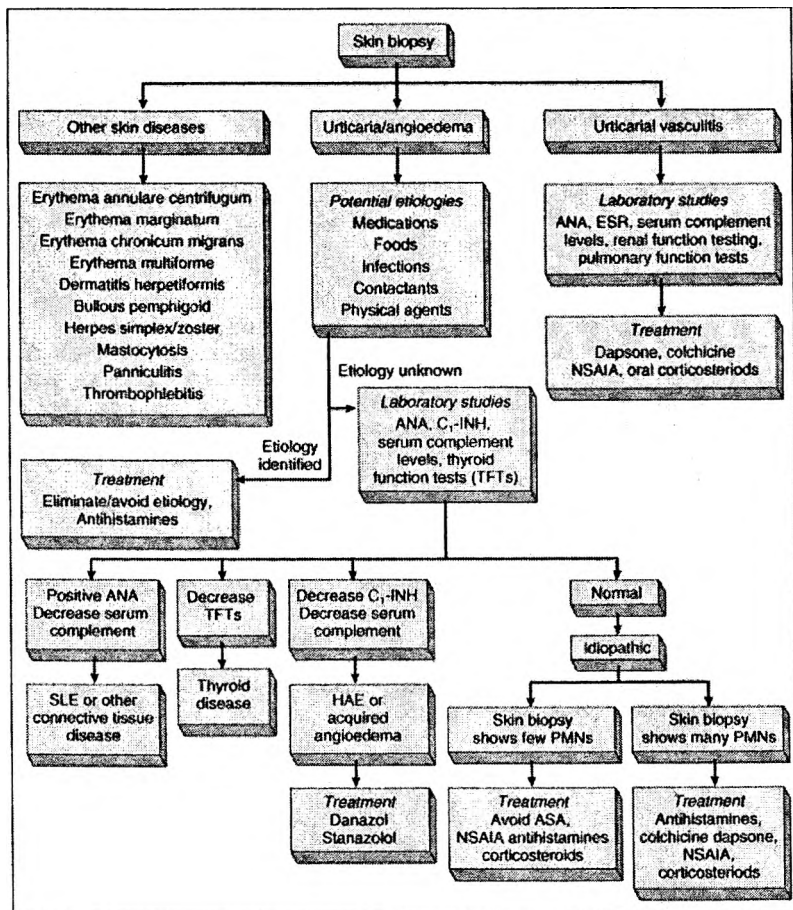
Figure 14-1. Algorithm for the diagnosis and treatment of chronic urticaria and angioedema. ANA, anti-nuclear antibody; C1, first component of complement; ESR, erythrocyte sedimentation rate; HAE, hereditary angioedema; C1 INH, C1 esterase inhibitor; NSAIA, nonsteroidal anti-inflammatory agent; PMN, polymorphonuclear neutrophils; SLE, systemic lupus erythematosus.
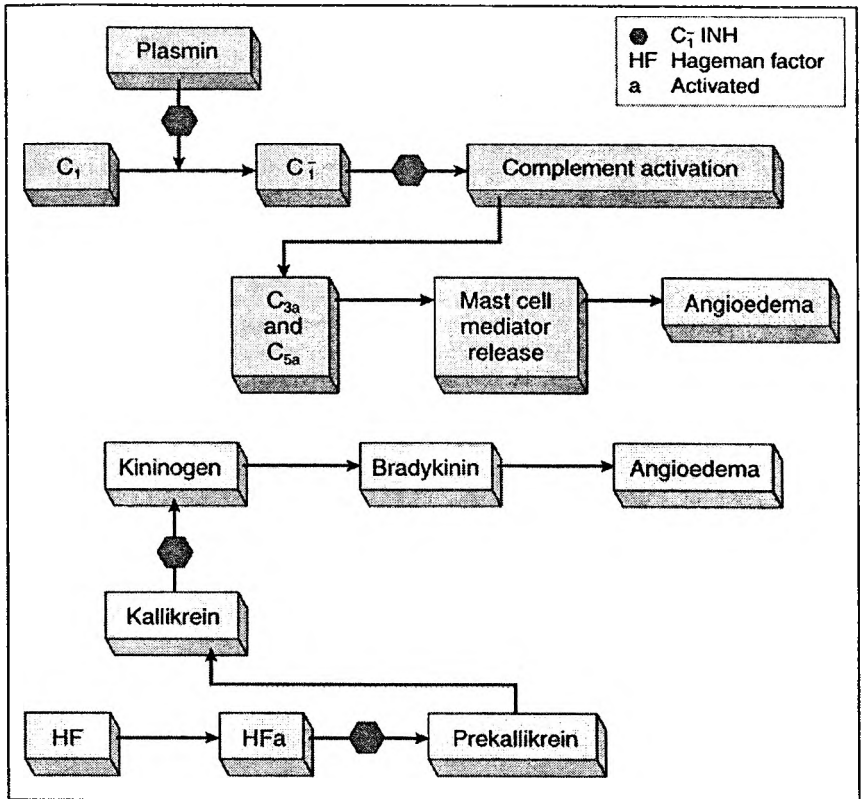
Figure 14-2. Pathogenesis of hereditary angioedema. Deficiency in the first component of complement (C1) esterase inhibitor (C1-INH) leads to uninhibited complement activation and anaphylatoxin (C3a, C5a) formation, which, in turn, stimulates mast cell mediator release. In addition, Hageman Factor activation also proceeds in the absence of C1-INH activity, which may result in the formation of the vasodilating agent bradykinin.

Box 15-1. Potential Mechanisms of Mast Cell Activation in Clinical Urticaria
Immunologic Mechanisms

- Antigen reaction with specific mast cell membrane IgE antibody
- Complement anaphylatoxin (C3a and C5a) stimulation of specific mast cell-associated receptors
- Eosinophil-derived major basic protein activation of mast cells
- Leukocyte-derived histamine releasing factor(s), stimulation of mast cells Antibodies to IgE and IgE receptors

Nonimmunologic Factors That Stimulate Mast Cells

- Neuropeptides (substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, neurokinin Y)
- Hormones (gastrin, estrogen, adrenocorticotropic hormone)
- Medications (aspirin, nonsteroidal anti-inflammatory agents, codeine, curare, succinylcholine, polymyxin B, thiamine)
- Physical stimuli (neat, cold, pressure, light)
- Venoms
- Radiocontrast media

Diagnosis

- The history is everything! The appearances of the lesions may give clues (distinctive lesions in cholinergic urticaria). Dermographism should be sought. Physical causes can usually be replicated in the clinic to confirm the diagnosis: pressure tests; ice cube test (wrap ice cube in plastic bag to ensure that it is cold not water that causes the problem).
- Other diagnostic tests should depend on likely cause.
- Allergy testing is rarely justified in chronic urticaria as the yield is low.
- Check thyroid function, acute-phase response, full blood count, and think of infective causes.
- For acute urticarias, foods may play a role, exclusion diets may help but only if there is a strong suspicion on clinical grounds. The role of natural dietary salicylates and/or preservatives in chronic urticaria is controversial.
- In cold urticaria, seek family history and check for cryoglobulins and causes thereof (electrophoresis of serum, search for underlying diseases, infections, connective tissue disease, lymphoproliferation).
- Autoantibodies (ANA, ENA, dsDNA, RhF) and complement studies (C3, C4) may be relevant in some instances. In SLE with urticaria, think of autoantibodies to C1q.
- Skin biopsy should be considered if there are atypical features if urticarial vasculitis suspected).

Testing for urticaria

Immediate tests	*Later tests*
Fut blood count—check for haematinic deficiency - MCV	Drug monitoring as required
Thyroid function	
Liver function	
Infection screen - Helicobacter	
Consider autoimmune serology	

Differential diagnosis of urticaria

- Urticaria of pregnancy (PUPPP)
- Urticarial vasculitis
- Figurative erythemas

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- Erythema multiforme
- Dermatitis herpetiformis
- Bullous pemphigoid
- Herpes simplex, herpes zoster
- Mastocytosis

PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY

The term *pruritic urticarial papules and plaques of pregnancy* (PUPPP) refers to an intense pruritic eruption that is occasionally observed in pregnant women. Characteristically, patients with this disorder develop erythematous, urticarial plaques and papules during the last trimester of pregnancy. Classically, these lesions begin centrally over the abdomen and extend to involve the thighs, buttocks, and distal extremities. The facial area is usually spared. In some patients, only the lower extremities are involved. Although the pathophysiologic mechanism for this disorder is unknown, skin biopsies of lesional tissue show histologic changes similar to those observed in other urticarial reactions and therefore suggest an important role for the mast cell. The material cutaneous lesions usually resolve shortly after delivery, and no associated abnormalities or adverse reactions have been reported in infants from mothers with PUPPP. Patients who develop PUPPP with their initial pregnancy are not necessarily at risk for recurrence of this disorder with subsequent pregnancies.

Systemic lupus erythematosus and other disorders

Urticaria lesions have the typical histologic changes of urticaria, while in others, there is evidence of leucocytoclastic vasculitis. Some patient with essential mixed cryoglobulinemia may also present initially with urticaria-like lesions following cold exposure. However, the presence of palpable purpuric lesions (vasculitis), Raynaud's phenomenon, and cutaneous ulterations helps to distinguish these patients from those with uncomplicated chronic urticaria.

Most patients with serum sickness develop an urticarial reaction pattern early in the course of disease. Histologically, these lesions may demonstrate changes typical of urticaria or may show more significant inflammation in the form of vasculitis. Urticarial vasculitis is distinguished from ordinary urticaria by the persistence of the lesions for >24 hours. Lesions usually fade to leave brown staining, due to erythrocyte extravasation. The hands, elbows, ankles, and knees are most frequently involved, and the patient often experiences pain or tenderness of cutaneous lesions in conjunction with pruritus. Joint pain and stiffness are also common and usually parallel skin disease activity. Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, and diarrhea, have been temporally associated with skin and joint involvement. Other symptoms encountered less frequently in patients with urticarial vasculitis include recurrent headaches, eye pain, and chest pain.

In addition to arthritis, other clinical signs of systemic involvement in these patients include generalized lymph-adenopathy, bronchospasm, uveitis, episcleritis, and, more rarely, neurologic findings such as pseudotumor cerebri, meningitis, and mononeuritis.

The diagnosis of idiopathic urticarial vasculitis is established by the histologic changes in the skin biopsy.

Urticarial-like papules and plaques also have been reported in children with juvenile rheumatoid arthritis, but, unlike common hives, these lesions are characteristically nonpruritic.

Lesions of acute and chronic urticaria also have been reported in patients with hypothyroidism, hyperthyroidism, and occult lymphomas.

Recurrent episodes of urticaria and angioedema have also been described in adolescents with the rare hereditary disorder originally described by Muckle and Wells.'s These children experience recurrent urticaria eruptions accompanied by chills and malaise. Progressive nerve deafness and amyloidosis of the kidney develop after a variable period. Schnitzler's syndrome represents a rare disorder characterized by nonpruritic urticarial papules and a monoclonal gammopathy. Patients aiso may experience a number of other signs and symptoms, including angioedema, fever, bone pain, weight loss, hepatospienomegaly, and lymphadenopathy. In addition to an IgM monoclonal

gammopathy, these patients also may have an elevated erythrocyte sedimentation rate and increased serum fibrinogen levels. Biopsies of lesional skin may show varying degrees of neuirophilic infiltrates with or without vasculitis.

Several other well-defined cutaneous diseases also should be considered in the differential diagnosis of urticaria or angioedema. The annular and arcuate morphology of some urticarial lesions must be distinguished from a group of disorders termed the figurative erythemas. This group includes erythema annulare centrifugum, erythema chronicum migrans, and erythema marginatum. In contrast to urticaria, usually these eruptions are nonpruritic. Erythema annulare centrifugum, which most closely resembles an urticarial reaction pattern, can be identified by a characteristic scaling ring that trails its advancing red border. Individual lesions of erythema multiforme may also assume an urticarial morphology. However, the more typical target-like lesions are usually also present.

Early in their course, some of the primary blistering disorders may appear urticarial. In particular, the autoimmune blistering diseases such as dermatitis herpetiformis and bullous pemphigoid may present as pruritic papules. Similarly, herpes simplex and herpes zoster may begin as pruritic, slightly painful urticarial lesions, and in some instances, the full clinical expression of grouped vesicles may not occur. Lesion arrangement (grouped) and, a focal anatomic distribution, however, provide important clinical characteristics for differentiating herpetic lesions from typical lesions of urticaria.

Mastocytosis

Patients with mastocytosis may have dermatographism or a spontaneous urticaria-like eruption in foci of cutaneous mast cell infiltrates. Unlike urticaria, lesions of mastocytosis are persistent and readily identified by their tan (in children) or reddish-brown (in adults) color. This condition has been called urticaria pigmentosa because of the appearance.

Classification of mastocytosis
- Cutaneous mastocytosis:
  - urticaria pigmentosa;
  - solitary mastocytoma;
  - diffuse cutaneous mastocytosis (rare);
  - telangiectasia macularis eruptive perstans.
- Systemic mastocytosis:
  - involvement of gut, bone marrow, bone.
- Mastocytosis in association with haematological disorders:
  - leukaemia, lymphoma, myelodysplastic syndrome.
- Lymphadenopathic mastocytosis with eosinophilic
- Mast cell leukaemia (very rare!).

Presentation
- Cutaneous involvement with itchy brown macules; Darier's sign = urticaria on rubbing or scratching cutaneous lesions. Dermographism.
- Systemic symptoms include: nausea, vomiting, diarrhoea, headache, shortness of breath, flushing, palpitations, loss of consciousness, malaise, and lethargy.
  - Systemic attacks triggered by heat, emotion, aspirin, opiates.
  - Evidence of associated haematological malignancy.
  - Symptoms may be confused with carcinoid and phaeochromocytoma.

Diagnosis of mastocytosis
- Biopsy of skin, bowel; bone marrow examination if systemic form expected; endoscopy will be required for gut involvement.

• Mast cell tryptase (serial measurements may be required); urinary methylhistamine is helpful, but not readily available. Exclude carcinoid by measurement of 5-HIAA, phaeochromocytoma by urinary catecholamines.

• Serum immunoglobulins and electrophoresis; urine electrophoreses.

• Blood film.

• Bone scan/MRI skeletal survey for infiltrations.

Treatment of mastocytosis

• High dose antihistamines (H1 and H2).

• Aspirin may reduce prostaglandin production causing flushing, but should be used with caution as it can directly activate mast cells; leukotriene antagonists (monteleukast) will prevent leukotriene-related symptoms.

• Oral disodium cromoglycate may help bowel symptoms.

• Caution with drug use: avoid opiates and other drugs directly activating mast cells (radiocontrast dyes, dextrans); anaesthesia needs to be approached carefully.

• Wasp/bee stings may lead to severe reactions.

• α-interferon (disappointing in most cases) and *c-kit* inhibitors (mast cells express increased c-*kit*) are being used experimentally. PUVA may help in skin lesions.

Treatment of urticaria

• Urticaria may be difficult to manage, especially cold urticaria. Commonest failing is inadequate dosage of antihistamines. The new antihistamines are safe in doses well above the recommended doses and do not interfere with cardiac potassium channels to cause prolonged QT interval.

• Acute urticaria should be treated with potent non-sedating antihistamines. Short-acting ones such as acrivastine may be appropriate for intermittent attacks. Potent long-acting non-sedating ones, such as fexofenadine, levocetirizine, and cetirizine (also said to have mast-cell stabilizing activity, of uncertain clinical significance), are useful for prophylaxis against frequent attacks. A few patients may still be sedated by these drugs.

• Loratidine and desloratidine have been reported by the EMEA to be associated with a small increase in minor malformations if taken in pregnancy.

• Doses up to 4 times the normal dose may be required in difficult cases.

• If these are unsuccessful alone, then the addition of an H2-blocker may be helpful, although the evidence is weak. There is no evidence to suggest whether ranitidine or cimetidine is preferable.

• Other therapeutic options include the following:

  • doxepin, an antidepressant with potent H1- and H2-blocking activity, and ketotifen and which has mast-cell stabilizing activity in addition to anti-H1 activity (it increases appetite and is sedating);

  • mirtazipine is also a valuable third-line agent and has antihistaminic properties;

  • calcium-channel blockers may have some beneficial effect as they stabilize mast cells (nimodipine is said to be better than nifedipine);

  • β_2-agonists (terbutaline) and phosphodiesterase inhibitors (theophylline) may help in rare cases;

  • oxypentifylline has been reported to reduce cytokine synthesis by macrophages and may be helpful;

  • colchicine is helpful in delayed pressure urticaria but is poorly tolerated; .

  • leukotriene antagonists may also be helpful in some patients;

  • resistant urticaria may respond to low dose warfarin (mechanism unknown).

• Non-familial cold urticaria may respond to cyproheptadine, calcium-channel blockers, β_2-agonists, and phosphodiesterase inhibitors, although responses tend to be poor.

• Familial cold urticaria does not respond to antihistamines, but may respond to NSAIDs.

- Steroids may be effective but should be used as a last resort as chronic therapy is not justified by the side-effects; danazol and stanozolol may be used as alternatives (with varying benefit). Short courses may be helpful for acute disease.
- Cyclosporin A may also be helpful, but the disease relapses once the drug is withdrawn. The side-effects (hypertension, nephrotoxicity) make it an undesirable drug for urticaria.
- High-dose IVIg has been used in resistant cases but the benefits are variable.
- Whenever chronic therapy is started, it is important to withdraw it at intervals to see whether it is still required in the light of possible spontaneous remission.
- Consider stress management programme.

QUESTIONS AND ANSWERS

1. How do CD8+T-cell subsets differ from CD4+ subsets?
CD8+ T cells are also divided into subsets based upon their cytokine profiles. CD8+ T cells that produce cytokines similar to CD4+ Th1 cells are designated T cytotoxic 1 (Tc1) cells, whereas those that produce cytokines similar to CD4+ Th2 cells are called T cytotoxic 2 (Tc2) cells.

2. Which T-cell subset is associated with oral tolerance?
Another type of Th cell, known asTh3, is preferentially induced by chronic oral administration of low doses of antigens. These cells synthesize large amounts of transforming growth factor-β, produce IL-10, and induce oral tolerance.

3. Explain the mechanisms by which CD8+ cells mediate cytotoxity.
CD8+ T cells exhibit two distinct mechanisms for inducing cytotoxicity: Fas ligand and perforin. Fas ligand on CD8+ cells engages Fas on the target cell, thereby initiating apoptotic pathways that lead to activation of caspase 8 (exogenous pathway) and caspase 9 (endogenous pathway). Both caspase pathways activate caspase 3, which induces apoptosis.
Alternatively, cytotoxic cells may interact with perforin, a membrane pore-forming molecule, to create pores in the target cell. Cytotoxic enzymes such as granzyme B and granulysin are transferred from the cytotoxic cell into the cytosol of the target cell, leading to cell death. In addition, granzyme B induces apoptosis by activating caspase 8, caspase 9, and caspase-activated DNAse (CAD), an endonuclease that cleaves DNA.

4. How does allergen-specific IgE testing compare with other tests for aeroallergens?
Allergen-specific IgE tests have been compared to skin testing. Modified RAST testing was found to be equivalent to skin prick testing and better than intradermal testing in predicting clinical reactivity to cat dander. The allergen-specific IgE testing was also found to have a sensitivity of 69%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 73% compared to cat allergen inhalation testing. A correlation was found between the concentration of dust mite-specific IgE and the concentration of dust mite allergen in the patient's bedding. There was a 77% chance of high dust mite allergen exposure when the concentration of dust mite allergen-specific IgE was > 2 kUa/L In general, allergen-specific IgE testing is comparable to allergic skin prick testing.

5. What is the prick-prick test?
The prick-prick test is a skin prick test in which the fresh food is pricked before pricking the patient's skin. This method may introduce proteins from the fresh food that is not available in the commercial extract. A prick from the fresh food must also be pricked on a patient without the pertinent history as a control. Spices may also be used after the material is ground into a power and solubilized with diluent.

6. What are the shock organs in anaphylaxis?
The clinical course of anaphylaxis is determined by organ system involvement. It is based on the immune response and the location of the smooth muscles affected by the release of the chemical mediators. In humans, the major organs affected by the anaphylaxis are heart and lung, with common and potentially fatal clinical reactions of cardiovascular compromise, respiratory failure, and laryngeal edema.

7. What common clinical conditions may mimic anaphylaxis/anaphylactoid reaction?
- Shock
- Hemorrhagic (massive gastrointestinal blood loss)

- Cardiogenic (acute myocardial infarction)
- Septic
- Vasovagal reaction
- Carcinoid syndrome
- Systemic mastocytosis
- Pheochromocytoma
- Hereditary angioedema
- Nonorganic causes
- Panic disorder
- Vocal cord dysfunction
- Globus hystericus

8. How can you differentiate a vasovagal reaction from true anaphylaxis or anaphylactoid response?
Vasovagal reactions may occur after an injection, and the usual clinical manifestations include dizziness, diaphoresis, pallor, weakness, sweating, nausea, hypotension, and bradycardia. Patients lack pruritus, urticaria, angioedema, tachycardia, and bronchospasm.

9. Which reactions are mediated by non-IgE mechanisms?
Complement activation and generation of anaphylotoxins (C3a, C4a, C5a): human plasma and blood products, gamma globulin.
Direct activation of mast cells or basophil mediators release: opiates, tubucurare, dextran, radiocontrast materials, fluorescein dye for angiography, and some chemotherapeutic agents.
Modulators of arachidonic acid metabolism: nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen, indomethacin).

10. Which reactions are mediated by an unknown mechanism?
Sulfites: food additives
Steroids: progesterone and hydrocortisone
Physical triggers: EIA, food-dependent EIA, systemic cold-induced urticaria, and systemic heat-induced urticaria
Systemic mastocytosis
Idiopathic anaphylaxis

11. What symptoms may be seen with overdose of first-generation antihistamines? Contrast the toxic effects in young children and adults.
Overdose in adults typically causes severe lethargy. Coma and death may occur. Anticholinergic effects may include dry mucous membranes, urinary retention, tachycardia, and decreased intestinal motility. The QTc interval may be prolonged, predisposing the patient to torsade de pointes.
In contrast, infants and young children may show paradoxical central nervous system stimulation with irritability, hyperactivity, hallucinations, and seizures.

12. What are the two basic classes of decongestants?
Oral decongestants include pseudoephedrine and phenylephrine; topical decongestants include oxymetazoline, xylometazoline, naphazoline, tetrahydrozoline, and phenylephrine.

13. What is the most effective class of medication used to treat allergic rhinitis?
A meta-analysis of 16 studies comparing intranasal steroids sprays to antihistamines showed a highly significant superiority of nasal steroids in controlling sneeze, itch, congestion, nasal discharge, and total nasal symptom score. In addition, compared to antihistamines, nasal steroids were equally effective at controlling ocular symptoms. The authors' conclusion based on efficacy, safety,

and cost was that intranasal steroids are preferred as first-line therapy for allergic rhinitis. Nasal steroids have also been shown to be more efficacious than cromolyn and montelukast.

14. Describe the mechanism of action of cromolyn sodium nasal spray. What is role in the treatment of allergic rhinitis?

Cromolyn sodium (Nasalcrom) inhibits mediator release from mast cells, reducing the allenii reaction ratherthan alleviating symptoms once they have begun. The protective effect of a single dose of cromolyn lasts for 4-8 hours. It is best to start cromolyn before the onset of the allergy season (e.g., spring) because the onset of sustained benefit takes several days to 2 weeks.

Suggested dosing is 1 spray in each nostril every 4 hours during the day. Cromolyn may also be used as an intermittent medication to pretreat infrequent exposures to the patient's known allergic triggers. Like antihistamines, cromolyn is more effective for reducing sneeze, itch, and rhinorrhea than it is for nasal congestion. In general, cromolyn is less effective than antihistamines and nasal steroids.

15. What should be considered first-line controller therapy for patients with moderate and severe persistent asthma?

The updated 2002 NAEPP guidelines stress that the combination controller regimen of low-to-moderate dose inhaled corticosteroids plus a long-acting β_2 agonist is equally or more efficacious in maintaining asthma control than high-dose inhaled steroids alone. This statement is supported by several recent clinical trials showing that the combination regimen best improves quality of life and symptoms and most effectively diminishes the number of exacerbations. This recommendation agrees with the recommendation to minimize dosing of inhaled steroids because of the possible, but as yet unproven, long-term side effects of high-dose inhaled steroids.

16. How can nocturnal awakenings be better controlled?

Since many medications lose their effect at these hours, nocturnal symptoms often become challenging to control. Moving the dose of inhaled corticosteroids to the afternoon hours, adding an inhaled long-acting β_2 agonist or anticholinergic bronchodilator, or offering a trial of a leukotriene inhibitor or theophylline before the patient retires to sleep are appropriate measures. A stepwise approach is often needed, and if one intervention does not ameliorate the symptoms, another agent should be added to the regimen.

17. What are the effects of pregnancy on asthma?

Asthma is the most commonly encountered lung disease during pregnancy. Approximately 1 % of pregnancies are complicated by asthma, and 1 of 500 pregnant women experience life-threatening consequences. In general, approximately one-third of pregnant women experience worsening of asthma during gestation, one-third remain the same, and one-third actually improve.

18. When should antibiotics be prescribed in acute exacerbations of asthma?

Common triggers of acute exacerbations of asthma include allergen exposure (e.g., dust mite, mold, pollens, cats), viral infections, and exercise. Evidence suggests that viral upper respiratory tract infections, namely rhinovirus, cause > 80% of asthma exacerbations in adults. The need for diagnostic chest radiographs or antibiotics for treatment of exacerbations is very uncommon. The 2002 NAEPP guidelines state that antibiotics are not indicated for the treatment of acute asthma exacerbations except when comorbid conditions dictate such use. Indications for antibiotic use include concomitant acute pyogenic sinusitis or acute bacterial bronchitis in patients with underlying COPD. In general, treatment focus is on appropriate steroid and bronchodilator therapy and trigger avoidance. Recent trials, however, have shown the benefits of macrolide therapy (clarithromycin, 1000 mg/d for 6 weeks or equivalent) in some severe asthmatics who have serologic evidence of Chlamydia pneumoniae or Mycoplasma pneumoniae Infection.

19. Explain the benefit of dry-powder inhalers (DPIs).

Dry-powder, breath-activated delivery devices are available for both inhaled steroid and bronchodilator medications, and combination formulations will soon be manufactured. They have gained favor among patients and physicians because of their ease of use and the elimination of CFC-containing MDIs. DPIs may benefit patients unable to master the hand-breath coordination of an MDI and improve airway deposition of drug in many patients with poor MDI technique. In addition, the automatic doses counter and simple packaging of DPIs make them appealing to patients and physicians. However, as with MDIs, the success of DPI delivery to the lower respiratory tract is still heavily dependent on patient effort.

20. What causes nocturnal awakenings in asthmatic patients?

Nocturnal symptoms of sleep wakefulness, cough, and wheezing are signs of poorly controlled asthma. The chronobiology of asthma in adults and children is well documented. Typically, PEFRs decrease significantly between 2 am and 6 am because of a natural diminution in circulating catecholamines and corticosteroids and a rise in vagal tone.

21. Describe hereditary angioedema.

Hereditary angioedema is a dominantly inherited disorder characterized by recurrent attacks i ii angioedema involving the skin, mucous membranes, and respiratory and gastrointestinal tracts. It is associated with a functional deficiency of the inhibitor of the first component of the complement system, the C1 esterase inhibitor. About 85% of patients have decreased levels of the inhibitor; the remaining patients have a normal level of the inhibitor, but it is nonfunctional. The condition can be diagnosed by clinical presentation, positive family history, and a characteristic complement profile (normal C1, C3, decreased C4) during attacks.

22. What is autoimmune urticaria?

Autoimmune urticaria designates a subset of patients with chronic urtiaria who have autoantibodies with histamine-releasing activity. The existence of these autoantibodies was recognized initially by the observation that sera from affected patients induced an immediate urticarial response on injection into their own skin. It was then shown that the sera induced histamine release from basophils and mast cells. It is now well established the autoantibodies responsible for this activity are those recognizing FceRI and, less commonly, IgE.

23. Describe contact urticaria (allergic or pseudoallergic).

Contact urticaria refers to lesions that develop following skin contact with substances ranging from low-molecular-weight organic compounds to macromolecules. Nonimmunoiogicai contact urticaria (NICU) occurs without previous sensitization. Inducing substances include preservatives and fragrances in foods, cosmetics, and topical medicaments. Immunologic (allergic) contact urticaria is due to immediate-type hypersensitivity and involves IgE specific for the contact allergens. It may be associated with systemic and potentially life-threatening symptoms. Natural rubber latex is one of the most notable allergens.

24. What is the role of foods in urticaria?

Foods are a common cause of acute urticaria, which is often identified by the patients themselves through association of the development of the lesions in proximity to ingestion of a particular kind of foods on several occasions. Symptoms begin within minutes to several hours after ingestion. GI and respiratory symptoms may accompany or precede the urticarial reaction IgE antibodies to food components are implicated. However, other mechanisms exist; for example, red wines may contain high concentrations of vasoactive amines, which can cause urticaria. The role of foods as a cause of chronic urticaria is controversial.

25. Do children outgrow IgE-mediated food allergies?

New data suggest that about 10% of children with peanut allergy become tolerant by age 5-6 years; however, if they are not tolerant by then, the allergy appears to be persistent through adulthood. Approximately 85% of children allergic to milk, soy, and egg tolerate the implicated food by age 3-5 years. If the reaction was anaphylactic and the level of IgE antibody is high, the development of tolerance is less likely. Most reactions to cow's milk are non-IgE-mediated GI reactions. In general, if a child has a low level of IgE to a food, there is a greater chance of developing tolerance when rechallenged later compared with children with high IgE levels. Incremental food challenges are quite useful and allow liberalization of the diet after 1-3 years ni avoidance. A child may still have a positive skin test or in vitro specific IgE assay and yet tolerate the food.

26. What is the immediate cause of death from food allergy?

Severe bronchospasm is frequently reported in the few available case series examining food allergy mortality. Symptoms can start out mild (hives) and then progress. Severe symptoms can persist for many hours before death. However, any of the following manifestations can result in death within minutes:

- Laryngoedema
- Oral angioedema blocking the airway
- Bronchospasm
- Hypotension/cardiovascular collapse

27. What are the risk factors for death from anaphylaxis to foods?

Failure to administer epinephrine early in the reaction. Many patients do not have self-injectable epinephrine because of failure of physicians to prescribe epinephrine or their own failure to carry it with them or keep the prescription up to date. In addition, many states do not allow all levels of emergency medical technicians to administer epinephrine in the field.

- Underlying asthma
- Peanut, tree nut, or seafood allergy
- Adolescent or young adult (may be related to denial of symptom severity)
- History of previous severe reactions
- Failure to activate the emergency medical system after recognizing a reaction due to denial of its potential severity
- Failure to recognize biphasic anaphylaxis, which occurs when a systemic reaction initially seems to respond completely to therapy, only to recur within an hour or two.
- Patient taking beta blockers and perhaps ACE inhibitors may have more severe anaphylaxis.

28. How is food allergy diagnosed?

A combination of history, physical examination, laboratory evaluation, skin prick testing, elimination diets, sometimes endoscopy and/oral food challenges. The history, which is most important, should focus on the age of onset, symptoms, time between ingestion and reaction, reproducibility (do the reactions occur every time the food is eaten?), presence of atopic dermatitis, asthma, allergic rhinitis, or other atopy. The history should also focus on conditions that may be in the differential diagnosis of food allergy or intolerance, such as gastrointestinal conditions (hiatal hernia, pyloric stenosis, gallstones). Subsequent evaluation is driven by the suspected pathophysiology of the reported adverse reaction.

29. Describe the role of aeroallergens and household allergens in atopic dermatitis.

Aeroallergens play more of a role as the atopic child grows older. Studies have shown worsening of symptoms with patch testing of aeroallergens. Inhalation of aeroallergens may exacerbate the skin disease. Sera from 95% of patients with atopic dermatitis had IgE to house dust mites compared with 42% of asthmatic patiente. House dust mite-specific lymphocyte stimulation is greatly elevated

in infants with atopic dermatitis. Recommendation of empiric avoidance of dust mite and animal dander may be warranted because avoidance improves symptoms.

30. What role do infectious agents play in flares of atopic dermatitis?
Patients with atopic dermatitis have an increased tendency for development of bacterial and fungal skin infections. In general, dry skin creates small fissures that can serve as an entry to skin pathogens. However, compared with other dry skin conditions, such as psoriasis, there is still an increased susceptibility for infections. A deficiency in antimicrobial peptides was found in the skin of patients with atopic dermatitis compared to the skin of patients with psoriasis, leading to a susceptibility to S. aureus. S. aureus is colonized on the skin of 90% of patients with atopic dermatitis compared with only 5% of healthy people. Empirical treatment with oral antibiotics often results in improvement, even if no active infection is seen. Observation of pustules indicates that S. aureus may be present.

31. How are bacterial skin infections treated?
An antibiotic with good staphylococcal coverage, such as cephalexin or dicloxacillin should be administered for 3-4 weeks. Some patients may require longer treatment (6-12 weeks). Bictroban can be used for early topical treatment and also can be applied to the nares of staphylococcal carriers who experience frequent relapses when antibiotics are discontinued. However, other topical antibiotics are of little therapeutic value and can lead to sensitization to the agents, particularly neomycin.

32. What mechanisms of immune damage have been associated with drug hypersensitivity?
The Gell and Coombs classification of human hypersensitivity provides models for understanding immunologic drug reactions. Type I reaction is IgE-mediated and constitutes an immediair hypersensitivity response. Type II hypersensitivity involves antibody-mediated cytotoxicity. Immune complex reactions are termed type III. Cell-mediated immunity causes type IV hypersensitivity. For the majority of suspected IDHRs, the exact mechanism of involvement of the immune system is not fully known, and some drug reactions may involve multiple pathways.

33. Describe the pathogenesis of type I hypersensitivity reactions.
Type I hypersensitivity reactions are true drug allergies. They are elicited by the binding of some from of the drug to specific IgE attached to Fcε receptors on mast cells. Degranulation and activation of the mast cell occur with release of histamine and other preformed and newly synthesized mediators of inflammation. Clinical findings include urticaria, angioedema, bronchospasm, and anaphylaxis.

34. Give examples of agents that may cause type I reactions.
Beta-lactams such as penicillin that can bind to human proteins and create allergenic haptens are the most common cause of type I drug hypersensitivity. Other drugs that may produce this type of reaction include proteins, generally of large molecular weight, such as:
- Antithymocyte globulin
- Chymopapain
- Heterologousantiserum
- Insulin
- Protamine
- Recombinant granulocyte-macrophage colony-stimulating factors (GM-CSF)
- Streptokinase
- Tetanus toxoid

35. Describe the mechanism of a type II hypersensitivity reaction.

Toxicity due to type II hypersensitivity is caused by antibodies directed against antigens on or near the cell surface. Specific antibodies are necessary to initiate this form of cytotoxic reaction, but in contrast to type I reactions, the antibodies are typically of the IgG or IgM class.

36. Give examples of type II reactions.

A major example of type II reaction is Coombs'-positive hemolytic anemia, in which penicillin exposure results in the production of antibodies directed against penicillin-coated erythrocytes, causing lysis of the cells. Other examples are:
- Granulocytopenia due to phenothiazines and sulfonamides
- Immune-induced thrombocytopenia due to sulfonamides, quinidine or heparin
- Methacillin-induced interstitial nephritis
- Methyldopa-induced immunohemolytic anemia

37. Give examples of a type III reaction.

Medications such as heterologous antiserum and other proteins with a long half-life in the body may elicit a type III reaction. The clinical manifestations typically resemble serum sickness (skin rash, fever, lymphadenopathy, and arthralgia) and occur between 1 and 3 weeks after drug administration. Penicillin and cefaclor have been associated with a serum sickness-like illness, although the mechanism of this syndrome appears to be more complex and, in the case of cefaclor, seems not to involve significant antigen-antibody reactions.

38. Describe the proposed pathogenesis of a type IV hypersensitivity reaction.

In type IV hypersensitivity, or delayed hypersensitivity, cell-mediated cytotoxicity is responsible for the various clinical symptoms. Both CD4+ and CD8+ T cells mediate type IV responses. The proposed mechanism involves binding of drug haptens to intracellular or extracellular proteins for presentation by MHC molecules to drug-specific T cells. Subsequent cytokine release by T cells, together with the production of other mediators of cytotoxicity, creates the inflammatory response that is seen in conditions such as delayed-type hypersensitivity skin disease. Subtypes of the delayed hypersensitivity response may account for a variety of IDMRs, including maculopapular erythematous (morbilliform) eruptions, pustular exanthems, and some bullous reactions.

39. Give examples of a type IV reaction.

Examples of delayed hypersensitivity include contact dermatitis induced by:
- Ethylenediamine
- Neomycin
- Topical anesthestics
- Topical antihistamines
- Topical corticosteroids

40. Define systemic mastocytosis.

Systemic mastocytosis is a clinical syndrome caused by the accumulation of mast cells in multiple organs, including skin, bone marrow, liver, and gastrointestinal tract. Clinical features of flushing, pruritus, and anaphylactic response may be associated with urticaria pigmentosa and may develop spontaneously or after taking NSAIDs, opiates, or alcohol. Other common features are osteoporosis, bone demineralization, and anemia due to bone marrow involvement.