Drug allergy

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Drug allergy is one type of adverse reaction to drugs and encompasses a spectrum of hypersensitivity reactions with heterogeneous mechanisms and clinical presentations. A thorough history is essential to the management of drug allergy. Laboratory testing has a very limited role in the management of drug allergy. Graded dose challenges and procedures to induce drug tolerance might be required in patients with drug allergy when there is a definite need for a particular agent. Management of reactions to specific agents, including β-lactam antibiotics, sulfonamides, local anesthetics, radiocontrast media, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and biologic modifiers, will be discussed in further detail. (J Allergy Clin Immunol 2010;125:S126-37.)

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Abbreviations used

ACE-I:	Angiotensin-converting enzyme inhibitor
ADR:	Adverse drug reaction
AERD:	Aspirin-exacerbated respiratory disease
ASA:	Acetylsalicylic acid
DILE:	Drug-induced lupus erythematosus
DRESS:	Drug rash with eosinophilia and systemic symptoms
NSAID:	Nonsteroidal anti-inflammatory drug
NSF:	Nephrogenic systemic fibrosis
PPL:	Penicilloyl-polylysine
RCM:	Radiocontrast media
SJS:	Stevens-Johnson syndrome
TEN:	Toxic epidermal necrolysis
TMP-SMX:	Trimethoprim-sulfamethoxazole

EPIDEMIOLOGY AND CLASSIFICATION OF ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment. ADRs are commonly encountered in both inpatient and outpatient settings. In a meta-analysis of inpatient ADR prospective studies, 15.1% of patients sustained ADRs during their hospitalizations, and 6.7% of patients experienced serious ADRs.[1] In a 4-week prospective cohort study of outpatients followed in primary care clinics, 25% of patients reported ADRs, 13% of which were serious.[2]

ADRs are categorized into predictable (type A) and unpredictable (type B) reactions. Predictable reactions are usually dose dependent, related to the known pharmacologic actions of the drug, and occur in otherwise healthy subjects. Predictable reactions account for about 80% of all ADRs and are subdivided into overdose, side effects, secondary effects, and drug interactions. Unpredictable reactions are generally dose independent, are unrelated to the pharmacologic actions of the drug, and occur only in susceptible subjects. Unpredictable reactions are subdivided into drug intolerance (an undesirable pharmacologic effect that occurs at low and sometimes subtherapeutic doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug), drug idiosyncrasy (abnormal and unexpected effect, usually caused by underlying abnormalities of metabolism, excretion, or bioavailability), drug allergy (immunologically mediated ADRs [including IgE-mediated drug allergy]), and pseudoallergic reactions (also called anaphylactoid reactions, which are due to direct release of mediators from mast cells and basophils rather than IgE antibodies).

The Gell and Coombs system of hypersensitivity is the most common method of classifying immunologically mediated ADRs. It is comprised of immediate-type reactions mediated by drug-specific IgE antibodies (type I), cytotoxic reactions mediated by drug-specific IgG or IgM antibodies (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (type IV). Type IV reactions can be subdivided into 4 categories involving activation and recruitment of monocytes (type IVa), eosinophils (type IVb), $CD4^+$ or $CD8^+$ T cells (type IVc), and neutrophils (type IVd).[3]

The pharmacologic interaction with immune receptors concept is a recently proposed addition to drug hypersensitivity classification. In this scheme a drug binds noncovalently to a T-cell receptor, which can lead to an immune response through interaction with an MHC receptor. In this scenario no sensitization is required because there is direct stimulation of memory and effector T cells analogous to the concept of superantigens.[4] Although these mechanistic classifications of drug-induced allergic reactions are useful, not all drug-induced allergic reactions can be categorized based on these limited mechanisms of hypersensitivity.

CLINICAL MANIFESTATIONS OF IMMUNOLOGICALLY MEDIATED ADRS

Drug-induced allergic reactions can affect numerous organ systems and manifest in a variety of reactions, including various drug-induced allergic syndromes, and many drug-induced allergic reactions can have more than 1 mechanistic pathway (Table I).

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TABLE I. Heterogeneity of drug-induced allergic reactions

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

Cutaneous manifestations are the most common physical manifestation of drug-induced allergic reactions; however, many other organ systems can be involved, including hematologic abnormalities, hepatitis, pneumonitis, lymphadenopathy, or arthralgias. Although drug-induced allergic reactions might present with noncutaneous physical findings, these findings are generally nonspecific and are not nearly as helpful in diagnosis and management decisions. Numerous cutaneous eruptions have been attributed to drug-induced allergic reactions and have been reviewed elsewhere.[5]

Because certain drug eruptions are associated with specific immunologic reactions, it is important to characterize the type of eruption in regard to determining the cause, further diagnostic tests, and management decisions. The most common cutaneous manifestation of drug-induced allergic reactions is a generalized exanthem (also know as a maculopapular eruption). Urticaria, angioedema, or both is another common cutaneous drug reaction that can be due to IgE-mediated reactions, serum sickness, pseudoallergic reactions, or other mechanisms (eg, bradykinin mediated). The most severe form of cutaneous drug reactions are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is another cutaneous, drug-induced, multiorgan inflammatory response that can be life-threatening. First described in conjunction with anticonvulsants, it has since been ascribed to a variety of other drugs. DRESS is atypical from other drug-induced allergic reactions in that the reaction develops later, usually 2 to 8 weeks after therapy is started; symptoms can worsen after the drug is discontinued; and symptoms can persist for weeks or even months after the drug has been discontinued.[6]

EVALUATION: HISTORY TAKING

A thorough history is an essential component in the evaluation of patients with suspected drug allergies. The history helps guide the clinician in the choice of diagnostic tests and whether it might be safe to reintroduce the medication. If possible, the original medical record that describes the drug reaction should be reviewed. The most important components of a drug allergy history are as follows.

- *What is the name of the medication?* Although obvious, not uncommonly, patients are unable to provide this basic piece of information. Reasons for this include passage of time and the fact that names of many medications sound similar, and patients who reacted to multiple drugs might confuse which drug caused which reaction.
- *How long ago did the reaction occur?* The time elapsed is important because some allergies, such as to penicillin, wane over time.

- *Which systems (eg, cutaneous, respiratory, and gastrointestinal) were involved in the reaction, and what were the characteristics?* If a cutaneous eruption occurred, what kind was it (eg, urticarial, morbilliform, bullous, or exfoliative)? Showing the patient pictures of different types of rashes might be helpful.
- *When during the course did the reaction occur?* Alternatively, was the onset of symptoms after the course was completed?
- *Why was the medication prescribed?* The indication is important because symptoms of the underlying disease might be misattributed to the medication (eg, a truncal rash during penicillin therapy for streptococcal pharyngitis).
- *Was the patient taking concurrent medications at the time of the reaction?* Antibiotics are usually blamed for reactions, but drugs such as opiates and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently coadministered and might be responsible instead.
- *What was the therapeutic management required secondary to the reaction?* Self-discontinuation of a medication suggests a milder reaction than if a patient required hospitalization. Some patients recall treatment they received more readily than the characteristics of the reaction itself.
- *Had the patient taken the same or a cross-reacting medication before the reaction?* Most allergic reactions require a period of sensitization, typically during a previous course that was tolerated.
- *Has the patient been exposed to the same or similar medication since the reaction?* For instance, some patients with a history of penicillin allergy report that later they tolerated a course of amoxicillin clavulanate (Augmentin; GlaxoSmithKline, London, United Kingdom), not realizing the latter is a penicillin-class compound.
- *Has the patient experienced symptoms similar to the reaction in the absence of drug treatment?* The most common situation is chronic recurrent idiopathic urticaria, which can be confused for drug allergy.
- *Does the patient have an underlying condition that favors reactions to certain medications?* Examples of such conditions include mononucleosis for ampicillin reactions and HIV infection for trimethoprim-sulfamethoxazole (TMP-SMX) reactions.

DIFFERENTIAL DIAGNOSIS IN DRUG ALLERGY

Drug-induced allergic reactions can present in numerous ways, affecting single organs or with multiorgan involvement. However, each clinical presentation is not unique or specific to drug-induced allergic reactions, and therefore other conditions might need to be considered based on the presentation. For example, a morbilliform eruption occurring in a child receiving amoxicillin for an upper respiratory tract infection might indeed be due to a viral exanthem and not a drug-induced allergic reaction. In addition, patients with multiple drug allergies might actually have an underlying chronic disease and are inappropriately labeled with multiple drug allergies. This frequently occurs in patients with underlying chronic urticaria or anxiety disorders but can also occur with other conditions, such as asthma, vocal cord dysfunction, idiopathic anaphylaxis, or rarely even mastocytosis.

LABORATORIES IN DRUG ALLERGY

Routine laboratory evaluation appropriate to the clinical setting might be useful for the evaluation of a patient with a suspected drug reaction, depending on the history and physical examination findings. Although eosinophilia is often suggestive of a drug-induced allergic reaction, most patients with drug-induced allergic reactions do not have eosinophilia, and therefore the absence of eosinophilia clearly does not exclude a drug-induced allergic cause. Autoantibodies might be helpful in the evaluation of drug-induced vasculitis (eg, antinuclear cytoplasmic antibody) and drug-induced lupus erythematosus (DILE). In the case of systemic DILE, antihistone antibody levels are frequently positive, whereas in patients with cutaneous DILE, anti-Ro/SSA, anti-La/SSB, or both levels are frequently positive.[7]

In cases of suspect anaphylaxis, a diagnosis of anaphylaxis might be made by detecting an increase in serum total tryptase levels above baseline values or in serum mature tryptase (also known as β-tryptase) levels, which peak 0.5 to 2 hours after drug administration and then decrease with a half-life of about 2 hours.[8] Additional methods for detecting systemic mast cell mediator release include obtaining 24-hour urine collections for major urinary metabolites of histamine or prostaglandin D_2.

For immediate hypersensitivity reactions mediated by IgE antibodies, demonstration of the presence of drug-specific IgE is usually taken as sufficient evidence that the patients is at significant risk of having a type I reaction if the drug is administered. This is helpful in the case of high-molecular-weight agents. In the case of small-molecular-weight drugs, validated and reliable skin test reagents are only available for penicillin. Haptenation of the β-lactam ring of penicillin to a protein (eg, penicilloyl-polylysine [PPL]) enhances the immunogenicity, with resultant improvement in the detection of specific IgE. The negative predictive value of penicillin skin testing (with PPL, penicillin G, and penicilloate and/or penilloate) for serious immediate-type reactions approaches 100%. However, insufficient knowledge about drug degradation products, metabolites, or both and how they are conjugated with body proteins has been an impediment to developing either skin or *in vitro* assays for assessing immune responses to most other small-molecular-weight drug chemicals. Specific IgE *in vitro* assays (eg, RASTs, ImmunoCAP, and Immulite) are available, although most are not adequately validated with unclear specificity and sensitivity and lack internal positive controls. In addition, *in vitro* assays for IgE to drugs are hampered because of difficulties with binding of drug allergens to solid-phase matrices.

The basophil activation test is a recently described method of evaluating expression of CD63 or CD203C on basophils after stimulation with an allergen. There are very limited data using this method to evaluate patients with possible drug allergies to β-lactam antibiotics, NSAIDs, and muscle relaxants,[9] and further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool. Drug patch testing might be useful for certain types of cutaneous drug reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions, but generally is not helpful for SJS or urticarial eruptions.[10] In complex cases in which multiple drugs are involved without a clear-cut temporal relationship, a skin biopsy might be useful. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy might not definitively exclude alternative causes.

TABLE II. Induction of drug tolerance procedures

Type of drug tolerance	Duration	Initial dose	Mechanisms	Example
Immunologic IgE (drug desensitization)	Hours	μg	Antigen-specific mediator depletion, downregulation of receptors	Penicillin Carboplatin, cisplatin, oxaliplatin
Immunologic non-IgE	Hours to days	mg	Unknown	TMP-SMX
Pharmacologic	Hours to days	mg	Metabolic shift, internalization of receptors	Aspirin
Nonimmunologic mast cell activation	Hours	μg	Unknown	Paclitaxel
Undefined	Weeks	μg-mg	Unknown	Allopurinol

INDUCTION OF DRUG TOLERANCE AND GRADED CHALLENGE PROCEDURES

In situations in which there is a definite medical need for a particular agent, no suitable alternative agent exists, and testing with high negative predictive value does not exist, there are primarily 2 options for the patient with a drug allergy. On the one hand, a procedure to induce temporary drug tolerance can be performed to allow the patient to take the drug safely. In contrast, a test dose or graded challenge can be administered to determine whether the patient is currently allergic to the particular drug.

The term *drug desensitizatio*n has been widely used and is defined as a procedure that modifies a patient's immune response to a drug, allowing him or her to take the drug temporarily in a safe manner. In cases such as IgE-mediated drug allergy (eg, to penicillin), the term drug desensitization is accurate in that patients are indeed sensitized to penicillin before the procedure and afterward typically have diminished or absent skin test reactions and hence are less sensitive or desensitized.[11] However, the term drug desensitization has also been used to describe a number of different protocols for patients with non–IgE-mediated drug allergies who in many cases are not truly sensitized initially but might react to the drug through various non–IgE-mediated or even nonimmune mechanisms. Recently, the term *induction of drug tolerance* has been proposed as a more appropriate term to encompass not only IgE-mediated desensitization procedures but other non–IgE-mediated desensitizations as well.[12] The term *drug tolerance* is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. Drug tolerance does not indicate either a permanent state of tolerance or that the mechanism involved was immunologic tolerance. Drug desensitizations for IgE-mediated drug allergy are indeed a form of immunologic drug tolerance. Induction of drug tolerance procedures modify a patient's response to a drug (through immunologic or other nonimmunologic mechanisms) to temporarily allow treatment with it safely. Induction of drug tolerance can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms (Table II).

All procedures to induce drug tolerance involve administration of incremental doses of the drug but vary considerably over the starting dose and duration of the procedure. Through various mechanisms, these procedures induce a temporary state of tolerance to the drug, which is maintained only as long as the patient continues to take the specific drug. Therefore this procedure would need to be repeated in the future if a patient requires the drug again after finishing a prior therapeutic course.

Graded challenge, or test dosing, is defined as a procedure to determine whether a patient will have an adverse reaction to a particular drug by administering lower than therapeutic doses over a period of time with observation for reactions. The rationale for starting with a lower dose is based on the concept that a smaller dose of allergen will result in a less severe and more easily treated reaction. Unlike induction of drug tolerance procedures, a graded challenge does not modify a patient's immunologic or nonimmunologic response to a given drug. Although it is not possible to be absolutely certain that a patient is not allergic to a drug because valid diagnostic tests are not available for most drugs, graded challenges are intended for patients who, after a full evaluation, are unlikely to be allergic to the given drug. Furthermore, the benefit of treatment with the drug should outweigh the risk of performing the graded challenge. The starting dose for graded challenge is generally higher than for induction of drug tolerance procedures, and the number of steps in the procedure might be 2 or several. The time intervals between doses are dependent on the type of previous reaction, and the entire procedure can take hours or days to complete. After a successful graded challenge and therapeutic course of the drug, future courses of the drug can be started without another challenge.

A typically safe starting dose for an IgE immune induction of drug tolerance (desensitization) procedure is about twice the dose used in the puncture or intradermal skin test used to document the IgE-mediated allergy. A typical starting dose for a graded challenge is 1/100th of the final treatment dose. This is in contrast to the starting dose for an IgE immune induction of drug tolerance, in which case the starting dose is often 1/10,000th of the final dose. Caution should be exercised when a graded challenge consisting of more than 4 or 5 steps is performed because it might inadvertently induce modifications of immune effector cells and therefore induce drug tolerance in the patient. In these circumstances future administrations of the drug should be made cautiously.

The choice of whether to introduce a clinically indicated drug through a graded challenge or through induction of drug tolerance mainly depends on the likelihood that the patient is allergic at the time of the procedure. Patients who, based on their history, diagnostic test results, or both, are unlikely to be allergic to a drug can undergo graded challenge. For example, if penicillin skin testing is unavailable and a patient with a history of a mild pruritic rash during penicillin treatment 20 years ago requires penicillin therapy, it would be reasonable to administer penicillin through a graded oral challenge. Patients who have a relatively higher likelihood of being allergic to a drug should undergo an induction of drug tolerance procedure. For example, if penicillin skin testing is unavailable and a patient with a recent history of penicillin-induced anaphylaxis requires penicillin, it should be administered through induction of drug tolerance. Graded challenge (or induction of drug tolerance) should almost never be performed if the reaction history is consistent with a severe non–IgE-mediated reaction, such as SJS, TEN, DRESS, hepatitis, or hemolytic anemia.

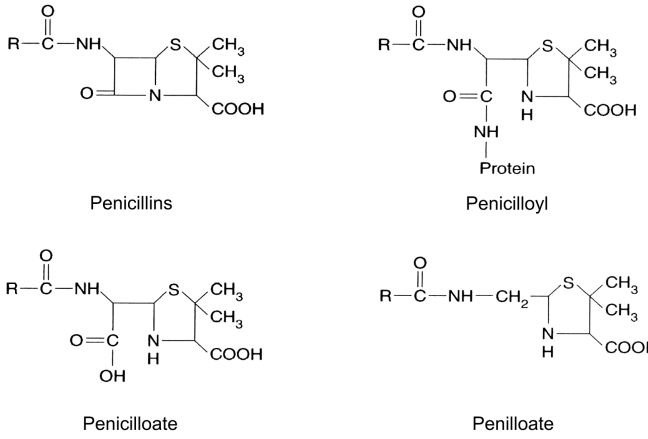

FIG 1. Chemical structures of major and minor penicillin allergenic determinants. The R-group distinguishes different penicillin compounds.

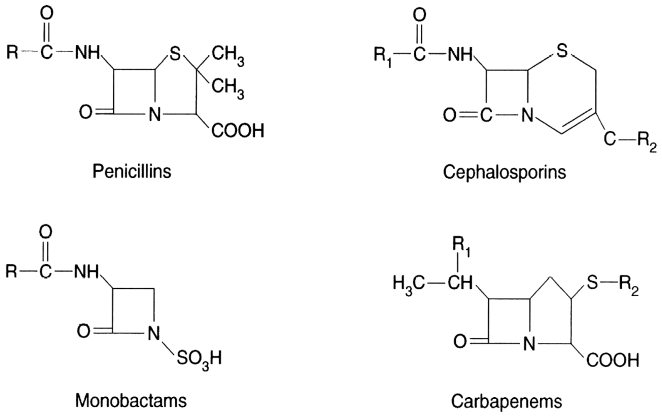

FIG 2. Chemical structures of β-lactam antibiotics.

MANAGEMENT OF COMMON ALLERGIC REACTIONS TO SPECIFIC AGENTS

β-Lactam antibiotics: Penicillins

Penicillin is the most prevalent medication allergy, with about 10% of patients reporting being allergic. When evaluated, however, approximately 90% of patients with a history of penicillin allergy are able to tolerate penicillins.[13,14] This observation is partly due to the fact that penicillin-specific IgE antibodies wane over time and many (but not all) patients outgrow their penicillin allergy. In addition, many patients were probably mislabeled as being allergic at the time of their reaction because symptoms and signs of an underlying illness can be confused for a penicillin-induced reaction. Patients labeled as allergic to penicillin are more likely to be treated with more expensive and broad-spectrum antibiotics (eg, quinolones and vancomycin),[15] which contributes to the development and spread of multiple drug-resistant bacteria and leads to higher health care costs.

The immunochemistry of penicillin was elucidated in the 1960s.[16] Under physiologic conditions, penicillin spontaneously degrades to a number of reactive intermediates that act as haptens and covalently bind to self-proteins, which then can elicit an immune response. Approximately 95% of penicillin degrades to the penicilloyl moiety, which is referred to as the major antigenic determinant (Fig 1). The remaining portion of penicillin degrades to several derivatives, and of these, penicilloate and penilloate are the most important to induce allergic responses. These 2 compounds, along with penicillin itself, are collectively known as the minor antigenic determinants, and they cover all clinically relevant allergenic determinants not covered by penicilloyl.

Less commonly, the R-group side chain, which distinguishes different penicillin compounds, can also serve as an allergenic determinant (Fig 2). This type of allergy results in patients who selectively react to amoxicillin, for example, but are able to tolerate other penicillins.[17] In contrast, patients allergic to the core β-lactam portion of penicillin cross-react to various penicillins. Selective allergy to amoxicillin or ampicillin is relatively common in parts of Southern Europe and quite infrequent in the United States; the reason for these differences in unknown.

Insight into the immunochemistry of penicillin has allowed for the development of validated skin test reagents to detect penicillin-specific IgE antibodies.[13,14] PPL was commercially available as Pre Pen from 1974 until 2004 and is expected to return to the market in 2009. Of the minor determinants, only penicillin G is commercially available. Some medical centers synthesize penicilloate and penilloate for local use. Amoxicillin or ampicillin should be included in the skin-testing panel when patients report reactions to these antibiotics.

The negative predictive value of penicillin skin testing is very high. In large-scale studies 1% to 3% of patients with negative skin test responses (with both major and minor determinants) had mild and self-limiting reactions on being challenged with the drug.[13,14] Some studies report that about 10% to 20% of patients with penicillin allergy have skin test reactivity only to penicilloate or penilloate.[13,14,18] The clinical significance of these findings is uncertain. Penicillin challenges of subjects with negative skin test responses to PPL and penicillin G[19] have similar reaction rates compared with those in subjects with negative skin test responses to the full set of major and minor penicillin determinants.[13,14]

Reaction history is a poor predictor of who will demonstrate a positive penicillin skin test response. Overall, about one third of patients with positive penicillin skin test responses report vague reaction histories.[20] Therefore any patient with a history of a possible IgE-mediated reaction to penicillin is a candidate for skin testing. Elective skin testing (when patients are well and not in immediate need of antibiotic therapy) should be considered. The medical care of patients labeled as having penicillin allergy can be compromised because of use of inappropriate antibiotics.[15] Patients who have positive responses should receive penicillins only through an induction of drug tolerance procedure. For patients with negative skin test responses, clinicians should consider a challenge with penicillin because without it, many patients are subsequently not treated with β-lactams because of fear on either the part of the patient or treating physician.

Resensitization after oral treatment with penicillin is rare in both pediatric and adult patients, including after repeated courses.[21,22] Hence routine repeat penicillin skin testing is not indicated in patients with a history of penicillin allergy who have tolerated 1 or more courses of oral penicillin. Consideration can be given to retesting individuals with recent or particularly severe previous reactions. Resensitization after high-dose parenteral treatment with penicillin might be more likely, but data are limited. Nevertheless, repeat penicillin skin testing in this situation might be warranted.[23]

TABLE III. Summary of studies of cephalosporin challenges in patients with a history of penicillin allergy without preceding penicillin allergy testing

Reference	History of penicillin allergy	No history of penicillin allergy	Cephalosporins administered
Dash, 1975[E1]	25/324 (7.7%)	140/17,216 (0.8%)	Cephalexin and cephaloridine
Petz, 1978[E2]	57/701 (8.1%)	285/15,007 (1.9%)	Cephalexin, cephaloridine, cephalothin, cefazolin, and cefamandole
Goodman et al, 2001[E3]	1/300 (0.3%)	1/2,431 (0.04%)	Cefazolin (in all but 1 patient)
Daulat et al, 2004[E4]	1/606 (0.17%)	15/22,664 (0.07%)	First generation (42%), second generation (21%), third/fourth generations (37%)
Fonacier et al, 2005[E5]	7/83 (8.4%)	Not reported	First generation (59%), second generation (8.4%), third generation (25%), fourth generation (7%)

Please see the Online Repository at www.jacionline.org for complete reference citations.

Without penicillin skin testing, the approach to patients with a history of penicillin allergy is based on the reaction history and likelihood of needing treatment with penicillins. Patients with a low likelihood of being allergic (eg, those with distant [> 10 years] or vague reaction histories) might receive penicillins through cautious graded challenge. On the other hand, patients with severe reaction histories (eg, anaphylaxis) or recent reactions should receive penicillins only through an induction of drug tolerance procedure.

β-Lactam antibiotics: Penicillin/cephalosporin cross-reactivity

Retrospective studies of administration of cephalosporins to patients with a history of penicillin allergy, without prior penicillin skin testing, showed much higher reaction rates in the 1970s compared to recently (Table III). Before 1980, cephalosporins were contaminated with trace amounts of penicillin, which would overestimate the cross-reactivity. Studies that rely on patient history to diagnose penicillin allergy are problematic because about 90% of these patients do not have penicillin allergy at the time of treatment with cephalosporins. Furthermore, some patients with severe penicillin reaction histories might have been denied treatment with cephalosporins.

Table IV summarizes studies in which patients with positive penicillin skin test responses were challenged with cephalosporins. Although these studies are of higher quality by virtue of proving type I penicillin sensitization before cephalosporin challenge, they still have limitations, including lack of control groups (eg, patients challenged with placebo or challenged with non–β-lactam antibiotics) and the fact that the challenges were not blinded. Patients might have an underlying propensity to react to unrelated drugs,[24] which can account for some reactions to cephalosporins in patients with penicillin allergy. In patients with documented allergic-like reactions to penicillins, the relative risk for allergic-like reactions was increased for both cephalosporins and sulfonamides.[25]

Ideally, management of cephalosporin administration to patients with a history of penicillin allergy includes penicillin skin testing (when available). About 90% of patients have negative penicillin skin test responses and can safely receive cephalosporins (as well as other β-lactams). Patients with positive penicillin skin test responses have a slightly increased risk of reacting to cephalosporins, and therefore they should be administered through graded challenge or an induction of tolerance procedure. When penicillin skin testing is not available, cephalosporins might be given through a full-dose or graded challenge, depending on the reaction history and the likelihood the patient has penicillin allergy. The reaction risk is very low, but rarely, anaphylactic reactions have been described.

Allergic cross-reactivity between amoxicillin and cephalosporins that share identical R-group side chains is higher than for patients with positive penicillin skin test responses. Twelve percent to 38% of patients proved to be selectively allergic to amoxicillin (ie, able to tolerate penicillin) reacted to cefadroxil.[26,27] Therefore patients with amoxicillin allergy should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, and cefatrizine) or receive them through induction of drug tolerance procedures. Similarly, patients with ampicillin allergy should avoid cephalexin, cefaclor, cephradine, cephaloglycin, and loracarbef or receive them through induction of drug tolerance procedures.

β-Lactam antibiotics: Penicillin/carbapenem cross-reactivity

Data on allergic cross-reactivity between penicillin and carbapenems are similar to those for penicillin/cephalosporins. Table V summarizes retrospective studies of carbapenem administration to patients with a history of penicillin allergy (no penicillin skin testing performed). The carbapenem reaction rate is somewhat higher in patients with a history of penicillin allergy. Table V also summarizes studies in which patients with positive penicillin skin test responses were challenged with carbapenems, and no patients experienced reactions (3 patients were not challenged because of positive carbapenem skin test responses).

The approach to carbapenem administration in patients with a history of penicillin allergy is analogous to that for cephalosporins. Patients with negative penicillin skin test responses can receive carbapenems safely. Patients with positive penicillin skin test responses should receive carbapenems through graded challenge, given that the chance of reacting is less than 1%. Without penicillin skin testing, carbapenems can be administered through graded challenge. Skin testing with carbapenems can be considered in patients with positive penicillin skin test responses or when penicillin skin testing is not performed.

Sulfonamides

Sulfonamides are defined as drugs with an SO_2-NH_2 moiety. Sulfonamide antibiotics also contain an aromatic amine at the N_4 position and a substituted ring at the N_1 position, whereas nonantibiotic sulfonamides do not. Beside penicillins, sulfonamide

TABLE IV. Summary of patients with positive penicillin skin test responses challenged with cephalosporins, not including patients with positive skin test responses to only amoxicillin or ampicillin (and not to major, minor, or both penicillin determinants)

	Cephalosporin			
Reference	**No. of patients**	**No. of reactions**	**Skin testing**	**Comment**
Girard, 1968[E6]	23	2 (8.7%)	No	Both reactions to cephaloridine
Assem and Vickers, 1974[E7]	3	3 (100%)	No	All reactions to cephaloridine
Warrington et al, 1978[E8]	3	0	Yes	
Solley et al, 1982[E9]	27	0	No	
Saxon et al, 1987[E10]	62	1 (1.6%)	No	Cephalosporin not noted
Blanca et al, 1989)[E11]	16	2 (12.5%)	No	Both reactions to cefamandole
Shepherd and Burton, 1993[E12]	9	0	No	
Audicana et al, 1994[E13]	12	0	Yes	
Pichichero and Pichichero, 1998[E14]	39	2 (5.1%)	No	Reaction to cefaclor and ?
Novalbos et al, 2001[E15]	23	0	Yes	
Macy and Burchette, 2002[E16]	42	1 (2.4%)	No	Reaction to cefixime
Romano et al, 2004[E17]	75	0	Yes	
Greenberger and Klemens, 2005[E18]	6	0	No	
Park et al, 2006[E19]	37	2 (5.4%)	No	Cephalosporins not noted

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TABLE V. Summary of carbapenem challenges in patients with a history of penicillin allergy without preceding penicillin allergy testing and in patients with positive penicillin skin test responses

	Carbapenem reaction rate			
Reference	**History of penicillin allergy (no penicillin ST)**	**No history of penicillin allergy**	**History of penicillin allergy (+ penicillin ST)**	***P* value**
McConnell et al, 2000[E20]	4/63 (6.3%)	NA	NA	NA
Prescott et al, 2004[E21]	11/100 (11%)	3/111 (2.7%)	NA	.024
Sodhi et al, 2004[E22]	15/163 (9.2%)	4/103 (3.9)	NA	.164
Cunha et al, 2008[E23]	0/110 (0%)	NA	NA	NA
Romano et al, 2006[E24]	NA	NA	0/110*	NA
Romano et al, 2007[E25]	NA	NA	0/103*	NA
Atanaskovic et al, 2008[E26]	NA	NA	0/107*	NA

Please see the Online Repository at www.jacionline.org for complete reference citations.
ST, Skin test response.

antibiotics are the most common cause of drug-induced allergic reactions.[28] They most commonly cause delayed cutaneous maculopapular/morbilliform eruptions, and IgE-mediated reactions are relatively infrequent. Sulfonamides are by far the most common cause of SJS and TEN.[29]

Patients infected with HIV have a greatly increased risk of cutaneous reactions from sulfonamide antibiotics, which is probably related to immunologic factors and frequent exposure to these antibiotics. The typical reaction to TMP-SMX in HIV-positive patients consists of a generalized maculopapular eruption that occurs during the second week of treatment and is usually accompanied by pruritus and fever. The incidence of skin rashes to TMP-SMX in healthy subjects is 3% to 5%, whereas reaction rates of 40% to 80% have been reported in patients with HIV.[28] Because TMP-SMX is the drug of choice for a number of HIV-associated infections (most notably prophylaxis and treatment of *Pneumocystis carinii*–induced pneumonia), it is not uncommon for HIV-positive patients with a history of reacting to sulfonamides to require treatment with the antibiotic. Consequently, various induction of drug tolerance procedures have been devised to safely administer TMP-SMX to HIV-positive patients with histories of reacting to the antibiotic.[30] The protocols vary greatly in terms of the starting dose, the incremental increase between doses, the time interval between doses, and the total duration of the desensitization; however, the success rates are comparable. Two studies compared the effectiveness of induction of tolerance versus rechallenge (single dose) in HIV-positive patients with documented reactions to TMP-SMX, and there were no differences in the success rates.[31,32] These results place into question the validity of previously reported induction of tolerance procedures that did not include a control group of patients who received full-dose TMP-SMX.

The N_4 aromatic amine is critical for the development of delayed reactions to sulfonamide antibiotics (through oxidation to hydroxyamines and nitroso compounds), and based on more limited data, the N_1 substituted ring appears to be important for IgE-mediated reactions.[28] Because nonantibiotic sulfonamides lack these structural components, they would not be expected to cross-react with sulfonamide antibiotics. Several clinical studies demonstrated no increased risk of reactions to nonantibiotic sulfonamides in patients with a history of allergy to sulfonamide antibiotics.[33]

Local anesthetics

IgE-mediated reactions to local anesthetics are extremely rare,[34] yet many patients are labeled allergic to all "caines" and denied access to these drugs. Most adverse reactions to local

anesthetics are due to nonallergic factors, such as vasovagal responses; toxic or idiosyncratic reactions caused by inadvertent intravenous epinephrine; or anxiety.[35] Local anesthetics are grouped into benzoate esters and amides. Based on patch testing, there is cross-reactivity among the benzoate esters (which do not cross-react with amides) but not among the amides. It is not known what, if any, relevance this has on immediate-type reactions to local anesthetics. If the reaction history is consistent with a possible type I reaction, skin testing followed by graded challenge tests can be performed with the same (epinephrine-free) local anesthetic that is intended to be used. Although there are differences in reported graded challenge procedures, a rapid and convenient protocol is as follows.[36] Skin prick testing is first performed with the undiluted anesthetic. If the response is negative after 20 minutes, an intradermal test is performed with 0.04 mL of 1:100 dilution of local anesthetic. If the response is negative after 20 minutes, a 1.0-mL subcutaneous injection of saline as a placebo is administered. If there is no reaction after 20 minutes, 1.0 mL of local anesthetic is administered, and the patient is observed for 20 minutes.

False-positive intracutaneous test results can occur in some patients.[37] Also, very rare patients can have positive skin test responses to methylparabens in local anesthetics, and some of these can be false-positive.[36] In these situations preservative-free local anesthetic should be used for skin testing/graded challenge.

Radiocontrast media

Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occur in about 1% to 3% of patients who receive ionic radiocontrast media (RCM) and less than 0.5% of patients who receive nonionic agents.[38] Severe life-threatening reactions are less common: 0.22% of patients receiving ionic RCM and 0.04% of patients receiving nonionic agents.[39] The fatality rate from RCM is about 1 to 2 per 100,000 procedures, and it is similar for both ionic and nonionic agents.[40] Risk factors for anaphylactoid reactions to RCM include female sex, asthma, and a history of a previous anaphylactoid reaction to RCM; β-blocker exposure, the presence of cardiovascular conditions, or both are associated with greater risk for more serious anaphylactoid reactions.[41]

The pathogenesis of anaphylactoid reactions is unrelated to "seafood allergy" (attributed to high iodine content); patients with food allergy require no special precautions before receiving RCM. RCM reactions are generally not mediated by specific IgE antibodies. RCM likely has direct effects on mast cells and basophils, leading to degranulation and systemic mediator release, which accounts for the clinical manifestations of anaphylactoid reactions. Complement activation might account for some reactions. A recent European trial suggests that some RCM reactions might be IgE mediated because approximately half of patients with immediate-type reactions to RCM had positive skin test responses, which were highly specific.[42]

Management of patients who require RCM and experienced prior anaphylactoid reactions includes the following: (1) determine whether the study is essential; (2) determine that the patient understands the risks; (3) ensure proper hydration; (4) use a nonionic, iso-osmolar RCM, especially in high-risk patients (asthmatic patients, patients taking β-blockers, and those with cardiovascular disease); and (5) use a pretreatment regimen that has been documented to be successful in preventing most reactions but is less successful in preventing recurrence of severe reactions.[43] Pretreatment is defined as the administration of medications before administration of a drug to lessen the likelihood and severity of a drug-induced allergic reaction. Medications used for pretreatment are thought to be effective because of blockade of receptors for mast cell mediators or through reduction in mast cell mediator release (mast cell stabilization). A typical pretreatment regimen consists of 50 mg of prednisone 13, 7, and 1 hour before the procedure; 50 mg of diphenhydramine 1 hour before the procedure; and either 25 mg of ephedrine or 4 mg of albuterol 1 hour before the procedure. However, the latter agents might not be favorable from a risk/benefit standpoint in patients with cardiovascular disease. The use of H_2 antagonists in the pretreatment regimen is controversial because it can increase the RCM reaction rate.[43]

Delayed reactions to RCM, defined as those occurring between 1 hour and 1 week after administration, occur in approximately 2% of patients.[44] These reactions most commonly manifest as mild, self-limited cutaneous eruptions and do not require any treatment.[44] The mechanism of delayed skin reactions to RCM appears to be T-cell mediated.[45] Rarely, more serious and life-threatening delayed reactions to RCM have been described, such as SJS and TEN.[45]

Anaphylactoid reactions to gadolinium occur less frequently than to contrast materials used for computed tomographic scans.[46] Premedication regimens consisting of corticosteroids and antihistamines have been successfully used.[47] Nephrogenic systemic fibrosis (NSF), also called gadolinium-associated systemic fibrosis, is a recently described devastating progressive systemic fibrosing disorder that afflicts patients with renal dysfunction who recently received gadolinium.[48] The mechanism of NSF has not been elucidated, but it is hypothesized that dechelation of gadolinium chelates attracts $CD34^+$, $CD45^+$, procollagen-positive circulating fibrocytes.[48] Gadolinium has been found in biopsy specimens of skin lesions. Pre-existing renal failure might facilitate the reaction by delaying the excretion of gadolinium chelates. There is no effective treatment for NSF, and affected patients have increased mortality.[48]

Angiotensin-converting enzyme inhibitor: Cough and angioedema

Angiotensin-converting enzyme inhibitors (ACE-Is) have 2 major adverse effects: cough and angioedema. The incidence of cough from ACE-Is ranges from 5% to 35%.[49] Cough occurs more commonly in women, nonsmokers, and Chinese patients. The cause for ACE-I–induced cough is unclear but might be related to bradykinin, substance P, or other mechanisms. ACE-I–induced cough is typically dry and might be associated with a tickling sensation in the throat. The cough can occur within hours of the first dose or within weeks or months of initiation of therapy. With discontinuation of the ACE-I, the cough usually resolves in 1 to 4 weeks and rarely lingers up to 3 months.[49] In patients for whom cessation of ACE-I therapy is not desirable, several pharmacologic agents have been reported in small case series to reduce coughing, including cromolyn, theophylline, NSAIDs, amlodipine, nifedipine, and ferrous sulfate.[49] ACE-I–induced cough is not dose related, and angiotensin II receptor blockers are not associated with an increased incidence of cough.[50]

The incidence of angioedema to ACE-Is is estimated to occur in 1 to 7/1,000 patients, and this risk is higher in African-Americans compared with that seen in whites.[51] ACE-I–induced

TABLE VI. Hypersensitivity reactions to aspirin and NSAIDs and cross-reactivity

Type of reaction	Underlying disease	Cross-reactivity with COX-1 inhibitors
Respiratory (AERD)	Rhinitis, nasal polyps, sinusitis, asthma	Yes
Urticaria/AE	Chronic urticaria	Yes
Urticaria/AE	None	Yes or no
Anaphylaxis	None	No

The cross-reactivity patterns depicted in this table are generally true, but exceptions can occur.
AE, angioedema.

angioedema is often unrecognized because its manifestation can occur anywhere between a few hours to 10 years after an ACE-I is first taken. A recent retrospective study found a mean of 1.8 years from initiation of an ACE-I until the onset of angioedema.[52] ACE-I–induced angioedema accounts for approximately one third of all patients presenting to the emergency department for angioedema.[53] Characteristically, ACE-I–induced angioedema involves the head and neck primarily, especially the lips and tongue; concomitant urticaria and pruritus are rare. In some cases laryngeal edema can cause fatalities. Reports of angioedema of the intestinal tract caused by ACE-Is have also been described. Bradykinin is a prominent mediator in both hereditary angioedema and ACE-I–induced angioedema.[54] ACE-Is are contraindicated in patients with hereditary angioedema. In patients with ACE-I–induced angioedema, angiotensin II receptor blockers are often used as alternative medications. Limited data suggest that in patients with angioedema, when taking an ACE-I, the risk of persistent angioedema when subsequently switched to an angiotensin II receptor blockers is less than 10%.[55] Treatment includes discontinuing the medication and careful management of the airway, and in some cases fresh frozen plasma has been useful.

Acetylsalicylic acid/NSAID reactions

Acetylsalicylic acid (ASA) and NSAIDs can cause a spectrum of drug-induced allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis. Some of these drug-induced allergic reactions exhibit cross-reactivity to other NSAIDs and aspirin, whereas some reactions might be drug specific (Table VI).

Aspirin-exacerbated respiratory disease (AERD) is a clinical entity characterized by ASA/NSAID-induced respiratory reactions in patients with underlying chronic respiratory diseases, such as asthma, rhinitis, sinusitis, and/or nasal polyposis. AERD has been previously referred to by a number of different terms, including aspirin sensitivity, aspirin intolerance, aspirin idiosyncrasy, aspirin-induced asthma, and aspirin or Samter's triad. AERD does not fit precisely into a specific category of ADRs, although it has often been referred to as a type of pseudoallergic reaction. AERD affects up to 20% of adult asthmatic patients, is more common in women, has an average age of onset around the age of 30 years, and usually starts with rhinitis, progressing to hyperplastic sinusitis and nasal polyposis.[56] Asthma might be present since childhood or might develop *de novo*, on average 2 years after the onset of nasal congestion and polyposis.

Fundamental to the pathophysiology of AERD is excessive production of cysteinyl leukotrienes, increased numbers of inflammatory cells expressing cysteinyl leukotriene 1 receptors, and greater airway responsiveness to cysteinyl leukotrienes. In addition, a number of genetic polymorphisms involving the leukotriene pathway have been reported to be associated with AERD, including the leukotriene C_4 promoter, the cysteinyl leukotriene 1 receptor promoter, and prostanoid and thromboxane receptor–related genes.[57] Administration of ASA leads to inhibition of COX-1, with a resultant decrease in prostaglandin E_2 levels. Prostaglandin E_2 normally inhibits 5-lipoxygenase, but with a loss of this modifying effect, arachidonic acid molecules are preferentially metabolized in the 5-lipoxygenase pathway, resulting in increased production of cysteinyl leukotrienes.

Within minutes of ingestion of therapeutic doses of ASA or NSAIDs, patients with AERD typically have both rhinoconjunctivitis and bronchospasm. The bronchospasm induced can be severe and result in respiratory failure with a need for intubation and mechanical ventilation. Gastrointestinal symptoms and urticaria are rare extrapulmonary manifestations of AERD. Patients with AERD will react to ASA and NSAIDs that inhibit COX-1. Selective COX-2 inhibitors almost never cause reactions in patients with AERD and can typically be taken safely.

There is no diagnostic *in vitro* or skin test for AERD. The diagnosis is usually established based on history, but when a definitive diagnosis is required, a controlled oral provocation challenge with ASA can be performed. A recent study showed that 100% of patients with a history of a severe reaction to aspirin (poor response to albuterol with need for medical intervention) had positive oral aspirin challenge esults.[58] Management of patients with AERD involves avoidance of aspirin and NSAIDs and aggressive medical, surgical, or both types of treatment of underlying asthma and rhinitis/sinusitis. A pharmacologic induction of drug tolerance procedure (also known as aspirin desensitization), during which tolerance to aspirin can be induced over a few days and then maintained chronically, is an important therapeutic option for patients with AERD and improves clinical outcomes for both upper and lower respiratory tract disease.[59,60]

Several other drug-induced allergic reactions to ASA or NSAIDs can occur. Patients with chronic urticaria/angioedema might have exacerbation of their urticaria/angioedema with ingestion of NSAIDs that inhibit COX-1 but typically tolerate COX-2 inhibitors. Patients without a history of underlying chronic urticaria/angioedema can have acute urticaria/angioedema with ingestion of aspirin or NSAIDs. Some of these patients demonstrate cross-reactivity to other COX-1 inhibitors, whereas others have selective reactions to a particular NSAID. Anaphylactic reactions to NSAIDs are typically drug specific, and these patients typically tolerate other NSAIDs.[61] Finally, some patients are not easily categorized who have blended reactions with overlap of various clinical features from the above well-described ASA/NSAID reaction syndromes.

HIV medications

Patients infected with HIV have an increased frequency of drug-induced allergic reactions, and the reasons behind this are likely multifactorial.[62] Drug exanthems from TMP-SMX are among the most common drug-induced allergic reactions in patients with HIV, as previously discussed. Antiretroviral medications have also been associated with numerous drug-induced allergic reactions, ranging from mild exanthems to life-threatening reactions, such as SJS or TEN.

Although many antiretroviral medications can cause drug-induced allergic reactions, abacavir deserves special mention because of the successful implementation of a pharmacogenetics approach to management. Abacavir is a nucleoside reverse transcriptase inhibitor that is associated with a hypersensitivity reaction in approximately 4% of treated patients, with an estimated mortality rate of 0.03%.[63] This multiorgan reaction includes symptoms such as fever, rash, malaise/fatigue, gastrointestinal symptoms, and respiratory symptoms. In 90% of cases, hypersensitivity reactions occurred within the first 6 weeks after initiation of abacavir. Rechallenge with abacavir resulted in recurrence of symptoms within hours of re-exposure, including hypotension in 25% of those rechallenge reactions. Because of the severity of reactions on rechallenge, hypersensitivity to abacavir is a contraindication to subsequent treatment with any formulation that includes it.

Investigations into genetic risk factors associated with these reactions discovered that several HLA alleles, most notably HLA-B*5701, were strongly associated with risk of abacavir hypersensitivity reactions.[64,65] The prevalence of HLA-B*5701 varies considerably by ethnicity and geography, with estimated US prevalences of 8% for whites, 1% for Asians, and 2.5% for African Americans.[66] A double-blind, prospective, randomized study of 1,956 predominantly white patients with HIV from 19 countries was performed to evaluate the utility of genetic screening before initiation of abacavir therapy.[67] Subjects were randomly assigned to undergo prospective HLA-B*5701 screening with exclusion for abacavir treatment if screened positive. Screening for HLA-B*5701 reduced the risk of hypersensitivity reaction to abacavir, with reaction rates of 3.4% in the screened group versus 7.8% in the control group. A North American study with a more racially diverse population demonstrated that genetic screening decreased the rate of abacavir hypersensitivity to less than 1%, which is lower than historical rates.[68] The ability to identify genetic predispositions to drug-induced allergic reactions and implement genetic screening tests, as in the case of abacavir hypersensitivity, might hold promise for preventing other drug-induced allergic reactions in susceptible persons.[69]

Cancer chemotherapeutic agents

Hypersensitivity reactions have been reported for most cancer chemotherapeutic agents.[70] The severity of reactions can range from mild cutaneous reactions to fatal anaphylactic reactions. Taxanes, such as paclitaxel and docetaxel, can cause anaphylactoid reactions (non–IgE-mediated anaphylaxis), frequently with the first administration. Pretreatment with antihistamines and corticosteroids will prevent reactions in greater than 90% of cases.[71] Platinum compounds, such as cisplatin, carboplatin, and oxaliplatin, typically cause hypersensitivity reactions after several treatment courses. Results of skin testing have been found to be positive in the majority of patients with immediate reactions to platinum-containing compounds, suggesting an IgE-mediated mechanism. Cetuximab is an mAb used to treat colorectal cancer and squamous cell carcinoma of the head and neck and has been associated with anaphylactic reactions. IgE antibodies to cetuximab have been found in the majority of anaphylactic reactions and are specific for an oligosaccharide, galactose-α-1,3 galactose, which is present on the Fab portion of the cetuximab heavy chain.[72] Procedures to induce drug tolerance have been reported to be successful and safe in platinum-containing compounds, taxanes, and other chemotherapeutics.[73]

Biologic modifiers

In the past decade, a number of biologic immune modulatory agents have been developed to treat various inflammatory diseases and tumors. They are comprised of proteins such as cytokines, mAbs, and fusion proteins of solubilized receptors. These agents differ from other drugs in that they are not small-molecular-weight compounds but large potentially immunogenic proteins. Their metabolism is different, many are naturally occurring proteins, and all have inherent immunologic effects. Because of all of these differences, a separate type of classification for adverse reactions to biologic agents has been proposed based on the mechanism of reactions.[74] High-dose reactions are related to high cytokine levels administered directly or from cytokines released (eg, capillary leak syndrome). Hypersensitivity reactions can be either antibody or cell mediated. Immune or cytokine dysregulation can result in secondary immunodeficiency, autoimmunity, or allergic/atopic disorders. Cross-reactive reactions can occur when the biologic agent is intended for a pathologic cell type but cross-reacts with normal cells. Finally, biologic agents can also result in nonimmunologic side effects. Interferons are an example of biologic agents capable of causing most of the above reactions, including high-dose flu-like symptoms, hypersensitivity reactions of urticaria, autoimmune reactions (including thyroid disease and psoriasis), and nonimmunologic effects, such as depression.

Capillary (vascular) leak syndrome is a rare but potentially fatal condition that has been attributed to a number of biologic agents, including IL-2, GM-CSF, and granulocyte colony-stimulating factor.[75] Clinical and biochemical findings can include fever, edema (peripheral, pulmonary, ascites, and pleural/pericardial effusions), weight gain, hypotension, hypoalbuminemia, and multiorgan failure. The mechanism of the endothelial damage with subsequent fluid and protein extravasation is unclear but appears to be related to the inherent biologic effects of these cytokines.

TNF-α antagonists include humanized and fully human mAbs to TNF-α (infliximab and adalimumab) and TNF-receptor fusion proteins (etanercept). Acute infusion reactions are a relatively common adverse reaction to infliximab, often after the first dose, usually occurring within 4 hours of the infusion, and characterized by symptoms including hypotension/hypertension, chest pain, dyspnea, fever, and urticaria/angioedema.[76] The pathophysiology of these reactions is not known but is usually not IgE mediated, although several cases of anaphylaxis have been reported. The majority of patients can continue the infusion with reduction in rate or with premedication.[77] Delayed serum sickness–like reactions with symptoms of fever, urticaria/angioedema, and myalgias have also been reported but are much less common. The presence of antibodies to infliximab has correlated with both acute and delayed infusion reactions to infliximab. Etanercept and, less commonly, adalimumab are associated with delayed injection site reactions that typically peak at 2 days, usually occur in the first 2 months of therapy, and rarely cause discontinuation of treatment. Recall injection site reactions at the sites of previous injections can also occur and can be T-cell mediated delayed-type hypersensitivity reactions.[78] In addition to the above-mentioned infusion- or injection-related reactions, a number of other immunologic adverse reactions have been reported with TNF-α

antagonists, including vasculitis, systemic lupus erythematosus, psoriasis, interstitial lung disease, ocular autoimmune diseases, sarcoidosis, and hepatitis.[79]

Omalizumab is an mAb to human IgE approved for the treatment of asthma. Anaphylactic reactions have been reported with omalizumab in less than 0.1% of treated patients.[80] Most, but clearly not all, anaphylactic reactions occur to the first 3 doses and within 2 hours of the injection.

Finally, although not often considered a biologic therapy, intravenous gamma globulin has been associated with a variety of infusion reactions. The most common infusion-related reactions include symptoms of headache, fever, chills, tachycardia, anxiety, nausea, dyspnea, arthralgia, and myalgias and rarely more serious signs, such as hypotension. Most infusion reactions are mild and rate related and occur 6 to 24 hours after an infusion. The mechanisms causing these reactions are postulated to involve activation of complement by immunoglobulin aggregates, antigen-antibody complexes, and contaminant vasoactive proteins.[81]

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Allergic skin diseases

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The skin is one of the largest immunologic organs and is affected by both external and internal factors, as well as innate and adaptive immune responses. Many skin disorders, such as atopic dermatitis, contact dermatitis, urticaria, angioedema, psoriasis, and autoimmune blistering disorders, are immune mediated. Most of these diseases are chronic, inflammatory, and proliferative, in which both genetic and environmental factors play important roles. These immunologic mechanisms might have implications for potential targets of future therapeutic interventions. (J Allergy Clin Immunol 2010;125:S138-49.)

Key words: *Allergic contact dermatitis, autoimmune blistering disease, atopic dermatitis, eczema, immune-mediated skin disorders, irritant contact dermatitis, psoriasis, urticaria*

The skin is one of the largest immunologic organs and is often a target for allergic and immunologic responses. Many skin disorders, such as atopic dermatitis (AD), contact dermatitis (CD), urticaria, angioedema, psoriasis, and autoimmune blistering disorders, are immune mediated, with abnormalities in innate and adaptive immunity. Most of these diseases are chronic, inflammatory, and proliferative, in which both genetic and environmental factors play important roles. These immunologic mechanisms might have implications for potential targets of future therapeutic interventions. This review will examine some recent research advances in allergic and immunologic skin diseases.

Abbreviations used

ACD:	Allergic contact dermatitis
AD:	Atopic dermatitis
AMP:	Antimicrobial peptide
ASST:	Autologous serum skin test
BHR:	Basophil histamine release
BP:	Bullous pemphigoid
CAPB:	Cocoamidopropyl betaine
CD:	Contact dermatitis
CIU:	Chronic idiopathic urticaria
CU:	Chronic urticaria
DC:	Dendritic cell
EH:	Eczema herpeticum
FDA:	US Food and Drug Administration
HBD:	Human β-defensin
ICD:	Irritant contact dermatitis
IDEC:	Inflammatory dendritic epidermal cell
IVIG:	Intravenous immunoglobulin
LC:	Langerhans cell
NACDG:	North American Contact Dermatitis Group
PDC:	Plasmacytoid dendritic cell
PPD:	Paraphenylenediamine
PV:	Pemphigus vulgaris
ROAT:	Repeat open application test
SCD:	Systemic contact dermatitis
TLR:	Toll-like receptor
T.R.U.E. TEST:	Thin layer rapid use epicutaneous test
TSLP:	Thymic stromal lymphopoietin

CONTACT DERMATITIS

Allergists and clinical immunologists are seeing increasing numbers of patients with eczema and CD and are performing more patch testing. Cohort population-based studies in Europe showed point prevalence rates of 0.7% to 18.6% for allergic contact dermatitis (ACD).[1,2] Allergists trained in patch testing are more confident about the clinical relevance of such testing, especially for the differential diagnosis of the common eczematous diseases.[3]

Pathophysiology

CD can be allergic (20%) or irritant (80%). The morphology, severity, and location of CD is affected by the innate allergenicity or irritancy of the allergen, the site and degree of contact, the thickness and integrity of the skin involved, exposure time, environmental conditions, the immunocompetency of the patient, and even genetics.

ACD is the prototype of the type IV cell-mediated hypersensitivity reaction. The allergens in ACD are usually small-molecular-weight molecules or haptens that conjugate with proteins in the skin and induce activated epidermal keratinocytes to release proinflammatory cytokines. The Langerhans cells endocytose, process, and combine specific hapten peptides with HLA class I molecules and then migrate to the draining regional lymph nodes, where they activate and sensitize naive $CD4^+$ T cells (T_H0 cells). Activated T_H cells then proliferate and generate clones of hapten-specific $CD4^+CD25^+$ regulatory and $CD8^+$ effector cells, which become either memory or effector cells. This is known as the afferent limb of the immune reaction. The $CD4^+$ regulatory/effector and $CD8^+$ effector cells then "home" to the original skin site and there function as the efferent limb of the immune response. Both $CD4^+$ and $CD8^+$ sensitized effector cells release proinflammatory cytokines/cytotoxins (INF-γ, TNF-α, GM-CSF, IL-2, perforin, and granzyme), which cause an intense perivascular inflammatory

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infiltrate and spongiosis. $CD4^+$ CCR10 chemokine–expressing memory lymphocytes are retained for long periods of time in the original ACD sites, accounting for the shortened latent period (anamnesis) on subsequent exposure. In mice mast cells at the site of ACD have been shown to recruit polymorphonuclear leukocytes to the site through the release of the mediators TNF-α and IL-8.

Irritant contact dermatitis (ICD) is the result of nonimmunologic, multifactorial, direct tissue reaction. T cells activated by means of nonimmune, irritant, or innate mechanisms release inflammatory cytokines (TNF-α, IL-1, IL-8, and GM-CSF) that contribute to the dose-dependent inflammation seen in patients with ICD.[4] There is usually a higher concentration of offending agents, such as solvents, detergents, chemicals, and alcohol. Lesions with erythema, edema, desquamation, and fissures are sharply demarcated typically and limited to the area in direct contact with the offending agent. They can burn or sting. Scratching, scrubbing, washing, excessive wetness, improper drying, perspiration, and extremes of temperature contribute to the reaction (Table I).

ACD and ICD frequently overlap because many allergens at high enough concentrations can also act as irritants. Impairment of the epidermal barrier layer, such as fissuring, can increase allergen entry into the epidermis.

TABLE I. Differentiation between ICD and ACD

Criteria	IICD	ACD
At risk	Anyone, especially if repeated exposure and occupational exposure	Previously sensitized and genetically predisposed
Mechanism	Nonimmunologic, direct tissue damage	Immunologic, delayed-type hypersensitivity reaction
Concentration of offending agent	Usually high, dose effect	Might be low threshold dose, all or nothing
Common causative agents	Water, soaps, solvents detergents, acids, bases, saliva, urine, stool	Poison ivy, poison oak, poison sumac, metals, cosmetics, medications, rubber, resins, adhesives
Risk if atopic	Increased	Decreased
Symptoms	Burning, stinging, soreness	Itching
Morphology	Erythema, edema, desquamation, fissures	Erythema, edema, vesicles, papules, lichenification
Demarcation	Usually sharp, limited to area in contact with agent	Sometimes sharp
Typical onset	Minutes to hour	Hours to days
Histology	Spongiosis, primarily neutrophilic infiltrates	Spongiosis, primarily lymphocytic infiltrates

Clinical evaluation

The diagnosis of ACD is suspected from the clinical presentation of the rash and the possible exposure to a contact allergen.

Face and eyelid. Fifty-five percent to 63.5% of eyelid dermatitis might be from ACD, 15% from ICD, less than 10% from AD, and 4% from seborrheic dermatitis.[5] Data collected by the North American Contact Dermatitis Group (NACDG) showed that in 193 (72%) of 268 patients with only eyelid dermatitis, gold was the most common allergen. Fragrances, preservatives, nickel, thiuram (rubber), cocamidopropyl betaine (CAPB) and amidoamine (shampoos), and tosylamide formaldehyde resins (nail polish) are other allergens to consider in the evaluation of eyelid dermatitis.[6] In patients with mixed facial and eyelid dermatitis, nickel, Kathon, and fragrance had the most positive patch test responses.[7,8]

Hands and feet. Hand dermatitis can be due to ICD, ACD, AD, dyshidrosis, or psoriasis. It can be extremely difficult to distinguish the cause of hand dermatitis, particularly because of tremendous overlap. Neither ACD nor ICD has pathognomonic clinical or histologic features. A thorough medical, work, and recreational history, together with a physical examination, ancillary laboratory tests, and patch tests, is critical in the evaluation of patients with hand eczema. Patch tests in patients with hand eczema showed that the relevant allergens include nickel sulfate (17.6%), potassium dichromate (7.2%), rubber elements (19.6%, including thiuram mix, carba mix, paraphenylenediamine [PPD], and mercaptobenzothiazole), and cobalt chloride (6.4%).[9] A Swedish study of 5700 patients showed that patients whose entire hands were involved were more likely to react to thiuram mix, PPD, chromate, and balsam of Peru. Patients with involvement of the fingers and interdigital spaces and those with palm involvement reacted more to nickel, cobalt, and 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one.[10]

The prevalence of hand eczema in patients with AD is 2- to 10-fold higher than that seen in nonatopic subjects, and 16% had nail dystrophy. The increasing prevalence of hand involvement with increasing age is probably due to increased water exposure and occupational insults, along with coexisting irritant dermatitis. Certain morphologic features can help distinguish the different contributing factors to hand eczema. Involvement of the dorsal hand and finger combined with the volar wrist suggest AD as a contributing causative factor.[11] ICD commonly presents as a localized dermatitis without vesicles in the webs of fingers; it extends onto the dorsal and ventral surfaces ("apron" pattern; Fig 1), dorsum of the hands, palms, and ball of the thumb. On the other hand, ACD often has vesicles and favors the fingertips, nail folds, and dorsum of the hands and less commonly involves the palms. ICD often precedes ACD, and therefore some pattern changes, such as increasing dermatitis from web spaces to fingertips or from palms to dorsal surfaces, should prompt patch testing or a repeat of it.[12]

Although ICD can cause dermatitis of the feet, ACD seem to be more common. ACD of the feet is usually located on the dorsum of the feet and toes (especially the hallux) but can also involve the sole and calcaneus. The interdigital areas are rarely involved. Humidity, heat, friction, and AD can contribute to or facilitate the development of CD of the feet. The most common positive patch test reactions in patients with ACD exclusively on the feet are rubber compounds (mercaptobenzothiazole mix, thiuram mix, carba mix, and PPD mix), with some patients sensitive to more than 1 of the agents. Other chemicals in footwear (eg, leather, adhesives, glues, and dyes) or in topical agents used for treatment (eg, creams, ointments, and antiperspirants) can cause ACD. Chemical agents used in the tanning and dyeing processes of leather (chrome), glues (colophony) used in soles and insoles, and nickel sulfate used in footwear buckles, eyelets, and ornaments[13] can be sensitizing agents.

Systemic contact dermatitis

Systemic contact dermatitis (SCD) is a systemic disease that demonstrates the inherent role of the skin as an immunologic organ. In the event that the suppressor function is inadequate, systemic administration of an allergen can lead to a full-blown effector

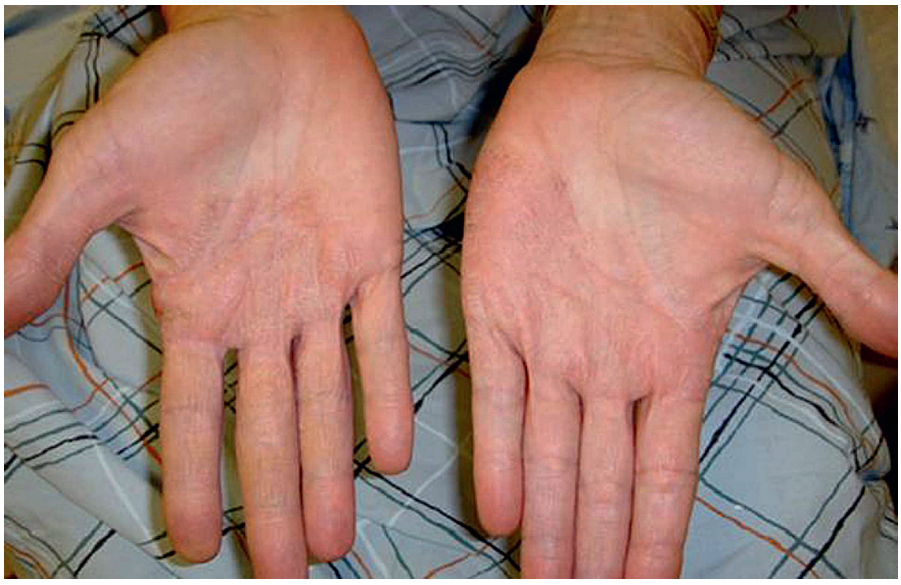

FIG 1. Irritant contact dermatitis of the hands: localized dermatitis without vesicles of webs of fingers extending onto the dorsal and ventral surfaces ("apron" pattern).

response. SCD is a localized or generalized inflammatory skin disease in contact-sensitized individuals exposed to the hapten orally, transcutaneously, intravenously, or by means of inhalation. It manifests as dermatitis at the cutaneous site of exposure, at previously sensitized sites (eg, an old lesion or the site of a previously positive patch test response), or in previously unaffected areas.[14] A variety of metals (cobalt, copper, chromium, gold, mercury, nickel, and zinc) have been found to cause SCD. The exposure type, duration, and environmental conditions (sweat and oxygen) in proximity to the metal are critical for mobilization of the ions inducing immune reactions. Medications reported to cause SCD include corticosteroids, antihistamines (diphenhydramine, ethylenediamine, hydroxyzine, and doxepin), miconazole, terbinafine, neomycin, gentamicin, erythromycin, pseudoephedrine, cinchocaine, benzocaine, tetracaine, oxycodone, intravenous immunoglobulin (IVIG), aminopenicillins, 5-aminosalicylic acid, naproxen, allopurinol, mitomycin C, 5-fluorouracil, and suxamethonium. In drug-induced SCD the clinical picture is frequently that of symmetric drug-related intertriginous and flexural exanthema. The criteria for the diagnosis of symmetric drug-related intertriginous and flexural exanthema include the following:

1 exposure to a systemic drug at first or repeated dosing (contact allergens excluded);
2 erythema of the gluteal/perianal area, V-shaped erythema of the inguinal/perianal area, or both;
3 involvement of at least 1 other intertriginous/flexural localization;
4 symmetry of affected areas; and
5 absence of systemic signs and symptoms.[15]

With alternative medicine's increasing popularity, more patients are using herbal preparations, homeopathy, and herbs in food, spices, and cosmetics that might contain plants and botanical extracts. Ragweed, chamomile, feverfew *(Tanacetum parthenium)*, *Arnica* species, marigold, *Echinacea* species, mugwort, cinnamon oil, vanilla oil, and balsam of Peru have been reported to cause SCD.

Occupational exposure

CD in the occupational setting can be benign and short lived or lead to severe disabling dermatitis. Patients with severe cases have poorer prognosis despite improvements in general working conditions, better availability of diagnostic patch testing, improved understanding of cutaneous biology, and treatment with topical and systemic steroids. ACD to nickel or chromium, a history of chronic dermatitis, delay of adequate treatment, a history of AD, and poor understanding by the worker of his or her disease is associated with a worse prognosis. Treatment of ACD in the workplace includes a timely diagnosis, identification of allergens or irritants, elimination of causal exposures, patient education, and use of therapeutic agents. AD is an important factor in susceptibility to persistent postoccupational dermatitis, and potential involvement of genetic predisposition to chemicals is observed. Two genomic screens[16,17] showed areas of genetic linkage on several chromosomes.

Patch testing. Patch testing is the only practical, scientific, and objective method for the diagnosis of ACD. It is indicated in patients with a chronic, pruritic, eczematous, or lichenified dermatitis in whom ACD is suspected. Patch test reactions are affected by oral corticosteroids (>20 mg of prednisone per day or its equivalent), cancer chemotherapy, or immunosuppressive drugs but not by antihistamines. Topical corticosteroids on the patch test site should be discontinued for 5 to 7 days before patch testing.

Sources of allergens. Commercially available, standardized patch testing allergens have been calibrated with respect to nonirritant concentrations and compatibility with the test vehicle. Test systems currently available are the thin-layer rapid-use epicutaneous test (T.R.U.E. TEST) and certain screening panels that are not US Food and Drug Administration (FDA) approved but conform to the standards of care recommended by CD experts. Commercial sources of customized patch testing materials include Smart Practice Canada (Calgary, Alberta, Canada); Hermal Pharmaceutical Laboratories, Inc (Hawthorne, NY); Dormer Laboratories, Inc (Rexdale, Ontario, Canada); and Trolab

Allergens (Omniderm Pharma Canada, Inc, Vaudreuil-Dorion, Quebec, Canada). The standardized allergens are loaded in Finn chambers or AllergEaze patch testing chambers (Haye's Service B.V., Alphen aan den Rijn, The Netherlands).

Number of allergens. Although the usefulness of patch testing is enhanced with the number of allergens tested, the ideal number of patch tests to be applied remains controversial. The T.R.U.E. Test contains 29 allergens, and the NACDG series ranges from 65 to 70 allergens. Studies show that the T.R.U.E. Test has higher false-negative reactions to neomycin, thiuram mix, balsam of Peru, fragrance mix, cobalt, and lanolin. Also, gold, bacitracin, methyldibromoglutaronitrile/phenoxyethanol, propylene glycol, bromonitropropane, cinnamic aldehyde, DMDM hydantoin, and ethylene urea/melamine formaldehyde have a prevalence of more than 2% in the NACDG 2004 but are not included in the current T.R.U.E. Test. Allergens not found on commercially available screening series in the United States frequently result in relevant reactions, and personal products are a useful supplement, especially in facial or periorbital dermatitis. The T.R.U.E. Test might serve as a triage or screening tool in an allergists' practice, but occupational exposures can benefit from early referral for supplemental testing.

Patch test technique. Patches are applied to upper or middle back areas (2.5 cm lateral to a midspinal reference point) free of dermatitis and hair and kept in place for 48 hours. Test results are read 30 minutes after removal of the patches to allow resolution of erythema caused by the tape, chamber, or both if present. A second reading should be done 3 to 5 days after the initial application. Thirty percent of relevant allergens eliciting negative reactions at the 48-hour reading elicit positive reactions in 96 hours. Irritant reactions tend to disappear by 96 hours. Metals (gold, potassium dichromate, nickel, and cobalt), topical antibiotics (neomycin and bacitracin), topical corticosteroids, and PPD can elicit positive reactions after 7 days. More than 50% of positive gold test results are delayed for about 1 week.

Nonstandardized patch tests, such as with the patient's personal products, allergens from cosmetics, or industrial allergens, might be needed. Leave-on cosmetics (makeup, perfume, moisturizer, and nail polish), clothing, and most foods are tested "as is," whereas wash-off cosmetics (soap and shampoo) are tested at 1:10 to 1:100 dilutions. Household and industrial products should only be tested after ascertaining their safety and patch test concentrations in the MSDS information.

Determining clinical relevance. The relevance of positive reactions to clinical ACD can only be established by carefully correlating the history, including sources of antigen in the patient's environment. A positive patch test reaction might be relevant to present or previous dermatitis, multiple true-positive results can occur, and mild responses can still represent an allergic reaction. A positive patch test reaction is considered to be a "definite" reaction of ACD if the result of a "use test" with the suspected item was positive or the reaction to patch testing with the object or product was positive, "probable" if the antigen could be verified as present in known skin contactants and the clinical presentation was consistent, and "possible" if skin contact with materials known to contain allergen was likely. Multiple sensitivities can occur when different allergens are present in different products used simultaneously. Likewise, concomitant sensitization of allergens can occur when multiple allergens are present in the same product; both processes induce sensitization. Cross-sensitization can also occur. Common combinations of positive patch test results are PPD and benzocaine (cross-sensitize); thiuram mix, carba mix, and mercapto mix (rubber products); quaternium 15 and paraben (quarternium-15, a formaldehyde releaser and formaldehyde are frequently combined and cosensitize); and cobalt and nickel (cobalt used in alloys with nickel and chromium and cosensitized). Patients older than 40 years are prone to multiple sensitivities.

TABLE II. Nickel content of certain foods

>50 μg	Soybean, boiled, ~1 cup: 895 μg Cocoa, 1 tbsp: 147 μg Cashew, ~18 nuts: 143 μg	Figs, ~5: 85 μg Lentils, ½ cup cooked: 61 μg Raspberry: 56 μg
20-50 μg	Vegetables, canned ½ cup: 40 μg Lobster, 3 oz: 30 μg Peas, frozen ½ cup: 27 μg	Asparagus, 6 spears: 25 μg Oat flakes, ⅔ cup: 25 μg Pistachios, 47 nuts: 23 μg
<20 μg	Strawberries, 7 medium: 9 μg Wheat bread, 1 slice: 5 μg Poultry, 3.5 oz: 5 μg Carrots, 8 sticks: 5 μg Apple, 1 medium: 5 μg	Cheese, 1.5 oz: 3 μg Yogurt, 1 cup: 3 μg Mineral water, 8 fl oz: 3 μg Mushroom, raw ½ cup: 2 μg Corn flakes, 1 cup: 2 μg

The repeat open application test (ROAT) might confirm the presence or absence of ACD. The suspected allergens are applied to the antecubital fossa twice daily for 7 days and observed for dermatitis. The absence of reaction makes CD unlikely. If eyelid dermatitis is considered, ROAT can be performed on the back of the ear.

SELECTED CONTACT ALLERGENS

Metals

Nickel. The prevalence rate of a positive patch test reaction to nickel in North America is consistently increasing. The most recent patch test data from the NACDG[18] reported that 18.7% of patients evaluated for ACD had a positive patch test reaction to nickel. Female subjects' sensitization to nickel is higher because of increased ear piercing. Laws regulating nickel products (eg, limiting the migration limit of nickel, the nickel ion release threshold of nickel-plated objects in prolonged contact with the skin, and the nickel content of post assemblies) in Europe appear to decrease sensitization in the younger population.

Evidence supports the contribution of dietary nickel to vesicular hand eczema.[19] A meta-analysis of SCD estimated that about 1% of patients with nickel allergy would have systemic reactions to the nickel content of a normal diet. Ten percent would react to exposures to 0.55 to 0.89 mg of nickel.[20] Foods with higher nickel content include soybean, fig, cocoa, lentil, cashew, nuts, and raspberry (Table II).

Gold. Previous NACDG data reported that 389 (9.5%) of 4101 patients had positive patch test reactions to gold. The most common sites of dermatitis were in the hands (29.6%); the face, with seborrheic distribution (19.3%); and the eyelids (7.5%).[21] Although mostly used for fashion appeal, gold is also an anti-inflammatory medication, is used in the electroplating industry, and is part of dental appliances. Patients with gold dental appliances (especially if present for more than 10 years) can present with oral symptoms. A subset of patients with facial dermatitis clear

with gold avoidance, mostly women with titanium dioxide in facial cosmetics, which adsorbs gold released from jewelry. Patients with gold allergy and eyelid dermatitis have cleared by not wearing gold jewelry, and therefore a trial of gold avoidance might be warranted with positive patch test reactions to gold. The avoidance period required for demonstrating benefit is long and might only be partially mitigating.[22]

Cosmetics

An individual is exposed to more than 100 chemical contactants in a typical day. Common allergens in these products include fragrances, preservatives, excipients, glues, and sun blocks.

Fragrance. Fragrance, the allergen of the year for 2007, is the most common cause of ACD from cosmetics and results in positive patch test reactions in 10.4% of patients. There are more than 2800 fragrance ingredients listed in the database of the Research Institute for Fragrance Materials, Inc,[23] and more new chemicals and botanical extracts are frequently used as fragrances. A manufacturer's label of "unscented" might erroneously suggest absence of fragrance when, in fact, a masking fragrance is present. "Fragrance-free" products are typically free of classic fragrance ingredients and are generally acceptable for the allergic patient. However, botanical extracts can be added to improve odor characteristics.

Because fragrances are complex substances, a perfume can contain hundreds of different chemicals that are difficult to identify individually. Fragrance mix I contains allergens found in 15% to 100% of cosmetic products[23] and might detect approximately 85% of subjects with fragrance allergy.[24] The addition of other commonly used fragrance ingredients (ylang ylang oil, narcissus oil, sandalwood oil, and balsam of Peru) increases the yield to 96%. The actual fragrance mix widely used in cosmetics and household products are seldom used in patch testing by the NACDG. Thus a positive patch test reaction to fragrance must correlate with distribution of the dermatitis and an evaluation of clinical relevance, such as a positive ROAT reaction.

Preservatives and excipients. Lanolin is a common component of consumer products. Unfortunately, its composition has not been fully characterized. Medicaments containing lanolin are more sensitizing than lanolin-containing cosmetics. It is a weak sensitizer on normal skin but a stronger sensitizer on damaged skin. Thus patients with chronic dermatitis, especially stasis dermatitis, are at higher risk of lanolin sensitivity.[25]

Cosmetic preservatives can be grouped into formaldehyde releasers and non–formaldehyde releasers. Paraben, a non–formaldehyde releaser, is the most commonly used preservative in cosmetics, as well as in pharmaceutical and industrial products, because of its broad spectrum of activity against yeasts, molds, and bacteria. Type I immediate hypersensitivity reactions (contact urticaria) and SCD from ingestion of paraben-containing medications or foods have been reported.[26]

Hair products. Hair products are second only to skin products as the most common cause of cosmetic allergy.

PPD is currently the most common cause of CD in hairdressers. In hair dye users the dermatitis often spares the scalp and usually involves the face near the hairline, eyelids, and neck. Nevertheless, generalized eruptions can occur. IgE–mediated contact urticaria and anaphylaxis, as well as lymphomatoid reactions, have also been reported. PPD cross-reacts with other chemicals, such as COX-2 inhibitor (celecoxib), sunscreens, and antioxidants used in the manufacture of rubber products (N-isopropyl-N′-phenyl-*p*-phenylenediamine). Theoretically, once oxidized, the PPD is no longer allergenic, but in reality, it is likely that PPD is never completely oxidized.[27] The FDA-required labeling and home-user tests appear to be predictive of PPD sensitization.[28] New hair dyes that contain FD&C and D&C dyes have very low levels of cross-reactivity with PPD and its other chemically related oxidative dyes (eg, Elumen Hair Color; Goldwell Cosmetics, Linthicum Heights, Md).

CAPB is an amphoteric surfactant often found in shampoos, bath products, and eye and facial cleaners. CAPB allergy typically presents as eyelid, facial, scalp, and/or neck dermatitis. Contaminants, such as amidoamine and dimethylaminopropylamine, which occur in the manufacture of CAPB, are thought to be allergens causing ACD. Positive patch test reactions to CAPB are often clinically relevant.[29]

Glycerol thioglycolate is the active ingredient in permanent wave solution. Unlike PPD, the thioglycolates might remain allergenic in the hair long after it has been rinsed out. Thus skin eruptions can continue for weeks after application of the permanent wave solution, and hairdressers allergic to it might be unable to cut permanent waved hair.

Medications

Antibiotics and antiseptics. Neomycin and nitrofurazone are potent sensitizers. Neomycin sulfate can cross-sensitize with gentamicin, kanamycin, streptomycin, spectinomycin, tobramycin, and paromomycin.

Corticosteroids. Although type I hypersensitivity reactions have been observed to corticosteroids, delayed-type hypersensitivity is by far the most common.[30] ACD to topical corticosteroids is rarely suspected from the history or from the appearance of the dermatitis, probably because of its anti-inflammatory action. Thus patients with a long-standing nonhealing dermatitis (eg, AD, stasis dermatitis, or chronic hand eczema) and patients with worsening of a previous dermatitis or an initial improvement followed by a deterioration of the dermatitis after application of corticosteroids should be evaluated for corticosteroid allergy. Patch tests for corticosteroid allergy should include the groups of simultaneously or cross-reacting corticosteroids,[31] as well as the vehicle and preservatives in the preparations. There is a 7-fold increase in frequency of a positive patch test reaction within a corticosteroid group. Cross-reactivity between groups A and D2 and groups B and D2 also has been reported.[32]

The optimal patch test concentration has not been worked out for most corticosteroids. A high patch test concentration of a potent corticosteroid might result in a false-negative test result on early readings because of its anti-inflammatory action. In such cases a lower concentration can be used if there is a strong suspicion of ACD, including corticosteroid-treated asthma and rhinitis. Patch tests to corticosteroids should include the patient's own commercial product. Thirty percent of the cases of ACD to corticosteroids might be missed if a delayed 7-day reading is not done.[33]

Surgical implant devices

The use of nickel in biomedical devices, especially in joint prostheses and endovascular stents, has led to increasing concern about the safety of permanent or semipermanent metal medical devices in suspected nickel-sensitized patients. Presently, there is high variability of care in terms of testing, recommendations, and, in some cases, selection of more expensive and less optimal

options. Unfortunately, there are no large, evidence-based, prospective case studies or expert panel consensus guidelines on this issue.[19]

In patients with ACD to orthodontics, nickel is the most common allergen. Stainless-steel arch wires are thought to release less amounts of nickel compared with flexible titanium-nickel arch wires. In a retrospective study of 131 patients suspected of coronary in-stent restenosis 6 months after 316L stainless-steel stent placement and patch testing 2 months after angioplasty, there were 11 positive patch test reactions in 10 (8%) of the patients. All 10 patients with a positive patch test reaction to metal (7 to nickel and 4 to molybdenum) had in-stent restenosis associated with clinical symptoms and a higher frequency of restenosis than seen in patients without metal allergy, suggesting that allergy to metals, nickel in particular, plays a relevant role in inflammatory fibroproliferative restenosis.[34] A prospective study of 174 patients with stents noted that patients with a recurrence of in-stent restenosis, although not after initial stent placement, had significantly greater positive patch test reactions to metals, most commonly nickel and manganese.[35] To date, the evidence for complications caused by nickel allergy is weak; proved cases are rare and remain on the case report level. The need for patch testing is controversial, and patch tests are not reliable in predicting or confirming implant reaction. A negative patch test reaction is reassuring for the absence of a delayed hypersensitivity reaction.

CD and patch testing in children

Although ACD is more common in teenagers, children as young as 6 months can be sensitized to contact allergen. The relevant allergens in children are similar to those in adults, with nickel, fragrance, and rubber being common sensitizers. The increasing rate of sensitization might be due to new trends in body piercing, tattooing, and use of cosmetic products. Adolescents constitute a significant portion of the population allergic to nickel. Kütting et al[36] recommend that ear piercing be delayed until after 10 years of age, presumably to allow for the development of immune tolerance. Children can tolerate the same patch test concentrations as adults, and polysensitization is common. Children with and without AD have the same rate of positive patch test reactions.

Treatment and prevention

Allergen identification to improve contact avoidance can be challenging, especially in work-related CD. Alternatives and substitutes to cosmetics should be offered to the patient to increase compliance. For patients with nickel allergy, barriers such as gloves and covers for metal buttons and identification of nickel by using the dimethyl-glyoxime test can be prescribed.

For supportive care and relief of pruritus, cold compresses with water or saline, Burrow solution (aluminum subacetate), calamine, and colloidal oatmeal baths might help acute oozing lesions. Excessive handwashing should be discouraged in patients with hand dermatitis, and nonirritating or sensitizing moisturizers must be used after washing.

A topical corticosteroid is the first-line treatment for ACD. For extensive and severe CD, systemic corticosteroids might offer faster relief. Studies on calcineurin inhibitors are limited, and their efficacy in patients with ACD or ICD has not been established. Oral antihistamines can be tried for pruritus, but oral diphenhydramine should not be used in patients with ACD to Caladryl (diphenhydramine in a calamine base) and hydroxyzine hydrochloride (Atarax) in an ethylenediamine-sensitive patient. Other modes of therapy are UV light treatment and immunomodulating agents, such as methotrexate, azathioprine, and mycophenolate mofetil.

OTHER IMMUNE-MEDIATED SKIN DISORDERS

Psoriasis

Psoriasis and AD have many similarities. They are common, chronic, inflammatory, and proliferative skin disorders in which both genetic and environmental factors play important roles. Psoriasis is primarily T_H1 mediated, whereas AD is generally thought to be T_H2 mediated. T cells in both diseases are triggered by conventional antigens and superantigens. Some studies suggest that group A streptococcus is a superantigen for acute guttate psoriasis, which is often preceded by or concurrent with infection[37,38] and is associated with an increase in serum antistreptococcal titers. Symptoms in patients with guttate psoriasis and AD frequently improve with systemic antibiotic therapy.

Although both psoriasis and AD have been associated with increased numbers of dendritic cells (DCs) in the skin, differences in DC populations, as well as the chemokine and cytokine environment, might have implications on potential targets for future therapeutic interventions. In patients with AD, myeloid DCs upregulate CCL17 and CCL18, which is in contrast to TNF-α and inducible nitric oxide synthase in patients with psoriasis.[39]

T_H17 cells have been implicated in the pathogenesis of psoriasis and other autoimmune inflammatory diseases.[37] Keratinocytes produce 2 T_H17 cytokines: IL-17A and IL-22. IL-23, which is overproduced by DCs and keratinocytes in patients with psoriasis, stimulates survival and proliferation of T_H17 cells within the dermis and drives keratinocyte hyperproliferation.

Autoimmune bullous diseases

Autoimmune blistering diseases are associated with antibodies against structural components of the skin and mucous membranes that maintain cell-to-cell and cell-to-matrix adhesion. In pemphigus vulgaris (PV), autoantibodies target the desmoglein adhesion molecule in the intercellular junctions and produce intraepithelial blisters. In bullous pemphigoid (BP) and epidermolysis bullosa acquisita, subepidermal blistering is associated with autoantibodies against the anchoring complex at the junction of the dermis and epidermis. Autoantibodies in patients with BP are formed against the basement membrane hemidesmosomal glycoproteins BP230 and BP180 and preferentially recognize phosphoepitopes in collagen XVII. In most subepidermal autoimmune blistering conditions, autoantibodies form deposits that cause the release of proteolytic enzymes through activation of the complement cascade, which destroys the basement membrane.[40]

Drugs containing sulfhydryl groups that cleave epidermal intercellular substances have resulted in the production of antibodies and blistering skin diseases. Penicillamine, furosemide, captopril, penicillin and its derivatives, sulfasalazine, salicylazosulfapyridine, phenacetin, nalidixic acid, and topical fluorouracil have been implicated.

The diagnosis of autoimmune bullous diseases requires the detection of tissue-bound and circulating serum autoantibodies by using various immunofluorescence methods, such as immunoblotting, ELISA, and immunoprecipitation.[41]

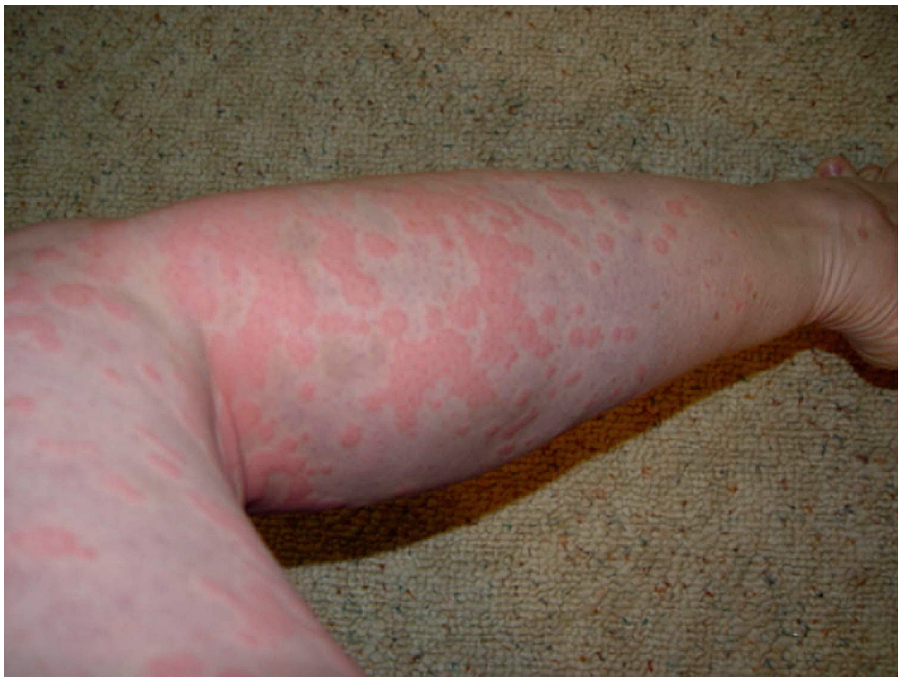

FIG 2. Urticarial skin lesions.

Treatment of PV includes long-term use of systemic corticosteroids to diminish autoantibody production, and only about 10% of patients achieve complete remission after initial treatment. Azathioprine, cyclophosphamide, methotrexate, mycophenolate, hydroxychloroquine, gold, and dapsone are other potential options. Rituximab, alone or in combination with IVIG, appears to be an effective therapy for patients with refractory PV and pemphigus foliaceus.

The mainstay of therapy in most patients with BP is oral corticosteroids at the lowest maintenance dose that will prevent new lesion formation and allow alternate-day therapy. A randomized trial suggests that patients with BP might have improved outcomes with topical rather than systemic corticosteroids, even in the presence of extensive disease.[42] Steroid-sparing agents, such as azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, dapsone, and tetracycline, can be used in combination with prednisone. In patients with cicatricial pemphigoid with involvement of the eyes, esophagus, or larynx, IVIG, etanercept, and infliximab have been used.

URTICARIA

Significant advances have occurred in our understanding of chronic urticaria (CU) since the last publication of the primer in 2003, but our understanding of this challenging illness is still imperfect. This review will cite pertinent recent review articles, and the reader is encouraged to find primary citations within these reviews. During the last 5 years, further evidence has accumulated that quality of life is severely affected in patients with CU, and these patients deserve our unqualified attention.[43,44] The most significant recent conceptual advances in our understanding of CU have been (1) the deepening appreciation that there is evidence of autoimmunity for a substantial number of patients and (2) a better understanding of the implications of diminished basophil function.[45-48]Nevertheless, it is still unclear whether the detected autoimmune phenomena or defects in basophil signaling contribute to the pathophysiology of CU and, if they do participate, what pathways are involved. Therapy of CU has also advanced, with more evidence supporting the efficacy of immunomodulatory drugs.[49,50]

Background

Urticarias are pruritic, edematous erythematous lesions of variable size that blanch under pressure (Fig 2). An episode of urticaria is a common phenomenon affecting 15% to 25% of individuals during their lives.[51] Most of these cases are acute in nature and are easily managed, but about 30% of patients continue to have frequent episodes of hives for more than 6 weeks and are considered to have chronic disease.[44] Approximately 40% of patients also have angioedema, swelling of the subdermis, that accompanies the urticarial lesions. In a smaller number, approximately 10%, angioedema is present without visible urticaria.[44] CU occurs more often in adults and affects women (75%) more than men. Based on the results of history, physical examination, laboratory testing, and provocative testing, CU has been further divided into IgE-mediated urticaria (approximately 1% to 5%) or the physical urticarias (approximately 20%) and idiopathic urticaria (75% to 80%). The idiopathic cases, chronic idiopathic urticaria (CIU), include 30% to 60% who have an autoimmune phenotype, but the evidence that autoimmunity is pathophysiologic in the same way that physical stimuli are considered directly related to the development of hives is not generally accepted.[44,47,52] For the purpose of this discussion, patients with autoantibodies will be considered to have idiopathic urticaria with evidence of autoimmunity.

Pathogenesis

The primary effector cells in patients with urticaria are mast cells, which are present in high numbers throughout the body,

including the subcutaneous tissue. Activated mast cells produce a wide variety of proinflammatory and vasodilatory substances, including the immediate (<10 minutes) release of histamine from granules and the production of leukotriene C_4 and prostaglandin D_2 from membrane phospholipids. There is also more delayed (4-8 hours) production and secretion of inflammatory cytokines, such as TNF-α, IL-4, and IL-5. The immediate products are responsible for pruritus, swelling, and erythema, whereas the later products lead to an influx of inflammatory cells.[47]

Lesions of acute urticaria are characterized by subcutaneous edema with widened dermal papillae and rare inflammatory cells. Lesions of CU, in addition to the presence of edema, are characterized by a perivascular inflammatory infiltrate consisting of $CD4^+$ and $CD8^+$ T lymphocytes, eosinophils, basophils, and neutrophils. A small number of patients with urticarial vasculitis present with atypical clinical features and have histologic evidence of vascular destruction.[47]

In small subgroups of patients, CU is driven by IgE/allergen interactions stimulating the high-affinity receptor for IgE (FcεRI) or by physical stimuli acting through nonspecific pathways. For CIU, the pathophysiology is still unclear. The earliest observations suggestive of an autoimmune mechanism was by Grattan and Humphreys,[43] who reported in 1986 that sera from a subset of patients with CIU could cause a wheal-and-flare reaction when injected intradermally into their own (autologous) skin. The results of this autologous serum skin test (ASST) are positive in approximately 40% of patients with otherwise idiopathic CU and generally in less than 5% of control subjects.[52] Two other *in vitro* tests of serum-derived activity that activates basophils have been published. Assay of serum-mediated expression of CD63 on donor basophils correlates with the basophil histamine release (BHR) assay and assay of serum-induced expression of the surface marker CD203c, which is correlated with both the BHR assay and the size of the ASST reaction. There is general consensus that these assays detect IgG autoantibodies to the α-chain of FcεRI (90%) or IgE.[46,52] These "functional" autoantibodies are distinct from immunochemical detection of IgG recognizing FcεRI (α-chain) in an ELISA or on immunoblotting because autoantibodies measured in this fashion are found in many healthy subjects.[45-48,52]

Although at first glance the importance of functional autoantibodies to FcεRI appears to be a good conceptual framework, there are a number of limitations.[45,48] The finding that some donor basophils work better than others and that mast cells and basophils do not always work with the same serum is a mystery and undermines the general applicability of these assays.[45,48]. Although *in vitro* tests are dependent on IgG in the serum, some sera that result in a positive ASST response can still produce a positive ASST response after removal of IgG by protein G, suggesting the presence of other histamine-releasing factors.[45,48] Discrepancies have been reported between *in vivo* ASST and *in vitro* BHR tests. For example, only about 50% of sera from patients with CIU who have a positive ASST response have a positive BHR response with single-donor basophils, whereas the correlation is better if the study is done with those who have the strongest ASST responses and more than 1 donor of basophils/mast cells is used in the assay.[48] If the autologous test is performed with plasma, 86% of patients have positive responses compared with 40% of those when the test is performed with serum, suggesting that the coagulation pathway might play a role.[45,48] The importance of autoantibodies has been questioned because there are only small differences between the clinical course of those with and those without evidence of functional autoantibodies and the autoantibodies can be detected in patients who are in remission.[47]

An entirely different view of the mechanisms underlying CIU comes from the observation that patients with CIU tend to be basopenic and that the basophils that are present are relatively resistant to activation by anti-IgE. This has led Brodell et al[47] to divide patients with CIU into 2 groups: responders and nonresponders. Although the patients with the responder phenotype complain of more itching, these defects resolve as disease activity lessens, and there are only modest differences in the clinical course of these 2 populations.[48] An additional interesting finding is that these subgroups do not segregate with the subgroups with and without evidence of autoimmunity.[48] As in the case of the subpopulation with evidence of autoantibodies, the knowledge of these subgroups has not resulted in changes in therapy.

Diagnosis

This discussion will focus on recently described laboratory tests for patients with CIU that either lead to a specific treatment regimen or allow the physician to reassure the patient that their hives are due to an intrinsic process and not an extrinsic cause. Several general approaches to the workup of patients with CU have been recently published.[43,44]

Many specialists look for evidence of autoimmunity. The most common tests ordered are those for anti-thyroid antibodies because results on these tests are abnormal in 15% to 20% of patients with otherwise idiopathic urticaria. Other tests for autoimmunity include the ASST and 2 new *in vitro* tests for antibodies that activate target basophils: the BHR test and a test for upregulation of the basophil surface marker CD203c. As mentioned above, patients with evidence of autoantibodies have been reported to have more severe disease, but the effect is small.[43,44] In patients who are desirous of knowing what might be contributing to their CU, knowledge of these autoantibodies might help them accept that CIU is a skin disease and is not caused by an exogenous trigger.

Yet another area of controversy is the detection of infection with *Helicobacter pylori*. This common infection is found in a minority of patients with CU. A meta-analysis of 10 studies provided evidence that eradicating *H pylori* from patients with CIU who have evidence of this infection is beneficial at resolving the urticaria.[43] The pathophysiologic link between infection with *H pylori* and urticaria is uncertain, leaving the general idea that low levels of immune complexes might be causative.[44]

Measurement of the ability of *ex vivo* basophils from patients with CIU to release histamine when triggered with anti-IgE is still a research test that might become clinically useful in the future.[48]

Treatment

For many patients with acute urticaria and for a few patients with CU, a specific trigger can be identified, and avoidance can be an effective approach. This is not the case for some patients with acute urticaria and most with CU. A generally accepted approach for those with acute urticaria is to suppress the hives with H_1-type antihistamines, with preference for low-sedating and nonsedating agents on a daily basis and potentially sedating antihistamines for rescue and at night. For some patients with severe acute urticaria

who are unresponsive to antihistamines, a brief course of oral corticosteroids is warranted.

Treatment of patients with CIU is much more complicated. Low-sedating and nonsedating type 1 antihistamines remain the mainstay of therapy, and their efficacy has been shown to be greater than that of placebo in multiple double-blind, placebo-controlled trials. Many specialists believe that it is important to treat underlying immunologic and infectious conditions that have been detected through a detailed history, a thorough physical examination, and selected laboratory evaluations. If the urticaria is controlled with standard doses of H_1 blockade, it is reasonable to continue this treatment for several months, occasionally stopping it briefly to see whether the hives have spontaneously resolved. For patients whose symptoms are not controlled by H_1 blockade, there are a variety of opinions as to what to do next. A brief course of oral corticosteroids might be warranted, but systemic corticosteroids are not an acceptable long-term treatment. The only treatment beyond antihistamines that has been proved to be effective in a double-blind, placebo-controlled fashion is cyclosporin A.[43,44,49] Because this is a fairly aggressive treatment, some specialists try a variety of other interventions before prescribing cyclosporine. The most common approach is to push the H_1 blockade by using these agents at 2 to 4 times the FDA-approved dose.[44] Other approaches include adding an H_2 blocker, a leukotriene pathway modifier, or both. Commonly tried immunomodulatory agents with a better side-effect profile than cyclosporine include hydroxychloroquine, sulfasalazine, colchicines, dapsone, mycophenolate, and omalizumab (anti-IgE); however, none of these have been formally proved to be effective. The decision to treat patients with CIU who have anti-thyroid antibodies and normal thyroid-stimulating hormone levels with L-thyroxine is controversial.[43,52] Antimetabolites, such as methotrexate, azathioprine, and the anti–B-cell drug rituximab have also been used. Reviews of these treatments and specific guidelines for use of many of these agents and for monitoring risks and side effects have been published recently.[43,44,49,50]

AD

The reader is referred to a number of excellent recent reviews on the pathophysiology and treatment of AD.[51,52] This section will therefore primarily focus on advances in our understanding of AD since the last primer was published.

Skin barrier dysfunction

During the past year, it has become well accepted that skin barrier dysfunction plays a critical role in the development of AD. This is largely because loss-of-function null mutations in the skin barrier gene filaggrin have been repeatedly demonstrated to be a major risk factor for the development of AD.[53-56] Filaggrin gene mutations are associated with persistent and more severe eczema, early onset of AD, and an increased risk of asthma in patients with a previous history of eczema.[57,58] Therefore this mutation contributes to the atopic march by enhancing systemic allergen sensitization through the skin. Defects in skin barrier function, however, likely result from a combination of factors, including a deficiency of skin barrier proteins, increased peptidase activity, the lack of certain protease inhibitors, and lipid abnormalities.[59-61] Furthermore, T_H2 responses have also been found to reduce filaggrin gene and protein expression.[62]

Innate immune response

Study of the innate immune response in patients with AD has been an active area of investigation. There is now considerable evidence that a defective innate immune response contributes to increased bacterial and viral infections in patients with AD.[63] Pattern-recognition receptors play a critical role in sensing the environment for invading pathogens. Toll-like receptors (TLRs) are prototypic pattern-recognition receptors that discriminate between diverse pathogen-associated molecular patterns. A polymorphism within the *TLR2* gene has been shown to be associated with severe forms of AD prone to recurrent bacterial infections and has been linked to TLR2 dysfunction.[64]

Keratinocytes and DCs in the epidermis represent the key cells involved in the skin innate immune response. AD skin contains an increased number of IgE-bearing Langerhans cells (LCs). Binding of IgE to LCs occurs primarily through high-affinity IgE receptors. In contrast to mast cells and basophils where the FcεRI is a tetrameric structure, the receptor on LCs consists of the α-chain, which binds IgE and γ-chain dimers containing an immunoreceptor tyrosine–based activation motif for downstream signaling, but lacks the classic β-chain.[65] Allergens that invade the skin are taken up by IgE molecules bound to FcεRI-expressing LCs for allergen presentation to T_H2 cells. The clinical importance of these IgE receptors is supported by the observation that the presence of FcεRI-expressing LCs bearing IgE molecules is required to provoke eczematous skin lesions through application of aeroallergens to uninvolved skin of patients with AD.

Human plasmacytoid dendritic cells (PDCs) are the only professional IFN-producing cells, and their responses to viral antigens are important for effective host defense against viral infections.[66] Human PDCs bear TLR7 and TLR9 on their cell surfaces. Furthermore, they express FcεRI. Because of a close interaction of FcεRI with TLR9, the amount of IFN-α and IFN-β released in response to TLR9 stimulation is profoundly downregulated in PDCs after FcεRI aggregation and allergen challenge *in vitro*.[67,68] Compared with psoriasis, CD, or lupus erythematosus, the frequency of PDCs in patients with AD is decreased.[69,70] This might account for the increased propensity of patients with AD to have disseminated viral skin infections.

Keratinocytes play an important role in the skin innate immune response by producing antimicrobial peptides (AMPs) in response to stimulation by invading pathogens and inflammation or trauma to the skin. Defensins and cathelicidins are broad-spectrum AMPs that act as natural antibiotics to kill a wide variety of bacterial, viral, and fungal pathogens.[63] Chronic inflammatory skin diseases, such as psoriasis or CD, demonstrate marked upregulation of cathelicidin and defensin expression in their skin lesions. In contrast, AD skin lesions are associated with very weak upregulation of human β-defensin (HBD) 2 and 3 and LL-37.[71] Expression of T_H2 cytokines, such as IL-4, IL-13, and IL-10, have been shown to downregulate AMP expression *in vitro* and might account for low AMP levels in the skin of patients with AD.[71,72] Moreover, reduced mobilization of human HBD3 accounts for defective killing of *Staphylococcus aureus* in patients with AD.[73] In addition to the propensity for bacterial infections caused by low HBD2, HBD3, and LL-37 expression, cathelicidin and HBD3 deficiency in patients with AD also contributes to severe viral infections, such as eczema vaccinatum caused by orthopoxvirus[74] and eczema herpeticum (EH).[75] In support of this concept, lower levels of cathelicidin are detected

in skin lesions of patients with AD with 1 or more episodes of EH in their history compared with patients with those seen in patients with AD without EH.

The adaptive immune response in patients with AD

Systemic immune response. Most patients with AD have peripheral blood eosinophilia and increased serum IgE levels. This is reflected in an increased frequency of peripheral blood skin-homing T_H2 cells producing IL-4, IL-5, and IL-13 but little IFN-γ. This might be due to selective apoptosis of circulating memory/effector T_H1 cells in patients with AD.[76]The decreased IFN-γ levels produced by T cells from patients with AD might be the result of reduced production of IL-18.[77] Furthermore, an inverse relationship between skin colonization with *S aureus* and spontaneous T cell–derived IFN-γ production has been observed.[78]

Biphasic T_H2-T_H1 cytokine skin response. Acute AD skin lesions are associated with the infiltration of T_H2 cells expressing increased levels of IL-4, IL-13, and IL-31, a pruritogenic T_H2 cytokine that correlates with severity of AD.[79] A number of determinants support T_H2 cell development in patients with AD. These include the cytokine milieu in which the T-cell development is taking place, the costimulatory signals used during T-cell activation, and the antigen-presenting cells. IL-4 promotes T_H2 cell development, whereas IL-12 induces T_H1 cells. AD keratinocytes participate in the adaptive immune response by expressing high levels of the IL-7–like cytokine thymic stromal lymphopoietin (TSLP), which activates myeloid DCs to promote T-cell expression of IL-5 and IL-13.[80] Skin-specific overexpression of TSLP in a transgenic mouse resulted in an AD-like phenotype, with the development of eczematous lesions containing inflammatory dermal cellular infiltrates, an increase in T_H2 $CD4^+$ T cells expressing cutaneous homing receptors, and increased serum levels of IgE,[81] suggesting an important role of TSLP in AD. DCs primed by TSLP might convert to strong inducers of T-cell responses of the T_H2 type *in vitro*,[82] so that enhanced TSLP release triggered by frequent allergen challenge might initiate and microbes might perpetuate T_H2 immune responses in patients with AD.

LCs bearing FcεRI are the major myeloid DC population present in nonlesional and acute AD skin. After IgE binding and internalization of the allergen, LCs migrate to peripheral lymph nodes, present the processed allergen to naive T cells, and initiate a T_H2 immune response with sensitization to the allergen. Concomitantly, aggregation of FcεRI on the surface of LCs *in vitro* promotes the release of chemotactic factors, which *in vivo* is thought to contribute to the recruitment of IgE receptor–bearing inflammatory dendritic epidermal cells (IDECs) into the epidermis. IDECs mainly present at inflammatory sites, produce high amounts of proinflammatory cytokines after FcεRI cross-linking, display a high stimulatory capacity to T cells, and serve as amplifiers of the allergic inflammatory immune response.[83] Moreover, stimulation of FcεRI on the surface of IDECs induces the release of IL-12 and IL-18 and enhances the priming of naive T cells into IFN-γ–producing T_H1 or T_H0 cells. These mechanisms might contribute to the switch from the initial T_H2 immune response in the acute phase to the T_H1 immune responses in the chronic phase of AD.

Regulatory T cells

Other T-cell types can also contribute to the magnitude and persistence of AD-related skin inflammation. Recent studies have examined the potential role of regulatory T cells. Mice deficient in forkhead box protein 3–positive regulatory T cells spontaneously have eczema.[84] Although one report found an absence of resident regulatory T cells in AD skin lesions,[85] another found increased numbers of regulatory T cells in AD skin.[86] Reefer et al[87] analyzed the properties of $CD25^{hi}$ T-cell subtypes in patients with AD associated with increased serum IgE levels. $CD25^{hi}$ T cells expressing regulatory T-cell markers (forkhead box protein 3, CCR4, and cutaneous lymphocyte-associated antigen) were increased in patients with AD compared with those seen in control subjects with low serum IgE levels. This phenomenon was linked to disease severity. Two subtypes of $CD25^{hi}$ T cells were identified on the basis of differential expression of the chemokine receptor CCR6. Activated $CCR6^{neg}$ cells secreted T_H2 cytokines, and coculture with effector T cells selectively enhanced IL-5 production. Moreover, induction of a T_H2-dominated cytokine profile on activation with bacterial superantigen was restricted to the $CCR6^{neg}$ subtype. These studies indicate that despite a regulatory phenotype, activated $CD25^{hi}$ T cells that lack expression of CCR6 promote T_H2 responses and might therefore contribute to the atopic immune response.

T_H17 cells

T_H17 cells have also been identified in AD skin lesions and might therefore contribute to skin inflammation in patients with AD.[88] However, their expression is significantly less than that seen in patients with psoriasis.[89] Furthermore, T_H2 cytokines, such as IL-4 and IL-13, inhibit IL-17–induced effects on generation of AMPs by keratinocytes.[90]

Management

Recent approaches to the management of AD have focused on the development of improved skin barrier creams, early dietary interventions, and novel immunomodulators that can reduce skin inflammatory responses.[51,91] There remains interest in treating infants with hydrolyzed infant formulas[92] or probiotics to control eczema early in life by directing allergic responses.[93-96] Perhaps the most interesting development is the observation that oral supplementation with vitamin D augments the innate immune response in patients with AD.[97] There also remains interest in the use of topical calcineurin inhibitors as an anti-inflammatory therapy. Promising novel anti-inflammatory therapies are also gaining attention. Although these require further controlled trials, they include lymphocyte function-associated molecule 3/IgG fusion protein[98] and anti-CD20.[99]

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Environmental and occupational allergies

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Airborne allergens are the major cause of allergic rhinitis and asthma. Daily exposure comes from indoor sources, chiefly at home but occasionally at schools or offices. Seasonal exposure to outdoor allergens, pollens, and molds is another important source. Exposure to unusual substances at work causes occupational asthma, accounting for about 5% of asthma in adults. Indoor and outdoor air pollutants trigger airway inflammation and increase the severity of asthma. Diesel exhaust particles increase the production of IgE antibodies. Identification and reduction of exposure to allergens is a very important part of the management of respiratory allergic diseases. The first section of this chapter discusses domestic allergens, arthropods (mites and cockroaches), molds, and mammals (pets and mice). Indoor humidity and water damage are important factors in the production of mite and mold allergens, and discarded human food items are important sources of proliferation of cockroaches and mice. Means of identifying and reducing exposure are presented. The second section discusses outdoor allergens: pollens and molds. The particular plants or molds and the amount of exposure to these allergens is determined by the local climate, and local pollen and mold counts are available to determine the time and amount of exposure. Climate change is already having an important effect on the distribution and amount of outdoor allergens. The third section discusses indoor and outdoor air pollution and methods that individuals can take to reduce indoor pollution in addition to eliminating cigarette smoking. The fourth section discusses the diagnosis and management of occupational asthma. (J Allergy Clin Immunol 2010;125: S150-60.)

Key words: *Allergens, indoor environment, mites, cockroaches, mice, pets, molds, pollens, humidity, water damage, air pollution, occupational asthma, climate change*

Abbreviations used
DEP: Diesel exhaust particle
ETS: Environmental tobacco smoke
HEPA: High-efficiency particulate air
NO_2: Nitrogen dioxide
SO_2: Sulfur dioxide

Two key factors influence the development and severity of allergic disease: host factors and environmental factors. Environmental factors include the specific allergens that are the targets of the IgE-mediated immune response, those elements of the environment that influence the presence of those allergens, and indoor and outdoor air pollutants. Also, environmental stimulants of innate immunity influence the development of allergic responses. Although pharmacologic treatments focus on host factors, interventions directed at environmental factors are critical for optimal management of allergic disease, as well as its prevention. Environments can be defined as domestic, outdoors, and occupational, and this chapter will focus on the identification of environmental exposures and methods of intervention for their control.

INDOOR DOMESTIC ALLERGY

Background

The primary indoor allergens that contribute to allergic disease include arthropod allergens, mammalian allergens (from either pets or pests), and fungal allergens.[1-5] Additionally, indoor pollutants can also influence host response to allergens and should be considered when developing environmental interventions.[6] Seasonal outdoor allergens can also play a role in the indoor environment when they penetrate into the indoor setting.[6]

Pathogenesis: Allergens

There is overwhelming evidence that indoor domestic allergens play a key role in allergic disease. The primary arthropod allergens associated with allergic disease are house dust mites and cockroaches.

House dust mite allergen. The 2 primary species of house dust mite associated with asthma are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. The prevalence of IgE sensitization to mites varies with the local environment; arid environments are associated with low-level sensitization (5%), whereas up to 60% of the population can be sensitized in humid locales. Exposure to mite allergens has been associated not only with the severity of allergic disease but also with disease pathogenesis.[3,4,6-8]

These microscopic arachnids do not bite humans or other animals but feed on human and animal dander and are found in bedding, upholstery, and carpeting. House dust mites require humid environments because they directly absorb water from the air, with critical relative humidity ranging from 55% to 75% depending on the ambient temperature. There are 2 major groups of mite allergens, with group 1 being derived from proteins found in the mite gut and group 2 being primarily male reproductive glycoproteins. A major source of mite allergens is mite fecal pellets. These allergens are found on particles that range from 10 to 20 μm in size, which means they tend to settle on surfaces and are not suspended in ambient air.[9,10]

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Cockroach allergen. Cockroaches represent another significant source of allergens, with the German cockroach *(Blatella germanica)* and the American cockroach *(Periplaneta americana)* being the most frequently encountered species in American homes. Cockroach allergy plays a critical role in asthma pathogenesis in the inner city, with the degree of sensitization being linked to the likelihood of requiring urgent or emergency treatment for asthma in urban populations. It has been reported that up 40% of urban children and 20% of suburban children are sensitized to cockroach allergens.[9,10]

Cockroaches tend to feed on discarded human food items. Thus they are attracted to locations in which such materials are readily available. Although they are found in single-family homes, they are more successful in townhomes and multifamily dwellings, which have a higher concentration of persons and, consequently, more discarded food. Cockroaches live in confined spaces, often in walls and between floors in large buildings, and are more active at night.[11]

Cockroach allergens derive from the bodies and feces of these insects. Like mite allergens, cockroach allergens tend to be found on larger particles (10-40 μm in diameter) and thus are more likely to be found in settled house dust rather than on suspended particles in ambient air. Cockroach allergen can be found in high concentrations on floors, carpets, counters, and other flat surfaces, especially in rooms that contain discarded or stored food. Cockroach allergens have also been reported in bedding, although this might be from passive transport of allergens from floor dust to the bed by persons living in cockroach-infested locations.[9,11]

Mouse allergy. Rodent allergens are also important allergens in the inner city, with mice being more common in domestic settings than rats because rats tend to stay outdoors. Mouse allergen exposure has been associated with decreased asthma control in inner-city residents. Mouse allergen has also been found in suburban settings and single-family homes but at levels that are typically 100- to 1,000-fold less than those reported in inner-city dwellings.

Mouse allergens are present in urine and are associated with pheromones and the mating behavior of these animals. Rodent urine is easily aerosolized, and thus rodent allergens can be found in smaller particles (<10 μm in diameter), which can be suspended in ambient air. Like cockroaches, feral mice tend to nest in small hidden spaces and are active primarily at night. Thus it is relatively rare to encounter these animals during the day. These animals are also attracted to discarded human food materials, and thus mouse allergen might be found in greater concentrations in areas where garbage is stored before disposal. In the event that mice are kept as pets, exposure to mouse allergen is similar to that of animal handlers and is principally in the bedding of the cages in which the animals are kept.[7,12-17]

Pet allergy. Mammalian pets are also a source of allergens, with dogs and cats being by far the most common pets in the United States. Common allergens derived from dogs and cats include Can f 1 and Fel d 1 and can be derived from saliva, dander, or other secretions. Like rodents, dog and cat allergens are found in small aerosolized particles (<10 μm in diameter) and can be found suspended in ambient air.[4,18-21] These allergens, especially those from cats, can be carried to other locations on the clothing of persons who own cats. It has also been reported that dog and cat allergens are found in house dust of homes with and without animals. Thus community exposure to these and probably many other domestic allergens likely contributes to exposure to these allergens outside of the home.[7,9]

There is a paradox that has developed with regard to the role that pets have in asthma and atopic disease pathogenesis. It has been argued that many persons with pet allergy do not have cats in their homes, and conversely, many persons who live with mammalian pets do not have clinical disease.[22,23] It has been reported that owning mammalian pets might actually be protective against the development of atopy.[24] Whether this is due to associated increases in domestic endotoxin levels (which, according to the hygiene hypothesis, would protect against atopy) or development of immunologic tolerance is unclear.[24] However, there is strong consensus that in persons with IgE sensitization to mammalian pets and clinical disease, increased exposure to pet allergen is deleterious.

Mold allergy. Mold is a term that encompasses hundreds of species of saprophytic fungi that can be found in the indoor environment. Molds require high humidity and moisture, adequate temperature, and nutrients. It is clear that IgE sensitization can occur to molds, and there is great interest in the role these allergens play in asthma exacerbation and pathogenesis. Quantifying mold exposure can be very complex and is not standardized for clinical practice. Methods for this include culture of spores from recovered environmental samples, spore counts, and assessment of fungal allergens in recovered house dust or other fungal products (eg, 1-3 β-glucans, which themselves exert health effects). Of note, mold spores are between 2 and 10 μm in size and thus can remain in ambient air for extended periods of time.

The variety of measures used in mold quantification has complicated the study of the role of indoor fungi in asthma. However, it is known that *Alternaria* species in outdoor settings is linked to increased asthma severity and airway reactivity. In the Inner City Asthma Consortium Studies indoor mold levels correlated well with outdoor levels, emphasizing that the outdoor environment plays an important role in establishing indoor mold levels. The National Academy of Science reviewed the relationship of mold and fungal exposures to asthma exacerbation and pathogenesis and stated that there was sufficient evidence that fungal allergen exposure caused disease exacerbation in sensitized subjects but that the existing data were inconclusive regarding the role of fungal exposures on disease pathogenesis.

Pathogenesis: Nonallergens

Indoor combustion. Combustion of biological matter results in notable indoor air pollution and often is due to burning of tobacco, wood, and other plant fuels.[25-28] Byproducts of plant-fuel combustion include particulates, which are rich in polyaromatic hydrocarbons, and other constituents that are converted intracellularly to a number of oxidant species.[29] Burning of wood in indoor stoves and fireplaces generates a number of particulates and oxidant gases and is strongly associated with increased respiratory tract illness. However, environmental tobacco smoke (ETS; side-stream smoke from the burning end of a cigarette and exhaled mainstream smoke from a smoker) is the most significant and remediable indoor air pollutant in the United States. An example of the effect of ETS on indoor particulate levels is shown in a study of 11 hospitality locations (primarily restaurants) in which smoking and nonsmoking sections were maintained. The

average concentration of particulate matter with a diameter in the range of 2.5 μm in smoking areas was 177 $\mu g/m^3$ versus 87 $\mu g/m^3$ in the nonsmoking section, which is still 29 times higher than that in truly smoke-free air and 6 times higher than that of local outdoor air.[30]

Exposure to ETS is unequivocally associated with exacerbation of asthma and is a notable contributing factor to disease severity and pathogenesis, with numerous reviews outlining the effect of ETS on asthma exacerbation and sensitization to allergens.[1,25,29,31-38] Experimental exposure to ETS augments nasal responses to allergen in atopic human subjects, with investigators reporting increased allergen-induced specific IgE and IgG4 levels; increased IL-4, IL-5, and IL-13 levels; decreased IFN-γ levels; and increased amounts of postallergen histamine in nasal lavage fluid.[39] Taken together, these studies provide initial mechanistic support to the epidemiologic reports suggesting that ETS exposure enhances the development of atopy and asthma.[29,40,41]

Another significant indoor pollutant is nitrogen dioxide (NO_2), which derives from use of natural gas appliances, especially if they are poorly maintained or poorly vented. Increased levels of NO_2 in domestic settings are associated with increased respiratory symptoms, such as cough, wheeze, production of phlegm, and bronchitis in exposed children, as well as an enhancement of the effect of viral infection in patients with asthma.[42-46]

Biological agents. Biological contaminants certainly contribute to poor air quality, including indoor endotoxin and products from gram-positive bacteria, and 1,3–β-glucans from molds might also affect airway inflammation in both atopic and nonatopic subjects. There are clearly 2 sides to the role that indoor biological agents might play in asthma because a great many articles have described the apparent protective effect that endotoxin and other agents have in the development of asthma. However, others have shown that increased indoor endotoxin levels are associated with increased respiratory tract illness in both allergic and nonallergic persons in both domestic[47] and occupational[48-50] settings. Endotoxin exposure seems to protect infants from asthma but increases it in adults. In domestic settings the number of animals (dogs, cats, and evidence of rodents) and persons living in the home correlate with the amount of endotoxin present.

Humidity. Indoor relative humidity is increasingly recognized as an important factor in determining asthma severity. Decreased levels of humidity are associated with decreased severity of asthma.[51-53] In a large cross-sectional study of fourth-grade schoolchildren in Munich, Germany, Nicolai et al[54] identified 234 children with active asthma, with 155 of these children undergoing lung function and nonspecific airway reactivity tests within a 3-year span. Dampness was associated with increased nighttime wheeze and shortness of breath but not with persisting asthma. Risk factors for bronchial hyperreactivity in adolescence included allergen exposure and damp housing conditions. Mite antigen levels were examined from homes of 70% of the asthma cohort and found to significantly correlate with dampness and bronchial hyperreactivity. However, the effect of dampness was not due to mite allergen alone because bronchial hyperreactivity remained significantly correlated with humidity, even when adjusting for mite allergen levels.

Diagnosis

General considerations. The items outlined in this diagnosis section have been reviewed extensively elsewhere.[7,9,55-57] Evaluation of environmental allergy involves a number of important elements: a clinical history consistent with allergic airway disease, the presence of IgE sensitization to suspect allergens, and determination of exposure to increased levels of environmental allergens, as well as nonallergenic factors that contribute to disease. Frequently, the clinical history includes a number of general points found in most patients with allergic airway disease. These include a history of recurrent respiratory disease, nighttime cough, exercise intolerance caused by cough or wheeze that occurs after aerobic exercise, and exacerbations associated with viral illness. However, other elements of the history might suggest strong environmental factors. This can include improvement of symptoms on vacation or other periods when the patient is away from his or her primary home or, conversely, worsening of symptoms when visiting a new environment. Although much of this discussion has focused on asthma, symptoms of allergic rhinitis and conjunctivitis can also increase at these times.

An environmental health history can be complicated by a number of factors. Many persons, especially children in dual custodial families, might live in more than 1 location on a regular or intermittent basis. Additionally, many patients might not be forthcoming regarding environmental factors in the home that could be relevant. Such factors can include increased symptoms with the addition of a new pet, smoking behavior of a parent (or the patient), or the presence of cockroaches or mice in the home. Patients can also be exposed to allergens in other settings in which they have less control, such as school buildings or work sites. For instance, it has been shown that allergen levels in day care settings might frequently exceed those levels shown to induce symptoms in domestic settings.

It is also important to establish that IgE-mediated processes are viable candidate mechanisms for a given subject's allergic disorders. Skin or serologic testing of allergen-specific IgE to appropriate allergens should be carried out for all patients presenting with a history consistent with allergic disease. Mite allergen testing should be conducted for most patients living in all but the most arid locations, many of which are above 5,000 feet in elevation. Testing for cockroach allergen should be considered for all patients but especially for those patients who live in multifamily dwellings or other institutional housing settings (eg, military barracks, colleges, and detention centers).

Testing for pet allergens should be considered for persons who own a pet or are going to move to a location in which a dog or cat has been owned by the previous occupants. Rodent allergy testing should be considered for those with indications for cockroach allergy. However, mouse allergens might be more widespread than previously thought. Mold allergens should be considered, especially for those living in damp environments. Although there are hosts of molds one might assess, *Alternaria*, *Aspergillus*, and *Penicillium* species are perhaps the most common indoor fungi. This list should also be expanded based on local mold populations. If there is doubt that respiratory symptoms are due to allergic asthma, other evaluations, including chest and sinus imaging, methacholine testing, and perhaps exercise testing should be considered.

Environmental history for mites. There are specific questions that are especially helpful to establish that specific allergen exposures might be contributing to disease. As noted above, house dust mites require humid environments and reasonably warm ambient temperatures. Additionally, if the amount of animal and human dander available to the mites is increased (many persons in a given bed, persons with eczema, and not

TABLE I. Domestic environmental interventions by allergen or pollutant source

	HEPA filter	Dehumidification and air conditioning	Washing bedding in hot water	Professional extermination	Removal of allergen source or contaminant	Cleaning of walls and floors	Securing food waste	Inspect crawlspace	Repair wall and floor cracks
House dust mites		xx	xx			xx		xx	
Cockroach				xx		xx	xx		xx
Pets	xx				xx	xx			
Mice	xx			xx		xx	xx		xx
Molds	xx	xx				XX		xx	
Tobacco smoke	xx				xx				

changing or washing sheets frequently), then the chance of mite allergen exposure is increased. Non–air-conditioned homes also have increased humidity, and this is an increased risk for mite allergen exposure. Indeed, it is not uncommon for persons to actively humidify the bedroom of an asthmatic subject, thinking that this intervention will be helpful. In fact, it often is exactly the wrong thing to do. Recently, home kits have been developed for use by homeowners to determine whether they have increased exposure to mite allergens.

Environmental history for cockroaches. Factors that might increase cockroach exposure include living in multifamily dwellings, the presence of available (open-pail or undisposed) waste food, and infestation with cockroaches in neighboring units of an apartment or condominium. Surveying the living space for cockroaches at night (they are less active during the day), especially in kitchen areas and places where food is consumed, is useful to confirm that cockroach infestation (and thus exposure) has occurred. Additionally, adhesive bait traps can be set, with recovered cockroaches serving as an indicator of total cockroach burden in the dwelling. If it remains unclear whether cockroach infestation has occurred, then a professional exterminator or entomologist can be consulted.

Environmental history for mice. Discovery of rodent droppings is the most common sign of an infestation. However, one might need to inspect crawlspaces, attics, and other hidden areas of the home to find mouse nests. Occasionally, mice can be found moving at night, and therefore nocturnal inspections might be helpful. Scratching sounds can also be heard with mouse infestation.

Environmental history for mold. Determining whether mold exposure is playing a role in a patient's disease is not standardized and can be frustrating. Demonstration of fungal colonies on drywall, caulking, and floor spaces suggests that molds might be playing an important role. Additionally, moisture plays a significant role in supporting mold populations. Homes that have been flooded or have been water damaged are more likely to harbor mold. Examination of plumbing for leaks might reveal an area that has been colonized by mold. Many environmental contractors offer testing for mold spore counts, often by sampling the ambient atmosphere and then determining how many fungal cultures are present. Unfortunately, such tests are not standardized, and it is difficult, if not impossible, to know what level of mold spores in ambient air represent a health risk. However, if one is interested in establishing whether a specific humidity intervention is useful, one might get a baseline assessment and undertake it again when the work is done.

Humidity and pollution. As noted above, there are a number of nonallergenic factors that can affect disease. Humidity and moisture control is one of these factors, and it has been briefly discussed with regard to mold exposures. The best way to determine whether the relative humidity is too high or too low is to measure it with a hygrometer or relative humidity gauge. Mechanical or electronic hygrometers can be purchased at a hardware store or building-supply store and will provide a good assessment of indoor relative humidity levels. Use of air conditioning and dehumidification are essential elements of humidity control in most temperate climates. Ideally, relative humidity should be no higher than 50% to 55% in the summer and 30% in the winter. Fireplaces can also be sources of water vapor, as well as other gases and particulates.

If persons who live in the house are smokers, this will be an important source of indoor pollutants. Although it is preferable that one does not smoke, there is reduced particulate pollution if smokers truly smoke outside. Many indoor air cleaners that are touted to decrease ambient air tobacco smoke are not very effective. Other indoor sources of pollution include gas stoves, furnaces, and artificial logs. Questions should focus on how well these devices are maintained and whether the exhaust is adequately ventilated.

Treatment

Interventions for environmental allergy can be focused on decreasing host reactivity to allergens (medically with inhaled or nasal corticosteroids, leukotriene inhibitors, antihistamines, short- and long-acting β-agonists, or allergen immunotherapy) and decreasing exposure to environmental allergens and adjuvants (Table I). Recent studies suggest that environmental interventions are most effective when an integrated approach is used in which the patient's specific allergen sensitivities and all of the appropriate environmental factors are simultaneously and appropriately addressed.

As noted in preceding sections, control of indoor humidity and moisture is essential for control of many allergens, including house dust mites and fungi, which are very sensitive to humidity. Air conditioning and dehumidification can be useful in decreasing humidity. Appropriate venting of kitchen and bathroom spaces is also an important intervention, as is checking for leaking plumbing fixtures and appropriate vapor shields in crawlspaces.

Indoor sources of combustion should also be assessed for their effect on indoor air quality. Fireplaces are sources of water vapor, particulates, and various gases, including carbon monoxide and nitrogen oxides, in homes. Gas stoves and furnaces can be sources of NO_2 and carbon monoxide. It is important that these sources of pollutants be well ventilated. There is also some evidence that smoking cigarettes only outside the home might decrease indoor particulate levels, although promotion of truly smoke-free homes is the optimal solution.

Some indoor activities have been associated with increased indoor pollutant and allergen levels, including use of humidifiers, gas cooking, sweeping, and smoking. Additionally, as noted

earlier, using air conditioning, keeping windows closed, and staying indoors decreases the likelihood that outdoor environmental agents (humidity, pollens, molds, ozone, and particulate matter) will infiltrate the indoor setting.

High-efficiency particulate air (HEPA) filters might be useful in decreasing exposure to certain allergens or pollutants. They are most helpful for agents found on particles small enough to be suspended in ambient air (generally <10 μm in diameter) and include allergens from mammalian pets or vermin, fungal spores, and particulates derived from wood or tobacco burning (although HEPA filtration should not be the preferred method of decreasing ETS exposure).

Measures used to control house dust mites depend on decreasing humidity, washing bedding in hot water (>130°F), and using mite-impermeable sheets, pillow covers, and mattress covers. However, some studies question the effectiveness of this latter approach. Cockroach control should involve professional extermination, removal of food sources, and checking walls, floors, and plumbing fixtures for holes or gaps and filling these to prevent these insects from entering the building again.[58-62] Ironically, control of mouse allergens includes many of the same concepts as control of cockroach allergen but should also include inspection of crawlspaces and other hidden areas for nests. Because of the large size of the particles that contain most mite and cockroach allergens, HEPA filters are not useful interventions for these exposures, although they can be useful for rodent allergen control.

Optimal control of pet allergen exposure involves removal of the pet and thorough cleaning of the home. However, even with these measures, pet allergens can persist for up to 6 months. Some have reported that washing pets on a regular basis (especially cats) might decrease allergen exposures. In the event that removal of an animal is not feasible, keeping the pet in an area of the home isolated from the patient's bedroom is often recommended.

Although some meta-analyses suggest that there is insufficient evidence to support the use of allergen control measures as a treatment for asthma, many recent studies demonstrate that maneuvers to decrease allergen levels in a domestic setting are effective in decreasing allergens and decreasing asthma severity.[61,62] These studies also suggest that integrated, multifaceted approaches are more effective than one approach alone.[63] An integrated approach includes establishing the IgE sensitization of the patient and designing an allergen control program to account for decreasing the relevant allergen and adjuvant agents that can affect disease.

OUTDOOR ALLERGENS AND CLIMATE CHANGE

Background

Airborne pollens and molds are important causes of allergic rhinitis and asthma and therefore have been a major focus of research since the 19th century. In as much as the details of each local climate determine which plants and molds will grow there, recently, there has been considerable interest in the effect of climate change on outdoor allergens.[64] The dates and amount of exposure to specific allergens at specific locations can be measured by using several methods. The most common is microscopic identification of the individual pollen grains and mold spores using Rotorod samplers or Burkard spore traps. Exposure to particular species of molds can also be determined by culturing of airborne particles. Particle size and allergen concentration can be determined by using filtration samplers with immunochemical assay of the filter.[64-66] Information about outdoor allergen concentrations at many locations is available from the National Allergy Bureau (www.aaaai.org/nab/).

Pollens

Tree pollens are shed in the spring, grass pollens in early summer, and weed pollens (especially ragweed) in late summer and fall. Pollen grains deposit on the nasal mucosa and release allergenic proteins to cause hay fever. Pollen grains are too large to be respirable, and therefore they do not reach the bronchi to cause asthma. Furthermore, the timing of pollen-induced asthma differs from that of hay fever in 2 ways: it starts later in the season and persists after the season ends. Also, it is worse during thunderstorms. Many of the important allergens of pollens lie on the outside of the cell membrane, the exine. They are not produced by the pollen cell itself but are stuccoed onto the exine by other cells of the male flower. A considerable amount of these allergens remain behind for weeks after the pollen is shed. Respirable bits of this part of the plant become airborne, especially from gusts of wind during thunderstorms. It is also possible that allergens extracted from pollen grains by raindrops can become airborne dust particles after drying.[67] This is one reason that asthma symptoms begin after hay fever symptoms and persist longer.

Molds

Allergy to outdoor molds, especially *Alternaria alternata*, is a more important cause of asthma than pollen.[68,69] Other important species include *Cladosporium*, *Penicillium*, *Aspergillus*, and *Helminthosporium*. Because air-sampling methods rely chiefly on mold spores, it is often assumed that the spores are the main source of the allergens. However, a spore is no more the whole organism than an acorn is an oak tree, and *Alternaria* species spores, like pollen grains, are too large to penetrate into the bronchi. More important sources of allergen-containing particles are the hyphae (which are fibrous and therefore stay suspended in the airstream) and dust from the area where the mold was growing and excreting digestive enzymes. This is important because mold proteases are not only allergens but also cause mast cell/eosinophil inflammation and promote IgE to other proteins through stimulation of protease-activated receptors.[64,66,70,71] Unfortunately, unlike the important pollen extracts, commercial mold extracts are not standardized and might not contain all the important allergenic molecules.[72] As a result, *in vitro* tests for IgE antibody to some molds (especially *Aspergillus* and *Penicillium* species but fortunately not *Alternaria* species) are more reliable than skin tests.

Climate change

Global warming is accelerating; an average warming of 1°C to 2°C is certain to occur in this century. If current emissions and land-use trends continue unchecked, increases in the prevalence and severity of asthma and related allergic diseases mediated through worsening ambient air pollution and increased pollen production are anticipated.[64] The sea will rise, and storms and drought cycles will increase. The pattern of change will vary regionally depending on latitude, altitude, rainfall and storms, land-use patterns, urbanization, transportation, and energy production.

TABLE II. What do we know about climate change and asthma?

What do we know?
Ambient air pollution increases the frequency and severity of asthma attacks and the number of symptomatic days.
Pollen, air pollution, and weather interact and affect the clinical expression of allergic disease.
Climate change is unequivocal, accelerating, and largely anthropogenic and will continue through at least the 21st century.
Climate change is measurably affecting the timing, distribution, quantity, and quality of aeroallergens and changing the distribution and severity of allergic disease.
Climate change alters local weather patterns, including minimum and maximum temperatures, precipitation, and storms, all of which affect the burden of allergic disease.
Warming temperatures promote production of ground-level ozone, which worsens asthma.
There are clinical interventions that can be used to minimize climate change–related increases in asthma and allergic disease (secondary prevention).
Greenhouse gas mitigation is the current global recommendation for stabilizing the climate (primary prevention).
What is still unknown?
Future air quality will be determined by energy and transportation choices, economic development, and population growth.
The degree to which human intervention and planning can minimize changes in vegetation and aeroallergen exposure remains unexplored.
The rate and magnitude of climate change in the future will depend on how rapidly and successfully global mitigation and adaptation strategies are deployed.
The outcome of crossing climate tipping points is unknown but potentially very grave for large portions of the global population.
New technologies addressing climate change and air pollution, as well as new medical treatments for asthma, allergic disease, or both could alter current predictions and trends.

Used with permission from Shea et al.[64]

Climate changes have profound effects on vegetation and floristic zones. Between 1990 and 2006, hardiness zones moved substantially northward in the United States because of the warming climate. In urban areas, where CO_2 levels were 30% higher and temperatures were 2°C higher than in matched rural areas, ragweed grew faster and larger and produced more pollen.[64] In general, increased temperatures produce earlier flowering and longer pollen production. Increased CO_2 levels produce pollen production and might cause some plant proteins to become more allergenic. Table II summarizes the effect of climate change on allergic respiratory disease.

Management

In addition to the usual pharmacologic treatment for allergic rhinitis and asthma, avoidance of exposure to outdoor allergens is an important part of management. The patient should be advised to stay indoors in an air-conditioned building as much as possible. Many patients find it practical to take their summer vacation in a location where there is little or no exposure. In exceptional cases in which asthma is unusually severe, such as *Alternaria* species–induced asthma in the Midwest, it might be advisable for the patient to move to a climate where *Alternaria* species is minimal, like the shores of the Pacific Ocean.

AIR POLLUTION AND ASTHMA

Increased exposure to respirable particulate matter (<10 μm in size) is associated with exacerbation of asthma across the world.[74-83] Studies performed in Utah clearly demonstrated the relationship between airborne particulates and occurrence of respiratory disease associated with the activity of a steel mill that was inactive for a year because of a labor dispute.[84,85] Occurrence of asthma and the level of particulates were less during the strike year compared with those during nonstrike years. The relationship of proximity to a roadway, and presumably vehicular traffic, is correlated with increased asthma. In a study of approximately 6,200 German children, traffic counts correlated with active asthma, cough, and wheeze.[51] In a study in the United Kingdom,[86] children less than 5 years old were more likely to be admitted to the hospital for asthma if they lived within 500 m from a heavily traveled road. The effects of specific pollutants are outlined below, and sources for many of these pollutants are listed in Table III.

Diesel exhaust and allergy

Diesel exhaust particles (DEPs) have been shown in numerous animal, *in vitro*, and human challenge studies to skew immune responses toward a T_H2 response.[72,73,87-90] It is thought that this effect of diesel results from oxidative stress generated by the conversion of polyaromatic hydrocarbons to quinones. In human subjects nasal challenge studies have shown that DEPs increased nasal IgE production. In subsequent studies, which are extensively reviewed elsewhere,[29,41,87-89] this group has reported that DEP challenge of the nasal mucosa causes increased T_H2 cytokine production by cells in recovered nasal lavage fluid. DEPs also enhance ragweed-specific IgE and IgG responses to ragweed allergen, which were characterized by increased expression of T_H2 cytokines and decreased expression of IFN-γ and IL-2. DEP challenge can also shift the primary immune responses of the nasal mucosa in human subjects toward a T_H2 phenotype, yielding allergen-specific IgE.[91]

Sulfur dioxide

The effects of sulfur dioxide (SO_2) have been extensively reviewed.[92-95] Total emergency department visits for respiratory problems and increased hospital admission rates have been linked with increased ambient exposure to SO_2. In children decreased lung function has been linked to increases in ambient SO_2 levels, and the likelihood of chronic asthma or obstructive lung disease likewise is associated with lifetime exposure to SO_2. However, in many of these studies, it is difficult to separate the effects of SO_2 from those of particulate air pollutants. Additionally, ambient SO_2 might contribute to acid aerosol (H_2SO_4) formation and might exert effects either as a gas or by contributing to H_2SO_4 particle formation.

TABLE III. Sources for air pollutants that cause asthma (source: http://www.epa.gov/air/emissions/index)

SO_2: Burning of coal, oil, and fossil fuels with a high sulfur content, usually power generation and industrial sites
NO_2: On- and off-road vehicle use, electricity generation, industrial processes, fossil fuel burning
Ozone: Derived from interaction of NO_2 and related nitrogen oxides with sunlight (UV light); thus this depends on vehicle use.
Particulate matter: Uncontrolled fire and planned wood combustion, road dust, electricity generation, and vehicle use

NO_2

There is a strong relationship between ambient air NO_2 levels and changes in lung function. NO_2 challenge enhances airway inflammation, primarily with an influx of airway PMNs. These effects are most notable at higher levels of NO_2 (4.0 ppm) and might affect the airway function of asthmatic subjects.[92-95] SO_2 also has an effect on the response to airway allergen in allergic asthmatic subjects.[96-99] Exposure to 0.4 ppm NO_2 and a combination of 0.2 ppm SO_2 and 0.4 ppm NO_2 have both been shown to enhance immediate bronchial responses of subjects with mild asthma to inhaled allergen. Exposure to NO_2 has also enhanced late-phase responses of asthmatic subjects to inhaled allergen. Likewise, exposure to 0.4 ppm NO_2 for 6 hours increases allergen-induced eosinophil cationic protein levels in the nasal airways of allergic asthmatic subjects. Taken together, these studies demonstrate that NO_2 can augment the acute response to allergen in atopic subjects.

Ozone

There is little debate that increased ambient air ozone levels induce exacerbations of asthma, as measured by hospitalizations, rescue medication use, and symptoms.[92,96-108] These events typically occur 24 to 48 hours after exposure to increased ozone levels. Even very low levels of ozone (less than the current National Ambient Air Quality Standard for ozone) have been linked to increased exacerbations of asthma.[109]

In controlled exposure studies human volunteers experience 2 primary effects of ozone: (1) a temporary restrictive defect characterized by decreased forced vital capacity and FEV_1, which are accompanied by a sensation of chest discomfort with deep breathing and enhanced nonspecific bronchial responsiveness, and (2) development of neutrophilic inflammation, which can be seen as early as 1 hour after exposure but persists for as long as 24 hours after exposure.[109,110] Despite the temporal relationship between these ozone responses, inflammatory and lung function changes do not correlate with each other, suggesting that they are mediated by different mechanisms.

In addition to changes in neutrophilic inflammation, ozone can induce selective increases in macrophages and monocytes,[103] and some investigators have found that ozone induces influx of monocytes and macrophages with increased expression of CD11b and CD14.[104] Overall, it seems likely that monocytes and macrophages might play an important and incompletely understood role in mediating the immunomodulatory effects of ozone. As with NO_2, ozone enhances the response to allergen challenge, with one report suggesting that an ozone exposure as low as 0.12 ppm for 1 hour increased the response to inhaled allergen.[106] Levels of 0.16 and 0.25 ppm ozone have also been shown to increase the response to inhaled allergen,[107,109] as does repeated challenge with ozone at levels o f 0.125 ppm.[109] Air pollution increases airway reactivity and bronchial inflammation.[110-117]

Pharmacologic interventions for the effects of pollutants on airway physiology

Rigorous studies of treatment interventions for environmental lung diseases have not been carried out on a large scale. Thus it is premature to suggest treatment guidelines for prophylaxis of pollutant-induced asthma exacerbation. However, there are reports that examine the effect of pharmacotherapy on responses to pollutants that might provide clues as to important mechanisms by which such agents affect airway disease.

Analgesics. Many investigators have shown in both animal and human studies that COX inhibitors, such as ibuprofen and indomethacin, inhibit ozone-induced decreases in spirometric results, with little effect on the neutrophilic response to ozone or airway hyperreactivity.[118-123] Volunteers treated with sufentanyl (a short-acting narcotic) shortly after ozone exposure were found to have a significant reversal in the ozone-induced decrease in lung function.[115] Taken together, these studies suggest that the immediate decrease in lung function caused by ozone exposure is a pain response, and for those susceptible to this action of ozone, analgesics might be helpful.

Anti-inflammatory agents and ozone. It is not surprising that agents with anti-inflammatory actions have been examined for their effect on the inflammatory response to pollutants, and these studies have been reviewed elsewhere.[116-126] Briefly, cromolyn sodium or nedocromil blunt immediate spirometric responses to SO_2, ETS, and endotoxin[127] in asthmatic volunteers. Inhaled glucocorticoids inhibit the effect of pollutants on airway inflammation. Corticosteroids have been shown to decrease ozone-induced inflammation in allergic asthmatic subjects and healthy volunteers.[124,128]

Antioxidants and ozone. It has been hypothesized that because pollutants exert oxidant stress, antioxidants might be useful interventions in pollutant-induced disease. Studies by Samet et al[129] examining the effect of an ascorbate-rich diet versus an ascorbate-depleting diet in human subjects suggest that antioxidants might be an important defense against the effect of ozone on lung function in healthy volunteers. Trenga et al[130] also examined the effect of vitamin E and C pretreatment on ozone-induced airway responsiveness by using an SO_2 challenge to induce bronchospasm after ozone exposure. Vitamin E and C therapy was also found to have a protective effect on airway function in asthmatic children after ozone exposure in Mexico City, especially in those children with the glutathione-S-transferase Mu null antioxidant genotype.[131,132] These studies suggest that antioxidants might play a role in protection against the effect of pollutants with oxidant activity.

Environmental interventions

One approach that subjects can take to decrease exposure to pollutants is to avoid or minimize outdoor activities during times when ambient air pollutant levels will be increased. The Air Quality Index for "criteria" pollutants can be found on a number of publicly available media sources, including the Web site for the US Environmental Protection Agency, as well as Web sites maintained by many state governmental agencies, and is generally updated on a daily basis. For ozone, the Air Quality Index has generally been

included as a routine part of television and print weather forecasts during the summer months, when ozone levels are increased.

In addition to personal avoidance strategies, public health approaches to decrease air pollutants have been shown to have a measurable effect on health outcomes. One example of this occurred in concert with the 1996 Olympic Games held in Atlanta. Coincident with attempts by the local government to decrease ozone generation by vehicle exhaust, there was not only a decrease in summer ozone levels but also a significant decrease in asthma morbidity noted during this time.[133] Likewise, in Dublin, Ireland, a ban on bituminous coal sales was implemented on September 1, 1990, to improve air quality.[134] In the 72 months after the ban, there was a 70% decrease in black smoke concentrations, a 5.7% decrease in nontrauma death rates, a 15.5% decrease in respiratory death rates, and a 10.3% decrease in cardiovascular death rates when compared with the 72 months preceding the ban.

OCCUPATIONAL ALLERGY

Background

The 2 main occupational allergies are contact dermatitis (see chapter 12 of this Primer)[135] and asthma. Hypersensitivity pneumonitis is uncommon. Farmers' lung has virtually disappeared because silos are no longer used to store food on dairy farms. Occupational asthma is the most common occupational respiratory disorder in industrialized countries, estimated to account for 5% to 15% of asthma cases in adults of working age, especially those with newly developed asthma. More than 250 agents have been reported to cause occupational asthma. The most frequent are isocyanates, flour and grain dust, airborne particles from other foods (especially fish), colophony and fluxes, latex, animals (especially laboratory animals), aldehydes, and wood dust (Table IV).[136-138] Development of asthma is often preceded by allergic rhinitis. Dust or low-molecular-weight compounds released into the outdoor air from the workplace can also cause asthma in the nearby community. Occupational asthma is distinguished from work-enhanced asthma and reactive airway disease syndrome, which are disorders caused by occupational exposure to airborne irritants.

Pathogenesis

High-molecular-weight agents elicit specific IgE antibody responses, and the cellular pathway of pathogenesis is the same as for all other IgE-mediated asthma. The pathogenesis of low-molecular-weight agents, such as isocyanates, is less clear. These patients often exhibit only the late-phase reaction and have more neutrophilia. However, $CD4^+$ lymphocytes do play a role, and some patients might have specific IgE and IgG4 antibodies.[139,140] Concomitant exposure to airborne agents that activate innate immunity enhances the likelihood of occupational asthma.[141,142] Cigarette smoking is another important risk factor, possibly also acting through innate immunity from its contamination with endotoxin.[143] The role of genetic susceptibility is complex and not a useful factor in diagnosis or management at this time.[144] The severity of asthma depends both on the concentration of the allergen in the air and the duration of exposure. Subjects with long-standing heavy exposure often continue to have asthma long after their exposure ceases.

TABLE IV. Some common occupational allergens

High molecular weight	Low molecular weight
Grain dust (including mites)	Diisocyanates (many sources)
Bakery dust	Acid anhydrides
Fish proteins	Western red cedar (plicatic acid)
Laboratory animals	Colophony
Bird proteins	Penicillins
Natural rubber latex	Nickel
Enzymes, especially detergents	Platinum
Mold proteins	Vanadium
Vegetable gums	
Soy bean dust	
Cotton, coffee, and other seed dusts	
Psyllium	

Diagnosis

By far the most important thing is to consider the possibility! Be sure to include details of the patient's occupation in the history of all adult patients with asthma. A history of symptoms improving when the patient is away from work is often more informative than symptoms occurring during work. Occupational asthma is distinct from work-enhanced asthma from exposure to air pollutants at the workplace. Once the diagnosis of occupational asthma is suspected from the history, additional diagnostic procedures include the following[136,145-147]:

- *Skin tests or in vitro tests for IgE antibody to high-molecular-weight allergens*. Unfortunately, standardized reagents are available for only a few occupational allergens, and therefore the material for the test might have to be improvised.
- *Peak flow measurements to correlate obstruction with exposure*. Many cases have a delayed-onset late-phase response and prolonged persistence after exposure, and therefore the peak flow needs to be measured at least 4 times a day for a long period that includes time off work.
- *Correlation of exhaled nitrous oxide concentration, sputum eosinophil counts, or both with exposure*. Again, the inflammation can persist after exposure ceases.

Specific bronchial challenge tests are often considered the gold standard, but for the practicing physician, they have several problems. The reagents are not readily available. Asthma medications inhibit a positive response, and therefore the test is reliable only in patients with mild disease who do not require daily medication. In patients who have not been recently exposed and are asymptomatic, the concentration required to elicit a positive response is 10 to 100 times higher than the concentration that elicits symptoms at work. Provocation tests are more useful for research centers to identify the cause of asthma in the workplace than for the practicing physician to diagnose individual patients' conditions.

Management

The key is avoidance, avoidance, avoidance,[137,145-147] but this is easier said than done.

First, consider the patient. The simplest thing is to change jobs. In fact, many subjects do this themselves, and therefore the prevalence of occupational asthma is often underestimated (ie, the "healthy worker effect").[148] Often, it is possible to continue working for the same employer at a different location, where exposure is less. If changing jobs is not feasible, protective air-fed helmets might be indicated. Simple masks are poorly effective.

The employer is key to avoidance. After the occurrence of occupational asthma at a workplace has been established, management has the responsibility of controlling the exposure, not only for the benefit of the particular subject but also for prevention of asthma in other employees. In many industries this control has been both feasible and effective, and occupational asthma there has been greatly reduced. Of course, the specific changes required depend on the details of the generation of the airborne causative agent. Monitoring of the effectiveness of the control measures involves measurement of the airborne allergen concentration. In those instances in which measurements have been practical (eg, latex and detergent enzymes), the concentration that elicits symptoms is in the range of 100 ng/m^3. Safe concentrations are 1 or at most 10 ng/m^3.

Pharmacologic treatment is the same as for all subjects with asthma. Unfortunately, many subjects with occupational asthma, especially those with more severe disease, continue to be symptomatic long after exposure has ceased. These subjects require the usual pharmacologic management of chronic asthma.

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Anaphylaxis

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Anaphylaxis occurs commonly in community settings. The rate of occurrence is increasing, especially in young people. Understanding potential triggers, mechanisms, and patient-specific risk factors for severity and fatality is the key to performing appropriate risk assessment in those who have previously experienced an acute anaphylactic episode. The diagnosis of anaphylaxis is based primarily on clinical criteria and is valid even if the results of laboratory tests, such as serum total tryptase levels, are within normal limits. Positive skin test results or increased serum specific IgE levels to potential triggering allergens confirm sensitization but do not confirm the diagnosis of anaphylaxis because asymptomatic sensitization is common in the general population. Important patient-related risk factors for severity and fatality include age, concomitant diseases, and concurrent medications, as well as other less well-defined factors, such as defects in mediator degradation pathways, fever, acute infection, menses, emotional stress, and disruption of routine. Prevention of anaphylaxis depends primarily on optimal management of patient-related risk factors, strict avoidance of confirmed relevant allergen or other triggers, and, where indicated, immunomodulation (eg, subcutaneous venom immunotherapy to prevent Hymenoptera sting–triggered anaphylaxis, an underused, potentially curative treatment). The benefits and risks of immunomodulation to prevent food-triggered anaphylaxis are still being defined. Epinephrine (adrenaline) is the medication of first choice in the treatment of anaphylaxis. All patients at risk for recurrence in the community should be equipped with 1 or more epinephrine autoinjectors; a written, personalized anaphylaxis emergency action plan; and up-to-date medical identification. Improvements in the design of epinephrine autoinjectors will help to optimize ease of use and safety. Randomized controlled trials of pharmacologic agents, such as antihistamines and glucocorticoids, are needed to strengthen the evidence base for treatment of acute anaphylactic episodes. (J Allergy Clin Immunol 2010;125:S161-81.)

Key words: *Anaphylaxis, allergic reaction, mast cell, basophil, IgE, Fc∈RI, histamine, tryptase, food allergy, medication allergy, venom allergy, epinephrine, adrenaline, H_1-antihistamine*

Abbreviations used
CNS: Central nervous system
COPD: Chronic obstructive pulmonary disease
CVD: Cardiovascular disease
NSAID: Nonsteroidal anti-inflammatory drug
OSCS: Oversulfated chondroitin sulfate
Siglec: Sialic acid-binding immunoglobulin-like lectin

This chapter focuses mainly on anaphylaxis in community settings. It provides an overview of epidemiology, pathogenesis, clinical diagnosis, confirmation of the triggers, and long-term management, including prevention of recurrences and emergency preparedness. It highlights recent advances published since the review of anaphylaxis published in the 2008 Mini-Primer.[1]

Anaphylaxis is currently defined as a serious allergic reaction that is rapid in onset and might cause death.[2] The diagnosis is considered to be highly likely when any one of 3 clinical criteria is fulfilled (Table I)[2]; the presence of reduced blood pressure or shock is not necessarily required. The terms anaphylactoid or pseudoanaphylaxis are no longer recommended for use.

EPIDEMIOLOGY

The lifetime prevalence of anaphylaxis from all triggers is estimated to be 0.05% to 2%.[3] The rate of occurrence appears to be increasing, especially in young people.[4-14] Accurate community-based population estimates are difficult to obtain because of underdiagnosis, underreporting, and miscoding, as well as use of different definitions of anaphylaxis and different methods of case ascertainment in the different populations studied.[15-17] Representative studies of anaphylaxis from all triggers in the general population are summarized in Table II.[3-12]

It is likely that anaphylaxis is underdiagnosed, especially if it is a patient's first episode, if there is a hidden or previously unrecognized trigger, or if symptoms are mild, transient, or both.[15] Patients might not be able to describe their symptoms if awareness, cognition, and judgment are impaired or if they are dyspneic or becoming unconscious. The presence of itching, flushing, hives, and/or angioedema is helpful in making the diagnosis; however, skin and mucosal symptoms and signs are absent or unrecognized in 10% to 20% of all anaphylactic episodes. Hypotension sometimes goes undocumented, especially in infants and young children.[15]

Underreporting and miscoding of anaphylaxis remain important issues.[15] Only 1% of emergency department visits for acute systemic allergic reactions receive the diagnosis of anaphylaxis; many are called acute allergic reactions, or acute hypersensitivity reactions.[16,17] In a recent nationally representative probability sample from hospital emergency departments in the United States, 57% of likely episodes of anaphylaxis to food did not receive an emergency department diagnosis of anaphylaxis.[13]

Death from anaphylaxis is considered rare[8,14,18-23]; however, underreporting of fatalities likely occurs for a variety of reasons.

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TABLE I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) AND at least 1 of the following:
A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
B. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
A. Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
C. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
A. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP*
B. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Adapted from reference 2.

BP, Blood pressure; *PEF*, peak expiratory flow.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 to 140 beats/min at age 1 to 2 years, from 80 to 120 beats/min at age 3 years, and from 70 to 115 beats/min after age 3 years. Infants and young children are more likely to have respiratory compromise than hypotension or shock.

These include incomplete clinical information, including lack of a history of concomitant diseases, concurrent medications, and drug or alcohol abuse, and absence of a detailed death scene investigation (eg, interview of witnesses).[22] Initial symptoms and signs in fatal episodes of anaphylaxis commonly include respiratory distress rather than circulatory collapse.[21] The autopsy findings might be nonspecific, and laboratory test results might be within normal limits; however, this cannot be used to exclude the diagnosis of anaphylaxis.[20-22]

PATHOGENESIS

Triggers of anaphylaxis

Triggers of anaphylaxis in the community are listed in Table III.[24-69] In many countries the most common food triggers are peanut, tree nuts, shellfish, fish, milk, egg, and sesame[24-26]; however, there are important geographic variations, and in some countries other foods, such as chestnut, rice, buckwheat, or chickpea, predominate.[27] Any food can potentially trigger anaphylaxis, including previously unrecognized triggers, such as quinoa,[28] dragon fruit,[29] or some fresh red meats containing carbohydrates.[30] Food triggers can be hidden (eg, substituted foods, cross-reacting foods, and cross-contacting foods).[26] Food triggers also include additives, such as spices, vegetable gums, and colorants (eg, carmine [cochineal])[31]; contaminants, such as dust mites[32]; and parasites, such as the live seafish nematode *Anisakis simplex*.[33]

Medication-triggered anaphylaxis can occur in patients of any age; however, it is particularly common in middle-aged and older adults. Antibiotics, especially β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and other agents, are often implicated, as are chemotherapeutic agents.[24,25,34-40] Newly recognized medication triggers include loperamide[37]; contaminants in medications, such as oversulfated chondroitin sulfate (OSCS)-contaminated heparin[38]; seemingly innocuous substances, such as vitamins and supplements containing folic acid[39]; and herbal treatments.[40] Perioperative medications,[41] iodinated contrast media[42] and medical dyes are becoming increasingly relevant triggers in community settings. Biological agents that trigger anaphylaxis include monoclonal antibodies (mAbs), such as cetuximab, infliximab, and omalizumab,[43-45] and allergens used in immunotherapy.[46,47] Vaccines to prevent infectious diseases seldom trigger anaphylaxis. If they do, the culprit is seldom the immunizing agent itself.[48-51] Rather, it is likely to be a protein excipient, such as gelatin or egg, or rarely another excipient, such as dextran.[48,51]

Venom from stinging insects (Order Hymenoptera, family Apidae [eg, honeybees]; family Vespidae [eg, yellow jackets, yellow hornets, white-faced hornets, and paper wasps]; and family Formicidae [eg, ants])[52-54] or, less commonly, saliva from biting insects (flies, mosquitoes, ticks, kissing bugs, and caterpillars) can trigger anaphylaxis.[54-57]

In health care settings ongoing efforts to prevent anaphylaxis from natural rubber latex have been relatively successful; however, in the community anaphylaxis is still occasionally reported after direct exposure to latex-containing gloves, condoms, rubber-handled racquets, balloons, latex-padded play pits, infant pacifiers, and bottle nipples. It also potentially occurs after ingestion of foods that cross-react with latex, such as banana, kiwi, papaya, avocado, potato, and tomato.[58]

Occupational allergens,[25] seminal fluid,[59] and, rarely, inhaled allergens, such as animal dander[60] or grass pollen, can also trigger anaphylaxis; some systemic absorption of these allergens likely occurs.

In addition, nonimmune perturbations of mast cells and basophils might lead to anaphylaxis. This potentially occurs after exercise[61,62] and/or exposure to cold air or water, heat, sunlight/UV radiation, insect venom constituents,[52,53] radiocontrast media,[34,42] ethanol, and some medications, including opioids, COX-1 inhibitors, and vancomycin.[24,25,34] In patients with exercise-induced anaphylaxis, food is a common cotrigger[61]; it is hypothesized that in these patients, food-sensitized immune cells are relatively innocuous until they are redistributed into the systemic circulation from gut-associated deposits during exertion.[62]

Idiopathic anaphylaxis is diagnosed when no triggers can be identified based on history, skin tests are negative, and serum specific IgE levels are absent or undetectable. Before this diagnosis is made, however, the possibility of a hidden or previously unrecognized trigger should be ruled out,[24,28-30,32,33,37-40,57] and the patients should be evaluated for mastocytosis and clonal mast cell disorders.[63-67]

Mechanisms

The underlying pathogenesis of human anaphylaxis commonly involves an immunologic mechanism in which IgE is synthesized

TABLE II. Epidemiology of anaphylaxis in the general population: All triggers

Author	Date	Description of study	Key findings	Comments
Yocum et al[4]	1999	Rochester Epidemiology Project, linked indexed medical records of the general population of Olmstead County, MN	During the years 1983-1987, the average annual incidence rate was 21/100,000 person-years, and the most common triggers were foods, medications, and insect stings.	Anaphylaxis frequently was not recognized by patients or physicians.
Simons et al[5]	2002	Dispensing data for all injectable epinephrine formulations over 5 consecutive years in a general population of 1.15 million in which all dispensings are recorded	Of this defined general population, 0.95% had injectable epinephrine dispensed for out-of-hospital treatment.	Dispensing rates were highest in those <17 years of age (1.44%) and lowest in those ≥65 years of age (0.32%). There was a male predominance to age 15 years and a female predominance after age 15 years.
Bohlke et al[6]	2004	Large health maintenance organization in the United States, 1991-1997; cases identified from automated database using ICD-9 codes 995.0, 995.6, 995.4, and 999.4 plus medical records review	The incidence rate was 10.5 anaphylactic episodes per 100,000 person-years.	After review of the sample using the additional ICD-9 codes 708.0, 708.9, 995.1, 995.3, and 695.1, the incidence rate was estimated at 68.4 cases/100,000 person-years.
Helbling et al[7]	2004	Investigated anaphylaxis with circulatory symptoms during a 3-year period, 1996-1998, in Bern, Switzerland (population, 940,000); allergy clinic medical records were reviewed, and emergency departments were contacted to identify additional cases.	Two hundred twenty-six people had 246 episodes of life-threatening anaphylaxis with cardiovascular symptoms, for an incidence rate of 7.9-9.6/100,000 person-years.	There were 3 deaths, resulting in a case fatality rate of 0.0001%.
Lieberman et al[3]	2006	Panel convened to review major epidemiologic studies of anaphylaxis	There was a frequency estimate of 50 to 2,000 episodes/100,000 person-years or a lifetime prevalence of 0.05% to 2%.	The largest number of incident cases were found in children and adolescents.
Poulos et al[8]	2007	Data on hospital admissions for anaphylaxis were extracted for the periods 1993-1994 to 2004-2005, respectively.	There was a continuous increase by 8.8% per year in the incidence rate of ED visits/hospitalizations for anaphylaxis and a steep increase in hospitalizations for food-triggered anaphylaxis in children <5 years of age.	In children, hospitalizations for food-induced anaphylaxis were an increasing concern.
Camargo et al[9]	2007	State-by-state dispensing data (filled prescriptions, including refills) for epinephrine autoinjectors in 2004 in the United States	State-by-state variation: average was 5.71 EpiPens per 1,000 persons (range from 2.7 in Hawaii to 11.8 in Massachusetts).	Regional variation was also noted: the rate was significantly higher in northern states (except Alaska) than in southern states.
Decker et al[10]	2008	Population-based incidence study from 1990-2000 in the Rochester Epidemiology Project (see Yocum et al study above in this table)	Overall age- and sex-adjusted incidence rate of 49.8/100,000 persons; the annual incidence rate increased from 1990 to 2000.	Age-specific rates were highest for ages 0-19 years (70/100,000 person-years).
Lin et al[11]	2008	Characterization of anaphylaxis hospitalizations in New York state in patients <20 years of age	During the study period, 1990-2006, the anaphylaxis hospitalization rate increased by more than 4-fold.	There was overall bimodal age distribution, with peaks in the very young and in teens.
Sheikh et al[12]	2008	Recorded incidence and lifetime prevalence of anaphylaxis in England were investigated by using QRESEARCH, a national aggregated primary health care database containing the records of >9 million patients.	Age/sex standardized incidence of anaphylaxis was 6.7/100,000 person-years in 2001 and increased by 19% to 7.9/100,000 person-years in 2005; lifetime age/sex standardized prevalence of anaphylaxis was 50/100,000 in 2001 and increased by 51% to 71.5/100,000 in 2005.	Adrenaline prescribing increased by 97% over this time.

This table summarizes selected publications during the past decade in which the rate of occurrence of anaphylaxis from all triggers in the general population was estimated. These estimates vary because of different definitions of anaphylaxis, different methods of case ascertainment, and the different populations studied.
ED, Emergency department; *ICD-9*, International Classification of Diseases–Ninth Revision.

in response to allergen exposure and becomes fixed to high-affinity receptors for IgE (FcεRI receptors) on the surface membranes of mast cells and basophils (Fig 1).[1,2,24,25,69-72] Aggregation of receptor-bound IgE molecules occurs on re-exposure to the allergen and results in cell activation and mediator release.[70-72] IgE also contributes to the intensity of anaphylaxis by enhancing the expression of FcεRI on mast cells and basophils.[70-72]

Rarely, other immunologic mechanisms that do not involve IgE are implicated in human anaphylaxis.[73] IgG-mediated

TABLE III. Mechanisms and triggers of anaphylaxis in the community

Immunologic mechanisms (IgE dependent)
Foods, such as peanut, tree nut, shellfish, fish, milk, egg, sesame, and food additives*
Medications, such as β-lactam antibiotics and NSAIDs, and biological agents†
Venoms, such as stinging insects (Hymenoptera)
Natural rubber latex
Occupational allergens
Seminal fluid (prostate-specific antigen)
Inhalants, such as horse, hamster, and other animal danders and grass pollen (rare)
Radiocontrast media‡
Immunologic mechanisms (IgE independent, formerly classified as anaphylactoid reactions)
Dextran, such as high-molecular-weight iron dextran†
Infliximab†
Radiocontrast media‡
Nonimmunologic mechanisms
Physical factors, such as exercise,§ cold, heat, and sunlight/UV radiation
Ethanol
Medications, such as opioids†
Idiopathic anaphylaxis
Consider the possibility of hidden or previously unrecognized allergens‖
Consider the possibility of mastocytosis/clonal mast cell disorder

Adapted from references 24-69.

*Food additives include spices, vegetable gums, colorants (carmine/cochineal), monosodium glutamate, sulfites, papain, and contaminants.

†Medications can potentially trigger anaphylaxis through an IgE-dependent immunologic mechanism, an IgE-independent immunologic mechanism, or direct mast cell stimulation. Biological agents include mAbs (eg, cetuximab and omalizumab), allergens, vaccines, and hormones (eg, progesterone).

‡Radiocontrast media potentially trigger anaphylaxis through an IgE-dependent immunologic mechanism or through activation of complement.

§With or without a food or medication cotrigger.

‖Includes foods, biting insect saliva, other venoms, medications, and biological agents. Save food or food label, insect or other relevant material, and save patient serum sample for customized *in vitro* tests, such as measurement of allergen-specific IgE (see the text for further details).

anaphylaxis has been reported due to high molecular weight iron dextran or infusion of chimeric, humanized, or human therapeutic mAbs, such as infliximab.[44,51] Complement-mediated anaphylaxis occurs in association with hemodialysis, OSCS-contaminated heparin,[38] protamine neutralization of heparin, liposomal drugs, or polyethylene glycols. Direct activation of the innate immune system might also contribute to triggering anaphylaxis.[74]

In addition, as noted previously, nonimmune activation of mast cells and basophils occurs.[24,25,34]

A trigger can lead to anaphylaxis through more than 1 mechanism; for example, radiocontrast media can trigger anaphylaxis through an immunologic IgE-dependent mechanism and through direct mast cell activation.[34,42] OSCS-contaminated heparin triggers anaphylaxis through activation of the complement system, leading to generation of kallikrein, bradykinin, and the complement protein-derived anaphylatoxins C3a and C5a; in addition, factor XII and the coagulation system are involved.[38,75]

Regardless of the immunologic or nonimmunologic triggering mechanisms and regardless of whether FcεRI or other receptors, such as G protein–coupled receptors or Toll-like receptors, are activated, mast cells and basophils play an important role in initiating and amplifying the acute allergic response. After IgE/FcεRI binding and receptor aggregation, multiple tyrosine kinases, including Lyn, Syk, and Fyn, are activated and exert both positive and negative regulation on the signal transduction cascade.[70,71,76] Calcium influx is the essential proximal intracellular event leading to mast cell degranulation and is controlled by both positive and negative regulation through calcium channels.[70,77] Mast cells and basophils release preformed chemical mediators of inflammation, including histamine, tryptase, carboxypeptidase A, and proteoglycans.[68,70,71,78,79] They also release newly generated mediators, such as leukotrienes, prostaglandins, and platelet-activating factor, and cytokines, such as IL-6, IL-33, and TNF-α, which is a late-phase mediator, as well as a preformed mediator.[68,70,71,80-84] Sphingosine-1-phosphate is now recognized as a circulating mediator in anaphylaxis, and in addition, it acts as a signaling component within the mast cell.[85] Once activated, the mast cell response is regulated by the balance of positive and negative intracellular molecular events that extend beyond the traditional kinases and phosphatases.

New discoveries in mast cell biology have the potential to improve the diagnostic and therapeutic approach to human anaphylaxis. For example, stem cell factor and its receptor Kit are fundamentally important in IgE/antigen-induced mast cell activation, and concurrent inhibition of Kit- and FcεRI-mediated signaling achieves coordinated suppression of human mast cell activation.[86] An orally effective compound has been identified that binds to Syk, downregulates the interaction of Syk with some of its macromolecular substrates, and inhibits FcεRI-induced mast cell degranulation *in vitro* and anaphylaxis *in vivo*.[87] Inhibitory sialic acid-binding immunoglobulin-like lectins (Siglecs) are expressed on human mast cells, on which Siglec-8 engagement results in inhibition of FcεRI-dependent mediator release without apoptosis.[88] Anti-IgE antibody potentially plays a therapeutic role by depleting free IgE, with consequent downregulation of FcεRI on mast cells and basophils and deflation of the intracellular activation signal triggered by IgE/FcεRI aggregation.[89] Basophil involvement in anaphylaxis will likely be further elucidated in the future because a monoclonal antibody directed against pro–major basic protein 1 has been identified.[90] The opening of the endothelial barrier through endothelial G_q/G_{11}-mediated signaling has been identified as a critically important process leading to symptoms of anaphylaxis in many body organ systems.[91]

There are few studies of the role of genetic factors in human anaphylaxis. Investigations in this area might improve our

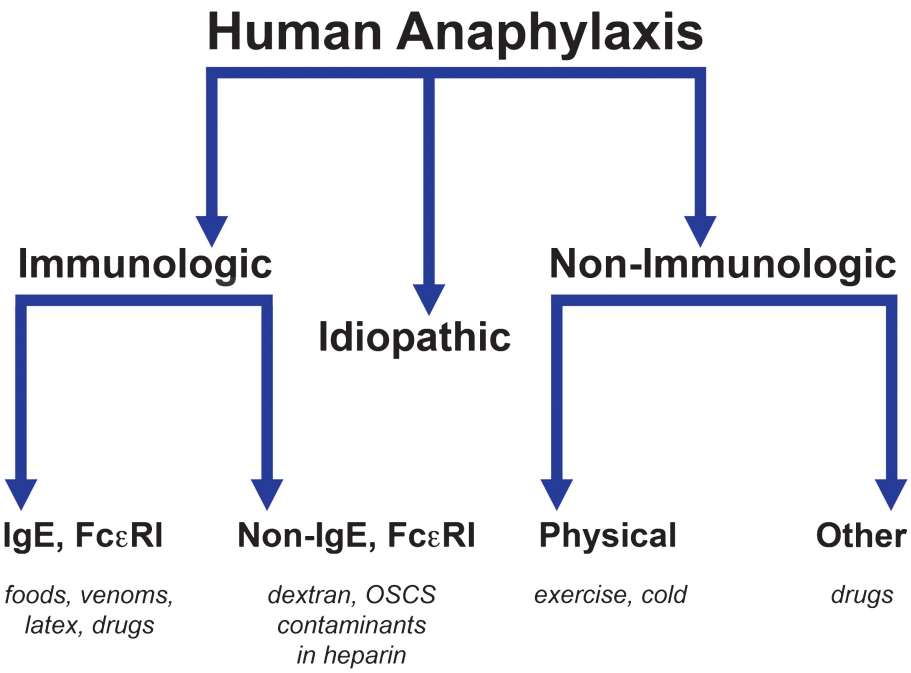

FIG 1. Mechanisms underlying human anaphylaxis. Anaphylaxis is commonly mediated through an immune IgE-dependent mechanism. Rarely, it occurs through another immune mechanism. Uncommonly, it occurs through direct (nonimmune) activation of mast cells. Idiopathic anaphylaxis, currently a diagnosis of exclusion, presents opportunities for identification of previously unrecognized triggers, elucidation of pathophysiologic mechanisms, and identification of patients with mastocytosis or clonal mast cell disorders.[69]

understanding of why anaphylaxis occurs in only a minority of persons who are sensitized to an antigen and why episodes vary greatly in severity from mild with spontaneous remission to severe and fatal.[92,93]

Patient-specific risk factors for severity and fatality

Patients might be at increased risk of anaphylaxis severity and fatality because of age, concomitant disease, concurrent medications, and other factors that are still being delineated (Table IV).[24,25,64-69,93-108]

In infants anaphylaxis is sometimes hard to recognize because they cannot describe their symptoms, and many of the signs of anaphylaxis in infancy, such as flushing and dysphonia after a crying spell, spitting up or loose stools after feeding, and loss of sphincter control, are ubiquitous in the healthy state.[94] Teenagers and young adults are at increased risk of anaphylaxis triggered by foods and possibly other agents because of inconsistent behaviors with regard to avoiding their confirmed relevant triggers and carrying epinephrine autoinjectors.[95] During pregnancy, anaphylaxis places the mother and especially the baby at high risk of fatality or permanent central nervous system (CNS) damage. During the first, second, and third trimesters, potential triggers of anaphylaxis are similar to those in nonpregnant women. During labor and delivery, the most common triggers are penicillins and other β-lactam antibiotics given as prophylaxis against neonatal group B streptococcal infection.[96] Elderly adults are at increased risk of fatality in anaphylaxis because of concomitant diseases, such as chronic obstructive pulmonary disease (COPD), and cardiovascular diseases (CVDs) and the medications used to treat them.[21,97-99]

In patients of any age, diseases that impede prompt recognition of triggers or symptoms potentially place patients at increased risk of anaphylaxis.[24,25,69,93] These include impaired vision or hearing, neurologic disorders, psychiatric disorders (including depression), autism spectrum disorder, developmental delay,[24,69] and use of medications, such as first-generation H_1-antihistamines (eg, diphenhydramine and chlorpheniramine), antidepressants, or CNS-active chemicals, such as ethanol or recreational drugs.[24,69]

Concomitant diseases, such as asthma or other chronic respiratory diseases, especially if severe or uncontrolled,[21,24,25,69] and also CVDs[97-99] and mastocytosis or clonal mast cell disorders,[64-67,100-103] are associated with increased risk of life-threatening or fatal anaphylaxis. Severe allergic rhinitis and severe eczema increase the risk of life-threatening anaphylaxis to some foods.[105] Concurrent medications, such as β-blockers and angiotensin-converting enzyme inhibitors increase the severity of anaphylaxis, and β-blockers potentially make anaphylaxis more difficult to treat.[24,25,98,99103,105]

In some patients severe or fatal anaphylactic episodes might be associated with defects in mediator degradation pathways and intracellular signaling pathways, as reflected, for example, in increased baseline serum tryptase levels (which are strongly associated with insect sting–triggered anaphylaxis),[67,103] increased baseline plasma histamine levels,[104] low serum angiotensin-converting enzyme activity,[105] and reduced platelet-activating factor acetylhydrolase activity.[80]

Other concomitant factors reported to increase the risk of an anaphylactic episode include exercise; exposure to extremes of temperature or humidity or high pollen counts; foreign travel or other disruption of routine; feeling unwell; fever; acute infection,

TABLE IV. Patient factors that increase risk of anaphylaxis severity and fatality

Age*
Infants: Underrecognition, underdiagnosis; no appropriate epinephrine auto-injector dose
Adolescents and young adults: ↑ Risk-taking behavior
Pregnancy: During labor and delivery, antibiotic prophylaxis against neonatal group B streptococcal infection is a common trigger
Elderly: ↑ Risk of fatality from medication and venom-triggered anaphylaxis
Comorbidities*
Asthma and other respiratory diseases, especially if severe or uncontrolled
CVDs, including hypertension
Mastocytosis† and clonal mast cell disorders†
Allergic rhinitis and eczema‡
Depression and other psychiatric diseases (might impair recognition of symptoms)
Thyroid disease (some patients with idiopathic anaphylaxis)
Concurrent medication/chemical use*
Potentially affect recognition of anaphylaxis
Sedatives/hypnotics/antidepressants/ethanol/recreational drugs
Potentially increase anaphylaxis severity
β-Blockers and ACE inhibitors
Other factors*
Exercise
Acute infection, such as upper respiratory tract infection
Menses
Emotional stress
Occupation, such as beekeeping
Priming effect of recent previous anaphylactic episode
Increased baseline plasma histamine levels (hyperhistaminemia)
Increased baseline serum tryptase levels
Reduced level of PAF AH activity, leading to increased PAF levels
Reduced level of ACE activity, leading to increased bradykinin levels

Adapted from references 68, 69, and 94-108.

ACE, Angiotensin-converting enzyme; *AH*, acetylhydrolase; *PAF*, platelet-activating factor.

*In some patients several factors might need to be present concurrently for risk to be increased, such as an elderly person plus cardiovascular disease plus β-blocker medication. In others concurrent triggers might be needed, such as food plus exercise.

†Suggested by increased baseline total tryptase levels.

‡Atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex but not for anaphylaxis triggered by insect stings, β-lactam antibiotics, or insulin.

such as an upper respiratory tract infection; emotional stress; menses (premenstrual and ovulatory phases); and/or ingestion of NSAIDs or ethanol.[20,32,61,62,106-108]

ASSESSMENT OF PATIENTS WITH A HISTORY OF ANAPHYLAXIS

Ideally, patients with a history of an acute anaphylactic episode should be referred to an allergy/immunology specialist with training and experience in risk assessment in anaphylaxis, including confirmation of the diagnosis, verification of the triggers, and evaluation of comorbidities and concurrent medications.

Clinical diagnosis of anaphylaxis

When patients are seen after an acute anaphylactic episode, the history of the episode should be confirmed and relevant emergency medical services and emergency department records should be reviewed.[24,25,68,69,93] The history should focus on recall of exposure to potential triggering agents or events, the minutes or hours elapsed between exposure and symptom onset, and the evolution of symptoms and signs. Involvement of body organ systems varies among patients and even in the same patient from one episode to another; however, review of anaphylaxis case series reveals some general patterns. Skin involvement is reported in 80% to 90% of episodes, respiratory tract involvement in up to 70%, gastrointestinal tract involvement in up to 45%, cardiovascular system involvement in up to 45%, and CNS involvement in up to 15% (Table V).[24,25,69,93]

The differential diagnosis of anaphylaxis includes common entities, such as acute generalized hives, acute asthma, syncope, panic attack, aspiration of a foreign body, and cardiovascular or neurologic events.[24,25] Postprandial syndromes, such as pollen-food syndrome and scombroidosis, also need to be considered, as do excess endogenous histamine syndromes, such as mastocytosis; flush syndromes, including perimenopausal flushing; nonorganic diseases, such as vocal cord dysfunction; and other diagnostic entities, some of which are rarely encountered (Table VI).[24-26,32,33,63-68,109,110] The differential diagnosis is age related to some extent. In infants foreign body aspiration, congenital malformations of the respiratory or gastrointestinal tracts, and apparent life-threatening event/sudden infant death syndrome need to be considered.[94] In middle-aged and elderly adults myocardial infarction, pulmonary embolus, and stroke are important considerations.[21,25,97]

Laboratory tests at the time of the acute anaphylactic episode

In some patients the clinical diagnosis of anaphylaxis can be confirmed by means of a blood test; for example, an increased plasma histamine level or serum total tryptase level. These tests are not specific for anaphylaxis (Table VII).[24,25,68,78,79]

Plasma histamine levels should optimally be measured 15 to 60 minutes after onset of symptoms of anaphylaxis. Special handling of the blood sample is required. Histamine and its metabolite, N-methylhistamine, can also be measured in a 24-hour urine sample.[68] Serum total tryptase levels should optimally be

TABLE V. Symptoms and signs of anaphylaxis

Cutaneous/subcutaneous/mucosal tissue
Flushing, pruritus, hives (urticaria), swelling, morbilliform rash, pilor erection
Periorbital pruritus, erythema and swelling, conjunctival erythema, tearing
Pruritus and swelling of lips, tongue, uvula/palate
Pruritus in the external auditory canals
Pruritus of genitalia, palms, soles
Respiratory
Nose: pruritus, congestion, rhinorrhea, sneezing
Larynx: pruritus and tightness in the throat, dysphonia and hoarseness, dry staccato cough, stridor, dysphagia
Lung: shortness of breath, chest tightness, deep cough, wheezing/bronchospasm (decreased peak expiratory flow)
Cyanosis
Gastrointestinal
Nausea, cramping abdominal pain, vomiting (stringy mucus), diarrhea
Cardiovascular
Chest pain, palpitations, tachycardia, bradycardia, or other dysrhythmia
Feeling faint, altered mental status, hypotension, loss of sphincter control, shock, cardiac arrest
CNS
Aura of impending doom, uneasiness, throbbing headache, dizziness, confusion, tunnel vision; in infants and children, sudden behavioral changes, such as irritability, cessation of play, and clinging to parent
Other
Metallic taste in the mouth
Dysphagia
Uterine contractions in postpubertal female patients

Adapted from references 24, 25, 93, and 94. Sudden onset of symptoms and signs is characteristic of anaphylaxis.

measured from 15 minutes to 3 hours after onset of symptoms. No special handling of the blood sample is required. The total tryptase level is typically increased in patients with anaphylaxis triggered by an injected medication or an insect sting and in those with hypotension and shock but is less likely to be increased in those with anaphylaxis triggered by food or in those who are normotensive.[68,78] Serial measurements of serum total tryptase and comparison with baseline levels obtained after the acute episode or available in stored serum might be more helpful than measurement at a single point in time.[68,78]

Other biomarkers reported to be useful in confirming an acute episode of anaphylaxis include serum mature β-tryptase; mast cell carboxypeptidase A3; chymase; platelet-activating factor; bradykinin; C-reactive protein; cytokines, such as IL-2, IL-6, IL-10, IL-33, and TNF-receptor I; and urinary cysteinyl leukotriene E4 and 9-α-11-β prostaglandin F_2.[68,72,80-84] Many studies of these potential biomarkers have included appropriate control groups, such as patients with severe acute asthma, but some have not. Biomarkers are released at different times after activation of mast cells and basophils, and patients experiencing anaphylaxis in community settings arrive in emergency departments at different time intervals after symptom onset; therefore measurement of a panel of different biomarkers might be useful.[68]

Confirmation of the triggers of anaphylaxis

An important aspect of risk assessment in patients who have experienced anaphylaxis in the community is confirmation of the trigger or triggers identified through a detailed history of antecedent exposures, so that the relevant specific trigger or triggers can be avoided and recurrences of anaphylaxis can be prevented (Table VIII).[24-26,34,52,58,61,68,69,93,111] Skin tests should be performed with validated instruments, techniques, and recording systems, preferably at least 3 to 4 weeks after the anaphylactic episode, to allow time for rearming of skin mast cells and recovery of mast cell releasability.[68] Measurement of allergen-specific IgE levels by using a quantitative method can be performed at any time during or after the acute anaphylactic episode; however, if the blood sample is obtained during or shortly after the episode from patients who have received intravenous fluid resuscitation, levels can be falsely undetectable or low because of the dilutional effect on circulating IgE. Negative tests for sensitization to a trigger in a patient with a convincing history of anaphylaxis from that trigger should be repeated weeks or months later. It is important to note that both positive skin tests and increased specific IgE levels indicate sensitization to the allergens tested but are not diagnostic of anaphylaxis or any other disease.[24-26,34,52,58,68,69]

If indicated, incremental challenge/provocation tests should be conducted in appropriately equipped health care facilities by professionals trained and experienced in patient selection, timing of the challenge, use of challenge protocols, and diagnosing and treating anaphylaxis. Before a challenge is performed, the potential risks and benefits should be discussed with the patient (or, for children, the caregivers) and documented in the medical record.[68,111]

Assessment of patients with food-triggered anaphylaxis. Skin prick tests with foods that elicit a wheal of 3 mm larger than that caused by the negative control (eg. saline) are considered positive. Commercially available food allergen extracts do not contain standardized allergens. Some food allergens, such as fruits and vegetables, are labile and degrade in glycerinated extracts during manufacture and storage; therefore skin prick tests with these allergens are often performed with fresh foods. Intradermal tests to foods are contraindicated because of lack of specificity (false-positive tests) and their potential for triggering anaphylaxis.[26,68,112] An exception to this might be use of intradermal tests to assess sensitization to fresh meat containing the carbohydrate galactose-α-1,3-galactose.[30]

In food-sensitized patients specific IgE levels have predictive values for positive (failed) or negative (passed) food challenge

TABLE VI. Differential diagnosis of anaphylaxis

Common entities	**Nonorganic disease**
Acute generalized hives	Vocal cord dysfunction
Acute asthma	Munchausen syndrome||
Syncope (faint, vasovagal episode)	
Panic attack	
Aspiration of a foreign body	**Shock**
Cardiovascular event (myocardial infarction, pulmonary embolus)	Hypovolemic Cardiogenic
Neurologic event (seizure, stroke)	Distributive (eg, spinal cord injury) Septic (might involve all of the above)
Postprandial syndromes	**Other**
Pollen-food syndrome*	Nonallergic angioedema
Scombroidosis†	Red Man syndrome (vancomycin)
Monosodium glutamate	Urticarial vasculitis
Sulfites	Hyper-IgE urticaria syndrome
	Progesterone anaphylaxis
	Pheochromocytoma
	Idiopathic systemic capillary leak syndrome
Excess endogenous histamine	
Mastocytosis/clonal mast cell disorders‡	
Basophilic leukemia	
Flush syndromes	
Perimenopause	
Carcinoid	
Autonomic epilepsy	
Medullary carcinoma thyroid	

Adapted from references 24-26, 63-68, 109, and 110.

*Pollen-food allergy syndrome, also termed oral allergy syndrome, is elicited by a variety of plant proteins, especially pathogen-related proteins that comprise a large number of class 2 allergenic proteins found in various fruits and vegetables. These plant proteins cross-react with airborne allergens. Typical symptoms include pruritus, tingling, and angioedema of the lips, tongue, palate, throat, and ears after eating raw, but not cooked, fruits and vegetables.

†This disease is due to histamine poisoning from fish, such as tuna, mackerel, saury, mahi-mahi, anchovies, and herring, that are stored at increased temperatures (30°C), at which bacteria such as *Morganella marganii* and *Klebsiella pneumoniae* produce histamine and *cis*-urocanic acid. Symptoms occur from minutes to hours after ingestion of the fish and last for hours. They include flush (especially of the face and neck), angioedema, nausea, vomiting, diarrhea, and hypotension. An important clue to the diagnosis is that more than 1 person eating the fish is usually affected. Skin prick tests to fish are negative, and fish-specific IgE levels are absent or undetectable.

‡Anaphylaxis might be the first manifestation of mastocytosis or a clonal mast cell disorder.

||Nonorganic diseases also include Munchausen syndrome by proxy in a child or other dependent, globus hystericus, and undifferentiated somatoform anaphylaxis.

tests. Allergen-specific IgE levels with greater than 95% predictive risk values of a positive (failed) food challenge result have been identified by using the ImmunoCAP (Phadia, Uppsala, Sweden). These levels are defined for cow's milk (≥15 kU/L), egg (≥7 kU/L), peanut (≥14 kU/L), tree nuts (≥15 kU/L), and fish (≥20 kU/L); in infants lower values have been established for milk (≥5 kU/L) and egg (≥2 kU/L).[26] Predictive values for allergen-specific IgE levels potentially differ from one immunoassay to another, and this can affect management decisions.[26,68,113]

A positive skin test, an increased serum IgE level, or both to a specific food document sensitization to that food. Such tests are not diagnostic of anaphylaxis because sensitization to 1 or more food allergens is common in the general population of healthy people who have no history of anaphylaxis. For example, 60% of young people have a positive skin prick test to 1 or more foods, yet most of those with positive tests have never experienced anaphylaxis from a food.[114] In addition, although positive skin tests and increased allergen-specific IgE levels correlate with an increased probability of clinical reactivity to specific foods, the results of these tests do not necessarily correlate with the risk of future anaphylactic episodes or with the severity of such episodes.[26,68]

Oral food challenge testing was extensively reviewed in the *Journal* in 2009.[111] Patients with a convincing history of anaphylaxis to a specific food and evidence of sensitization to that food should not undergo oral food challenge tests because of their high risk of anaphylaxis from such tests. Others, such as those with an equivocal history, low or moderate evidence of sensitization, or both, might benefit from a physician-monitored incremental oral food challenge. A positive (failed) challenge provides a sound basis for continued avoidance of the food. A negative (passed) challenge allows introduction or reintroduction of the specific food into the patient's diet.[111]

Unproved or disproved diagnostic methods, such as electrodermal skin testing and kinesiology, remain in use for assessment of patients with food allergy.[115]

In the future, *in vitro* tests that will distinguish reliably between sensitization without risk of clinical reactivity versus sensitization with risk of clinical reactivity might be available. These include measurement of allergen-specific basophil reactivity,[116] assessment of sensitization by using recombinant allergens,[117] peptide microassay-based immunoassays to map IgE and IgG_4 binding to sequential allergen epitopes,[117-119] or assessment of allergen-specific cytokine or chemokine production.[68]

Assessment of medication- or biological agent–triggered anaphylaxis. Any medication or biological agent can potentially trigger anaphylaxis. For most agents, the antigenic determinants have not been characterized or validated; indeed, the relevant immunogenic prodrugs, haptens, metabolites, and unidentified degradation products or contaminants are often unknown.[34,38,68] For most medications, with the exception of some β-lactam antibiotics, appropriate reagents are not commercially available for use in skin tests, measurement of medication-specific IgE levels, or other *in vitro* tests.[34,68] Customized tests and physician-monitored challenge/provocation tests performed in specialized centers therefore play a central role in assessment of patients with a history of anaphylaxis triggered by a medication.[34,68,120-122]

For assessment of anaphylaxis triggered by vaccines to prevent allergic diseases, skin prick tests should be performed not only with the immunizing agent but also with the relevant excipients in the culprit vaccine, such as gelatin in measles vaccines or egg in some influenza vaccines and in yellow fever vaccine.[48,68]

Assessment of stinging insect–triggered anaphylaxis. Standardized Hymenoptera venoms, such as honeybee, yellow jacket, yellow hornet, white-faced hornet, and paper wasp, are available for skin testing. Skin prick tests, if negative, should be followed by intradermal tests.[52-54] Use of dialyzed venoms in skin tests is reported to improve the identification of venom-sensitized patients.[123] For fire ant-triggered anaphylaxis, whole-body extracts are used as skin test reagents.[54,55] Measurements of venom-specific IgE levels and fire ant whole-body extract–specific

TABLE VII. Laboratory tests: Acute anaphylactic episode

Histamine*
Obtain blood sample within 15 minutes to 1 hour of symptom onset* (use wide-bore needle, keep sample cold (at 4 degrees C), centrifuge it promptly, and freeze plasma promptly).
Twenty-four-hour urine histamine and N-methylhistamine measurements might also be helpful.
Total tryptase* (pro, pro′, and mature forms of α/β-tryptases)
Obtain blood sample within 15 minutes to 3 hours of symptom onset.
Consider comparing the levels measured during the acute episode with a baseline level.†
If higher during the acute episode than in baseline serum, the diagnosis of anaphylaxis is confirmed.‡
If within normal limits during the acute episode, the diagnosis of anaphylaxis cannot be excluded.
Total tryptase level can be measured in postmortem serum.§
Additional laboratory tests‖

Adapted from references 24, 25, 68, 78, 79 and 81.
*Increases of histamine and tryptase levels are not specific for anaphylaxis. For example, histamine levels are increased in patients with scombroid poisoning and tryptase levels are increased in patients with myocardial infarction, trauma, amniotic fluid embolus, and sudden infant death syndrome.
†Obtained 24 hours after resolution of the acute event or on stored serum, if available (levels are stable for ≥1 year if stored at -20 degrees C).
‡If greater than 11.4 ng/mL in both acute and baseline sera, the diagnosis of mastocytosis or clonal mast cell disorder should be considered.
§Blood samples should be obtained from femoral vessels and not the heart; the level needs to be correlated with the clinical history because, as noted above, increased levels are also found in other clinical situations, such as myocardial infarction, trauma, amniotic fluid embolism, and sudden infant death syndrome.
‖When sorting out the differential diagnosis of anaphylaxis, the detailed clinical history and physical examination might suggest the need for additional laboratory tests to confirm or rule out diseases such as mastocytosis, basophilic leukemia, carcinoid (serum serotonin level and urinary 5 hydroxyindoleacetic acid), medullary carcinoma of the thyroid/vasoactive polypeptide–secreting gastrointestinal tumor (substance P and vasointestinal polypeptide), pheochromocytoma (free metanephrine in plasma and urinary vanillylmandelic acid), hereditary angioedema (C4 and C1 esterase inhibitor), or diagnostic imaging to confirm or rule out hydatid cysts. Investigation of the complement cascade (C4a, C5a, and C3a), the contact system (bradykinin, high-molecular-weight kininogen, kallikrein–C1-inhibitor complexes, and factor XIIa–C1-inhibitor complexes), and coagulation pathway (factors V, VIII, and fibrinogen), although usually not performed, might support the clinical diagnosis of anaphylaxis; however, these tests also appear to lack specificity.

TABLE VIII. Confirmation of a potential trigger for an anaphylactic episode

Allergen skin tests
Percutaneous (prick or puncture)*
Intradermal (intracutaneous) for selected allergens such as insect venoms and β-lactam antibiotics†
Allergen-specific serum IgE levels
Quantitative ELISAs‡
Allergen challenge tests§
Most commonly performed with foods or medications
Other challenge tests
Exercise‖
Cold
Heat
Sunlight
Work up of patients with idiopathic anaphylaxis (in whom detailed history of antecedent events/exposures does not yield any clues about triggers and skin test results and allergen-specific IgE measurements are negative)
Search for a previously unrecognized trigger
Measure serum baseline total tryptase levels (normal value, <11.4 ng/mL)
Inspect skin closely for evidence of urticaria pigmentosa
Consider bone marrow biopsy (perform c-Kit mutational analysis in addition to usual stains for identification of spindle-shaped mast cells in clusters)

Adapted from references 24-26, 34, 52, 58, 61, 67, 100-102, and 111.
*Allergens for skin testing should be selected on the basis of the history. Standardized extracts are available only for some Hymenoptera venoms and some inhalant allergens. Patients should discontinue H_1-antihistamines 7 days before skin testing. Many people in the general population are sensitized to allergens (eg, 60% of teens to food and as many as 28.5% of adults to venom).
†Intradermal tests are generally contraindicated in food allergy because of the high likelihood of false-positive results and the possibility of triggering anaphylaxis.
‡Available commercially for foods, insect venoms, and latex but not for most medications or biological agents. Refer to predictive values, where available, for foods such as peanut, tree nuts, fish, milk, and egg.
§Open, single-blind, or double-blind depending on clinical history and allergen. *"First do no harm"*: challenge *only* if assessment (clinical history, skin tests, and/or measurement of allergen-specific IgE levels) indicate that the patient is at low risk for anaphylaxis. Perform *only* under medical supervision in a hospital or other health care facility.
‖Assessment of cotriggers, such as a food, medication, or cold exposure, is needed.

IgE levels are commercially available. Some patients with a history of Hymenoptera sting–triggered anaphylaxis have negative skin test responses to insect venoms but increased specific IgE levels to venoms and *vice versa*.[52,124] Challenge/provocation tests with stinging and biting insects are potentially dangerous and are used only in research.[52-57,68,125]

Positive intradermal tests to stinging insect venoms, increased venom-specific IgE levels, or both occur in up to 28.5% of the general adult population, most of whom do not have systemic symptoms after an insect sting.[52-54,68] It is therefore critically important that the test results be interpreted in the context of the clinical history. Cross-reacting carbohydrate derivatives between venom allergens and plant

or other nonvenom allergens might account for many of these positive test results. In some centers additional tests used to assist in interpretation of positive test results include consideration of total IgE levels as well as venom-specific IgE levels,[125] and measurement of basophil activation markers, such as CD63 or CD203c after incubation with different concentrations of venom.[53,68,125]

Conversely, venom skin tests might be negative and venom-specific IgE levels might be absent or undetectable in patients with a convincing history of insect sting–triggered anaphylaxis. Negative tests might be due to rare IgE- or non–IgE-mediated reactions to a protein or peptide constituent[127] such as melittin in honeybee venom or mastoparan in vespid venom; variability of intradermal testing; anergy in patients tested within a few weeks of the sting; decrease in the immune response to venom over time in patients stung many years before testing; or increased patient vulnerability to anaphylaxis. As noted previously, risk of severe or fatal anaphylaxis increases with older age; concurrent diseases, including CVDs; and concurrent use of medications, such as β-blockers or angiotensin-converting enzyme inhibitors,[52,53,97,103] as well as in patients with mastocytosis, clonal mast cell disorders, or increased baseline tryptase levels.[52,53,72,100-103] If the baseline total tryptase level is greater than 11.4 ng/mL (the new upper limit of normal), meticulous examination for cutaneous mastocytosis is indicated, and if the level is greater than 20 ng/mL, a bone marrow biopsy is indicated, even if cutaneous manifestations are absent.[67] Also, in some patients clinical risk of anaphylaxis is increased by factors such as a recent sting; a previous severe systemic reaction to a sting; a sting on the head, neck, or throat; or the entomology of the stinging insect.[52-54,68,103]

Assessment of anaphylaxis from other triggers. For assessment of anaphylaxis triggered by natural rubber latex, skin prick tests should be performed with commercial latex allergens, where available, or with extracts of rubber products, such as natural rubber latex gloves, where commercial allergens are not available. Consideration should be given to testing with foods that cross-react with latex, such as banana, kiwi, papaya, avocado, potato, and tomato.[58,68] Latex-specific IgE antibodies can also be measured.

For assessment of exercise-triggered anaphylaxis, skin tests should be performed with potential food allergen cotriggers.[61] An exercise intensity threshold can be defined in an exercise challenge test to diagnose food-dependent exercise-induced anaphylaxis.[128]

Assessment of idiopathic anaphylaxis. When a meticulous history of antecedent exposures and events does not yield any clues about potential triggers and when allergen skin tests are negative and specific IgE measurements are absent or undetectable to selected common allergens, patients are said to have idiopathic anaphylaxis. Before making this diagnosis, physicians should consider the possibility of a hidden or previously unrecognized trigger. Sensitization to a novel trigger for which there is no commercially available test allergen can be identified through a history of the event and confirmed by objective tests. These potentially include skin testing the patient and 1 or more controls with crude extracts of the suspected culprit allergen (although there is no quality assurance that such extracts contain the relevant allergenic components) and/or development of customized, sensitive, specific ELISAs and other *in vitro* tests, including gel electrophoresis and IgE immunoblotting, for identification of specific IgE to the suspect allergen.[63,68,69]

The serum total tryptase level should be measured in all patients with idiopathic anaphylaxis.[63-68,78,100-103] This important screening test for mastocytosis reflects the increased burden of mast cells in all forms of this disease.[78]

MANAGEMENT OF PATIENTS AT RISK FOR ANAPHYLAXIS IN COMMUNITY SETTINGS

Long-term preventive measures include optimal management of relevant comorbidities, such as asthma, other chronic respiratory diseases, CVDs, and mastocytosis and clonal mast cell disorders.[63-67,97-102] These measures also include discussion of the relative benefits and risks of concurrent medications (eg, β-blockers, angiotensin-converting enzyme inhibitors, and others that are widely and effectively used in the management of CVDs) with the patient and his or her cardiologist and documentation of the rationale for treatment decisions in the patient's medical record.[97-99,103]

With the exception of venom immunotherapy for patients with insect sting–triggered anaphylaxis, current recommendations for prevention of anaphylaxis and emergency preparedness for treatment of anaphylaxis in the community are based on expert opinion and consensus rather than on randomized, double-blind, placebo-controlled trials. Preventive strategies for anaphylaxis in community settings that involve trigger avoidance and immunomodulation are summarized in Table IX.[1,2,24-26,34,52,54,58,69,93,129-153] Follow-up at regular intervals is an important aspect of long-term risk reduction.

Long-term risk reduction: Prevention of anaphylaxis

Anaphylaxis triggered by food. Written personalized information about avoidance of confirmed relevant food triggers, including lists of common hidden sources of the food or foods and high-risk situations, such as buffet and catered meals and unlabeled desserts, baked goods, and candies, should be provided. Patients should be directed to resources that provide up-to-date, consistent information about avoidance of the specific food or foods (Table IX).[26,129] Food avoidance measures potentially decrease quality of life for those at risk of anaphylaxis and for their caregivers[130,131] because of lifestyle changes that disrupt activities, uncertainty about ambiguities in advisory labeling,[132] and anxiety about the risk of accidental exposures.[26,133] Strict avoidance of many foods potentially leads to nutritional deficiencies.[26] Some patients at risk for anaphylaxis to foods, or their caregivers, turn to complementary and alternative medicine for relief.[115]

Allergen-specific oral immunotherapy is currently a research procedure for prevention of anaphylaxis triggered by food. Clinical trials with foods such as milk, egg, or peanut have been conducted in carefully selected patients in appropriately equipped food allergy research centers by physicians and other health care professionals who have experience in performing food challenges, administering oral immunotherapy, and diagnosing and treating anaphylaxis.[108,112,134-141] A few of the studies have had a double-blind, placebo-controlled design.[137] Adverse effects have been common with some oral immunotherapy dosing regimens, especially on the initial dose escalation day and on subsequent dose build-up days.[141]

In some of these studies, clinical desensitization to a food has been accompanied by long-term, food-specific humoral and cellular changes,[138,140] including decreased titrated skin prick tests, decreased basophil activation, decreased IgE levels, and increased IgG_4, IL-10, IFN-γ, and TNF-α levels.[140] Studies in progress will resolve the issue as to whether oral immunotherapy for food-triggered anaphylaxis leads not only to clinical desensitization but also to true immunologic tolerance in which patients

TABLE IX. Preventive strategies for anaphylaxis in community settings

Allergen-specific trigger avoidance based on history of exposure and confirmation of sensitization (strength of recommendation = C)
Foods,* including additives and contaminants
Medications and biological agents†
Insect stings and bites
Natural rubber latex*
Inhalants
Seminal fluid
Occupational allergens
Other
Nonimmunologic triggers: avoid relevant exposure (strength of recommendation = C)
Exercise-induced anaphylaxis‡
Cold air or water
Heat
Sunlight/UV radiation
Medications, such as opioids
Ethanol
Immunomodulation
Food: Currently, oral immunotherapy is a research procedure supervised by physicians in specialized food allergy centers (strength of recommendation pending).
Insect venoms: allergen-specific immunotherapy (strength of recommendation = A)
Medications†: desensitization (strength of recommendation = B)
Seminal fluid: desensitization (strength of recommendation = C)
Idiopathic anaphylaxis (for frequent episodes only; strength of recommendation = C)
Oral glucocorticoid, such as prednisone; H_1-antihistamine, such as cetirizine (used for prophylaxis)

Adapted from reference 153 and others; see text for details.

*These Web sites consistently provide accurate up-to-date information: the Food Allergy and Anaphylaxis Network (www.foodallergy.org); the American Latex Allergy Association (www.latexallergyresources.org); the American Academy of Allergy, Asthma & Immunology (www.aaaai.org); and the American College of Allergy, Asthma & Immunology (www.acaai.org).

†Avoid the medications suspected of triggering anaphylaxis and substitute a non–cross-reacting medication, preferably from a different therapeutic class. If this is not possible, desensitization should be performed (eg, for β-lactam antibiotics, NSAIDs, and chemotherapy drugs).

‡Avoid relevant cotriggers, such as food, medication, cold air, or cold water.

remain desensitized even if the food is not eaten on a regular basis.[112,134,135]

Future directions in specific immunotherapy to food and other allergens that trigger anaphylaxis might include allergen administration through the sublingual route, "engineered" recombinant protein allergens, a mixture of major recombinant allergens, CpG-oligonucleotide–conjugated allergens, peptides or polymers of major allergens, and other novel approaches.[112]

Immunomodulatory approaches that are not specific for a particular food allergen are also being studied. Food Allergy Herbal Formula-2, a well-characterized mixture of Chinese herbs that prevents food-induced anaphylaxis and leads to long-lasting immunologic tolerance in a murine model, has now entered clinical trials.[142] Subcutaneous injections of anti-IgE antibody potentially provide an increased margin of protection against food and other allergen triggers of anaphylaxis for many, although not all, patients at risk (Table IX).[143]

Medication- or biological agent–triggered anaphylaxis. For anaphylaxis triggered by a medication or a biological agent, avoidance is critically important. An alternative non–cross-reacting agent, preferably from a different therapeutic class but sometimes from the same class, can often be substituted effectively and safely.[34] Where this is not possible, desensitization with the offending agent is indicated.[34,144] Standardized 12-step desensitization protocols in which antigens are introduced in an incremental manner over several hours have been published for some agents, such as β-lactam antibiotics or other antibiotics, aspirin or other NSAIDs, insulin, and chemotherapeutic agents, including taxanes and platins, as well as mAbs.[144] Once achieved, desensitization is maintained through regular administration of the medication. Immunologic tolerance does not occur, and if the medication is discontinued, symptoms can recur when it is restarted.[144] Desensitization should be conducted in an appropriately equipped health care facility staffed by health care professionals who are trained and experienced in using desensitization protocols and in the recognition and treatment of breakthrough symptoms, including those of anaphylaxis.[34,144] The cellular and molecular mechanisms underlying temporary desensitization without immunologic tolerance are not yet fully understood.[144]

In patients with a history of vaccine- or vaccine component–triggered anaphylaxis who have negative skin tests to the vaccine and its components, it is highly unlikely that IgE antibody is present. The vaccine can therefore be administered in the usual manner; however, it is prudent to observe such patients for 1 hour afterward instead of the customary 30 minutes. In patients with a positive history and positive skin tests, a suitable alternative vaccine is sometimes available; for example, egg-free seasonal influenza vaccine and egg-free pandemic A/H1N1 vaccine grown in mammalian cell culture systems are now available in some countries. If a suitable alternative vaccine is not available, the culprit vaccine should be administered in an appropriately equipped and staffed health care facility by using a graded-dose protocol (Table IX).[48]

Stinging insect–triggered anaphylaxis. For anaphylaxis triggered by stinging insects, avoidance of exposure involves several approaches. Yellow jacket, hornet, or wasp nests or fire ant mounds in the vicinity of the patient's home should be professionally exterminated. Awareness of high-risk outdoor work or leisure activities, such as gardening, camping, picnicking, or barbecuing,

is important. When outdoors, appropriate protective clothing, including shoes and socks, should be worn. Personal insect repellents, such as DEET, are not effective in preventing insect stings in contrast to their efficacy in preventing insect bites.[54]

In most patients with Hymenoptera venom–triggered anaphylaxis, a 3- to 5-year course of subcutaneous injections of the relevant standardized insect venom or venoms significantly reduces the risk of anaphylaxis from a subsequent sting and provides long-lasting protection.[52-54,124] This potentially curative treatment is underused.[53] In children a 98% protection rate can be achieved, and the effect lasts for decades after venom injections are discontinued.[52,145] Use of purified extracts potentially reduces large local reactions during venom immunotherapy.[146] Venom immunotherapy can be safely administered to all those at risk, including high-risk patients with mastocytosis or clonal mast cell disorders, although a slow rate of dose escalation is often necessary in such patients.[147,148] Anti-IgE antibody is reported to be useful in controlling reactions to venom immunotherapy in patients with mastocytosis.[149] For prevention of anaphylaxis from fire ant stings[54,55] or from insect bites,[54,57] subcutaneous injections of the relevant whole-body extracts are used.

In adults venom immunotherapy significantly reduces sting-induced cutaneous systemic reactions and is therefore indicated for patients with sting-induced generalized urticaria and no other systemic symptoms.[52,124] It also reduces large local reactions to stings and might be considered for at-risk patients who cannot totally avoid insect exposure, such as beekeepers, and/or those who experience frequent or severe large local reactions.[150] In children, venom immunotherapy is not indicated either for sting-induced generalized urticaria without other systemic symptoms or for large local reactions (Table IX).[145]

Anaphylaxis induced by other triggers. Avoidance of the relevant specific confirmed trigger is the key to prevention of anaphylaxis recurrence, such as avoidance of natural rubber latex[58] or occupational allergens.[1,2,24,25,69] Desensitization provides short-term immunomodulation for patients at risk of anaphylaxis to seminal fluid.[59] In the future, regular subcutaneous injections of anti-IgE antibody might be indicated for patients with anaphylaxis triggered by various allergen triggers. For anaphylaxis induced by some nonimmune triggers, such as cold, heat, sunlight/UV radiation, or ethanol, avoidance of the trigger is the key to prevention of recurrences (Table IX).[25]

Exercise-triggered anaphylaxis. Strategies for prevention of exercise-induced anaphylaxis include strict avoidance of relevant cotriggers, such as food, medication, or ethanol ingestion and cold air or cold water exposure, and awareness of other potential concomitant risk factors, such as acute infection, emotional stress, menses (premenstrual and ovulatory phases), extremes of temperature and humidity, and high pollen counts. Additional precautions include never exercising alone, discontinuing exertion immediately when the first symptom of anaphylaxis is noted, always carrying 1 or more epinephrine autoinjectors, and carrying a cell (mobile) phone for calling 911/emergency medical services during activities such as long-distance running or cross-country skiing. Premedication and warm-up are not effective in preventing exercise-induced anaphylaxis (Table IX).[24,25,61]

Idiopathic anaphylaxis. Immunomodulation with pharmacologic agents is often recommended for patients with frequent episodes of idiopathic anaphylaxis, which is defined as more than 6 per year or more than 2 per 2 months. One example of a prophylaxis regimen involves 60 to 100 mg of prednisone each morning for 1 week, followed by 60 mg on alternate mornings for 3 weeks and then gradual tapering of the dose over 2 months, in addition to an H_1-antihistamine, such as 10 mg of cetirizine daily.[63] Anti-IgE antibody injections have been reported to be helpful in patients with idiopathic anaphylaxis and in anaphylaxis with no apparent trigger that occurs in patients with mastocytosis. (Table IX)[151,152]

Long-term risk reduction: Emergency preparedness for anaphylaxis recurrences in the community

Those at risk for anaphylaxis in the community and their caregivers should be prepared to recognize episodes that occur despite best efforts to avoid the relevant trigger and other preventive measures and to provide prompt life-saving first-aid treatment of such episodes.[2,24-26,34,52,54,69,93,153] Emergency preparedness involves carrying 1 or more epinephrine autoinjectors, having an anaphylaxis emergency action plan, and wearing appropriate medical identification.[1,2,24-26,54,69,153]

Epinephrine (adrenaline): the medication of choice. For treatment of an anaphylaxis recurrence in the community, injection of epinephrine is the first-aid medication of choice, as recommended in all anaphylaxis guidelines. The rationale for this is summarized in Table X.[24,154,156-162] Most guidelines recommend injecting epinephrine from an autoinjector intramuscularly in the midanterolateral aspect of the thigh. The first aid dose of epinephrine is 0.01 mg/kg of a 1 mg/mL (1:1,000) dilution to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child. This dose can be repeated every 5 to 15 minutes, as needed.[154,155,163-165] Patients should not suddenly sit or stand after receiving an epinephrine injection because this can lead to the empty inferior vena cava/empty ventricle syndrome and sudden death.[166]

In patients with anaphylaxis, epinephrine has potent life-saving α_1-adrenergic vasoconstrictor effects on the small arterioles and precapillary sphincters in most body organ systems.[156] It decreases mucosal edema, thereby preventing and relieving upper airway obstruction, and it also prevents and relieves hypotension and shock (Table X).[156-160] In addition, its β_1-adrenergic effects lead to increased force and rate of cardiac contractions, and its β_2 effects lead to increased bronchodilation and decreased release of mediators, such as histamine and tryptase, from mast cells and basophils.[156]

Prompt injection is important. In most countries the highest epinephrine dose currently available in an autoinjector is 0.3 mg. This dose is low compared with the initial adult dose of 1 mg epinephrine used in cardiopulmonary resuscitation and is unlikely to be effective if anaphylaxis has progressed to the point at which cardiopulmonary resuscitation is needed. Delayed injection of epinephrine is associated with fatal anaphylaxis[18-21] and also contributes to the increased likelihood of biphasic anaphylaxis, which is defined as symptom recurrence 1 to 72 hours (usually within 8 hours) after resolution of the initial symptoms despite no further exposure to the trigger.[167-169]

The best way of providing first-aid treatment with epinephrine (adrenaline) for anaphylaxis in the community is by using an autoinjector; however, currently available autoinjectors have a number of limitations. Only 2 fixed epinephrine doses, 0.15 mg and 0.3 mg, are available in autoinjector formulations in most countries (EpiPen, Dey, LP, Napa, Calif; Twinject, Shionogi & Co, Ltd, Osaka, Japan; Anapen, Lincoln Medical, Salisbury, Wiltshire, United Kingdom). The 0.15 mg dose is too high for

TABLE X. Epinephrine (adrenaline): Medication of first choice for anaphylaxis

Strength of recommendation	B-C
Pharmacologic effects when given by injection (oral administration is ineffective because of rapid metabolism in the GI tract)	At α_1-receptor
	↑ Vasoconstriction/↑ vascular resistance in most body organ systems
	↑ Blood pressure
	↓ Mucosal edema (larynx)
	At β_1-receptor
	↑ Heart rate
	↑ Cardiac contraction force
	At β_2-receptor
	↓ Mediator release
	↑ Bronchodilation
	↑ Vasodilation
Practical aspects	↓ Mucosal edema and relieves upper airway obstruction
	↓ Wheezing
	↓ Hives
	↑ Blood pressure and prevents and relieves hypotension and shock
Potential adverse effects (after usual dose of 0.01 mg/kg to a maximum of 0.5 mg [adults] IM)*	Anxiety, pallor, tremor, palpitations, dizziness, and headache; these symptoms indicate that an appropriate pharmacologic dose has been injected.
Potential adverse effects (after overdose, such as IV bolus dose, overly rapid IV infusion, or erroneous administration of a concentrated epinephrine solution 1:1,000 [1 mg/mL] by the IV route)†	Pulmonary edema, hypertension, angina, myocardial infarction, ventricular arrhythmias; note that the latter 3 adverse effects also potentially occur in untreated anaphylaxis when subclinical coronary artery disease is unmasked, because the heart itself is a potential target organ in anaphylaxis.‡
Comment: why the intramuscular route is preferred	Epinephrine has a vasodilator effect in skeletal muscle.‡
	Skeletal muscle is well vascularized.
	After intramuscular injection into the vastus lateralis, absorption is rapid, and epinephrine reaches the central circulation rapidly.
	Rapid absorption is critical in anaphylaxis in which the median time to respiratory or cardiac arrest is 15 minutes (venom) to 30 minutes (food).

Adapted from references 24 and 154-162.

GI, Gastrointestinal; *IM*, intramuscular; *IV*, intravenous.

*The epinephrine dose recommended for initial treatment of anaphylaxis is lower than the dose recommended for initial use in cardiopulmonary resuscitation and is unlikely to be effective after cardiac arrest has occurred. Ideally, epinephrine doses should be stated concentrations (ie, milligrams per milliliter) rather than as ratios; however, both methods are in common use.

†Intravenous infusion of epinephrine presents a high risk of harmful side effects. It should be given only by physicians who are trained and experienced in the dose titration of vasopressors (preferably by using an infusion pump) against continuous hemodynamic monitoring.

‡Epinephrine enhances blood flow in coronary arteries because of increased myocardial contractility and increased duration of diastole. This action and the vasodilator effect in skeletal muscle produced by endogenous epinephrine are well-recognized aspects of the fight-or-flight response.

infants and children weighing less than 15 kg. The 0.3 mg dose is too low for children weighing more than 30 kg and for teens and adults. In the United Kingdom a 0.5 mg epinephrine dose is available in the Anapen. Autoinjectors with 1.43 cm needles might not achieve intramuscular injection in some children and adults, as ascertained by using computed tomographic scans of the thigh to measure the distance from the skin to the surface of the vastus lateralis muscle.[170,171] The force of the injection likely also contributes to intramuscular deposition and rapid absorption of epinephrine.[172]

Health care professionals need to be trained to use epinephrine autoinjectors correctly and safely in order to train and coach those at risk for anaphylaxis and their caregivers in how to use them correctly and safely.[173] Unintentional injections from epinephrine autoinjectors into fingers, thumbs, and hands by patients self-injecting or by caregivers injecting children or others have been reported to poison control centers with increasing frequency in the past decade. These unintentional injections might not only result in injury but also in partial or complete loss of the epinephrine dose for the person having an anaphylactic episode, the so-called "lost dose hazard."[174,175] Epinephrine autoinjectors with improved design, including needle protection features, are being introduced.

Up to 20% of patients who receive an initial first-aid dose of epinephrine for treatment of anaphylaxis in the community are reported to require a second dose, either because of ongoing symptoms or because of biphasic anaphylaxis.[167-169,176-178] Most patients with anaphylaxis respond promptly to epinephrine injections; the potential reasons for apparent lack of response in a minority of patients are summarized in Table XI.[158,166,170,171,175,178-181]

Transient pharmacologic effects of epinephrine, such as pallor, tremor, anxiety, palpitations, headache, and dizziness, that occur within 5 to 10 minutes after injection are usually mild and confirm that a therapeutic epinephrine dose has been given. Serious adverse effects, such as pulmonary edema or hypertension, are usually attributable to epinephrine overdose. Although they can occur after administration by any route, they are most commonly reported after either an intravenous bolus dose, an overly rapid intravenous infusion, or an intravenous injection of a concentrated 1 mg/mL (1:1,000) epinephrine solution instead of the dilute 0.1 mg/mL (1:10,000) epinephrine solution appropriate for intravenous infusion.[24,154]

TABLE XI. Reasons for apparent lack of response to epinephrine

Physician-related factors
Error in diagnosis*
Empty ventricle syndrome†
Patient-related factors
Rapid anaphylaxis progression
Patient taking a medication that interferes with optimal epinephrine effect, such as an α-adrenergic blocker or β-adrenergic blocker
Epinephrine-related factors
Epinephrine autoinjector not available‡
Epinephrine autoinjector not prescribed by physician
Epinephrine autoinjector not affordable (prescription not picked up)
Injected too late
Dose too low on a milligram per kilogram basis
Dose too low because of injection of epinephrine that is past the expiry date§
Injected using incorrect technique, such as not enough force
Injection route not optimal‖
Injection site not optimal
Adverse reaction to sodium metabisulfite preservative in the epinephrine solution (rare)

Adapted from references 158, 166, 170, 171, 175, and 178-181.

*For example, if epinephrine is injected for a disease, such as nonallergic angioedema or food protein–induced enterocolitis, that would not be expected to respond well to it.

†Occurs when the epinephrine injected cannot circulate in the body because the patient is suddenly placed upright and the vena cava (and ventricle) empties.

‡In many countries life-saving epinephrine autoinjectors are not available for those at risk of anaphylaxis. Existing alternatives cannot be depended on to produce high tissue concentrations of epinephrine rapidly. These include having a patient or caregiver draw up epinephrine from an ampule, use of a syringe prefilled with epinephrine, or use of an epinephrine metered-dose inhaler.

§The maximum shelf-life of EpiPen and Twinject autoinjectors is 12 to 18 months. The maximum shelf life of AnaPen autoinjectors (available in the United Kingdom) is 18 to 24 months. The maximum shelf life of a syringe prefilled with epinephrine in a physician's office is 3 to 4 months. *In vitro* degradation (breakdown) products of epinephrine are ineffective in patients with anaphylaxis.

‖Epinephrine through other routes, such as subcutaneous injection or inhalation from a metered-dose inhaler or nebulizer and compressor is not recommended for the treatment of anaphylaxis because it is more difficult to achieve high plasma and tissue concentrations rapidly when these routes are used.

Traditionally, many physicians have been reluctant to inject epinephrine in middle-aged or older patients with anaphylaxis because of concerns regarding cardiac adverse effects. In fact, the heart is a potential target organ in anaphylaxis. In healthy people mast cells are present throughout the myocardium (between myocardial fibers, around blood vessels, and in the coronary artery intima).[72,97] In patients with coronary artery disease, the number and density of cardiac mast cells is increased because mast cells are also present in atherosclerotic plaques, where they contribute to atherogenesis.[97] Histamine, leukotrienes, platelet-activating factor, and other mediators released after mast cell stimulation potentially lead to coronary artery spasm.[97] Patients with anaphylaxis can present with acute coronary syndrome secondary to either vasospasm or acute plaque rupture and thrombus formation. In patients with coronary artery disease, the use of epinephrine requires caution; however, concerns about its potential adverse effects need to be weighed against the cardiac risks of untreated anaphylaxis and the knowledge that epinephrine injection usually enhances blood flow in the coronary arteries because its β_2-adrenergic action leads to increased myocardial contractility and increased duration of diastole compared with systole (Table X).[24,25,97,161,162]

Other medications. More than 40 H_1-antihistamines are available for use,[182] and many of these medications are recommended for use in anaphylaxis; in some anaphylaxis guidelines, dosage regimens are provided for up to 7 different H_1-antihistamines. H_1-antihistamines do not prevent or relieve upper or lower airway obstruction, hypotension or shock.[182,183] After oral administration, their onset of action ranges from 1 to 3 hours.[182] The rapid improvement in symptoms sometimes attributed to oral H_1-antihistamines likely reflects spontaneous resolution of the anaphylactic episode. First-generation, potentially sedating H_1-antihistamines, such as diphenhydramine, chlorpheniramine, and promethazine, have a poor benefit/risk ratio.[182,184] When self-administered in patients with anaphylaxis, these medications potentially impair self-recognition of symptoms. When given to a child, they potentially complicate interpretation of CNS symptoms and signs, such as drowsiness. An H_1-antihistamine might be useful as an adjunctive measure to relieve residual hives that have not disappeared after epinephrine injection (Table XII).[153,183]

β_2-Adrenergic agonists do not have a vasoconstrictor effect and do not decrease mucosal edema, prevent or relieve upper airway obstruction, hypotension or shock. They are potentially useful when administered by nebulization as an adjunctive measure to relieve residual bronchospasm that has not disappeared after epinephrine injection (Table XII).[154]

Glucocorticoids are traditionally given to prevent and relieve biphasic or protracted anaphylaxis (Table XII).[185]

Emergency preparedness in the community: Additional measures. Almost 40% of persons at risk of anaphylaxis in the community reportedly use a written anaphylaxis emergency action plan.[178] Most plans list common symptoms and signs of anaphylaxis and emphasize the importance of using the epinephrine autoinjector promptly and of calling 911 or emergency medical services promptly (download from www.aaaai.org).[69,186] Plans should be personalized for each at-risk patient by listing comorbidities and concurrent medications, describing the epinephrine autoinjector and dose prescribed for the patient, and providing appropriate contact telephone numbers, such as those of family members.[69,186] Plans need to be updated and discussed with the patient, and if relevant, his or her caregivers, on a regular basis. Formal evaluation of the clinical efficacy and cost-effectiveness of these plans is needed.[187]

TABLE XII. Adjunctive medications for the treatment of anaphylaxis

Medication (example)	H_1-antihistamines* (oral, such as cetirizine; IV, such as diphenhydramine)	H_2-antihistamines* (ranitidine)	β_2-Adrenergic agonists* (salbutamol [albuterol])	Glucocorticoids* (oral, such as prednisone; IV, such as methylprednisolone)
Strength of recommendation*	C	C	C	C
Pharmacologic effects	At H_1-receptor	At H_2-receptor ↓ Gastric acid secretion	At β_2-receptor	↓ Late-phase allergic response to allergen
	↓ Itch (skin, mucus membranes)	↓ Vascular permeability	↑ Bronchodilation	
	↓ Flush	↓ Hypotension		
	↓ Hives	↓ Flushing		
	↓ Sneezing	↓ Headache		
	↓ Rhinorrhea	↓ Tachycardia		
		↓ Chronotropic and inotropic activity		
		↓ Mucus production (airway)		
Practical aspects	↓ Itch and hives but not life-saving in anaphylaxis	Small additive effect (10% or so) when used in conjunction with an H_1-antihistamine for ↓ in vascular permeability, ↓ flushing, and ↓ hypotension	↓ Wheeze, cough, and shortness of breath but do not ↓ upper airway obstruction or relieve hypotension and are not life-saving in anaphylaxis	Effects take several hours; used to prevent biphasic or protracted anaphylaxis; however, there is no evidence from high-quality randomized controlled trials that this occurs.
Potential adverse effects (usual doses)	First-generation drugs cause sedation and impair cognitive function.	Ranitidine: unlikely cimetidine: potentially causes hypotension if infused rapidly	Tremor, tachycardia, dizziness, jitteriness	Unlikely to occur during a short 1- to 3-day course
Potential adverse effects (overdose)	Coma, respiratory depression	Unlikely	Headache, hypokalemia	Unlikely
Comment	Many different H_1-antihistamines and different dose regimens are listed as adjunctive medications in anaphylaxis guidelines.	Not mentioned in most anaphylaxis guidelines; an H_2-antihistamine should not be used alone in anaphylaxis; if used, it should be given with an H_1-antihistamine.	Deliver by nebulization and face mask.	Different glucocorticoids and different dose regimens are used; these medications are unlikely to play a role in the initial minutes to hours of an anaphylactic episode.

There are no randomized double-blind, placebo-controlled trials of any of these medications in the treatment of acute anaphylaxis episodes. The route of administration of H_1-antihistamines and glucocorticoids depends on the severity of the anaphylaxis episode. Adapted from reference 153.
*For use in anaphylaxis.

Those at risk for anaphylaxis in the community should wear medical identification jewelry that provides worldwide access to a patient registry service 24 hours a day, 365 days of the year, so that health care professionals treating them can obtain relevant information about their triggers, concomitant diseases, and concurrent medications if needed. An anaphylaxis wallet card listing relevant confirmed triggers, concomitant diseases, and concurrent medications is available at www.aaaai.org.[69,153]

An approach to anaphylaxis education for health care professionals, people at risk of anaphylaxis and their caregivers, and the general public is outlined in Table XIII.[69,153,188,189] The consistent message in anaphylaxis education should be that anaphylaxis is potentially a killer allergy, not a trivial lifestyle disease, and that prompt treatment is life-saving.[69,153]

Anaphylaxis education projects are now becoming a priority in some communities. The main goal of these efforts is to teach people to act promptly, recognize anaphylaxis, use an epinephrine autoinjector correctly and safely, call for help, transfer the patient to a health care facility, and also to recommend follow-up, preferably with an allergy/immunology specialist. Examples of specific education projects are those focusing on anaphylaxis after omalizumab injection in a physician's office,[190] and on follow-up of patients with anaphylaxis who are treated in the emergency department.[191] Many patients discharged from an emergency department after anaphylaxis treatment still do not receive a prescription for self-injectable epinephrine or a referral to a specialist physician.[192] Lack of access to epinephrine autoinjectors for children experiencing anaphylaxis in schools remains a concern.[188,189,193,194]

EMERGENCY MANAGEMENT OF ACUTE ANAPHYLAXIS IN A HEALTH CARE FACILITY

Emergency management of anaphylaxis in a health care facility is reviewed in depth elsewhere.[154,155,163,164] In any physician's

TABLE XIII. Anaphylaxis education

Health care professionals
Who: physicians, nurses, pharmacists, emergency medical technicians, and first responders
What: definition of anaphylaxis (new); shock not necessarily a criterion for diagnosis
Common triggers
Emergency preparedness
Recognition of evolving symptoms and signs; can be difficult in those unable to describe their symptoms, such as infants, or patients with dysphonia, dyspnea, or shock; severity varies among patients and in the same patient from one episode to another
Treatment: promptly and simultaneously inject epinephrine, activate 911 or emergency medical services,* and place patient on the back or in position of comfort with lower extremities elevated
When: at regular intervals
Key messages: Anaphylaxis can kill rapidly (within 15 minutes after an insect sting and within 30 minutes after ingestion of a food trigger). Inject first-aid dose of epinephrine promptly. Especially, do not hesitate if the patient has trouble breathing, throat tightness, or altered level of consciousness.
People at risk for anaphylaxis
Who: those who have experienced anaphylaxis previously and are at risk for recurrences and their families; for teens and young adults, their peers
What: triggers of anaphylaxis, prevention of episodes (trigger specific), emergency preparedness—recognize symptoms and signs, inject epinephrine; activate emergency medical services,* notify family
Hands-on epinephrine autoinjector training and coaching
When: teachable moments in the weeks or months after an anaphylactic episode and then at yearly intervals or more often
Key messages: Death from anaphylaxis can occur within minutes. Promptly inject epinephrine, activate emergency medical services* Place the patient on the back or in a position of comfort with lower extremities elevated.
General public
Who: educators, coaches, camp directors, child care providers, food industry workers, restaurant workers, and transportation workers
What: Anaphylaxis occurs in infants, children, teens, and adults who appear to be in excellent health until exposed to their trigger. Symptoms that mandate immediate treatment are sudden difficulty breathing, throat tightness, and altered level of consciousness.
When: at regular intervals, such as the start of academic year for educators; a highly publicized fatal episode of anaphylaxis increases public awareness.
Key messages: Anaphylaxis is a killer allergy. Promptly inject epinephrine, activate emergency medical services*. Place the patient on the back or in a position of comfort with lower extremities elevated.

Adapted from references 69, 153, 166, 188 and 189.
*Transport of the patient to an emergency department.

TABLE XIV. Reasons for lack of randomized controlled trials in patients with anaphylaxis

Anaphylactic episodes are unpredictable.
Anaphylaxis commonly occurs in community settings (eg, home, restaurant, and school).
Baseline measurements of vital signs and oxygenation are often not available.
Symptoms and signs vary from one person to another and from one episode to another, even in the same person, with regard to time of onset after exposure to trigger (minutes to hours), body organ systems involved, severity, and duration.
Symptoms sometimes resolve spontaneously because of endogenous production of epinephrine, endothelin I, and angiotensin II.
Randomized placebo-controlled trials would be unethical for epinephrine, although randomized placebo-controlled trials of H_1-antihistamines, H_2-antihistamines, and glucocorticoids might be conducted in the future.
Rarely, even with prompt and optimal treatment and monitoring, anaphylaxis can be fatal.

Adapted from reference 200.

office or clinic where allergen skin tests or allergen challenge/provocation tests are performed or allergen-specific immunotherapy, anti-IgE antibody injections or vaccine injections are given, it is important to develop and rehearse an anaphylaxis management plan, train the staff, and ensure availability of essential medications (within expiry date), as well as essential supplies and equipment.[195]

The basic principles of anaphylaxis management in a health care facility include rapid assessment of the patient's airway, breathing, circulation, and orientation/mentation; examination of the skin; and estimation of body weight/mass. Initial treatment involves discontinuing exposure to the trigger, if relevant (eg, discontinuing administration of an intravenous medication or biological agent), and then prompt and simultaneous intramuscular injection of epinephrine in a first-aid dose of 0.01 mg/kg to a maximum adult dose of 0.5 mg, calling for help (either a resuscitation team or 911/emergency medical services, whichever is appropriate), and placing the patient on the back or in a position of comfort with the lower extremities elevated.[154,155,166,195] Administration of supplemental oxygen by face mask at a rate of at least 6 to 8 L/min, airway management, and insertion of 1 or more large-bore (no. 14 or 16) needles or intravenous catheters for infusion of large volumes of fluid, such as 0.5 to 1 L of 0.9% (isotonic) saline in 5 to 10 minutes to an adult, should be performed if needed.[154,155,163,195] Most anaphylaxis guidelines recommend administration of an adjunctive medication such as an H_1-antihistamine, a nebulized β_2-adrenergic agonist, and a glucocorticoid[154,155,163-166] and some also recommend an H_2-antihistamine.[163]

It has also been suggested that epinephrine and other vasopressors should be administered intravenously only by physicians who are trained, experienced, and equipped to administer these potent medications effectively and safely; that is, to titrate the rate of infusion (preferably by using an infusion pump), according to

the patient's hemodynamic response assessed by means of continuous, noninvasive cardiac and blood pressure monitoring and pulse oximetry.[154,155] If it is used, intravenous epinephrine should only be given by slow infusion (not a bolus) of a dilute solution, 0.1 mg/mL (1:10,000) that is appropriate for intravenous use, and not the concentrated 1 mg/mL (1:1,000) dilution that is appropriate for intramuscular injection.[154] Physician confusion between dilute and concentrated epinephrine solutions potentially leads to dosing errors and fatality.[196] Existing studies do not permit a conclusion with regard to whether any one vasopressor is superior to another in preventing mortality in critically ill patients with shock.[197] Even in the hands of intensive care specialists, use of intravenous vasopressors might not improve outcomes and might increase fatality rates.[198,199]

FUTURE DIRECTIONS IN THE PHARMACOLOGIC MANAGEMENT OF ANAPHYLAXIS

Recommendations for the treatment of acute anaphylactic episodes are based on expert opinion rather than on randomized controlled trials in patients experiencing anaphylaxis at the time of the study. The reasons for lack of randomized controlled trials of pharmacologic interventions in anaphylaxis are summarized in Table XIV.[200]

It is important to note that the evidence base for epinephrine injection in the treatment of anaphylaxis is stronger than the evidence base supporting the use of H_1-antihistamines, H_2-antihistamines, or glucocorticoids in anaphylaxis.[160,165,183,185] Recommendations for prompt epinephrine injection are based on fatality studies, epidemiologic studies, observational studies, nonrandomized controlled studies in patients actually experiencing anaphylaxis, randomized controlled studies in patients not experiencing anaphylaxis at the time of the study, *in vitro* studies, and studies in animal models.[157-160,200]

The World Health Organization (www.who.int) and the World Allergy Organization,[159] as well as all anaphylaxis guidelines,[154,155,163-165] are in universal agreement that epinephrine injection is fundamentally important in anaphylaxis management. Placebo-controlled trials of epinephrine are therefore clearly unethical. Recommendations for the maximum initial dose of epinephrine or the route of injection differ among the guidelines, however, and in the future, it might be possible to conduct randomized trials comparing different first-aid epinephrine doses or different routes of injection.[200]

In contrast to the consensus about epinephrine, there is no consensus among published anaphylaxis guidelines with regard to the use of H_1-antihistamines, H_2-antihistamines, or glucocorticoids in the treatment of anaphylaxis. Many different H_1-antihistamines in a variety of dose regimens are recommended.[183] Several different glucocorticoids in a variety of dose regimens are recommended.[185] H_2-antihistamines are not mentioned in most guidelines.[165] In the future, it might therefore be possible to conduct randomized placebo-controlled trials of these medications in acute anaphylaxis episodes.[200]

If randomized controlled trials are conducted, in addition to the intervention being tested, it will be critically important to take rigorous appropriate precautions to ensure that all patients have prompt, optimal, standard-of-care treatment with epinephrine injections, are placed in the recumbent position or a position of comfort with lower extremities elevated; and have appropriate treatment with supplemental oxygen, airway management, and high-volume intravenous fluid resuscitation, as well as continuous noninvasive monitoring of heart rate, blood pressure, and oxygenation.[154,155,163,164,166,190,195]

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Primary immunodeficiencies

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In the last years, advances in molecular genetics and immunology have resulted in the identification of a growing number of genes causing primary immunodeficiencies (PIDs) in human subjects and a better understanding of the pathophysiology of these disorders. Characterization of the molecular mechanisms of PIDs has also facilitated the development of novel diagnostic assays based on analysis of the expression of the protein encoded by the PID-specific gene. Pilot newborn screening programs for the identification of infants with severe combined immunodeficiency have been initiated. Finally, significant advances have been made in the treatment of PIDs based on the use of subcutaneous immunoglobulins, hematopoietic cell transplantation from unrelated donors and cord blood, and gene therapy. In this review we will discuss the pathogenesis, diagnosis, and treatment of PIDs, with special attention to recent advances in the field. (J Allergy Clin Immunol 2010;125:S182-94.)

Key words: *Primary immunodeficiency, T-cell immunodeficiency, antibody deficiency, innate immunity defects, immunoglobulin replacement therapy, hematopoietic cell transplantation, gene therapy*

Primary immunodeficiencies (PIDs) comprise more than 130 different disorders that affect the development, function, or both of the immune system.[1] In most cases PIDs are monogenic disorders that follow a simple mendelian inheritance; however, some PIDs recognize a more complex polygenic origin. Disease penetrance and expression variability and interactions between genetic and environmental factors can also contribute to the phenotypic diversity of PIDs.

With the exception of IgA deficiency (IgAD), all other forms of PID are rare and have an overall prevalence of approximately 1:10,000 live births; however, a much higher rate is observed among populations with high consanguinity rates or among genetically isolated populations.

PIDs are classified according to the component of the immune system that is primarily involved.[1] Defects in adaptive immune responses include antibody deficiency syndromes and combined immunodeficiencies (CIDs). Defects of innate immunity comprise disorders of phagocytes, Toll-like receptor (TLR)–mediated signaling, and complement. All of these forms are characterized by increased susceptibility to recurrent infections, severe infections, or both, with distinctive susceptibility to various types of pathogens depending on the nature of the immune defect. In addition, some forms of PIDs present with immune dysregulation, and others (immunodeficiency syndromes) have a more complex phenotype in which immunodeficiency is only one of multiple components of the disease phenotype. For each of the various categories of PIDs, we will review cause and pathogenesis, clinical and laboratory features, prognosis, and treatment.

PATHOGENESIS AND CLINICAL FEATURES

CIDs

CIDs comprise a heterogeneous group of disorders with impaired development, function, or both of T lymphocytes associated with a defective antibody response.[2] The latter might result from intrinsic defects in B lymphocytes or might reflect inadequate T_H cell activity. In the most severe forms of CID (also known as severe combined immunodeficiency [SCID]), there is a virtual lack of functional peripheral T cells, whereas residual number, function, or both of T lymphocytes are present in other forms of CID.[2] Patients with SCID present early in life with infections of bacterial, viral, or fungal origin (Table I). Pneumonia caused by *Pneumocystis jiroveci* is common; however, interstitial lung disease might also be due to cytomegalovirus (CMV), adenovirus, respiratory syncytial virus, or parainfluenza virus type 3. Many infants with SCID have chronic diarrhea, leading to failure to thrive. Skin rash might reflect graft-versus-host disease caused by maternal T-cell engraftment in infants with SCID[3] or tissue damage caused by infiltration by activated autologous T lymphocytes, as typically seen in Omenn syndrome. In addition, some forms of SCID are associated with distinctive features in other systems.

SCID defects are classified according to the immunologic phenotype and are categorized into (1) SCID with absence of T lymphocytes but presence of B lymphocytes (T^-B^+ SCID) or (2) SCID with absence of both T and B lymphocytes (T^-B^- SCID). Both main groups of SCID include forms with or without natural killer (NK) lymphocytes. Regardless of the immunologic phenotype (T^-B^- or T^-B^+), patients with SCID present with similar clinical features, including early-onset severe respiratory tract infections, chronic diarrhea, and failure to thrive. SCIDs have a prevalence of approximately 1:50,000 live births and are more common in male subjects, reflecting the overrepresentation of X-linked SCID (SCIDX1), the most common form of SCID in human subjects.

The pathogenesis of SCID reflects distinct mechanisms that affect various steps in T-cell development (Fig 1).[2] Impaired survival of lymphocyte precursors is observed in reticular dysgenesis (RD) and in adenosine deaminase (ADA) deficiency. Both forms are inherited as autosomal recessive traits and are characterized by extreme lymphopenia. In addition, patients with RD also have severe neutropenia and sensorineural deafness. RD is a very rare form of SCID and is caused by mutations of the adenylate kinase 2 gene *(AK2)*.[4,5] This mitochondrial enzyme regulates levels of adenosine diphosphate. Adenylate kinase 2 deficiency

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Abbreviations used

AD: Autosomal dominant
ADA: Adenosine deaminase
AID: Activation-induced cytidine deaminase
AIRE: Autoimmune regulator
ALPS: Autoimmune lymphoproliferative syndrome
ANC: Absolute neutrophil count
AR: Autosomal recessive
AT: Ataxia-telangiectasia
BCR: B-cell receptor
BTK: Bruton tyrosine kinase
CD40L: CD40 ligand
CGD: Chronic granulomatous disease
CHS: Chediak-Higashi syndrome
CID: Combined immunodeficiency
CMV: Cytomegalovirus
CSR: Class-switch recombination
CVID: Common variable immunodeficiency
DC: Dendritic cell
DGS: DiGeorge syndrome
DHR-123: Dihydrorhodamine-123
DP: Double-positive
FOXP3: Forkhead box protein 3
HCT: Hematopoietic cell transplantation
HIES: Hyper-IgE syndrome
HLH: Hemophagocytic lymphohistiocytosis
ICOS: Inducible T-cell costimulator
IgAD: IgA deficiency
IPEX: Immune dysregulation–polyendocrinopathy–enteropathy–X-linked
IRAK: IL-1 receptor–associated kinase
IVIG: Intravenous immunoglobulin
JAK: Janus kinase
LAD: Leukocyte adhesion deficiency
MBL: Mannose-binding lectin
MMR: Mismatch repair
MSMD: Mendelian susceptibility to mycobacterial disease
NADPH: Reduced nicotinamide adenine dinucleotide phosphate
NHEJ: Nonhomologous end-joining
NK: Natural killer
PID: Primary immunodeficiency
RAG: Recombinase-activating gene
RD: Reticular dysgenesis
SBDS: Schwachman-Bodian-Diamond syndrome
SCID: Severe combined immunodeficiency
SCIDX1: X-linked severe combined immunodeficiency
SCIG: Subcutaneous immunoglobulin
SCN: Severe congenital neutropenia
SHM: Somatic hypermutation
STAT: Signal transducer and activator of transcription
TACI: Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TAP: Transporter of antigenic peptide
TCR: T-cell receptor
THI: Transient hypogammaglobulinemia of infancy
TLR: Toll-like receptor
TREC: T-cell receptor excision circle
Treg: Regulatory T
UNG: Uracil N-glycosidase
WAS: Wiskott-Aldrich syndrome
WASP: Wiskott-Aldrich syndrome protein
XLA: X-linked agammaglobulinemia

results in increased apoptosis of myeloid and lymphoid precursors. ADA is an enzyme of the purine salvage pathway that mediates conversion of adenosine (and deoxyadenosine) to inosine (and deoxyinosine). In the absence of ADA, high intracellular levels of toxic phosphorylated metabolites of adenosine and deoxyadenosine cause apoptosis of lymphoid precursors in the bone marrow and thymus.[6,7] ADA deficiency accounts for 10% to 15% of all forms of SCID. Clinical manifestations of ADA deficiency extend beyond the immune system (deafness, behavioral problems, costochondral abnormalities, and liver toxicity), reflecting the fact that ADA is a housekeeping enzyme. Purine nucleoside phosphorylase is another enzyme of the purine salvage pathway. Purine nucleoside phosphorylase deficiency is rare (1% to 2% of all forms of SCID). In this disease immunologic abnormalities become progressively manifest within a few years after birth and are more pronounced in T than in B lymphocytes.[6] Progressive neurological deterioration and autoimmune hemolytic anemia are typically observed.

Defects of cytokine-mediated signaling are responsible for the majority of SCID in human subjects. SCIDX1 accounts for 40% of all cases of SCID and is caused by mutations of the IL-2 receptor γ gene *(IL2RG)*, which encodes for the common γ chain (γc) shared by cytokine receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. In particular, IL-7 mediates expansion of early thymocyte progenitors, whereas IL-15 plays a role in NK cell development.[8] Accordingly, patients with SCIDX1 lack both T and NK cells, whereas they have a normal number of circulating B lymphocytes.[9] The γc is physically and functionally coupled to the intracellular tyrosine kinase Janus kinase (JAK) 3, which delivers γc-mediated intracellular signaling. Hence defects of JAK3 result in an autosomal recessive form of SCID with an immunologic phenotype undistinguishable from that of SCIDX1.[10] Mutations of the *IL7R* gene (encoding for the α chain of the IL-7 receptor) abrogate T-lymphocyte development but leave B-cell and NK cell development intact.[11]

Expression of the pre–T-cell receptor (TCR) is a critical landmark during thymocyte development. Similar molecular mechanisms govern expression of the pre-TCR and of the pre–B-cell receptor (BCR) in developing T and B lymphocytes, respectively.[12] In particular, recombinase-activating gene 1 (RAG1) and RAG2 proteins mediate DNA cleavage at the TCR and immunoglobulin heavy and light chain loci, thus initiating V(D)J recombination. Several DNA repair proteins complete this process, allowing assembly of variable (V), diversity (D), and joining (J) elements. Defects of pre-TCR and pre–BCR expression account for a significant fraction of autosomal recessive T^-B^- SCID in human subjects and might reflect mutations in the *RAG1* and *RAG2* genes (which account for 4% to 20% of all cases of SCID) or in genes that encode proteins involved in nonhomologous end-joining (NHEJ) and DNA repair, in particular Artemis, DNA protein-kinase catalytic subunit, Cernunnos/XLF, and DNA ligase IV.[2,12-15] In all of these diseases, development of NK cells proceeds normally, so that NK lymphocytes represent almost all of the circulating lymphocytes, but generation of T and B lymphocytes is severely compromised. However, a leaky phenotype, with residual development of T and B lymphocytes, is typically seen in patients with Cernunnos/XLF deficiency.[16] Genetic defects that affect the NHEJ pathway are characterized also by increased cellular radiosensitivity with extraimmune manifestations (microcephaly, facial dysmorphisms, and defective tooth development).[17]

TABLE I. Type of infections associated with major categories of PIDs

Organism	Antibody deficiencies	CIDs	Phagocytic defects	Complement deficiencies
Viruses	Enteroviruses	All, especially: CMV, respiratory syncytial virus, EBV, parainfluenza type 3	No	No
Bacteria	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Neisseria meningitidis, Mycoplasma pneumoniae*	As for antibody deficiencies, also: *Salmonella typhi*, *Listeria monocytogenes*, enteric flora	*S aureus, P aeruginosa, Nocardia asteroides, S typhi*	As for antibody deficiencies: especially *N meningitidis* in deficiency of late components
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous, including BCG	No
Fungi	No	*Candida* species, *Aspergillus* species, *Cryptococcus neoformans, Histoplasmosis capsulatum*	*Candida* species, *Aspergillus* species	No
Protozoa	*Giardia lamblia*	*Pneumocystis jiroveci, Toxoplasma gondii, Cryptosporidium parvum*	No	No

Mutations of the CD3δ, CD3ϵ, and CD3ζ components of the CD3 complex affect signaling through the pre-TCR and hence cause SCID.[18] Few cases of mutations of the tyrosine phosphatase CD45, which mediates signaling in both T and B lymphocytes, have been also reported.[19,20]

Defects in T-cell development that occur beyond the $CD4^+CD8^+$ double-positive cell stage result in CID with residual numbers of T lymphocytes. Mutations of the ζ chain–associated protein of 70 kDa (ZAP-70) tyrosine kinase in human subjects compromise positive selection of $CD8^+$ thymocytes, thus causing severe deficiency of circulating $CD8^+$ T lymphocytes. $CD4^+$ T cells are generated and exported to the periphery; however, their proliferative response to stimulation through the TCR is drastically impaired.[21]

Positive selection of $CD8^+$ thymocytes is dependent on low-affinity recognition of self-peptides in the context of class I MHC molecules. The transporters of antigenic peptides 1 and 2 (TAP1/2) and tapasin shuttle newly synthesized peptides across the endoplasmic reticulum, where they are loaded onto HLA class I molecules and are then directed to the cell membrane. Mutations in the *TAP1*, *TAP2*, or tapasin genes cause selective $CD8^+$ cell deficiency.[22] However, this defect is rarely severe, reflecting residual MHC class I expression. The clinical phenotype of MHC class I deficiency is often marked by midline granulomatous lesions and vasculitis.

Defective expression of MHC class II molecules impairs positive selection of $CD4^+$ lymphocytes. This disease can be caused by mutations in 4 genes that encode for transcriptional activators of MHC class II genes. The disease is more common in certain geographic regions (North Africa). It is characterized by $CD4^+$ cell lymphopenia and has a progressive and severe clinical course.[23]

Recently, novel genetic defects have been identified in patients with other rare forms of CID. Calcium flux is essential to mediate the response of various cell types, including mature lymphocytes, to activatory stimuli. Genetic defects of *STIM1* (a sensor of calcium release from the endoplasmic reticulum) and *ORAI1* (a component of the calcium-release activated channels) cause inability of T lymphocytes to respond to TCR-mediated activation.[24,25] Muscular cells are also affected, causing myopathy.

The signal transducer and activator of transcription (STAT) 5b is a transcription factor that is activated in response to IL-2 and other cytokines and growth factors, including growth hormone. Mutations of *STAT5B* result in a rare form of immunodeficiency with short stature. Because IL-2 plays a critical role in immune homeostasis, STAT5b deficiency is often associated with autoimmune manifestations.[26]

Hypomorphic mutations in genes that are typically associated with SCID can allow residual T-cell development. In these cases impaired cross-talk between thymocytes and thymic epithelial cells might compromise mechanisms of central tolerance, with failure to delete autoreactive T cells and impaired generation of regulatory T (Treg) cells.[27,28] Accordingly, autoimmune or dysreactive manifestations are common, with infiltration of target tissues by activated and oligoclonal T lymphocytes. Omenn syndrome, which is caused by mutations in *RAG1/2* or other genes, is the prototype of these conditions and is characterized by erythroderma, lymphadenopathy, and inflammatory gut disease. Hypomorphic *RAG* mutations have been also associated with a novel phenotype characterized by granuloma formation, EBV-related lymphoma, and survival into late childhood.[29]

Idiopathic CD4 lymphopenia is defined based on a persistently low $CD4^+$ T-cell count ($<0.3\times10^9$/L in adults and $<1.0\times10^9$/L in childhood). It is a diagnosis of exclusion: infections sustained by HIV or other T-cell lymphotropic viruses, immunosuppressive treatment, or underlying autoimmune disease must be ruled out. Most patients with idiopathic CD4 lymphopenia are adults. Clinical features include opportunistic (caused by *P jiroveci*, *Cryptococcus neoformans*, *Candida* species, and mycobacteria) and viral infections.[30] Naive $CD4^+$ T cells are affected more than memory $CD4^+$ lymphocytes. Some degree of hypogammaglobulinemia is common.

CD40 ligand (CD40L) deficiency is inherited as an X-linked trait. CD40L is predominantly expressed by activated $CD4^+$

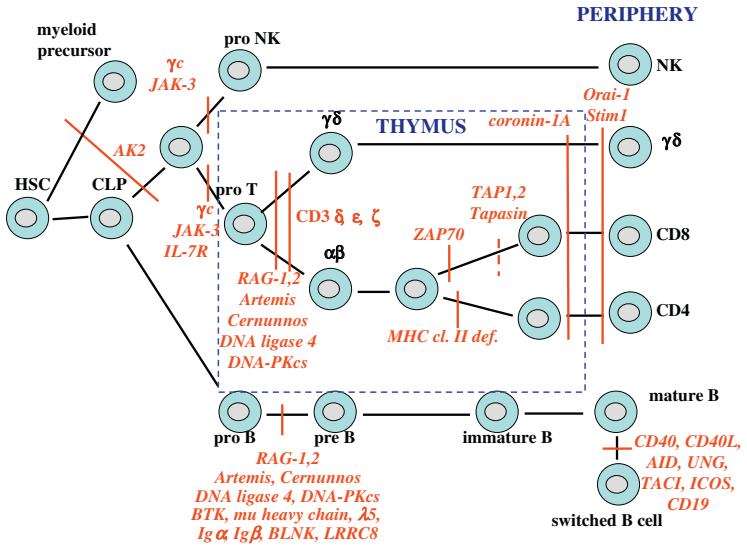

FIG 1. Blocks in T-and B-cell development associated with PIDs.

T lymphocytes and interacts with CD40, which is expressed by B lymphocytes, monocytes, dendritic cells (DCs), and other cell types. CD40L-CD40 interaction is a key signal in driving B-cell activation and, combined with interleukin-mediated signaling, promotes class-switch recombination (CSR). Accordingly, male subjects with CD40L deficiency have a severe defect of all immunoglobulin isotypes other than IgM. In addition, CD40L-CD40 interaction also promotes DC maturation and IL-12 secretion, favoring T-cell priming and production of IFN-γ, a key molecule in the defense against intracellular pathogens. Therefore patients with CD40L deficiency are also prone to opportunistic infections (*P jiroveci* and *Cryptosporidium parvum*), making CD40L deficiency a form of CID.[31] Neutropenia, which is usually associated with a block at the promyelocyte-myelocyte stage of differentiation in the bone marrow, is found in 65% of the patients with CD40L deficiency. A similar phenotype has been reported in patients with CD40 deficiency, a rare PID with autosomal recessive inheritance.[32]

T-cell immunodeficiencies caused by thymic defects

DiGeorge syndrome (DGS) is a developmental defect of the third and fourth pharyngeal pouches and arches, resulting in impaired development of the thymus and parathyroid glands, conotruncal heart abnormalities, facial dysmorphisms, feeding difficulties, and increased frequency of psychiatric disorders in childhood and adulthood.[33] In different series hemizygous deletion of chromosome 22q11 has been observed in 35% to 90% of patients; a minority of patients show deletion of 10p13-14. In most cases (referred to as "partial DGS"), there is mild-to-moderate T-cell deficiency, reflecting residual thymic development. Complete DGS with athymia is rare (1% of all cases) and presents with SCID-like features. Atypical complete DGS includes presentation with development of oligoclonal T cells that undergo extensive *in vivo* activation and infiltrate target organs, mimicking that observed in Omenn syndrome.

Forkhead box N1 (FOXN1) is a transcription factor required for thymic epithelial cells development. Autosomal recessive *FOXN1* deficiency has been reported in a few patients and is characterized by SCID associated with alopecia and nail dystrophy.[34]

Impaired egress of mature thymocytes has been reported in a single patient with mutations in coronin-1A, a regulator of actin cytoskeleton.[35]

Finally, Good syndrome is characterized by the association of hypogammaglobulinemia with thymoma. Opportunistic infections (candidiasis, CMV, and recurrent herpes simplex virus infections) and autoimmune cytopenia (especially red cell aplasia, neutropenia, or both) are common.[36]

Antibody deficiencies

Defective antibody production causes increased susceptibility, mostly to bacterial infections (Table I) that typically involve the upper and lower respiratory tract (otitis, sinusitis, and pneumonia) but might also cause abscesses in the skin or other organs, meningitis, urinary tract infections, and arthritis. Recurrent viral infections are also common. Intestinal *Giardia* species infection can cause protracted diarrhea. Antibody deficiencies might depend on a variety of defects that interfere with B-cell development, maturation, and/or function (Fig 1).[31]

Signaling through the pre-BCR is an essential step in B-cell development. The pre-BCR is composed of immunoglobulin heavy μ chains, surrogate light chains (V-preB and λ5), and the signal-transducing subunits Igα (CD79a) and Igβ (CD79b). This complex recruits a number of intracytoplasmic proteins, among which are the adaptor molecule B cell linker protein (BLNK) and Bruton tyrosine kinase (BTK). Defects in BTK account for X-linked agammaglobulinemia (XLA), the most common form (85%) of early-onset agammaglobulinemia in human subjects. Mutations in the immunoglobulin heavy μ chain gene *(IGHM)* are the second most common cause (5%), whereas only a few patients have been identified with defects in λ5, Igα, Igβ, and BLNK.[31,37] In all of these cases, there is a block at the pro-B to pre-B stage of differentiation in the bone marrow, resulting in virtual absence (<1%) of circulating B lymphocytes. However, the defect is often incomplete in patients with XLA, and few B cells might be identified in peripheral blood. A chromosomal translocation involving the leucine-rich repeat-containing protein 8 gene *(LRRC8)* has been reported in 1 patient in whom congenital agammaglobulinemia with developmental arrest at the pro–B-cell

stage was associated with facial dysmorphisms.[38] In addition to bacterial infections, patients with agammaglobulinemia are uniquely susceptible to enteroviral infections (which might cause meningoencephalitis or severe dermatomyositis) and mycoplasma (arthritis). Fortunately, both these complications are rare in patients treated appropriately with replacement immunoglobulins.

Maturation of the antibody response is marked by 2 key processes: CSR and somatic hypermutation (SHM).[39] During CSR, the μ chain is replaced by other immunoglobulin heavy chains, resulting in the production of IgG, IgA, and IgE, which have distinct physicochemical and biologic properties. SHM is the process by which point mutations are introduced in the variable region of the immunoglobulin genes, leading to increased binding affinity for antigen (affinity maturation). Although CSR and SHM are independent and distinct processes, they both occur in the germinal centers and are triggered by similar signals, such as CD40L-CD40 interaction and TLR-mediated signaling. CSR involves active transcription through the heavy chain constant-regions loci, with formation of DNA/RNA hybrids that leave one strand of DNA accessible to changes and cleavage. Induction of CSR promotes transcription of the activation-induced cytidine deaminase gene *(AICDA)*, which encodes a DNA-editing enzyme (also known as activation-induced cytidine deaminase [AID]) that replaces deoxycytidine residues with deoxyuracil. The resulting mismatch in the DNA is recognized by the enzyme uracil N-glycosylase (UNG), which removes the deoxyuracil residues, leaving abasic sites that are resolved by means of DNA repair mechanisms. Similar events occur during SHM; however, the mechanisms of DNA repair between these processes are distinct.[39] In particular, DNA repair during CSR involves proteins of the NHEJ pathway, as well as the Ataxia-Telangiectasia Mutated (ATM), Meiotic Recombination 11 (MRE11) and Nijmegen Breakage Syndrome 1 (NBS1) proteins. Furthermore, the DNA mismatch repair (MMR) system also participates in CSR. In contrast, SHM involves error-prone DNA polymerases and the MMR pathway. Mutations in the *AICDA* and *UNG* genes account for B-cell intrinsic defects of CSR, resulting in absent or very low levels of serum IgG, IgA, and IgE, whereas IgM levels are often increased (thus resulting in a hyper-IgM phenotype).[39] The vast majority of AID and all of the few cases of UNG deficiency reported thus far are inherited as autosomal recessive traits; however, few cases of mutations in the C-terminal region of AID have autosomal dominant inheritance.[31,39] SHM is differently affected by AID versus UNG deficiency; in particular, SHM is abolished in the former (with the exception of mutations that affect the C-terminus of the AID molecule), whereas it is preserved but biased (with lack of mutations at A:T residues) in UNG deficiency.[39]Impaired CSR with reduced levels of IgG, IgA, and IgE is also observed in patients with ataxia-telangiectasia (caused by mutations of the *ATM* gene), ataxia-telangiectasia–like syndrome (*MRE11* mutations), Nijmegen breakage syndrome (*NBS1* mutation), and ligase IV syndrome in keeping with the role that these proteins play in CSR.[39,40] Also, mutations of Post-Meiotic Segregation increased *2 (PMS2)*, which is involved in MMR, cause impaired CSR, which is associated with high susceptibility to malignancies and café au lait spots.[41] In spite of these advances, a significant proportion (about 15%) of CSR defects currently grouped under the definition of hyper-IgM syndrome remain genetically undefined.[39]

Common variable immunodeficiency disorders (CVIDs) are the most common form of clinically significant PIDs and present mainly in adults, although they can also be observed in children. CVIDs are defined by reduced levels of 1 or more isotypes and impaired antibody production in response to immunization antigens or natural infections.[42] CVIDs are a diagnosis of exclusion of all known causes of poor antibody production or low serum immunoglobulin levels. In addition to recurrent infections of the respiratory tract (sinusitis, otitis, bronchitis, and pneumonia) caused by common bacteria (eg, nontypeable *Haemophilus influenzae* and *Streptococcus pneumoniae*), some patients with a CVID are highly prone to autoimmmune manifestations (cytopenias and inflammatory bowel disease), granulomatous lesions, lymphoid hyperplasia, and tumors (especially lymphomas).[42-44] There is now clear evidence that CVIDs include a group of clinically and genetically heterogeneous conditions. CVIDs are mostly sporadic; however, autosomal dominant and autosomal recessive forms are also possible. Although most patients with a CVID have a normal number of B lymphocytes, some (12%) will turn out to have differentiation defects. Among those who do have B cells, some have reduced switched memory ($CD27^+IgD^-$) B lymphocytes and a low rate of SHM[45]; this might turn out to be due to a T- or B-cell failure. Most cases of CVIDs remain genetically undefined and might well turn out to be polygenic. Several studies of familial cases of CVIDs have shown association with the MHC region; however, the underlying gene defect has not been clearly identified. Mutations of the *T*umor *N*ecrosis *F*actor *R*eceptor *S*oluble *F*actor *13B (TNFRSF13B)* gene, which encodes the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), a member of the TNF receptor family, have been identified in 15% of the patients, most often in heterozygosity,[31,42,46] and have been found to be present in the general population as well. TACI is expressed by B lymphocytes and interacts with 2 ligands: the B-cell activating factor (BAFF) and a proliferation–inducing ligand (APRIL). In particular, APRIL/TACI interaction promotes B-cell activation and CSR. Disruption of the *tnfrsf13b* gene in mice leads to lymphoid proliferation, and lymphoid hyperplasia and granulomatous lesions are often seen in patients with a CVID. Nine patients have been identified with mutations in the inducible T-cell costimulator gene *(ICOS)*.[47] ICOS is expressed by activated T cells and interacts with ICOS ligand expressed by B lymphocytes. This interaction promotes B-cell activation and antibody production. Finally, a few cases of CVIDs are due to mutations of the *CD19* gene.[48] The CD19 protein forms a complex with CD21, CD81, and CD225 and decreases the threshold of BCR-mediated activation. CD19 deficiency does not affect B-cell development, as shown by a normal number of circulating $CD20^+$ lymphocytes in CD19-deficient patients.

IgAD is the most common PID, with approximately 1:700 affected individuals worldwide. Both partial and complete forms of IgAD are known. The pathophysiology of IgAD remains poorly understood, although association with MHC alleles and higher frequency within families with a CVID have been reported. Approximately two thirds of adults with IgAD are asymptomatic, but the remaining might experience recurrent infections, autoimmunity, or allergy.[49] Adult patients with IgAD and a history of infections often have associated defects of IgG subclasses, especially IgG2. However, children are more likely to have delayed maturation of immunoglobulin synthesis and will not progress to significant immunodeficiency. IgG subclass

deficiency might also occur without abnormalities in other isotypes. The pathophysiology of IgG subclass deficiency remains unknown in most cases; interstitial deletions on both alleles of the immunoglobulin heavy chain constant region have been reported in a minority of patients, most of whom have been infection free.

Specific antibody deficiency is characterized by impaired antibody production (especially to carbohydrate antigens) without abnormalities in total immunoglobulin levels or in B-cell numbers. The pathophysiology of this disorder, which is associated with recurrent upper and lower respiratory tract infections,[50] remains unclear.

Patients with transient hypogammaglobulinemia of infancy (THI) have low immunoglobulin levels that spontaneously return to normal, usually within 2 years of age, although this is very variable.[51,52] Although many subjects with THI remain asymptomatic, this condition is associated with a higher rate of recurrent infections, especially upper respiratory tract infections of viral origin. The pathophysiology of THI is unknown. In a prospective study of infants who presented with hypogammaglobulinemia, a low number of memory B cells and inability to produce IgG *in vitro* were associated with persistence of hypogammaglobulinemia and increased risk of infection beyond 2 years of age.[51]

Immunodeficiency with immune dysregulation

Some forms of immunodeficiency are characterized by significant autoimmune manifestations, reflecting disturbance in immune homeostasis.[53,54] Central immune tolerance is achieved through deletion of autoreactive T-cell clones in the thymus. The autoimmune regulator (AIRE) protein is a transcription factor expressed by mature medullary thymic epithelial cells. AIRE drives expression of tissue-restricted antigens that are presented by medullary thymic epithelial cells and thymic DCs to nascent T lymphocytes, thereby permitting deletion of T-cell clones that recognize self-antigens with high affinity. Mutations of the *AIRE* gene disrupt this protein, causing autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome.[55] Hypoparathyroidism and adrenal insufficiency are prominent autoimmune manifestations of this autosomal recessive disorder. Treg cells mediate suppression of immune responses to self-antigens in the periphery. Generation of Treg cells in the thymus is controlled by the transcription factor forkhead box protein 3 (FOXP3). Mutations of the *FOXP3* gene cause immune dysregulation–polyendocrinopathy–enteropathy–X-linked (IPEX) syndrome, with severe and early-onset autoimmune enteropathy, insulin-dependent diabetes, and eczema.[56] In typical cases the disease evolves rapidly, unless treated with hematopoietic cell transplantation (HCT). IL-2 plays an important role in immune homeostasis and upregulates expression of FOXP3 by $CD4^{+}CD25^{hi}$ Treg cells. Mutations of the *IL2RA* gene, which encodes for the α chain of the IL-2 receptor, cause immunodeficiency with IPEX-like features.[57] Peripheral immune homeostasis is also based on apoptosis of autoreactive lymphocytes in the periphery. Interaction between Fas ligand, expressed by activated lymphocytes and Fas (CD95) triggers intracellular signaling pathways that ultimately result in activation of caspases and cell death. Mutations of Fas are the predominant cause of autoimmune lymphoproliferative syndrome (ALPS), with lymphadenopathy, hepatosplenomegaly, and autoimmune cytopenia.[58] There is an increased risk of malignancies (especially B-cell lymphomas), which occur in 10% of the patients with Fas mutations.[59] ALPS is most often inherited as an autosomal dominant trait and is caused by dominant-negative mutations that interfere with the signal-transducing activity of Fas trimeric complexes. Somatic mutations of the Fas gene have been reported in a few cases. A rare variant of Fas is caused by Fas ligand mutations. In a few patients, mutations of caspase-8 and caspase-10 have been identified also.[60,61] IL-2 starvation induces apoptosis through a mechanism that depends on the proto-oncogene Neuroblastoma RAS viral oncogene homolog (NRAS). Mutations of this gene have been identified in a single family with ALPS.[62] A significant fraction of patients with ALPS remain genetically undefined.

Immunodeficiency with impaired cell-mediated cytotoxicity

The cytotoxic activity of T and NK lymphocytes depends on the expression of cytolytic proteins that are assembled into granules and transported through microtubules to the lytic synapse that is formed on contact with target cells. Some forms of immunodeficiency are characterized by impairment of the mechanisms of transport, docking, or release of the lytic granules. These disorders are frequently associated with defective intracellular transport of melanin, resulting in immunodeficiency with pigmentary dilution disorders.[63] The Chediak-Higashi syndrome (CHS) is an autosomal recessive disease caused by mutations of the Lysosomal Trafficking regulator *(LYST)* gene. In addition to impaired cytotoxicity, the phenotype of CHS includes the presence of giant lysosomes in leukocytes, gray-silvery hair, and peripheral neuropathy that reflects primary involvement of the nervous system.[64] Cytotoxicity defects characterize also the autosomal recessive forms of hemophagocytic lymphohistiocytosis (HLH) because of deficiency of perforin (which forms the cytolytic pores on contact with target cells), Munc13-4 (involved in intracellular transport of lytic granules), and syntaxin 11 (presumably involved in permitting fusion of the cell membrane between cytotoxic lymphocytes and target cells). In these diseases the inability to extinguish inflammatory reactions results in sustained and excessive production of T_H1 cytokines and IFN-γ in particular. This inflammatory reaction characterizes the life-threatening "accelerated phase" of the disease with hemophagocytosis. A similar phenotype has been occasionally observed also in Hermansky-Pudlak syndrome type 2, a condition with oculocutaneous albinism, severe neutropenia, and tendency to bleeding, which is caused by mutations of the β component of the adaptor-related protein complex 3 (AP3) involved in sorting of granules to the endosomal pathway.[65]

The X-linked lymphoproliferative disease, mainly caused by EBV infection, might be due to mutation of the *SH2D1A* gene, which encodes an adaptor protein involved in intracellular signaling in T and NK lymphocytes,[66] or of the *BIRC4* gene, which encodes for the X-linked inhibitor of apoptosis.[67] More recently, an autosomal recessive form of the disease has been identified that is caused by mutations of *ITK*, an intracellular tyrosine kinase expressed in T lymphocytes.[68] All of these 3 forms of lymphoproliferative disease share a lack of NK T cells, suggesting a possible role of these rare populations of lymphocytes in controlling EBV infection.

Defects of innate immunity: Phagocytes, TLRs, leukocyte signaling pathways, and complement

Phagocytic cell defects. Phagocytes play a key role in the defense against bacteria and fungi; accordingly, patients with defects of phagocytic cell number, function, or both experience recurrent and severe infections of fungal (especially *Candida* and *Aspergillus* species) and bacterial origin. Respiratory tract and cutaneous infections predominate, but deep-seeded abscesses are also common. Recurrent oral stomatitis is present in most cases.

Severe congenital neutropenia (SCN) is defined as a neutrophil count that is persistently less than 0.5×10^9 cells/L. A variety of genetic defects might cause SCN in human subjects.[69] The most common form of SCN is due to mutation of the *ELA2* gene, which encodes neutrophil elastase. This disease might be sporadic or autosomal dominant and is associated with a block at the promyelocyte-myelocyte stage in the bone marrow. Some *ELA2* mutations cause cyclic neutropenia, with oscillations in neutrophil count, which reach a nadir approximately every 21 days, resulting in periodicity of the infections. *ELA2* mutations carry an increased risk of myelodysplasia and myeloid leukemia associated with somatic mutations in the granulocyte colony-stimulating factor receptor *(GCSFR)* gene. Among autosomal recessive forms of SCN, HAX1 deficiency (identified also in the original SCN pedigree reported by Kostmann et al) causes increased apoptosis of myeloid cells. Some *HAX1* mutations cause also increased neuronal cell death, leading to a severe neurological phenotype.[70] Increased apoptosis caused by intracellular unbalance of glucose levels is also observed in myeloid cells from patients with mutations in the glucose-6-phosphatase catalytic subunit 3 gene *(G6PCS3)* or in patients with glycogenosis 1b caused by defects of the *G6PT1* gene, which encodes a G6P transporter. Heart and urogenital defects and prominence of superficial veins are part of the *G6PCS3* deficiency phenotype.[71] More rarely, autosomal recessive SCN is due to p14 deficiency; this form is associated with partial oculocutaneous albinism and short stature. Mutation of the Growth Factor Independent 1 *(GFI1)* gene, encoding a myeloid transcription factor, causes a rare form of autosomal dominant SCN; T and B lymphopenia is also observed. A rare X-linked recessive form of SCN with increased risk of myelodysplasia is caused by activating mutations of the Wiskott-Aldrich syndrome protein gene *(WASP)*. Finally, X-linked neutropenia, heart defects, and growth retardation are features of Barth syndrome, which is caused by mutation of the Tafazzin gene *(TAZ)* with mitochondrial defects.

Chronic granulomatous disease (CGD) represents the prototype of defects of phagocyte function and is caused by defects in the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex.[72] In 75% of cases, CGD is inherited as an X-linked trait caused by mutations in the X-linked *CYBB* gene, which encodes the $gp91^{phox}$ component of NADPH oxidase. Autosomal recessive forms caused by defects of the $p22^{phox}$, $p47^{phox}$, and $p67^{phox}$ components are also known. The $gp91^{phox}$ and $p22^{phox}$ proteins are located in the phagosome membrane, where cytosolic $p47^{phox}$ and $p67^{phox}$ are translocated after phagocytic cell activation. Assembly of the NADPH complex is regulated by 2 glutathione triphosphatases, Rac2 and Rap1, and defects of Rac2 have been identified in 1 patient with CGD-like disease. After phagocytosis, induction of the NADPH oxidase complex results in production of microbicidal compounds (superoxide radicals and hydrogen peroxide) and activation of lytic enzymes (cathepsin G, elastase, and myeloperoxidase), resulting in intracellular killing of bacteria and fungi. Patients with CGD experience recurrent and often severe infections (skin, liver and perirectal abscesses, pneumonia, and lymphadenitis). *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia*, and *Nocardia* species are responsible for most of the bacterial infections, whereas *Candida* and *Aspergillus* species cause most of the fungal infections. Patients with CGD are also at higher risk for mycobacterial infections. The sustained inflammatory response observed in patients with CGD is also responsible for the granulomatous manifestations of the disease that recur, especially in hollow organs, even in the absence of infections, causing gastric outlet obstruction, noninfective colitis, and hydronephrosis.[72]

Leukocyte adhesion deficiency (LAD) includes a series of syndromes characterized by impaired trafficking of leukocytes.[73] LAD1 is due to mutations of the *ITGB2* gene, which encodes the β_2 integrin component (also known as CD18) shared by the lymphocyte function–associated antigen 1, complement receptor 3, and complement receptor 4 molecules. These β_2 integrins mediate stable adhesion between leukocytes and endothelial cells, permitting transendothelial passage of leukocytes that can thus reach the sites of infection/inflammation. LAD2 is caused by mutations in a GDP-fucose transporter. In this disease defective fucosylation of proteins results in a lack of expression of Sialyl-Lewis-X, the ligand for E-selectin. This defect causes impaired rolling of leukocytes along the endothelium.[73] Finally, LAD3 is caused by mutations of kindlin-3, which is involved in inside-outside integrin signaling.[74] All 3 forms of LAD are inherited as an autosomal recessive trait, and they all present early in life with very severe infections and lack of pus formation. Impaired wound healing (even after minor trauma) and severe periodontitis are typically present. In addition, patients with LAD2 have short stature, facial dysmorphisms, mental retardation, and Bombay blood-type phenotype, reflecting the generalized defect of fucose metabolism. LAD3 is associated with increased bleeding caused by platelet functional defects.

Defects of TLRs. TLRs are a series of molecules that are expressed at the cell surface or endosomal membrane and mediate recognition of pathogen-associated molecular patterns, such as LPS, glycolipids, and single- or double-stranded RNA. The classical pathway of TLR activation involves the adaptor molecules MyD88 and the intracellular kinases IL-1 receptor–associated kinase (IRAK) 4 and IRAK-1 and ultimately results in the induction of nuclear factor κB and production of inflammatory cytokines (IL-1, IL-6, TNF-α, and IL-12). TLR-3, TLR-7, TLR-8, and TLR-9 can activate an alternative pathway that involves the adaptor molecules TRIF and the UNC-93B protein, resulting in the induction of type 1 interferons (IFN-α/β). Surprisingly, mutations in genes involved in TLR-mediated signaling result in a selective susceptibility to pathogens in human subjects. In particular, *IRAK4* and *MYD88* gene mutations (both inherited as autosomal recessive traits) have a similar phenotype, with severe and invasive pyogenic infections early in life, often without significant inflammatory response.[75,76] Infections tend to become less frequent later in life. Heterozygous mutations in *TLR3* and biallelic mutations in *UNC93B* have been identified in patients with selective susceptibility to herpes simplex encephalitis, with reduced production of type 1 IFN.[77,78]

Defects of the IL-12/IFN-γ signaling pathway. The immune response against mycobacteria is based on secretion of

IL-12 by macrophages. IL-12 binds to a specific receptor expressed by T and NK lymphocytes and induces secretion of IFN-γ that triggers macrophage microbicide on binding to the IFN-γ receptor. Defects of the IL-12/IFN-γ axis account for mendelian susceptibility to mycobacterial disease (MSMD).[79] Mutations might affect the IL-12 p40 subunit, the IL-12 receptor β1 chain, both chains of the IFN-γ receptor (encoded by the *IFNGR1* and *IFNGR2* genes), and the *STAT1* gene, which encodes a transcription factor downstream of the IFN-γ receptor. Different mutations in these genes account for autosomal dominant and autosomal recessive variants of MSMD. In addition, mutations in the *IKBKG* gene, encoding the IKK-γ (also known as NF-κB essential modulator, NEMO) regulatory component of the nuclear factor κB signaling pathway, also cause increased susceptibility to mycobacterial disease associated with CID, impaired CSR, and ectodermal dystrophy.[80] NEMO deficiency is inherited as an X-linked trait. All forms of MSMD are characterized by increased susceptibility to environmental mycobacteria (*Mycobacterium avium*, *Mycobacterium kansasii*, and *Mycobacterium fortuitum*) and to BCG vaccine strain. *Salmonella*, *Listeria*, and *Histoplasma* species infections can also be observed, especially in patients with *IL12RB1* mutations. Complete STAT1 deficiency causes susceptibility to severe viral infections in addition to MSMD.[81]

Complement defects. A variety of inherited defects of complement components have been reported.[82] Deficiency of the early components of the classical pathway of complement (C1q, C1r, C1s, C4, C2, and C3) causes autoimmune manifestations resembling systemic lupus erythematosus. C2 and C3 deficiencies also lead to increased risk of infections caused by capsulated bacteria. Defects of late components (C5-C9) are associated with recurrent and invasive neisserial infections. A similar phenotype is observed in patients with defects of factor D or of properdin, 2 components of the alternative pathway of complement activation. Deficiencies of the regulatory components Factor H and Factor I cause membranoproliferative glomerulonephritis and recurrent atypical hemolytic-uremic syndrome. The latter can also be caused by deficiency of membrane cofactor protein, a C3b/C4b-binding molecule of the complement system with cofactor activity for the Factor I–dependent cleavage of C3b and C4b. Deficiency of the mannose-binding lectin (MBL), a component of the MBL-dependent pathway of complement, has been associated with increased risk of recurrent bacterial infections, especially during the first years of life. However, it is more plausible that MBL deficiency plays a contributory role in patients who have additional risk factors. Mutations of the MBL-associated serine-protease-2 gene *(MASP2)* have been also linked to increased occurrence of infections. Finally, deficiency of the C1 esterase inhibitor, a regulatory component of the classical pathway of complement activation, does not cause immunodeficiency but hereditary angioedema, with recurrent episodes of edema that might involve the mucosa of the larynx and the gut, as well as the face and the extremities. These manifestations reflect uncontrolled release of bradykinin caused by lack of inhibition by C1 esterase inhibitor of the kallikrein-kinin system.

Immunodeficiency syndromes

The term immunodeficiency syndromes applies to several disorders in which other clinical features are present in addition to immunodeficiency. The Wiskott-Aldrich syndrome (WAS) is an X-linked disease characterized by eczema, immunodeficiency (with increased susceptibility to infections, autoimmunity, and lymphoid malignancies), and congenital small-sized thrombocytopenia.[83] However, only one third of the patients present all of the elements of this triad. WAS is cased by mutations in the *WASP* gene, which encodes a regulator of actin cytoskeleton the expression of which is restricted to hematopoietic cells. Hypomorphic mutations of the *WASP* gene, especially in exons 1 and 2, are often associated with a milder variant of the disease isolated X-linked thrombocytopenia.[83] In contrast, transactivating mutations of *WASP* cause X-linked neutropenia and myelodysplasia (see above).

Several immunodeficiencies are caused by defects in mechanisms that sense, repair, or both DNA breaks. Some of these defects are associated with SCID (see above). Ataxia-telangiectasia is an autosomal recessive disease caused by mutations of the ataxia-telangiectasia mutated gene *(ATM)*.[84] Patients with ataxia-telangiectasia have ataxia, ocular telangiectasia, increased risk of infections, and tumors. The immunodeficiency is marked by a progressive decrease of T-lymphocyte counts and function and hypogammaglobulinemia. Typically, levels of α-fetoprotein are increased. A similar phenotype, although without the increase in α-fetoprotein levels, is observed in patients with mutations in the *MRE11* gene, which is involved in DNA repair. The Nijmegen syndrome associates immunologic findings with microcephaly, "bird-like" facies, short stature, and increased occurrence of malignancies and is due to mutations in the Nibrin gene *(NBS1)*.[85] Ligase IV (LIG4) syndrome is due to defects of the *LIG4*gene, which encodes a factor involved in the DNA repair phase of the NHEJ process. Patients with LIG4 syndrome present with microcephaly, facial dysmorphism and increased susceptibility to tumors, and a variable degree of immunodeficiency that ranges from SCID/Omenn syndrome to hypogammaglobulinemia with impaired CSR to moderate or even very modest defects of T- and B-cell immunity.[86] Immunodeficiency–centromeric instability–facial anomalies syndrome is most often due to mutations of the DNA methyltransferase 3B gene *(DNMT3B)*. From an immunologic standpoint, immunodeficiency–centromeric instability–facial anomalies syndrome is characterized by recurrent bacterial and opportunistic infections, hypogammaglobulinemia, and a reduced number of T and B lymphocytes.[87]

The hyper-IgE syndrome (HIES) is characterized by eczema, increased occurrence of cutaneous and pulmonary infections sustained by *S aureus* (with formation of pneumatoceles) and *Candida* species, and markedly increased IgE levels.[88] Life-threatening superinfection of pneumatoceles by *Aspergillus* and *Scedosporium* species is common. Sporadic autosomal dominant and autosomal recessive forms are known. The autosomal dominant HIES associates defective shedding of primary teeth, scoliosis, higher risk of bone fractures, joint hyperextensibility, characteristic facial appearance, and vascular abnormalities with aneurysms and is due to dominant-negative heterozygous mutations of the *STAT3* gene.[89] STAT3 is a transcription factor that is activated in response to activation of the JAK-STAT signaling pathway through cytokine and growth factor receptors that contain the gp130 protein. Biologic responses to IL-6 and IL-10 are decreased, and development of T_H17 cells is impaired, resulting in poor secretion of IL-17, IL-21, and IL-22. The phenotype of autosomal recessive HIES is different. These patients might also have viral disease but do not present with skeletal or dental abnormalities. Vasculitis and autoimmunity are common in autosomal

recessive HIES. In one case of autosomal recessive HIES, mutations of the tyrosine kinase 2 gene *(TYK2)*, encoding one of the members of the JAK family upstream of STAT3, were demonstrated.[90] However, most cases of autosomal recessive HIES remain genetically undefined.

Veno-occlusive disease with immunodeficiency syndrome is a CID associated with early-onset severe liver disease and profound hypogammaglobulinemia and is caused by a mutation of the gene encoding the nuclear body protein Sp110.[91]

Immuno-osseous dysplasias include cartilage hair hypoplasia, Schimke disease, and Shwachman-Bodian-Diamond syndrome (SBDS). Cartilage hair hypoplasia is caused by mutations of the RNAse mitochondrial ribonucleoprotein gene *(RMRP)*. It is characterized by short-limbed dwarfism, sparse hair, and frequent occurrence of anemia or other forms of bone marrow failure associated with a variable degree of immunodeficiency, ranging from SCID to virtually normal immune function.[92] Schimke disease (caused by mutations of *SMARCAL1*)[93] associates short stature and progressive renal disease. SBDS is characterized by exocrine pancreatic insufficiency, bone marrow failure, and metaphyseal chondrodysplasia and is caused by a mutation of a gene involved in ribosome biogenesis.[94] Neutropenia is a prominent feature of SBDS and might cause severe infections.

Warts-hypogammaglobulinemia-infections-myelokathexis syndrome is an autosomal dominant disease caused by heterozygous mutations of the *CXCR4* chemokine receptor, which cause sustained and inappropriate signaling mediated by the ligand CXCL12. CXCL12-CXCR4 interaction is important in the governance of leukocyte trafficking. In patients with Warts-hypogammaglobulinemia-infections-myelokathexis, there is retention of mature neutrophils in the bone marrow (myelokathexis), resulting in severe neutropenia. Trafficking of B lymphocytes is also affected, causing B-cell lymphopenia and a variable degree of hypogammaglobulinemia. Patients are highly prone to papillomavirus infections (warts).[95]

DIAGNOSTIC APPROACH TO PIDS

The main forms of PID (CIDs, antibody deficiencies, and defects of innate immunity) are characterized by different susceptibilities to pathogens (Table I). Accordingly, medical history (with particular regard to type, location, age at onset, and severity of infections) might provide important insights into the possible underlying mechanisms of immunodeficiency. Additional aspects of past medical history might also help. Certainly a history of HIV infection is very important in the differential diagnosis of SCID. Also, a history of seizures during neonatal age should prompt one to consider DGS.

Family history is also important in the approach to PIDs because of the monogenic nature of most forms of these disorders. However, most patients with PIDs do not have a positive family history because they represent *de novo* mutations or the first occurrence of an autosomal recessive disease.

Physical examination can also provide important hints. Patients with agammaglobulinemia show absence of tonsils and other lymphoid tissues. Partial albinism characterizes pigmentary dilution disorders, ataxia and ocular telangiectasias are observed in ataxia-telangiectasia, microcephaly is common in PIDs associated with defects in DNA repair, petechiae and other bleeding manifestations associated with eczema are highly suggestive of WAS, and patients with immuno-osseous disorders have short stature. Generalized erythroderma is typical of Omenn syndrome but can also occur in IPEX, in SCID with maternal T-cell engraftment, in atypical complete DGS, and occasionally in NEMO deficiency.

Clinical immunologic laboratory tests are very important to validate the suspicion of PID. Lymphopenia, and marked reduction of T-lymphocyte counts in particular, is a hallmark of SCID, but HIV infection must be excluded in all cases. It is very important to compare lymphocyte counts with those of age-matched healthy control subjects. The presence of maternal T-cell engraftment or of residual autologous T cells in patients with CID might result in relatively preserved (and even normal) T-lymphocyte counts and hence confound the picture; however, in these cases most circulating T lymphocytes have an activated/memory ($CD45R0^+$) phenotype, and there is a virtual lack of naive ($CD45RA^+$) T lymphocytes. T-cell receptor excision circles (TRECs), consisting of circularized signal joints, are a byproduct of V(D)J recombination and are exported to the periphery by newly generated T lymphocytes that leave the thymus. Levels of TRECs in circulating lymphocytes are particularly high in newborns and infants (reflecting active thymic function) and progressively decrease with age. No TRECs are detected in infants with SCID; assessment of TREC levels by means of PCR has been proposed for newborn screening of SCID,[96] and a pilot study has been recently started in Wisconsin and Massachusetts.[97] In addition to the severe T-cell lymphopenia, *in vitro* response to mitogens is absent in patients with SCID; however, the number and proliferative responses of circulating T lymphocytes are often variable in patients with other forms of CID.

Evaluation of patients with putative antibody deficiency should include enumeration of B lymphocytes, measurement of total immunoglobulins, and assessment of specific antibodies to both protein and polysaccharide antigens. B lymphocytes (identified based on CD19 or CD20 expression) are absent in patients with congenital agammaglobulinemia, some adult patients with CVIDs, and patients with thymoma. Differential diagnosis includes some forms of SCID and myelodysplasia. Immunoglobulin serum levels should be compared with values of age-matched control subjects. It is important to remember that during the first months of life, IgGs are predominantly of maternal origin. Therefore apparently normal IgG serum levels can be detected during the first 2 to 3 months of life, even in patients with impaired ability to produce antibodies. There is large variability in the ability to produce IgA, and some individual attain normal levels only after the first few years of life. Demonstration of very low levels of serum IgG and IgA, with normal to increased serum IgM levels, is suggestive of CSR defects caused by either intrinsic B-cell problems (AID or UNG deficiency) or impaired cross-talk between T and B lymphocytes (CD40L or CD40 deficiency or NEMO defect). The term hyper-IgM syndrome, which is commonly used to identify these disorders, is in fact misleading because the majority of patients with these disorders have normal IgM serum levels.

Determination of serum levels of IgG subclasses has limited value and should not be used as a screening assay. More important information is provided by the assessment of antibody titers. In particular, antibodies to tetanus toxoid and diphtheria toxoid represent robust assays to measure the antibody response to protein (T-dependent) antigens. It is important to remember that use of conjugated vaccines to pneumococcus, *H influenzae*, or meningococcus elicits T-dependent responses,

even if the antibodies are ultimately directed against polysaccharide antigens. Therefore pneumococcal polysaccharide vaccine should be used to test the antibody response to polysaccharide (T-independent) antigens. If basal antibody titers appear nonprotective, a boosting immunization should be performed, followed by repeat measurement of specific antibodies 4 weeks later. A 4-fold increase of specific antibodies is considered indicative of robust antibody production. Isohemagglutinins are antibodies directed against the polysaccharide moieties of AB0 blood group antigens and represent "natural" anti-polysaccharide antibodies. However, isoagglutinin titers are often low in the first 2 years of life, thus limiting the value of this test in infancy.

The occurrence of severe bacterial and fungal infections since early life, especially if associated with a history of gingivostomatitis, should prompt consideration of disorders of neutrophil numbers, functions, or both. The absolute neutrophil count (ANC) is markedly reduced in all forms of SCN. If infections recur approximately every 3 weeks, the possibility of cyclic neutropenia should be entertained. In this case ANCs should be evaluated once a week for 6 consecutive weeks to identify possible decreases in the neutrophil count. Diagnosis of CGD is most commonly based on evaluation of dihydrorhodamine-123 (DHR-123) oxidation, as assessed by means of flow cytometry. This assay is quantitative and objective and also permits identification of carriers of X-linked CGD, who have 2 populations of neutrophils, only one of which is capable of mediating DHR-123 oxidation. Patients with autosomal recessive CGD often have very modest but detectable levels of activity, as detected by using this assay. Diagnosis of LAD1 is straightforward and is based on flow cytometric evaluation of CD18 expression on the surface of leukocytes. Partial defects (2% to 10% of normal density of CD18 molecules at the cell surface) are associated with a moderate form of the disease that permits more prolonged survival.

Investigation of patients with putative TLR-signaling defects can be facilitated by using a screening assay to measure IL-6 and TNF-α production on stimulation of whole blood with TLR agonists or by the failure of affected neutrophils to shed CD62 ligand following stimulation *in vitro*.[98]

Measurement of hemolytic activity of the classical (CH50) and alternative (AP50) pathways of complement, as well as of C3 and C4 levels, might guide in the diagnosis of complement deficiencies. However, as for other forms of PIDs, gene mutations might allow production of nonfunctional proteins, so that ultimately the diagnosis of deficiency of single complement components can rely on appropriate functional assays. The importance of measuring MBL levels is less well defined because of the uncertainties on the pathogenic role of this deficiency, if isolated.

Flow cytometric assays targeted to disease-associated proteins might help define the diagnosis,[99] as discussed above for assessment of CD18 expression in patients with LAD1. Impaired expression of CD40L is typically observed following *in vitro* activation of $CD4^+$ T cells in patients with CD40L deficiency. Patients with IPEX usually lack circulating Treg cells, which are defined as $CD4^+CD25^{bright}$ cells that express intracellular FOXP3. However, a minority of patients with IPEX show residual expression of nonfunctional FOXP3 protein. Caution should be used in the enumeration of Treg cells because FOXP3 can also be expressed by activated T lymphocytes. Protein-specific flow cytometric assays can also be used in the diagnosis of WAS (lack of WASP protein), SCIDX1 (absence of γc), XLA (lack of BTK protein in monocytes), and HLH caused by perforin deficiency. However, interpretation of these assays should take into account that some mutations are permissive for residual protein expression.

Increase of $TCR\alpha\beta^+CD4^-CD8^-$ (double-negative) T cells is suggestive of ALPS; increased levels of Fas ligand and IL-10 represent additional biomarkers of this disease.[100]

Functional assays are also important. In addition to *in vitro* proliferative response to mitogens and antigens for the diagnosis of CID, specific antibody responses in patients with hypogammaglobulinemia, and DHR-123 oxidation in the diagnosis of CGD, other clinically relevant functional assays include the demonstration of markedly reduced NK cytotoxicity (measured against K562 erythroleukemic target cells) in patients with familial forms of HLH and impaired Fas-mediated apoptosis in patients with ALPS.

In the last years, genetic tests have become more widely available. Identification of specific mutations is important not only to confirm the diagnosis but also to guide genetic counseling and to facilitate carrier detection and prenatal diagnosis. However, it should be noted that not all DNA changes are necessarily disease causing; some might represent polymorphisms, rare variants, or disease-contributing variations. These non–disease-causing DNA changes contribute to the heterogeneity of clinical and immunologic phenotypes associated with PIDs, and overall, they make genotype-phenotype correlation less stringent. Analysis of mRNA and protein expression and functional studies are often warranted to define in better detail the possible pathogenicity of specific gene mutations. However, it is important to recognize that in some cases (eg, patients with SCID), the urgency of the condition might require that patients be treated aggressively, even if definition of the genetic defect is still under way.

TREATMENT

Infants with a suspicion of SCID or other CIDs require prompt intervention with use of cotrimoxazole to prevent *Pneumocystis* infection, prophylactic use of antifungal drugs, immunoglobulin replacement therapy, and aggressive treatment of any infectious episodes. Nutritional support is often necessary. Immune suppression helps in controlling the inflammatory reactions associated with Omenn syndrome. Only irradiated and filtered blood products should be used in patients with SCID because of the high risk of otherwise fatal graft-versus-host disease and of transmitting infections (CMV in particular). Use of live attenuated viral vaccines must be avoided to prevent uncontrolled vaccine-associated infections. Ultimately, permanent cure of SCID depends on HCT. When performed from an HLA-identical sibling, HCT can allow greater than 90% long-term survival and very robust and long-lasting immune reconstitutition.[101] HCT from HLA-mismatched related donors provides excellent results when performed in the first 3.5 months of life[102]; however, the outcome is less satisfactory in older patients. Encouraging results have been reported with HCT from matched unrelated donors.[103] It is important to distinguish typical forms of SCID (T^-B^- or T^-B^+) from the most severe forms of CID. Although HCT is required in both, the presence of residual autologous T cells in patients with CID has important implications, both because it might cause symptoms associated with immune dysregulation and

because chemotherapy is usually needed to eliminate autologous T cells before HCT. Nonetheless, some forms of CID are characterized by worse outcome after HCT. In particular, reduced survival and a higher rate of complications after HCT have been reported in patients with radiation-sensitive SCID, Omenn syndrome, MHC class II deficiency, and ADA deficiency who did not have HLA-matched siblings.

Gene therapy has been shown to be effective for patients with ADA deficiency and with SCIDX1, leading to survival with immune reconstitution.[104,105] However, 5 of the 20 infants with SCIDX1 treated at 2 centers have experienced clonal proliferation caused by insertional mutagenesis, calling for the development of novel and safer vectors. Enzyme replacement therapy with weekly intramuscular injections of pegylated bovine ADA is available for patients with ADA deficiency.[106] Thymic transplantation from unrelated donors has been shown to restore T-lymphocyte development in patients with complete DGS.[107] Alternatively, unmanipulated bone marrow transplantation from HLA-identical siblings can also allow T-cell reconstitution caused by expansion of mature T lymphocytes contained in the graft.[108]

Treatment of antibody deficiency is based on immunoglobulin replacement therapy. This can be performed with intravenous or subcutaneous preparations (intravenous immunoglobulin [IVIG] and subcutaneous immunoglobulin [SCIG]). Both are effective in reducing the incidence of infections. The usual dose of IVIG is 400 mg/kg per 21 days, but higher doses might be needed in patients with bronchiectasis or enterovial meningoencephalitis. SCIG is administered at the dose of 100 mg/kg/wk; potential advantages of SCIG include a lower rate of adverse reactions and more stable IgG trough levels.[109] On the other hand, IVIG might be more useful when there is a need to administer higher doses (as in the treatment of patients with bronchiectasis or with associated autoimmune complications). Although no studies have been performed to support the use of continuous antibiotic prophylaxis in patients with antibody deficiency, they might be beneficial in patients with bronchiectasis and recurrent sinusitis.

Defects of neutrophils require regular antibiotic and antifungal prophylaxis. Cotrimoxazole and itraconazole are efficacious in the treatment of CGD, and injection of IFN-γ might further reduce the incidence of severe infections. Overall survival in patients with CGD is now around 90%.[72] HCT is the treatment of choice for LAD and can be proposed for patients with CGD who have HLA-matched family donors. Use of HCT from Matched Unrelated Donors or cord blood in patients with CGD remains controversial, although recent reports have shown that it can correct severe inflammatory complications.[110] Gene therapy has been attempted in a few patients with CGD, although because of the lack of selective advantage for gene-corrected cells, only a very small fraction of cells in the periphery carry the transgene if no conditioning regimen is used. In a recent trial with nonmyeloablative conditioning, clonal expansion caused by insertional mutagenesis has been reported.[111] Regular subcutaneous administration of recombinant granulocyte colony-stimulating factor can increase ANCs in patients with SCN. Management of HIES is based on hygiene and regular prophylaxis of staphylococcal and fungal infections.[88]

Patients with WAS should be treated with infusion of immunoglobulins, antibiotic prophylaxis, and appropriate measures to prevent severe bleeding episodes (eg, use of helmets).[83] However, the ultimate therapy of WAS is represented by means of HCT. Excellent results have been obtained with HCT from HLA-identical related donors. Results of MUD-HCT are also good, but mixed chimerism is associated with an increased rate of autoimmune complications.[112] Demonstration of lack of WASP protein expression might help identify high-risk patients who should be treated with HCT; in contrast, the approach to patients with XLT is more controversial.

HCT should be used without delay in patients with familial forms of HLH and in those with X-linked lymphoproliferative disease. Immunosuppressive treatment is required to treat the accelerated phase of the disease both in patients with X-linked lymphoproliferative disease and in those with PIDs with defective cytotoxicity associated with pigmentary dilution. Although HCT can cure the hematologic and immunologic manifestations of the disease, it does not prevent progressive neurological deterioration in patients with CHS.

Finally, although all patients with immunodeficiency associated with autoimmunity benefit from immunosuppressive treatment, alternative strategies can be considered, depending on the severity of the underlying defect. In particular, HCT is needed in patients with IPEX, whereas the significant splenomegaly of ALPS might require splenectomy.

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Secondary immunodeficiencies, including HIV infection

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Extrinsic factors can adversely affect immune responses, producing states of secondary immunodeficiency and consequent increased risk of infections. These immunodeficiencies, which can be encountered in routine clinical practice, arise from a number of conditions, such as treatment with glucocorticoids and immunomodulatory drugs, surgery and trauma, extreme environmental conditions, and chronic infections, such as those caused by HIV. The most common cause of immunodeficiency is malnutrition, affecting many communities around the world with restricted access to food resources. Protein-calorie deficiency and micronutrient deficiencies have been shown to alter immune responses; of note, recent progress has been made in the influence of vitamin D deficiency in causing failure of immune activation. Other categories of disease that might present with secondary immunodeficiency include metabolic diseases and genetic multisystemic syndromes. The immune defects observed in secondary immunodeficiency are usually heterogeneous in their clinical presentation, and their prognosis depends on the severity of the immune defect. Management of the primary condition often results in improvement of the immunodeficiency; however, this is sometimes not possible, and the risk of infections can be reduced with prompt antimicrobial treatment and prophylaxis. (J Allergy Clin Immunol 2010;125:S195-203.)

Key words: *Secondary immunodeficiency, immunosuppression, lymphopenia, AIDS*

Secondary immunodeficiencies are far more common than primary immunodeficiencies, which are, by definition, caused by genetic defects affecting cells of the immune system.[1] Secondary immunodeficiencies result from a variety of factors that can affect a host with an intrinsically normal immune system, including infectious agents, drugs, metabolic diseases, and environmental conditions. These deficiencies of immunity are clinically manifested by an increased frequency or unusual complications of common infections and occasionally by the occurrence of opportunistic infections (Fig 1). The secondary immunodeficiencies have a wide spectrum of presentation, depending on the magnitude of the offending external condition and on the host susceptibility. For example, the immunodeficiency induced by the use of corticosteroids and other immunosuppressive drugs depends on the dose used[2,3] and, to a lesser degree, on concomitant disease processes of the host, such as the presence of sepsis. AIDS, resulting from infection by HIV, is the best known secondary immunodeficiency largely because of its prevalence and its high mortality rate if not treated. However, the most common immunodeficiency worldwide results from severe malnutrition, affecting both innate and adaptive immunity.[4] The restoration of immunity in secondary immunodeficiencies is generally achieved with the management of the primary condition or the removal of the offending agent. We summarize reports of immune defects occurring in a variety of clinical scenarios (Table I), with special emphasis on HIV infection. We selected diseases and conditions based on their frequent presentation in general medical practice and their relevance for allergists and immunologists. We do not discuss immunomodulating mAbs and fusion proteins, which are covered in Chapter 28 of this primer.[5]

Abbreviations used
GvHD: Graft-versus-host disease
HAART: Highly active antiretroviral therapy
IRIS: Immune reconstitution inflammatory syndrome

EXTREMES OF AGE: NEWBORN PERIOD AND ADVANCED AGE

Newborn period

Neonates have an increased susceptibility to common and opportunistic infections and sepsis compared with older children.[6] There is an inverse association of infection susceptibility and the age of prematurity. In early life there are fewer marginal-zone B cells in lymphoid tissue and a decreased expression of CD21 on B cells, thus limiting the ability of B cells to develop specific responses.[7] Although they can develop humoral responses to some antigens after exposure *in utero*, impaired immunity in newborns can be attributed to the relative lack of maturity of secondary lymphoid organs, including the lymphoid tissue associated to mucosa in the gastrointestinal and respiratory tracts. This immaturity is related to the absence of memory cell development because of the relative isolation provided by the maternal environment. In addition, premature infants are more vulnerable to infections because of the absence of maternal IgG transfer before 32 weeks of gestational age. Other significant recent observations described at this early age are related to innate immunity mechanisms, such as a decreased neutrophil storage pool, as defined by the ability of neutrophilia to develop in response to an infection; decreased *in vitro* neutrophil functions (ie, phagocytosis, oxidative burst, chemotaxis, and adhesion); capacity to develop a neutrophil extracellular trap[8]; decreased natural killer cell activity; decreased Toll-like receptor signaling; decreased production of cytokines; and reduced complement components.

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Advanced age

Among the elderly, some subjects experience malignancies and an excessive number of infections caused by viruses and bacteria, reflecting a decrease in the immune defenses, particularly in the cellular compartment. Decreased delayed-type hypersensitivity skin reactions and decreased lymphocyte proliferative responses to mitogens can be demonstrated in this patient population. This relative impairment of the immune response has been linked to the development of T-cell oligoclonality together with a limited capacity of the thymus to generate naive T cells and therefore reduced responses to new antigens. Oligoclonal expansion of $CD8^+$ T cells begins in the seventh decade of life, which results in the skewing of the T-cell repertoire and an increased number of differentiated memory $CD8^+$ T cells.[9] Advanced age is similarly associated with a restricted B-cell diversity repertoire and a limited response to vaccines; however, there is also an increased number of total memory B cells and increased total IgG levels. The innate immunity might be compromised in the elderly, with increased breakdown of skin and mucosal barriers and slow healing processes caused by metabolic and endocrinologic changes associated with aging. A diminished production of hematopoietic growth factors has been postulated to occur in the elderly, resulting in decreased ability to upregulate the production and function of macrophages and neutrophils.[10] Some subjects are at higher risk of infections when these immunologic defects are combined with other environmental factors, such as malnutrition or the concomitant presence of chronic inflammation caused by autoimmunity or persistent infections.[11] Progress in understanding the aging-associated immune defect is of importance to optimize protective immunity against preventable infectious diseases.[12]

MALNUTRITION

Worldwide, protein-calorie malnutrition is the most common cause of immunodeficiency.[13] Malnutrition can result from limited access to food sources and chronic diseases that induce cachexia, such as neoplastic diseases. Diarrhea caused by infections and respiratory tract infections are common. T-cell production and function decrease in proportion to the severity of hypoproteinemia; however, specific antibody titers and immune responses to vaccines can be detected in a malnourished subject for a relatively prolonged period. Eventually, these immune responses decrease if malnutrition persists. The deficiency of micronutrients (eg, zinc and ascorbic acid) contributes to increased susceptibility to infections through the weakening of barrier mucosa, therefore facilitating a pathogen's invasiveness.[14,15] Other essential molecules have been shown to have specific roles in the immune system; for example, vitamin D appears to be necessary in the macrophage activity against intracellular pathogens, remarkably *Mycobacterium tuberculosis* (Fig 2).[16] Correction of the nutritional deficiencies often results in the resolution of these immunologic defects.

METABOLIC DISEASES: DIABETES MELLITUS AND UREMIA

Many disease processes originating from dysfunctional metabolic pathways significantly affect the cells involved in the immune response. Diabetes mellitus and uremia resulting from kidney or liver disease are 2 common metabolic disorders with known deleterious effects on immunity. Optimal control of the metabolic abnormality usually leads to improved immune function. The defective immune functions reported in patients with diabetes mellitus include defective phagocytosis and macrophage chemotaxis *in vitro*, T-cell anergy demonstrated by delayed hypersensitivity skin tests, and poor lymphoproliferative response to mitogens caused by chronic exposure to hyperglycemia.[17] Impaired glucose metabolism, insufficient blood supply, and denervation are other factors that contribute to the increased susceptibility to infection in patients with diabetes, who present most commonly with skin sores, bacterial and fungal respiratory tract infections, and systemic viral diseases.

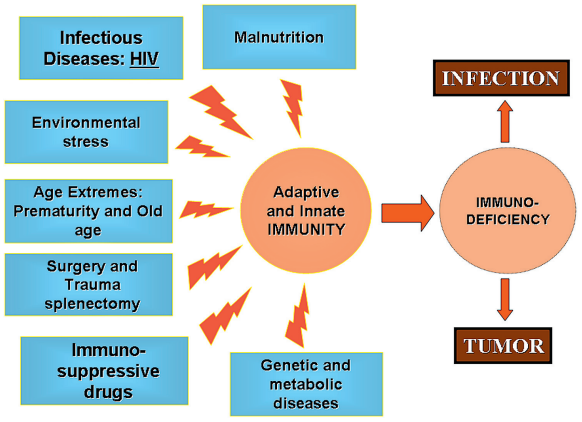

FIG 1. Extrinsic factors leading to defects of immune function.

Uremic patients experience increased incidence and severity of infections compared with the general population. Even when disparities in age, sex, race, and diabetes mellitus were taken into account, mortality rates in patients undergoing dialysis attributed to sepsis were higher by a factor of 100 to 300.[18] The need for dialysis procedures and use of vascular devices are independent risk factors for invasive infections. Multiple defects of the innate and adaptive immunity have been described to have a role in the increased frequency of infections, summarized as immune hyporesponsiveness and a state of chronic activation. The diminished capacity to generate memory antibody responses, regardless of repeated vaccination, and defective phagocyte chemotaxis and microbicidal activity *in vitro* are examples of the immune defects present in uremic patients.[19,20]

INHERITED DEFECTS OTHER THAN PRIMARY IMMUNODEFICIENCIES

Diseases caused by genetic defects might not primarily affect the immune system, but they can present with impaired immunity to infections resulting from metabolic and cellular dysfunction, such as poor expression of adhesion molecules or defects in the DNA repair machinery. The molecular mechanisms leading to immunologic defects remain not well defined. Genetic syndromes are relatively rare, and usually only a subset of patients present with an immune defect of clinical severity that increases their risk of infections or malignancies. The disease processes caused by chromosomal number abnormalities are the most common within the genetic disorders. As an example, patients with Down syndrome or trisomy of chromosome 21 present with increased incidence of infections, although they are usually not severe, including skin abscesses, periodontitis, and upper respiratory

TABLE I. Selected causes of secondary immunodeficiencies

Condition	Effect on immune function
Extremes of age	
Newborn period	Immature lymphoid organs Absent memory immunity Low maternal IgG levels in premature infants Decreased neutrophil storage pool Decreased neutrophil function Decreased natural killer activity
Advanced age	Decreased antigen-specific cellular immunity T-cell oligoclonality Restricted B-cell repertoire
Malnutrition	Decreased cellular immune response Weakened mucosal barriers
Metabolic diseases	
Diabetes mellitus	Decreased mitogen-induced lymphoproliferation Defective phagocytosis Decreased chemotaxis
Chronic uremia	Decreased cellular immune response Decreased generation of memory antibody responses Decreased chemotaxis
Genetic syndromes: trisomy 21	Defective phagocytosis Defective chemotaxis Variable defects of antigen-specific immune responses
Anti-inflammatory, immunomodulatory, and immunosuppressive drug therapy: corticosteroids, calcineurin inhibitors, cytotoxic agents	Lymphopenia Decreased cellular immune response and anergy Decreased proinflammatory cytokines Decreased phagocytosis Decreased chemotaxis Neutropenia (cytotoxic agents) Weakened mucosal barriers (cytotoxic agents)
Surgery and trauma	Disruption of epithelial and mucosal barriers T-cell anergy caused by nonspecific immune activation
Environmental conditions UV light, radiation, hypoxia, space Flight	Increased lymphocyte apoptosis Increased secretion of tolerogenic cytokines Cytopenias Decreased cellular immunity and anergy Stress-induced nonspecific immune activation
Infectious diseases: HIV infection	T-cell lymphopenia Decreased cellular immune response and anergy Defective antigen-specific antibody responses

tract infections. T- and B-cell number and function are variably affected.[21] Neutrophils isolated from patients with Down syndrome have shown defects in chemotaxis and phagocytosis *in vitro*. Most recent studies have focused on the overexpression of the gene Down syndrome critical region 1 *(DSCR1)* and its role in contributing to phagocyte dysfunction.[22] Patients with Turner syndrome (complete or partial absence of the second X chromosome) also have an increased number of respiratory tract infections, and hypogammaglobulinemia can be identified, although this immune defect is not consistently demonstrated in these patients. The gene defects involved in the decrease of immunoglobulin production are not known.

In other genetic diseases, such as cystic fibrosis, caused by deleterious mutations in the cystic fibrosis transmembrane conductance regulator, the increased susceptibility to sinusitis and pneumonia is explained by defective mechanisms of innate immunity.[23] Patients with cystic fibrosis have an impaired airway mucous clearance caused by the thickness of the mucous secretions, which favors the development of respiratory infections caused by *Pseudomonas* species. It is recommended that patients receive prompt antibiotic therapy when infection is suspected, and antibiotic prophylaxis should be prescribed to those patients with recurrent infections to reduce the number of infectious episodes.

ANTI-INFLAMMATORY, IMMUNOMODULATORY, AND IMMUNOSUPPRESSIVE DRUG THERAPY

The use of drugs to ameliorate undesirable immune responses is common in clinical practice as a consequence of the increasing prevalence of inflammatory conditions. These diseases include the categories of autoimmune disorders, allergic disorders, transplant rejection, and graft-versus-host disease (GvHD). Broadly, we can study these drugs by dividing them into biologic, physical, and chemical categories. The chemical agents are the most available clinically and have in common their ability to inhibit lymphocyte proliferation and their lack of specificity for the immune response causing the particular illness of interest.

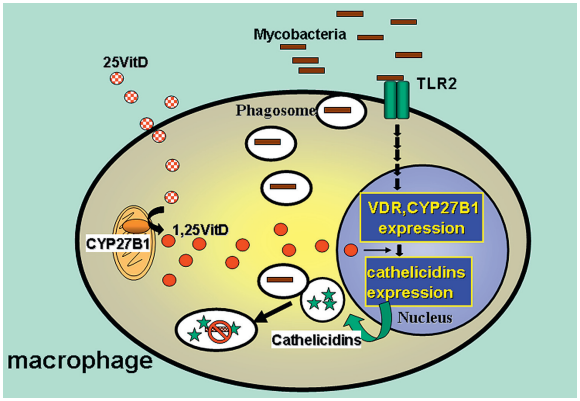

FIG 2. Role of vitamin D *(VitD)* in macrophage activation. Toll-like receptor 2 *(TLR2)* activation increases expression of CYP21B1, a mitochondrial enzyme that converts vitamin D into its active form, 1,25OH vitamin D, and vitamin D nuclear receptor *(VDR)* expression, which when bound to 1,25OH vitamin D promotes cathelicidin synthesis. Cathelicidins are intracellular bactericidal proteins.

Biologic immunosuppressive drugs have been developed to increase the immune specificity by targeting specific components of the immune response, such as cytokines or a particular lymphocyte subset. Physical agents (ie, UV light and ionizing radiation) can also be used to ablate immune responses.

In addition, there are drugs that might have an immunosuppressive effect that is not clearly related to the pharmacologic activity of the molecule. Its occurrence is not predictable and varies within different patient populations. Well-known examples of this drug mechanism are the development of hypogammaglobulinemia in patients receiving antiepileptic drugs and the leukopenia seen in patients taking trimethoprim-sulfamethoxazole.

Based on their structure and mechanism of action, most molecules with immunosuppressive activity can be grouped into corticosteroids, calcineurin inhibitors, and cytotoxic drugs. The adverse side effect of these drugs is that they tend to weaken the cellular immune response, rendering patients more susceptible to fungal and viral infections (acute, chronic, and reactivated).

Corticosteroids

The corticosteroids include both glucocorticoid and mineralocorticoid molecules. Only the glucocorticoids have significant anti-inflammatory activity. Glucocorticoids are well known for their variety of applications in both general and subspecialty medicine to reduce tissue damage caused by an excessive inflammatory response. The range of potency of the different molecules of this group and their routes of administration is diverse, each designed to different applications. For example, betamethasone is 25 times more potent than cortisol and can be used in topical, oral, and injectable preparations. Glucocorticoids bind a cytosolic receptor, which then translocates to the nucleus to act as a transcription factor affecting the expression of a number of genes, resulting in an anti-inflammatory effect (Fig 3).[24] The bound complex-glucocorticoid receptor modulates signal transduction pathways, resulting in the activation of the transcription factors nuclear factor κB, nuclear factor of activated T cells, and activator protein 1. It has been suggested that glucocorticoids might also cause an effect on cell function by interacting with the cell membranes, which could explain observed clinical benefits when used as "pulse therapy," with doses higher than required for receptor saturation. The overall results are decreased cytokine production (IL-1, IL-6, and TNF-α) and impaired leukocyte chemotaxis, cell adhesion, phagocytosis, and lymphocyte anergy. Lymphopenia occurs as a result of the proapoptotic activity and inhibition of IL-2–mediated proliferative responses. When used at large doses, antibody responses and delayed-type hypersensitivity responses are reversibly suppressed. This wide range of immune defects renders the patient susceptible to viral, bacterial, and fungal infections, according to the degree of immunosuppression and the administration route. Examples of these are oral candidiasis, a frequent complication of the use of inhaled steroids, and herpes zoster disease, which often presents with chronic use of systemic corticosteroids.

Calcineurin inhibitors

Calcineurin inhibitors bind cytoplasmic proteins from the immunophilin family and inhibit their interaction with calcineurin, which is essential for the activation of IL-2 transcription and T-cell function (Fig 4). The advantage of these drugs over corticosteroids and cytotoxic drugs is to spare macrophage and neutrophil functions, reducing the spectrum of susceptibilities to infections. However, these drugs cause respiratory tract and skin infections, usually of viral cause, to occur with increased frequency. The most common adverse effects of calcineurin inhibitors are hypertension and renal dysfunction; less common but more serious is the increased frequency of lymphoproliferative disorders and skin neoplasias. The first drug in this category was cyclosporine, which has been extensively used to prevent organ transplant rejection,[25] GvHD, and corticosteroid-resistant autoimmune disorders. Other agents with a similar mechanism of action and immune selectivity are tacrolimus and pimecrolimus. The latter is the most recent member of this group, and it was developed for topical use in the treatment of severe atopic dermatitis. An agent with a similar name, sirolimus or rapamycin, also binds an immunophilin but does not inhibit calcineurin. Instead, sirolimus inhibits the IL-2–induced response by inhibiting the mammalian target of rapamycin, a protein essential for cell activation and proliferation.

Cytotoxic agents

Cytotoxic agents were conceived to control neoplastic cell growth and ablate the bone marrow for transplantation. They have progressively found their niche in the immunosuppressive drugs category because of the selectivity conferred by the proliferative nature of the immune response, and their application has extended to autoimmune and inflammatory disorders, including GvHD and the prevention of graft rejection.[26] The most common drugs used for these applications are the alkylating agent cyclophosphamide and the antimetabolites methotrexate, mycophenolate, azathioprine, and 6-mercaptopurine. Other drugs with predominant use in autoimmune disorders are sulfasalazine, hydroxychloroquine, and leflunomide.[26] These compounds interfere with the synthesis of DNA, arresting the cell cycle and inducing apoptosis. Generally, they inhibit both T- and B-cell proliferation and therefore any new immune responses. In addition, depending on the dose used, they inhibit cellular and antibody responses resulting from previous sensitizations. The major limitation of the use of these agents is their toxicity to other hematopoietic and nonhematopoietic cells, with development of cytopenias, gastrointestinal

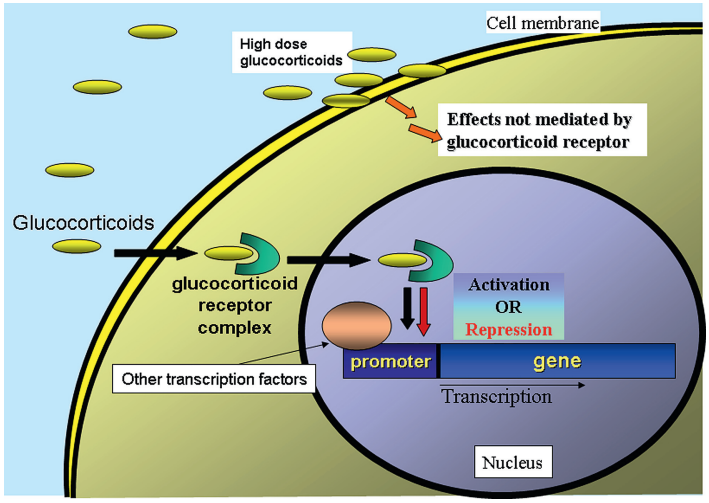

FIG 3. Molecular mechanism of action of glucocorticoids. A cytosolic receptor binds glucocorticoids and translocates them to the nucleus, where they either activate anti-inflammatory genes or inhibit proinflammatory genes. At high doses, corticosteroids can also affect cell function by non–receptor-dependent mechanisms.

mucosa, and skin deterioration. These cytopenias contribute to the state of secondary immunodeficiency and susceptibility to infections.

SURGERY AND TRAUMA

Surgery and trauma cause disruption of epithelial barriers and cell destruction that triggers an inflammatory response to promote healing and local microbicidal activity.[27,28] Microorganisms contain surface pathogen–derived molecules that activate pattern-recognition receptors expressed on antigen-presenting cells and other immune cells to induce cytokine and chemokine release and recruitment of the adaptive immune system.[29] Massive tissue injury further increases activation of proinflammatory mechanisms in response to the presence of toxic byproducts of cell death.[30] In this inflammatory response Toll-like receptors play a central role in activating immune cells, resulting in the release of inflammatory cytokines, such as IL-6 and TNF-α. If this response is severe, trauma patients might experience the adult inflammatory respiratory syndrome in the lung or the systemic inflammatory response syndrome when there is multiorgan failure. The inflammatory response observed in patients with severe trauma develops gradually: loss of epithelial barriers, vasodilatation and increased vascular permeability, cellular activation and increased adhesion to endothelia, and a neuroendocrine stress response. At the same time, injured patients are relatively immunosuppressed because of nonspecific cell activation leading to an anergic immune state and because of increased levels of cortisol induced by stress in addition to the loss of containment provided by epithelial barriers. This process occurs within the context of a delicate balance of inflammatory and counterinflammatory mechanisms.[31]

Patients who have undergone splenectomy deserve special consideration because they are particularly susceptible to infections by encapsulated bacteria, such as *Streptococcus pneumoniae*. The mortality for sepsis in splenectomized patients is between 50% and 70%, emphasizing the need to avoid splenectomy when possible. Patients who are scheduled for elective splenectomy should receive antipneumococcal, anti–*Haemophilus*

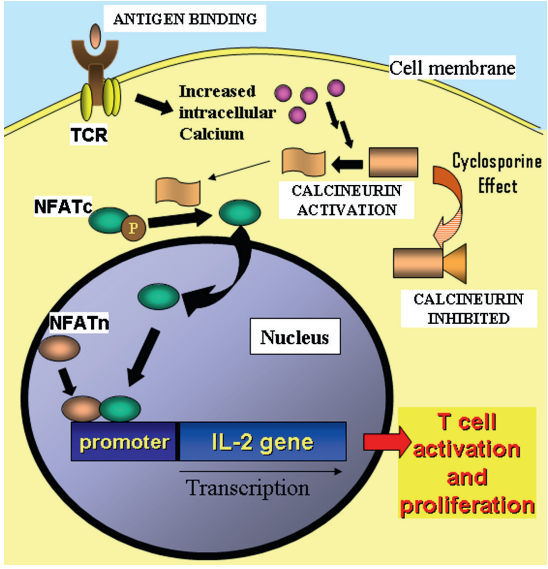

FIG 4. Effect of cyclosporine on T cells. Inhibition of calcineurin activity by cyclosporine results in decreased activation of IL-2 transcription. *TCR*, T-cell receptor; *NFAT*, nuclear factor of activated T cells; *NFATc*, cytoplasmic monomer; *NFATn*, nuclear monomer.

influenzae, and antimeningococcal immunizations at least 2 weeks before surgical intervention.[32]

ENVIRONMENTAL CONDITIONS: UV LIGHT, IONIZING RADIATION, HIGH ALTITUDE, CHRONIC HYPOXIA, AND SPACE FLIGHTS

There is increased awareness of potential adverse effects caused by chronic exposure to inhospitable environmental conditions, such as extreme cold or high altitude. It has been recommended to avoid exposure to sunlight because of increased risk of malignancies; however, beneficial effects of sunlight have also been observed, particularly in patients with skin inflammatory conditions, such as psoriasis.[33] The biologic effect

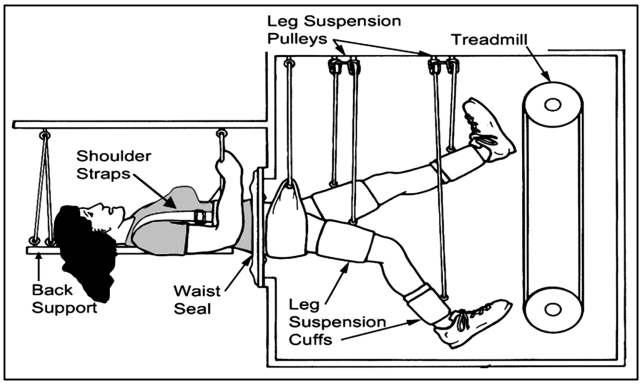

FIG 5. Human model to test the effects of microgravity. Volunteers are maintained in bedrest position for 60 days to mimic the affects of microgravity in space. Exercise is used as a countermeasure.

of sunlight in inflammation is mediated by UV light, which induces T-cell apoptosis, nonspecific release of tolerogenic cytokines from antigen-presenting cells in the epidermis, and differentiation of regulatory T cells; hence UV light is used in the treatment of eczema and the skin manifestations of autoimmune disorders.

The immunosuppressive effect of ionizing radiation affects all blood cell lineages by depleting the bone marrow and inducing cytopenias, whereas the humoral response and phagocytosis are considered radioresistant.[34] However, continuous exposure to radiation eventually weakens all immune functions. Animal experiments of space radiation similar to that human subjects would experience during long-duration space flights have demonstrated a weakness of T cell–mediated immunity and reactivation of latent viral infections.[35] Other adverse conditions, such as chronic hypoxia at high-altitude locations and long-duration space flights, might affect immunity by causing physical and mental stress. Confinement, isolation, and sleep-cycle alterations induce chronic stress, which disturbs the corticoadrenal regulation and increases cortisol levels. In human subjects space flight–equivalent models, including acute sleep deprivation, have been shown to increase blood levels of inflammatory cytokines and suppression of IL-10 secretion.[36] Prolonged bedrest (ie, 60 days) with head-down tilt, a model of microgravity in space, has produced a significant increase of serum TNF-α soluble receptor levels in female volunteers (Fig 5).[37] Interestingly, vigorous exercise served as an effective countermeasure in negating this effect.

INFECTIOUS DISEASES

Transient periods of immunosuppression have been associated with viral infections since the 1900s, when it was observed that tuberculin skin test results became negative in patients with measles during the acute phase of the infection. Some infectious agents or their toxins and metabolites might be present in excess amounts to activate the immune system, leading to a nonresponsive state, such as the T-cell anergy observed after toxic shock syndrome induced by staphylococcal superantigen. Tissue destruction caused by microbial-induced damage or inflammatory reaction to a particular infection facilitates access for other microbes to develop secondary infections. Infections with measles virus, CMV, and influenza virus can induce lymphopenia and also T-cell anergy; however, these are transient and usually less severe than the immunodeficiency seen in AIDS. One additional mechanism of immune compromise is infection of the bone marrow by viral and bacterial organisms producing neutropenia or pancytopenia, particularly in immunocompromised hosts.[38]

HIV INFECTION: AIDS

Background

Without antiretroviral drug treatment, HIV infection almost always progresses to the advanced stage of the disease called AIDS that is characterized by profound lymphopenia and susceptibility to infections with opportunistic pathogens. HIV is transmitted sexually, for the most part, but it is also transmitted parenterally among intravenous drug users and vertically from mothers to their infants.[39] Initially recognized during the early 1980s in a handful of cases, it is currently estimated that more than 30 million persons are infected with HIV worldwide. Two thirds of these subjects are living in the sub-Saharan region of Africa, and approximately half of them are women and children (Fig 6).[40] The HIV epidemics in North America and Europe have shown decreasing trends in the last decade, thanks to massive education campaigns and the use of potent anti-HIV drugs. However, more than 56,000 new cases of HIV infection were reported in the United States in the last HIV infection survey by the Centers for Disease Control and Prevention, and approximately half of these were in subjects younger than 25 years.[41] There is an increasing number of reports of viral multidrug resistance and clinical complications caused by the chronic use of antiretroviral drugs.[42]

Virology

HIV is a double-stranded, enveloped RNA retrovirus from the group lentiviruses, with a tropism for human $CD4^+$ expressing cells, including T cells and macrophages.[41] Two HIV types have been identified, HIV-1 and HIV-2, and both cause human disease. HIV-2 is more prevalent in West Africa and might take more time from infection to the development of immunodeficiency than HIV-1. The HIV genome contains 3 structural genes (*gag*, *pol*, and *env*) and 6 regulatory genes (*tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*). Gag protein is split by the HIV protease into the proteins named capsid (p24), matrix, nucleocapsid, p6, and p2, all of which form the viral particle and stabilize the viral genome. Pol protein is also split to produce 3 enzymes: integrase, reverse transcriptase, and the protease that cleaves the viral proteins. After the viral genomic RNA is converted into DNA by the reverse transcriptase, the integrase facilitates the incorporation of the viral DNA into the host genome and uses the host cell's replication mechanisms to produce more virions. The Env protein is also cleaved to produce 2 envelope proteins named gp120 and gp41, which are involved in the binding to CD4 and the chemokine receptors CXCR4 and CCR5 on the cell surface. Tat protein increases the transcription of HIV genes by 100-fold, whereas Rev protein allows the expression of the different HIV genes by regulating mRNA splicing.

The roles of the other regulatory genes have only been clarified in the last few years. Nef protein downregulates CD4 and MHC class I surface expression on the membranes of infected cells, probably facilitating escape from immune surveillance. Vif is a protein that induces the degradation of APOBEC3 G, a cytosine deaminase that causes mutations during viral transcription. Vpr

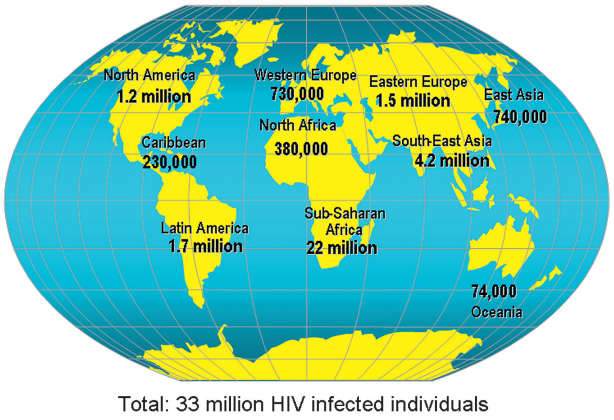

FIG 6. Worldwide prevalence of HIV infection. Adapted from the United Nations Programme on HIV/AIDS.[40]

and Vpu proteins seem to facilitate the intracellular transport of viral proteins for viral particle formation.

Immunopathogenesis

HIV infection begins with the binding of the HIV gp120 protein to the CD4 molecule and the chemokine receptor CCR5 on target cells. Infected cells migrate to the lymph nodes, where initial replication and infection of nearby $CD4^+$ T cells occur.[43] During acute HIV infection, the gut-associated lymphoid tissue is severely depleted, with predominant loss of memory $CD4^+$ T cells and with high viremia and immune activation.[44,45] HIV induces T-cell lymphopenia through several mechanisms: HIV-induced apoptosis, viral cytopathic effect, apoptosis caused by nonspecific immune activation, and cytotoxicity to HIV-infected cells. An additional form of cell death named autophagy, in which organelles are sequestered and directed toward lysosomal pathways, has been shown to be induced by HIV Env protein in uninfected T cells.[46] The acute phase of HIV infection occurs 1 to 6 weeks after infection, with nonspecific symptoms, such as fever, fatigue, myalgia, and headaches. The period of clinical latency that follows is characterized by a virtual absence of signs or symptoms until symptomatic disease occurs and can last as long as 10 years. Levels of several cytokines are increased and contribute to determine the degree of control of HIV viremia. Higher viral loads at the initial stage predict shorter clinical latency. Without anti-HIV drug treatment, $CD4^+$ T-cell counts progressively decrease, and the host usually succumbs to infections with opportunistic organisms that take place because of the immune deficiency. Investigators have been able to demonstrate the production of specific anti-HIV $CD4^+$ T cells and $CD8^+$ T cells, as well as neutralizing anti-HIV antibodies; however, these immune responses are eventually overcome by viral escape strategies. At this stage, patients present with fever, weight loss, diarrhea, lymphadenopathy, and fungal and viral skin infections, indicating compromise of the immune system. When the peripheral $CD4^+$ T-cell count is less than 200 cells/mL, the patient can present with any of a number of infections that define AIDS, such as *Pseudomonas jiroveci*–induced pneumonia, histoplasmosis, toxoplasmosis, and coccidioidomycosis.[47] If the patient does not receive antiretroviral treatment, repeated infections that are difficult to manage lead to the patient's death. A small proportion of HIV-infected patients remain asymptomatic and do not have AIDS. These patients are called long-term nonprogressors and have been the focus of multiple studies to understand the basis of their protection. Those who maintain low levels of HIV (ie, <50 RNA copies/mL) without treatment are called elite controllers.[48] This immunity appears to be explained by different viral and host factors. The best known of these factors is the inherited defect in the gene encoding the CCR5 receptor, a T-cell surface molecule that is necessary for HIV cell entry. *CCR5* gene mutations have been found with significant prevalence in persons of Northern European ancestry. Other factors identified in long-term nonprogressors include a low number of activated $CD8^+$ T cells,[49] the presence of particular HLA haplotypes, and viral mutations that result in low virulence. The diagnosis of HIV infection is made by using a sensitive ELISA to detect antibodies against the HIV protein p24. A positive HIV ELISA result is confirmed by using the more specific Western blot, which detects antibodies to several HIV proteins, or the detection of HIV DNA sequences by PCR. Rapid diagnostic tests to rule out HIV infection use serum, saliva, or urine with similar sensitivity and specificity to the ELISA and can be performed in the office or at home. Infants and children up to 18 months of age born to HIV-infected mothers should be evaluated with an HIV DNA PCR test because the presence of passively acquired maternal antibodies in the serum of the child can result in a positive HIV ELISA test result, even if the child is not infected with HIV. Other useful laboratory tests are genotyping and phenotyping assays. Genotyping identifies HIV mutations that confer viral resistance to antiretroviral drugs. Phenotyping measures the inhibitory action of anti-HIV drugs on the isolated HIV strain, which is similar to a bacterial susceptibility assay. These assays define anti-HIV drug susceptibility profiles of viral strains isolated from infected patients and help in the design of the combination of drugs with the most probability to have a therapeutic effect in a particular patient.

Treatment

In adults specific anti-HIV therapy is recommended when the patient has an AIDS-defining illness, the $CD4^+$ T-cell count is less than 350 cells/mm^3, or the HIV viral load is greater than 100,000 copies/mL. Caution should be exercised in other clinical situations because of the development of viral resistance to the antiretroviral agents and significant drug-induced adverse effects, including allergic and metabolic syndromes.[50,51] In children treatment is considered for any HIV-infected infant because disease progresses faster than in older children. For children older than 12 months, the criteria are similar to those in adults: presence of an AIDS-defining illness, $CD4^+$ T-cell count of less than 15% of PBMCs, or viral load greater than 100,000 copies/mL.[52] Anti-HIV drug classes are defined according to their mechanism of action: nucleoside reverse transcriptase inhibitor, nonnucleoside reverse transcriptase inhibitor, protease inhibitor, and cell fusion inhibitor. In the last 2 years, CCR5 inhibitors and integrase inhibitors have been added to the arsenal of anti-HIV medications.[53,54] Combinations of 3 synergistic anti-HIV drugs from 2 different classes are known as highly active antiretroviral therapy (HAART). HAART protocols have been effective in reducing viremia and restoring normal T-cell counts, with drastic reduction of mortality and number of infections; however, they do not eradicate HIV and need to be administered continuously for life. As an adjuvant treatment to improve baseline immunity, the

administrations of IL-7 and IL-2 have been independently tested to increase $CD4^+$ T-cell counts, with promising results.[55,56]

Immunologic reactions associated with anti-HIV treatment

The immune reconstitution inflammatory syndrome (IRIS) is a severe inflammatory response to existing opportunistic infections that can be observed in 15% to 25% of patients with AIDS 2 to 3 weeks after starting HAART treatment.[57] The management of IRIS consists of corticosteroid therapy and simultaneous treatment of the opportunistic infections; however, IRIS might not occur if these infections are recognized and treated before starting the HAART therapy. A similar clinical observation is the increased incidence of asthma in HIV-infected patients receiving HAART, up to 3 times the rate of HIV-negative control subjects.[58]

Drug-allergic reactions have an increased prevalence in this patient population. Urticarial or maculopapular rashes, which occasionally present as the Steven-Johnson syndrome, occur in as many as 60% of patients with HIV receiving trimethoprim-sulfamethoxazole and in 17% of those receiving the antiretroviral nevirapine.[59] Abacavir is a nucleoside reverse transcriptase inhibitor that causes a multiorgan hypersensitivity syndrome characterized by fever, rash, diarrhea, myalgia, and arthralgia in as many as 14% of patients who take this drug. This has a strong association with the presence of HLA B5701. This syndrome presents within the first weeks of treatment and can be fatal; however, it usually resolves after 72 hours of discontinuing the drug.

HIV vaccine

The failure of current antiretroviral therapy to eliminate the HIV virus emphasizes the need of preventive measures to control the HIV pandemic. Research for an effective anti-HIV vaccine has yielded several lessons; perhaps the most important is the need to demonstrate the development of specific cellular immunity and humoral responses and include mucosal protective immunity.[60] The first vaccine candidates were based on strategies that had worked for other infectious diseases, such as inactivated virus and HIV proteins conjugated to adjuvants. These were able to induce only weak neutralizing antibody activity and did not provide significant protection against HIV infection in clinical trials. Live attenuated simian immunodeficiency virus strains have been demonstrated to protect macaques from simian immunodeficiency virus challenge; however, there are safety concerns related to the extraordinary capacity of HIV for recombination, which might lead to wild-type revertant strains. A novel approach using an adenovirus-based vaccine expressing HIV proteins elicited strong anti-HIV immunity; however, it was unable to demonstrate a protective effect over placebo in a phase I/II clinical trial with more than 3,000 subjects.[61]

Prevention measures

Considerable resources have been placed on educational campaigns to control the HIV epidemics. Preventive interventions that have been useful are using condoms, providing intravenous drug users with free sterile needles, screening blood products, and administering antiretroviral agents to HIV-infected pregnant women and their infants. Avoidance of breast-feeding has been recommended on the basis of the increased risk of transmitting the virus through breast milk; however, this might be revised in communities with poor resources, where it has been demonstrated that breast-feeding up to 1 month in combination with antiretroviral therapy does not increase early transmission and provides immune and nutritional support to the newborn.[62] Other preventative interventions are male circumcision, with a reduction of the risk of HIV infection in heterosexual males by 50% to 60%,[63] and topical anti-HIV microbicidals as an alternative to the use of condoms.[64] The control of this deadly disease will only result from a combined effort of researchers and physicians developing and using anti-HIV drugs effectively and educators working in the promotion of safe behavioral practices in communities at risk.

CONCLUSION

There is an increased awareness of the variety of factors that can affect the immune response. When evaluating a patient with increased frequency or severity of infections suggesting immunodeficiency, physicians should consider that secondary immunodeficiencies are far more common than primary immune defects of genetic cause. A detailed clinical history might uncover the condition affecting the immune system, such as infection, malnutrition, age extremes, concomitant metabolic or neoplastic diseases, use of immunosuppressive drugs, surgery and trauma, and exposure to harsh environmental conditions. Because of its prevalence and clinical progression, HIV infection should be considered and ruled out. The specific immune defects and clinical presentation in other secondary immunodeficiencies are usually heterogeneous, affecting both the innate and the adaptive immunity. The immune impairment improves with the resolution of the primary condition.

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Immunologic rheumatic disorders

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We provide the basics for clinicians who might be called on to consider the diagnosis of diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) in their practice. We will emphasize clinical recognition and first-line laboratory testing. Only characteristics of the classic rheumatic inflammatory diseases (ie, RA, seronegative spondyloarthropathy, SLE, antiphospholipid syndrome, Sjögren syndrome, scleroderma, and polymyositis/dermatomyositis) will be covered. In the past decade, treatment for RA and seronegative spondyloarthropathy has substantially improved. Their treatment has been revolutionized by the use of methotrexate and, more recently, TNF inhibitors, T-cell costimulation modulators, and B-cell depletion. The goal of RA treatment today is to induce a complete remission as early as possible in the disease process, with the mantra being "elimination of synovitis equals elimination of joint destruction." The hope is that if the major mediators of Sjögren syndrome, SLE, or scleroderma can be identified and then blocked, as in the example of TNF inhibitors in patients with RA, more specific treatments will become available. Thus RA has become an excellent model of this evolving paradigm. Through the identification of major mediators in its pathogenesis, novel and highly efficacious therapeutic agents have been developed. (J Allergy Clin Immunol 2010;125:S204-15.)

Key words: *Rheumatoid arthritis, seronegative spondyloarthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren syndrome, scleroderma polymyositis, dermatomyositis, and inclusion-body myositis*

Abbreviations used

ACA:	Anticentromere antibody
ACLA:	Anticardiolipin antibody
ANA:	Antinuclear antibody
Anti-CCP:	Anti–cyclic citrullinated peptide
APA:	Antiphospholipid antibody
APLS:	Antiphospholipid syndrome
aPTT:	Activated partial thromboplastin time
AS:	Ankylosing spondylitis
β2GP1:	β_2-glycoprotein 1
DM:	Dermatomyositis
DMARD:	Disease-modifying antirheumatic drug
dRVVT:	Dilute Russell viper venom time
IBD:	Inflammatory bowel disease
IBM:	Inclusion-body myositis
IVIG:	Intravenous immunoglobulin
JIA:	Juvenile idiopathic arthritis
JRA:	Juvenile rheumatoid arthritis
MRI:	Magnetic resonance imaging
NSAID:	Nonsteroidal anti-inflammatory drug
PM:	Polymyositis
PsA:	Psoriatic arthritis
RA:	Rheumatoid arthritis
RF:	Rheumatoid factor
Scl:	Scleroderma
SLE:	Systemic lupus erythematosus
SNSA:	Seronegative spondyloarthropathy
SS:	Sjögren syndrome
USpA:	Undifferentiated spondyloarthropathy
VDRL:	Venereal disease research laboratory

In this chapter we will provide the basics for clinicians who might be called on in their practice to consider the diagnosis of diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We will emphasize clinical recognition and first-line laboratory testing. Characteristics of the classic rheumatic inflammatory diseases (ie, RA and its variants, seronegative spondyloarthritis [SNSA], SLE, antiphospholipid syndrome [APLS], Sjögren syndrome [SS], scleroderma [Scl], and polymyositis [PM]/dermatomyositis [DM]) will be covered.

To begin, some general principles relative to these disease entities will be outlined to place them in the overall context of autoimmune and chronic inflammatory disorders. First, although often described as autoimmune diseases and displaying immunologic features, the cause and pathophysiology of these diseases are poorly understood. Infections, toxins, and drugs have been implicated as well, but there is no consensus about causation. The standard textbook explanation is that an interplay among genetic, hormonal, environmental, and immunologic factors produces these illnesses.

Second, these diseases are probably more accurately described as syndromes. Does each category represent one entity with a single cause? More likely, we are dealing with clinical syndromes with similar phenotypes, resulting from many distinct insults.

Third, female subjects have these syndromes more commonly than male subjects and often do so relatively early in adult life. The responsible hormonal or reproductive predisposing factors remain unknown.

Fourth, these diseases feature autoantibodies, and the antigenic reactivity profile of each is helpful in establishing the diagnosis. In most cases, though, we are lacking direct proof that the

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autoantibodies are pathogenic rather than bystander phenomena. It is also unknown, for example, whether an autoantibody to human native DNA develops in response to autologous, viral, or bacterial RNA/DNA or even to other materials (phospholipids) that structurally resemble DNA. Moreover, approximately 20% of patients with RA have negative rheumatoid factor (RF) and anti–cyclic citrullinated peptide (anti-CCP) antibody test results. Only 40% to 50% of patients with SLE have anti-DNA antibodies, although 99% have positive antinuclear antibody (ANA) test results. A substantial fraction, approximately one third, of patients with SS, Scl, and PM/DM are also serologically negative. Either there are as yet undiscovered antibodies, or autoantibodies are not mandatory players in the pathogenesis. Furthermore, positive but usually low-to-moderate titers of ANAs and RFs are commonly detected in most chronic inflammatory diseases.

Fifth, for unclear reasons, these diseases tend to pick an organ system (RA, synovial joints; SS, exocrine glands; Scl, skin; and PM/DM, muscle) to damage. The autoantibody profile, although facilitating disease classification, does not tell us why the skin is a major target in patients with Scl or the synovial-based joints are major targets in patients with RA. Multiorgan involvement is particularly characteristic of SLE, probably because of immune complex deposition in vascular structures.

Sixth, except for Scl, these diseases generally respond to anti-inflammatory and immunosuppressive drugs. Such a response, of course, does not mean that the immune system was at fault initially but does imply a role for immunologically mediated inflammation in producing tissue damage. A persistent stimulus or an overactive inflammatory response mediated by the innate or adaptive arms of the immune system could be the responsible process.

In the past decade, RA is the entity for which treatment has substantially improved. The management of RA has been revolutionized by the regular use of methotrexate and, more recently, use of this agent in combination with a TNF inhibitor, a T-cell costimulation modulator, or B-cell depletion therapy. The goal of RA treatment today is to induce a complete remission as early as possible with the objective of eliminating the synovitis to prevent joint destruction. The hope is that if the major mediators of SS, SLE, or Scl can be identified and then blocked, as per the example of TNF inhibitors in patients with RA, more specific and efficacious treatments await us. Thus RA has become an excellent model for this evolving paradigm. Through the identification of key players in pathogenesis, novel and effective therapeutic agents have been developed, and more are anticipated.

RA

General information

RA is a symmetric inflammatory polyarthritis that affects approximately 1% of the population and accounts for significant morbidity and mortality. RA occurs worldwide, increases in incidence with age, and affects women about 3 times more often than men. Although the cause of RA is unknown, we have learned much about the inflammatory process that leads to joint destruction and how we might selectively target this process.

Clinical features

The clinical presentation and course of RA are variable. Patients most often have an insidious onset of symmetric joint pain, swelling, and morning stiffness that worsens over several weeks. Generalized malaise and fatigue accompany active inflammation. Progressive joint damage from suboptimally controlled RA leads to deformities and increasing disability.

Physical findings in patients with RA include symmetric joint inflammation early in the course of the disease and later manifestations of joint destruction with chronic disease. Classically, RA causes synovitis in the metacarpophalangeal, proximal interphalangeal, and wrist joints in a symmetric distribution. Clinically, this is manifested as swelling, warmth, tenderness, and loss of range of motion and grip strength in the hands. Range of motion can be restricted in deeper joints, in which demonstration of other signs is not possible. RA commonly affects the knees, shoulders, ankles, and feet, as well as the hips and cervical spine.

Extra-articular manifestations of RA include subcutaneous rheumatoid nodules, vasculitic skin ulceration, sicca symptoms of dry eyes and dry mouth, pulmonary nodules and pulmonary interstitial fibrosis, mononeuritis multiplex, and Felty syndrome (triad of RA, neutropenia, and splenomegaly). However, with the discovery of more effective treatments, extra-articular manifestations of RA are less common than in previous decades.

Immunologic features and disease pathogenesis

The underlying cause of RA remains incompletely understood. Data from the past decade support an immune-mediated process leading to joint inflammation and destruction. Genetic studies have demonstrated links to major MHC class II molecules. In particular, patients with the shared epitope, which is found in the hypervariable region of the HLA-DR β chain, are more likely to have RA than those without it. Environmental factors, such as cigarette smoking, have been identified as risk factors for RA. Other, yet to be identified genetic and environmental factors are likely also involved. The purported scenario is that a genetically susceptible subject is exposed to particular environmental, hormonal, or infectious factors. Proinflammatory cytokines, including IL-1, IL-6, and TNF-α, have been linked to RA and thus provide new therapeutic targets.[1]

The pathogenesis of joint destruction in patients with RA includes synovial immune complex deposition, neutrophil infiltration, angiogenesis, and T-cell activation.[2] Blocking T-cell costimulation by antigen-presenting cells is a recently developed strategy for treating RA that provides evidence for the importance of T-cell activation in pathogenesis. Additionally, leukocytes, including macrophages, are subsequently activated and propagate the cytokine-rich inflammatory environment. The synovial membrane enlarges to form the pannus, which begins to invade the cartilage and bone. Finally, proliferation of the pannus leads to more profound cartilage destruction, subchondral bone erosions, and periarticular ligamentous laxity. Cytokine-stimulated osteoclast activity leads to erosions and periarticular osteoporosis.

The search for specific immunologic mechanisms has led to the discovery of autoantibodies in patients with RA. The role of these autoantibodies and their respective autoantigens in pathogenesis is unknown. The long-recognized RF, a polyclonal IgM directed against the Fc portion of IgG, is found in about two thirds of patients with RA. It binds to IgG-containing immune complexes and augments immunoinflammatory responses. RF is present in all subjects but in higher amounts in patients with RA. The key autoantibody convincingly associated with RA is against citrullinated peptides. In the past decade, measurement of the anti-CCP antibody has become recognized as a highly specific and fairly sensitive diagnostic test for RA. It occurs in approximately 60%

TABLE I. American College of Rheumatology criteria for the classification of rheumatoid arthritis

1. Morning stiffness lasting >1 hour
2. Swelling of ≥3 joints observed by a physician
3. Symmetric distribution of joint involvement
4. Involvement of the wrists, metacarpophalangeal joints, and proximal interphalangeal joints, sparing the distal interphalangeal joints
5. Positive RF test result
6. Rheumatoid nodules on extensor tendon surfaces
7. Radiographic changes (periarticular osteopenia and erosions)

For the diagnosis of RA, a patient should have at least 4 of the 7 criteria. Criteria 1 through 4 must be present for at least 6 weeks.

of patients with RA and is more specific than RF for the diagnosis of RA. RF and anti-CCP antibodies can be identified in patients years before they have clinical disease, suggesting that the disease process begins long before it is clinically apparent. The mechanisms that facilitate the transition to clinical disease are unknown but are likely varied and multiple.

Diagnosis

The American College of Rheumatology classification criteria for the diagnosis of RA (Table I) were designed for inclusion of patients in clinical studies and not for routine clinical diagnosis. In fact, an important limitation of these criteria is that they were derived from hospitalized patients with established RA and have not been validated for the diagnosis of "early RA." However, for the clinician unfamiliar with RA, they are beneficial as guidelines for the evaluation of patients with suspected RA. In practice, a patient with symmetric inflammatory polyarthritis of the small joints of the hands with a positive RF test result, CCP antibody test result, or both likely has RA. In fact, if both RF and CCP antibody test results are positive, the diagnosis of RA is almost certain. A positive RF test result, anti-CCP antibody test result, or both in a patients with RA portends more aggressive clinical disease and radiographic damage. Nonspecific indicators of inflammation, such as erythrocyte sedimentation rate and C-reactive protein level, might be increased and might also correlate with the severity of clinical disease.[2]

Recent studies support the value of early recognition and aggressive treatment of RA to limit long-term disease sequelae. If there is a clinical suspicion of RA,[3] prompt referral to a rheumatologist and immediate initiation of therapy to prevent damage is recommended.

Treatment

The goals of treatment in patients with RA are to control inflammation, prevent progressive joint destruction, preserve and improve performance of activities of daily living, and alleviate pain. Medical treatment includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and corticosteroids. Nonpharmacologic treatment, including patient education, physical therapy, occupational therapy, orthotics, and surgery, is also important in the management of RA.

Initiation of DMARD therapy within 3 months of diagnosis is currently recommended. DMARDs suppress immune-mediated inflammation by decreasing the activity of target cells (eg, lymphocytes) or specifically targeting cytokine pathways. Commonly used DMARDs include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. When maximal dosing of a DMARD provides suboptimal disease control, addition of other DMARDs often improves effectiveness. Routine monitoring for RA disease activity and drug toxicity is mandatory.

"Biologic DMARDs" targeting TNF-α include the fusion protein etanercept; the mAbs infliximab, adalimumab, and golimumab; and the pegylated TNF receptor fusion protein certolizumab pegol. Other currently available biologic DMARDs include abatacept (a cytotoxic T-lymphocyte antigen 4 fusion protein that blocks T-cell costimulation by antigen-presenting cells), rituximab (an mAb to CD20 that depletes B cells), and the IL-1 receptor antagonist anakinra. Tocilizumab is an mAb to the IL-6 receptor recently approved for the treatment of RA.

Corticosteroids in low doses (≤10 mg of prednisone) are effective for promptly reducing the symptoms of RA, but care should be taken to use the lowest effective dose. Corticosteroids are appropriate in patients with significant limitations in their activities of daily living, particularly early in the course of disease while awaiting the efficacy of the generally slower-acting DMARDs.

NSAIDs, including the selective COX-2 inhibitors, are commonly added to treatment regimens for pain relief and to decrease inflammation. However, they should be used with caution because of their potential to increase cardiovascular risk, which is increased anyway in patients with RA.

JUVENILE IDIOPATHIC ARTHRITIS

Clinical features

Juvenile idiopathic arthritis (JIA; formerly juvenile rheumatoid arthritis [JRA]) represents a family of inflammatory articular disorders that occur before the age of 16 years. Six distinct presentations have been described in patients with JIA. There are 2 subtypes of the polyarthritis (≥5 joints, previously called polyarticular-onset JRA): those with positive RF test results, who generally have more severe disease, and those with negative RF test results. Patients with 4 or fewer joints involved are said to have oligoarthritis (previously called pauciarticular-onset JRA). Young girls with oligoarthritis and a positive ANA test result are at increased risk for chronic iritis. Systemic disease (previously called systemic-onset JRA or Still disease) is characterized by intermittent fever, hepatosplenomegaly, lymphadenopathy, leukocytosis, pleuropericarditis, and the classic "Still rash," a faint, evanescent, salmon-colored eruption that tends to occur during periods of fever. The Koebner phenomenon refers to the fact that this rash can be elicited by stroking the skin. Adult Still disease is a similar syndrome occurring in adults. Differential diagnosis includes SLE, spondyloarthropathy, infectious arthritis, Henoch-Schönlein purpura, vasculitic syndromes, inflammatory bowel disease (IBD), leukemia, sickle cell anemia, and hemophilia.

TABLE II. Characteristics of the seronegative spondyloarthropathies

Disease	Pattern of arthritis	Cutaneous involvement	Other features
AS	Axial: sacroiliitis, continuous involvement of lumbar through cervical spine		
PsA	1. Distal interphalangeal arthritis	Psoriasis, nail pitting associated with distal interphalangeal arthritis	Onset of arthritis before, simultaneous with, or after psoriasis; cervical spine involvement without lumbar spine involvement
	2. Peripheral oligoarthritis		
	3. Symmetric polyarthritis		
	4. Arthritis mutilans		
	5. Spondylitis and sacroiliitis		
Reactive arthritis	Asymmetric oligoarthritis, lower extremity > upper extremity	Keratoderma blennorrhagica, circinate balanitis, psoriasis-like nail changes	Onset days to 6 wk after bacterial gastroenteritis or genitourinary *Chlamydia* species infection
IBD-associated spondyloarthritis	Axial: spondylitis, sacroiliitis Peripheral:		Equal prevalence in men and women
	1. oligoarthritis		
	2. polyarthritis		
USpA	Spondylitis, sacroiliitis, and/or peripheral arthritis		

Enthesitis-related arthritis is characterized by arthritis, enthesitis, and at least 2 of the following: sacroiliac joint tenderness, inflammatory pain of the spine, HLA-B27 positivity, uveitis, or family history of painful uveitis, spondyloarthropathy, or inflammatory bowel disease (IBD). Psoriatic arthritis (PsA) includes children with arthritis who either have psoriasis or a family history of psoriasis.

Immunologic features

RF (see RA) test results are positive in 5% to 10% of older patients with polyarticular symmetric disease. ANA (see SLE) test results tend to be positive in young girls with oligoarthritis and chronic inflammatory eye disease.

Treatment

The medications used for the treatment of JIA include many of the same ones used for the treatment of RA: NSAIDs, prednisone, sulfasalazine, hydroxychloroquine, methotrexate, TNF inhibitors, anakinra, and abatacept. A pediatric rheumatologist should be consulted. The chronic iridocyclitis in patients with JIA is usually asymptomatic until visual loss occurs from glaucoma because of a chronic increase of intraocular pressure. Children with JIA should undergo an eye examination every 3 to 12 months by an ophthalmologist.

SERONEGATIVE SPONDYLOARTHROPATHIES

General information

The seronegative spondyloarthropathies (SNSAs) are a group of inflammatory arthropathies affecting axial and peripheral joints sometimes associated with extra-articular features (Table II). They include ankylosing spondylitis (AS), PsA, reactive arthritis, and IBD-associated arthritis. Patients with undifferentiated spondyloarthropathy (USpA) have features of the SNSAs but do not fulfill the diagnostic criteria for any of them.

Clinical features

The spondyloarthropathies are more common in men than in women. Onset is generally before the fifth decade. Patients present with inflammatory symptoms affecting the spine, the peripheral joints, and/or the entheses (tendon or ligament insertions). Inflammatory back pain has gradual onset, is associated with morning stiffness, and is improved by activity. Sacroiliitis is common and often presents with buttock pain. Peripheral arthritis is typically asymmetric and affects 3 or fewer joints of the lower extremities. Dactylitis or "sausage digit" reflects inflammation of the soft tissue of an entire digit and is frequently seen in patients with PsA and reactive arthritis.

Inflammatory eye disease is commonly seen in the SNSAs, including conjunctivitis, which is generally benign, and anterior uveitis (iritis), which can threaten vision and should be evaluated by an ophthalmologist. A majority of patients with SNSAs have bowel inflammation, usually asymptomatic,[4] and 30% of patients with IBD have SNSAs.[5] Among patients with psoriasis, a recent cross-sectional study revealed a 19% prevalence of PsA.[6]

Levels of acute-phase reactants are often increased in patients with SNSAs. HLA-B27 levels are positive in about 90% of white subjects with AS and in 70% with USpA. Early sacroiliitis is visible on magnetic resonance imaging (MRI), but plain radiographic evidence of sacroiliitis can take years to develop. Sacroiliitis is usually symmetric in patients with AS but can be asymmetric in patients with PsA or USpA. Plain radiographs of the spine show bridging syndesmophytes in patients with advanced AS, with the "bamboo spine" appearance reflecting complete spine fusion. Syndesmophytes in patients with PsA are often nonmarginal and asymmetric in contrast to those seen in patients with AS.

Immunologic features

HLA-B27 is associated with the SNSAs, but only a small percentage of subjects with HLA-B27 have SNSAs, suggesting interplay between genetic and environmental factors. HLA-B27

transgenic rats have SNSA-like disease spontaneously, suggesting a critical role for HLA-B27 in pathogenesis, although the nature of that role is unknown.[7] Interestingly, the B27 transgenic rats did not have SNSA-like disease when raised in a germ-free environment.[8] HLA-B27 on the surface of antigen-presenting cells preferentially binds certain antigens. One hypothesis is that arthritogenic peptides bind HLA-B27 and cross-react with autoantigens.

IBD-associated arthritis might provide a model for pathogenesis of the SNSAs. Arthritis is thought to result when gut inflammation increases intestinal permeability in a susceptible host, allowing absorption of bacterial or other material that increases secretory IgA levels and activates lymphocytes and macrophages. Exactly how this initiates musculoskeletal inflammation is unknown. A similar breach of normal barriers to foreign proteins likely occurs in the gut or the genitourinary tract in patients with reactive arthritis and possibly in the skin in patients with PsA. The asymptomatic bowel inflammation seen in patients with AS might be analogous to IBD-associated increased intestinal permeability.

Diagnosis

Early diagnosis is beneficial because of the availability of effective therapy for the SNSAs. A definitive diagnosis of AS can be made on the basis of inflammatory back pain lasting more than 3 months in the setting of radiographic sacroiliitis. MRI is more likely than a plain radiograph to reveal early sacroiliac inflammation. A patient with inflammatory spine pain or peripheral synovitis who also has one of the following likely has an SNSA and should be referred to a rheumatologist: psoriasis, IBD, acute infection (gastroenteritis, urethritis, or cervicitis) preceding the arthritis, enthesopathy, radiographic sacroiliitis, or a family history of a SNSA.[9]

Treatment

NSAIDs frequently reduce symptoms in patients with the SNSAs. Peripheral joint involvement in patients with the SNSAs often responds to the oral DMARDs used to treat RA, particularly sulfasalazine. The anti-TNF medications etanercept, infliximab, adalimumab, and golimumab have demonstrated considerable efficacy for axial disease. Another TNF inhibitor, certolizumab, is approved for use in IBD and can benefit IBD-associated arthritis. Current data suggest that the TNF inhibitors do not slow the spinal radiographic changes of the SNSAs.[10,11] Local glucocorticoid injections in inflamed joints or entheses, except for the Achilles tendon insertion, can be effective.[12]

Despite the possible role of infections in the pathogenesis of the SNSAs, antibiotics are ineffective in the treatment of these conditions, except in treating the gastrointestinal or genitourinary tract infections that lead to the development of reactive arthritis.

Physical therapy is beneficial in maintaining function and reducing pain. Because of the risk of restrictive lung disease resulting from thoracic spine disease, smoking cessation is important. Joint replacement is beneficial when more conservative measures fail for severe pain or impaired function.

SLE

General information

SLE is a multisystemic "autoimmune" disease affecting the joints, skin, heart, lungs, central nervous system, kidneys, and hematopoietic system. In 99% of patients, it is associated with a positive ANA test result by means of indirect immunofluorescence with the Hep-2 epithelial tumor cell line as substrate. Young women of childbearing age are most commonly affected; drug-induced disease also occurs but is rare today. The most common mistake made in establishing the diagnosis of SLE is inappropriate emphasis on the positive ANA test result in the absence of clinical features of this disease. The ANA test is sensitive but not specific for SLE.

Clinical features

SLE has protean manifestations. The clinical skills of a physician might be tested when assessing whether a patient has this diagnosis.[13] The American College of Rheumatology has articulated 11 clinical classification criteria, of which 4 must be satisfied for the diagnosis. However, these criteria were established for the purpose of including patients in clinical trials and not for making the initial diagnosis in clinical practice. Although these criteria can serve as a general guide for recognizing the clinical features of SLE, "counting criteria" is no substitute for clinical judgment in making the diagnosis of SLE (Table III). Alopecia, Raynaud phenomenon, and systemic complaints, such as fever and fatigue, are other common manifestations of SLE. APLS (see below) is frequently encountered in patients with SLE, particularly in the setting of thromboembolic disease and neuropsychiatric events.

Immunologic features

The immunopathology of SLE has been the subject of many sophisticated and intricate hypotheses, which unfortunately have been impossible to prove or disprove. SLE is characterized by immune complex deposition, of which the best example is glomerulonephritis. The other central concept in the immunopathology of SLE is the presence of autoantibodies; although their presence is indisputable, they might not always be pathogenic but rather epiphenomena. The autoantibodies associated with SLE are perhaps the most confusing and misunderstood characteristics of this disease.[14] The ANA test by means of indirect immunofluorescence is so sensitive that a negative test result effectively rules out the diagnosis of SLE. (Note: The ELISA ANA testing now available is not recommended for screening because 10% to 20% of patients with SLE might have negative results with this currently unsatisfactory method.) The indirect immunofluorescence technique often produces low-to-moderate titers of ANA in patients with chronic inflammatory conditions and sometimes in healthy subjects; thus reduced specificity is the price paid for the high sensitivity of this test. The higher the titer, the more likely SLE or a related syndrome is present. Therefore the ANA test is most useful in testing the clinical hypothesis that a patient might have SLE in that a negative test result excludes the diagnosis, whereas a positive test result means that a diagnosis of SLE is possible but not established. If the ANA test is used as a screen for autoimmune disease, a positive ANA test result has little or no immediate significance, especially in the absence of clinical evidence of SLE.

Antibodies to double-stranded DNA, by contrast, have lower sensitivity but high specificity: a high titer of anti-DNA antibodies makes the diagnosis of SLE very likely, although a negative anti-DNA test result does not exclude the diagnosis because 50% of patients with SLE never have anti-DNA

TABLE III. American College of Rheumatology classification criteria for SLE*

1. Malar rash: fixed malar erythema, flat or raised, sparing nasolabial folds
2. Discoid rash: erythematous raised patches with keratotic scaling and follicular plugging
3. Photosensitivity: skin rash as an unusual reaction to sunlight
4. Oral or nasopharyngeal ulcers
5. Arthritis: nonerosive
6. Serositis: pleuritis or pericarditis
7. Renal disorder: proteinuria (>0.5 g/d or >3+) or cellular casts
8. Neurologic disorder: seizures or psychosis
9. Hematologic disorder: hemolytic anemia or leukopenia (<4,000/mL), lymphopenia (<1,500/mL), or thrombocytopenia (<100,000/mL)
10. Immunologic disorder: anti–double-stranded DNA, anti-Smith, false-positive test result for syphilis, or positive lupus erythematosus (LE) cell preparation (a test rarely performed)
11. Abnormal titer of ANA by means of immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

*Note that these are classification criteria and not diagnostic criteria. The diagnosis of SLE is based on the physician's overall evaluation. SLE often presents with a positive ANA test result and single organ system involvement. Diagnosis by counting criteria is not how one makes an initial diagnosis of SLE.

antibodies. There are 2 common techniques for detecting anti-DNA antibodies. The *Crithidia luciliae* technique is an indirect immunofluorescence test analogous to the ANA test. The *Crithidia* organism contains a kinetoplast that is comprised of pure double-stranded DNA, a convenient target for anti-DNA antibodies when the organisms are fixed to a microscope slide. The other technique is an ELISA, which is a quantitative assay with the potential to allow processing of large numbers of samples rapidly in an automated fashion.

Another highly specific assay for the presence of SLE is anti-Smith, which reacts with one of the soluble extractable nuclear antigens. It occurs in approximately 25% of patients with SLE. Anti-ribonucleoprotein can be seen in some cases of SLE, especially in the setting of myositis, but is classically associated with mixed connective tissue disease when present in high titers. Anti-Ro (SSA) is observed in approximately 25% of patients with SLE, especially those with subacute cutaneous lupus erythematosus, an annular erythematous rash that heals without central scarring, in contrast to discoid lupus erythematosus rash, which does produce scarring. Anti-Ro and anti-La are serologic markers for the neonatal lupus syndrome, which is characterized by congenital heart block, thrombocytopenia, and an annular rash. This is an excellent example of pathogenic antibodies in the mother that cross the placenta and induce disease in the newborn. Ironically, about 50% of the mothers of babies with neonatal lupus do not clinically have SLE yet carry the autoantibodies. Nevertheless, neonatal lupus only occurs in 15% to 20% of the children born to mothers with SLE who have positive anti-Ro/La test results, and of those, approximately 15% have skin disease and 1% to 2% have congenital heart block.

Serum complement levels C3 and C4 might be decreased in patients with active disease because of complement consumption by immune complexes, especially in the setting of active glomerulonephritis. Levels usually increase with clinical improvement, although they do not always normalize. The total hemolytic complement assay is not particularly sensitive for detecting complement consumption but is valuable in detecting an isolated complement component deficiency (C1q, C1r, C1s, C4, or C2), which usually presents with an SLE-like syndrome (albeit rare, occurring in 0.5% to 1% of patients with SLE).

More recently, an IFN-α signature, meaning activation of many genes by increased levels of this cytokine, has been recognized in a substantial fraction (approximately 50%) of patients with SLE. Treatments designed to interfere with this process are awaited. Lastly, whole-genome screens have identified many additional targets for therapeutic intervention.

Treatment

A common misconception is that all patients with SLE require therapy with systemic corticosteroids, when in fact, milder manifestations of the disease can be treated with less potent medications. Rash can be effectively treated with topical corticosteroids, but care must be taken to avoid use of fluorinated corticosteroids on the face because of the potential for the development of subcutaneous atrophy. Hydroxychloroquine can be effective for control of skin disease, as well as for arthritis. NSAIDs and low daily doses of prednisone (10-20 mg) can bring relief from arthritis and milder cases of pleurisy and pericarditis; more severe cases require high daily doses of corticosteroids (40-60 mg of prednisone). Kidney disease that threatens renal function is typically treated with high-dose corticosteroids and intermittent intravenous cyclophosphamide or oral mycophenolate mofetil. Treatment decisions must be individualized for the particular clinical situation.

APLS

General

APLS can occur as part of SLE or as an idiopathic isolated entity. Ten percent to 30% of patients with SLE have antiphospholipid antibodies (APAs), and of those, 30% to 50% have APLS. Conversely, about 50% of patients with APLS have SLE. Serologic hallmarks of this prothrombotic disorder have been recognized for a long time as the biological false-positive test result for syphilis and the lupus anticoagulant. It was not, however, until the early 1980s that a clinical syndrome consisting of venous and arterial thrombotic events and recurrent miscarriages was widely recognized as being related to these tests. Thus we have the paradox of a clinical syndrome featuring excessive clotting diagnosed by the prolongation of a coagulation test that might be expected to lead to excessive bleeding.

Clinical features

These patients are usually young and middle-aged women, with or without lupus, who present with a prothrombotic medical

history. The second major feature is a history of multiple miscarriages, especially in the second and third trimesters. A patient might have only venous or arterial thromboses, miscarriages, or a combination thereof. The most common problem is deep venous thrombosis, whereas on the arterial side, strokes and transient ischemic attacks are prominent. However, any vessel can be involved, leading to infarctions of the gut, heart, adrenals, and extremities. Miscarriages most likely relate to thrombosis of placental vessels, leading to infarction, placental insufficiency, and a small fetus. Livedo reticularis, which is observed in about one third of patients, is readily apparent on physical examination. Patients with APLS also commonly have thrombocytopenia, which is sometimes severe, but usually in the 75,000/mm^3 to 150,000/mm^3 range.[15] The diagnosis should be strongly considered in young women with no explanation for their thromboses or if the thromboses are in unusual sites. Catastrophic APLS is rare. It occurs when there are acute, multiple, diffuse, simultaneous vascular infarcts, often with a lethal outcome.

Cause and pathogenesis

How APAs induce thrombosis is unknown. Inhibition of protein C activation, activation of platelets, alterations in prostaglandin synthesis, and stimulation of endothelial cells have been proposed. There is *in vitro* evidence to support each possibility. In a murine model animals injected with APAs from patients display fetal wastage caused by placental destruction by antibodies and complement. Patient-derived APAs also facilitate thrombus formation in other murine organs.

Laboratory tests

Four tests for APAs are lupus anticoagulant, anticardiolipin antibodies (ACLAs), antibody to β_2-glycoprotein 1 (β2GP1), and the false-positive venereal disease research laboratory (VDRL) tests. In the lupus anticoagulant test the activated partial thromboplastin time (aPTT) is prolonged but is not corrected by mixing with normal plasma (to rule out a factor deficiency); it is, however, normalized by addition of phospholipids (to compensate for the phospholipids tied up by the APA). The failure of the prolonged aPTT to correct with the addition of normal plasma combined with correction of the prolonged aPTT by the addition of phospholipid defines the phenomenon referred to as "lupus anticoagulant."

Another test for this is the dilute Russell viper venom time (dRVVT). This is analogous to the aPTT, except that dilute Russell viper venom replaces activated thromboplastin as the stimulus for the intrinsic coagulation pathway. The advantages of the dRVVT are that it is more sensitive for the detection of smaller amounts of APA than the aPTT (the dRVVT might be prolonged even with the aPTT is not) and that it can be performed in the setting of therapeutic anticoagulation. ACLAs are detected by using an ELISA, which can measure IgG, IgM, and IgA ACLAs. Medium-to-high titers of IgG are most diagnostic.

Another ELISA detects antibodies to β2GP1, a plasma protein that binds negatively charged phospholipids; the ACLAs in patients with APLS are often directed to β2GP1. It might function as an anticoagulant through its binding to phospholipids, and therefore interference with its function by antibodies could induce thrombosis.

Finally, the "false-positive VDRL" (so-called because the fluorescent treponemal antibody [FTA] test result is negative for syphilis) reflects the presence of antibodies that react with cardiolipin.

Treatment

Among patients with asymptomatic APA, the risk of thrombosis is 0% to 3.8% annually.[16] Aspirin has not been shown to be effective in preventing first thrombosis. Other risk factors for thrombosis, including smoking and oral contraceptive use, should be addressed. Once a thrombosis has occurred, recurrence is common, and patients are usually treated indefinitely with oral anticoagulants. Although some patient subsets respond solely to aspirin, most require prolonged warfarin therapy in which the international normalized ratio goal is 2.0 to 3.0, although there is controversy as to how high the target international normalized ratio should be. Treatment is usually successful in preventing further episodes. Regimens using heparin, aspirin, intravenous immunoglobulin (IVIG), and prednisone are used as monotherapy and in various combinations to treat recurrent pregnancy wastage. Patients who have recurrent vascular thrombosis despite adequate oral anticoagulation are also treated in this manner. Catastrophic APLS is managed with a combination of anticoagulation, high-dose corticosteroids, plasma exchange, IVIG, and, in some instances, immunosuppression with cyclophosphamide or rituximab.[3] It has a very high mortality rate.

SS

Background

SS is a chronic autoimmune disease affecting the exocrine glands, particularly the lacrimal and salivary glands (autoimmune exocrinopathy). SS affects approximately 0.3% to 0.6% of the population worldwide and is one of the most common autoimmune diseases. With a female/male ratio of 9:1, SS exhibits one of the highest female/male ratios among the autoimmune diseases and has a peak incidence in the fourth and fifth decades. SS can occur alone, when it is called primary SS, or in association with another defined autoimmune disease (eg, SLE, RA, or Scl), when it is termed secondary SS.[17]

Clinical features

The most common symptoms are dry eyes (xerophthalmia) and dry mouth (xerostomia), together called sicca symptoms. Patients present with symptoms of ocular discomfort and visual disturbance caused by tear film instability and inflammation of the ocular surface.[18] Patients complain of difficulty eating dry foods. Decreased salivary flow leads to frequent dental caries and accelerated periodontal disease. The most prominent sign of SS is swelling of the parotid gland, which can be unilateral or bilateral and is often recurrent. The most common cutaneous finding in patients with SS is dry skin; less commonly, palpable purpura, urticaria, and annular lesions occur. Arthralgias are common. Pulmonary manifestations of SS include dryness of the airways, hyperreactive airway disease, interstitial lung disease, lymphoproliferative diseases, pulmonary hypertension, and amyloidosis.[19] Nonspecific interstitial pneumonia, a type of interstitial lung disease, is the most common pulmonary pathology seen in patients with primary SS.[20]

Dysphagia, esophageal webs and/or dysmotility, chronic atrophic gastritis, and rarely ischemic colitis caused by vasculitis are gastrointestinal features of SS. Neurologic complications in patients with SS are varied and include meningitis, myelopathy, cranial neuropathy, sensorimotor polyneuropathy, and mononeuritis multiplex. The syndrome of pure sensory neuropathy is characteristic of primary SS.[21] Patients who have SS are at risk for lymphomas, usually low-grade, non-Hodgkin, mucosal associated lymphoid tumor–associated lymphomas.[22,23] Certain patient characteristics are predictive of lymphoma, including low C4 levels, especially at the time of presentation[24]; recurrent glandular swelling; palpable purpura; and increased IgM levels.[24,25] Such patients require close observation and monitoring for malignant changes.[25] A recent study in Sweden and a meta-analysis found the relative risk for lymphoma in patients with primary SS to be between 16 and 18 compared with the general population.[26,27] Infants of mothers with SS with a high titer of antibodies to SSA/Ro have an increased risk of congenital heart block.

Pathogenesis

Recent evidence suggests that glandular epithelial cells play a central role in the pathogenesis of SS.[28] The glandular epithelial cells found in patients with SS are immunologically activated, expressing MHC class I and II molecules and B7 costimulatory molecules. These epithelial cells release proinflammatory cytokines and chemokines that attract lymphocytes into the affected glands, producing the characteristic periductal, focal, lymphocytic infiltrate with T_H cells, B cells, and plasma cells observed in SS. The initial event that stimulates the activation of these glandular epithelial cells is unknown, but persistent viral infections might play a role.[29] Chronic HIV and hepatitis C infection can lead to a glandular pathology similar to that found in patients with idiopathic SS, and patients infected with such viruses often have sicca symptoms and glandular swelling.

Diagnosis

Antibodies to Ro/SSA and La/SSB are the best-characterized serologic features of SS. Anti-La antibodies are almost invariably accompanied by anti-Ro antibodies because of the physical association of these molecules in Ro/La ribonucleoprotein particles, but anti-Ro antibodies frequently occur in the absence of anti-La antibodies. Anti-Ro antibodies are present in approximately 70% and anti-La antibodies in 40% of patients with primary SS. Anti–thyroid microsomal and anti–gastric parietal cell antibodies are seen in a third of patients with primary and secondary SS. Other antibodies reported in patients with SS include perinuclear antineutrophil cytoplasmic antibodies and antibodies directed against carbonic anhydrase, proteasomal subunits, α-fodrin, and the muscarinic M3 receptor.[30] Positive test results for ANA and RF are present in 60% to 80%, and polyclonal hypergammaglobulinemia is demonstrable in 50% of patients with primary SS.

Diagnosis of primary SS according to the current American European Consensus Group criteria requires that at least 4 of the following 6 criteria be present: subjective xerophthalmia, subjective xerostomia, objective tests of xerophthalmia, objective evidence of salivary gland dysfunction, presence of either anti-Ro/SSA or anti-La/SSB antibodies, and histopathologic criteria for SS on minor salivary gland biopsy. One of the 4 criteria must be either positive by means of serology or positive by means of histopathology.[31] Xerophthalmia is often demonstrated by using the Schirmer test, in which a standardized strip of filter paper is placed for 5 minutes between the eyeball and the lateral part of the inferior eyelid. The test result is positive when the wetting is 5 mm or less in 5 minutes. Saliva production tests, the results of which are considered positive when 1.5 mL or less of whole saliva is collected in 15 minutes, although highly specific for SS, are rarely done in clinical practice.

Treatment

The mainstay of treatment of dry eye disease in patients with SS is lubrication with a variety of artificial tear supplements. Recently, topical cyclosporine 0.05% emulsion has been approved for and shown to be effective in patients with decreased tear production caused by inflammation, including those with SS. In patients with inadequate response to artificial tears, punctal occlusion performed by an ophthalmologist might help retain the instilled artificial tears. Attention to dental hygiene and use of topical fluorides might retard dental caries and periodontal disease. Orally administered secretagogues improve dry mouth symptoms better than dry eye symptoms, and their use is mainly limited by their cholinergic side effects of sweating and diarrhea. Pilocarpine, the first approved secretagogue for SS, was shown in a prospective, randomized clinical trial to be effective in improving symptoms of dry mouth, with a smaller effect on symptoms of dry eye.[32] Cevimeline, another secretagogue, might be better tolerated than pilocarpine and is effective in treating symptoms of both dry eyes and mouth.[33]

Arthralgias might respond to nonsteroidal anti-inflammatory agents or antimalarial agents. Systemic steroids and cytotoxics are mainly used for treatment of extraglandular complications, such as vasculitis, pulmonary disease, and neurologic involvement. Two randomized controlled trials, one with infliximab and another with etanercept, showed a lack of efficacy of these TNF antagonists in patients with primary SS.[24,25] Recently, rituximab, an anti-CD20 mAb, has shown efficacy in the treatment of primary SS in 3 open-label studies and 1 randomized controlled trial, indicating that B-cell modulation might be a promising new treatment strategy for this disease.[26,34,35]

SCL

General information

Scl (also called systemic sclerosis) is a systemic disorder characterized by excess collagen deposition in the skin and viscera, along with vascular abnormalities, including vasospasm and microvascular occlusion. There are 2 subsets of Scl with differing clinical presentations and prognosis: limited and diffuse Scl. A localized form of disease can occur, and there are several Scl-like disorders that must be distinguished from Scl (Table IV). Scl has a peak age at onset of 35 to 65 years and a female/male ratio of approximately 3:1.

Clinical features

The hallmark of both limited and diffuse Scl is thickening of the skin. In limited disease this is gradual in onset and, by definition, is limited to the hands, face, forearms, and feet (Table V). In diffuse disease both the pace and extent of skin

TABLE IV. Classification of Scl

Systemic sclerosis
Diffuse Scl
Limited Scl
Localized Scl
Morphea Scl
Linear Scl
Scl-like syndromes
Graft-versus-host disease
Diabetic cheiroarthropathy
Eosinophilic fasciitis
Scleredema
POEMS syndrome
Carcinoid
Drug induced
Bleomycin
Tryptophan
Occupational and environmental
Silica
Solvents
Trichlorethylene
Perchlorethylene
Vinyl chloride
Toxic oil
Nephrogenic systemic fibrosis

POEMS, Polyneuropathy, organomegaly, endocrinopathy/edema, M-protein, and skin abnormalities.

TABLE V. Comparison of limited and diffuse Scl

Manifestation	Limited	Diffuse
Site of skin involvement	Distal and face only	Distal and proximal
Pace of skin involvement	Slow	Rapid
Telangiectasias	+++	+ (late)
Calcinosis	+++	+ (late)
Tendon friction rubs	0	+++ (early)
Pulmonary hypertension	++	(+/−)
"Renal crisis"	0	++
ACA	+++	0
Survival (10 y)	>70%	<50%

thickening are more extreme, with involvement of the entire trunk and upper and lower extremities. Calcinosis and telangiectasias occur in both forms of the disease but later in diffuse disease. Musculoskeletal features of this disease include acro-osteolysis, myositis, and severe flexion contractures from skin and tendon involvement, particularly in diffuse disease.

Raynaud phenomenon is nearly universal among patients with Scl. In limited disease it can precede skin changes by months to years, but in diffuse disease the onset of both symptoms is usually nearly simultaneous. Raynaud phenomenon occurs in 10% to 20% of the general population, most of whom have no underlying or associated disorder. The differential diagnosis includes Scl and other connective tissue diseases; exposure to percussive or vibratory equipment; drugs, including ergots and sympathomimetics; and cryoglobulinemia.

Esophageal dysmotility is the most common gastrointestinal manifestation and can present with dysphagia, reflux, or stricture. Decreased small-intestine motility can also occur, resulting in bacterial overgrowth, diarrhea, and malabsorption. Large-intestine involvement presents as constipation or pseudo-obstruction.

Pulmonary parenchymal fibrosis is common but often asymptomatic and occurs in both forms of the disease. Approximately 10% to 30% of patients experience pulmonary hypertension, more commonly in those with limited disease. Cardiac involvement includes arrhythmias, microvascular ischemia, and congestive heart failure. Patients with diffuse Scl are at risk for "renal crisis," with hypertension, microangiopathy, and renal insufficiency without nephritis. Cardiopulmonary disease is the most common cause of death in both forms of Scl.

Immunologic features

The pathogenesis of Scl is unknown, but immune mechanisms appear to play a role. Polyclonal hypergammaglobulinemia is common. Approximately 80% of patients have ANA in a centromere or nucleolar pattern. Anticentromere antibody (ACA) is strongly associated with limited disease; anti–Scl-70 is more common with diffuse disease. Antibody to RNA polymerase III is strongly associated with renal crisis. There is an increased frequency of other autoimmune disorders, including hypothyroidism, primary biliary cirrhosis, and SS.

Microvascular occlusion is another hallmark of this disease. Endothelial cell activation results in increased levels of IL-1, which upregulates adhesion molecule expression. Platelet activation causes release of connective tissue growth factor, fibroblast-activating factor, platelet-derived growth factor, and TGF-β. TGF-β stimulates endothelin and fibroblast synthesis. Fibroblasts proliferate abnormally and also secrete increased amounts of collagen and fibronectin. Levels of tissue inhibitor of metalloproteinase 1, an inhibitor of procollagenase, are increased, resulting in decreased remodeling of tissue collagen matrix. The net result is an overproduction of collagen, endothelial fibrosis, and relative tissue ischemia.

Diagnosis

The diagnosis of Scl is made on clinical grounds, with Raynaud phenomenon and skin thickening as diagnostic clues. ACA or anti–Scl-70 antibody testing can be used to confirm the clinical suspicion. Skin biopsy is rarely needed. Occasionally, the diagnosis of "scleroderma sine scleroderma" is made in the setting of Raynaud phenomenon and severe esophageal dysmotility without skin thickening, particularly if ACA or anti–SCL-70 is present. Baseline and periodic pulmonary function tests and echocardiograms are useful in monitoring disease and guiding treatment.

Treatment

Treatment of patients with Scl is symptomatic and problem oriented. Management of Raynaud phenomenon includes avoiding cold exposure, nicotine, caffeine, and sympathomimetics. Raynaud phenomenon might respond partially to vasodilators, including calcium-channel blockers. Losartan and sildenafil might also be useful. Ischemic digital ulcers can be managed with cervical sympathetic blockade; prostacyclin infusion; phosphodiesterase-5 inhibitors, such as sildenafil; and meticulous local skin care. Arthritis and serositis generally respond to NSAIDs, which must be used cautiously. Corticosteroids are reserved for resistant symptoms. Use of moderate- to high-dose steroids might increase the risk of hypertensive crisis. This complication is treated with angiotensin-converting enzyme inhibitors. Proton pump inhibitors are used for esophageal symptoms and should be prescribed to all patients because of

TABLE VI. Myositis-specific autoantibodies

Autoantibody	Associated clinical manifestations	Response to therapy	Frequency in myositis
Antisynthetase (anti–Jo-1 is most common)	Antisynthetase syndrome: myositis, arthritis, fever, interstitial lung disease, "mechanic's hands," Raynaud phenomenon	Moderate	20% to 30%
Anti-SRP	Myalgias and severe weakness with cardiac involvement	Poor	<5%
Anti–Mi-2	Classic dermatomyositis	Good	5% to 10%

SRP, Signal recognition particle.

the high frequency of reflux and aspiration. Promotility agents can also be added. There is no definitive treatment for the skin thickening. Occupational therapy is of value in maintaining hand function. Pulmonary hypertension might respond to prostacyclin analogs, phosphodiesterase 5 inhibitors, or the endothelin 1 receptor blocker bosentan.[36] Patients with inflammatory interstitial lung disease might derive modest benefit from treatment with cyclophosphamide.[37]

POLYMYOSITIS, DERMATOMYOSITIS, AND INCLUSION BODY MYOSITIS

General information

PM, DM, and inclusion-body myositis (IBM) are the major distinct forms of idiopathic inflammatory myopathies.[38] These diseases are characterized by inflammation and weakness of skeletal muscle. The inflammatory myopathies are rare, with an incidence of approximately 1 in 100,000. Other categories of inflammatory myopathies include DM of childhood, PM and DM associated with neoplasia, and PM or DM associated with connective-tissue diseases, such as Scl, SLE, and mixed connective tissue disease.

Clinical features

PM and DM affect women more often than men, usually after the second decade of life. These inflammatory myopathies cause muscle weakness that is proximal and symmetric and progresses over weeks to months. Patients typically have difficulty climbing stairs, rising from a chair, or lifting objects above their heads. Neck flexor weakness or dysphagia can occur, but facial or ocular muscle involvement is rare. Systemic manifestations (fatigue, anorexia, and fever) are common. Up to 50% of patients have extramuscular involvement, usually cardiac (conduction defects and cardiomyopathy) or pulmonary (alveolitis and respiratory muscle weakness).

DM has skin findings that distinguish it from other myopathies. A lilac discoloration of the eyelids (heliotrope rash), often with periorbital edema, and erythematous papules over the knuckles (Gottron sign), elbows, knees, and ankles are characteristic. The DM lesions of the elbows and knees can resemble psoriasis. A macular rash of the face or upper anterior chest (V sign), upper back, or shoulders (shawl sign) is also seen in DM and is frequently photosensitive. Dilated nailfold capillary loops at the base of the fingernails can be visualized with a handheld ophthalmoscope set at +40 diopters. The skin of the fingers might be rough and cracked, with dark, "dirty" lines ("mechanic's hands"). Skin lesions can exist without evidence of muscle weakness (amyopathic DM).

The antisynthetase syndrome of DM or PM is characterized by some or all of the following manifestations in the setting of antisynthetase antibody positivity: acute onset of disease, constitutional symptoms, interstitial lung disease, inflammatory arthritis, mechanic's hands, rash, and Raynaud phenomenon. Myositis can be mild or even absent in some patients with this syndrome.

As opposed to PM and DM, IBM is more common after age 50 years and affects men twice as often as women. IBM commonly presents with weakness and atrophy that might be distal and asymmetric and progresses over months to years. This type of myopathy does not respond to treatment as well as PM, but stabilization or modest improvement of muscle weakness can sometimes be achieved.

The association between myopathies and cancer is stronger with DM than with PM; multiple studies have demonstrated an increased malignancy incidence in both patients with DM and those with PM. An appropriate workup includes a thorough history and physical examination, including pelvic examinations for women and age-appropriate malignancy screenings for the breast, colon, and prostate. Whereas most experts agree that an exhaustive search for occult malignancy is not indicated, one group reported 11 malignancies in 24 patients who underwent computed tomographic scans of the chest, abdomen, and pelvis after the diagnosis of DM or PM.[39] This finding highlighted the concept that primary DM and PM might be clinically difficult to distinguish from malignancy-associated PM/DM and that a thorough evaluation is warranted in the appropriate setting. Furthermore, malignancy risks continued to be increased 3 years after the PM/DM diagnosis, necessitating ongoing close monitoring during this period.

DM is by far the most common inflammatory myopathy in children. Up to 40% of children with DM have calcinosis of the skin and muscle.

Immunologic features

Muscle biopsy specimens from patients with PM reveal $CD8^+$ T-cell infiltrates in the endomysium. In contrast, muscles affected by DM show $CD4^+$ T-cell and B-cell infiltrates in the perimysium and perivascular area. DM appears to be a vasculopathy with immune complex deposition and the complement membrane attack complex in vessel walls.

Recently, dendritic cells have been identified by means of immunohistochemistry in muscle biopsy specimens of inflammatory myopathies.[40] These cells are the professional antigen-

presenting cells and might play a central role in recruiting T and B cells and promoting their activation. Furthermore, cytokine profiling of inflammatory myositic lesions revealed an interferon signature, which is consistent with the hypothesis that dendritic cell activation is one major pathogenic step in inflammatory myositis. Lastly, autoantibodies, such as myositis-specific antibodies, might be an epiphenomenon associated with dendritic cell activation.

Nevertheless, myositis-specific autoantibodies define subgroups of patients with more uniform clinical features and prognosis (Table VI).[41,42] Although these autoantibodies are specifically increased in patients with inflammatory myopathies, they target ubiquitous antigens. These autoantibodies can be found in patients before the development of weakness, and their titers can vary with disease activity. However, there is no direct evidence to support a pathogenic role. The most prevalent myositis-specific antibodies are targeted to aminoacyl-tRNA synthetases. The most common of the antisynthetases is the anti–Jo-1 antibody. Other well-characterized antibodies include the anti–signal recognition particle that targets a cytoplasmic ribonucleoprotein complex and is associated with cardiac involvement and poor prognosis. In addition, anti–Mi-2, which targets a helicase involved in regulating transcription, is associated with classic DM skin manifestations. Other immunologic features include the presence of ANA, increased levels of immunoglobulins in the serum, and the infiltration of muscle by lymphocytes.

Diagnosis

The diagnosis of PM and DM is based on history and physical examination, focusing on identifying proximal muscle weakness, and on the laboratory markers of muscle damage, especially creatine kinase. Electromyography reveals changes characteristic of myopathy, such as insertional irritability, positive sharp waves, fibrillations, and polyphasic small-amplitude muscle unit potentials. A common approach is to perform electromyography unilaterally and then obtain muscle biopsy specimens on the contralateral side in the muscle groups with the most abnormal findings to avoid the artifact of inflammatory cells in the muscle into which an electromyographic needle has been inserted. Alternatively, MRI can be used to direct muscle biopsy because it can demonstrate areas of active muscle inflammation, thus reducing the risk of sampling error. A muscle biopsy specimen with inflammatory cells, fibrosis, necrosis, regeneration, and atrophy of muscle cells confirms the diagnosis of PM. The biopsy specimen in patients with DM is more likely to demonstrate perivascular infiltration of T and B lymphocytes and perifascicular atrophy. With IBM, light microscopy shows basophil-rimmed vacuoles, and electron microscopy demonstrates cytoplasmic inclusions.

Treatment

Corticosteroids are the mainstay of treatment.[43] Initial daily prednisone doses of up to 100 mg are used and are tapered according to clinical response, serum creatine kinase levels, and side effects. Methotrexate and azathioprine are used as steroid-sparing agents, often being initiated simultaneously with high-dose corticosteroids or because of inadequate response. Up to 90% of patients with PM/DM have at least a partial response to treatment. IBM is also treated with prednisone, methotrexate, and azathioprine but with more modest expectations for clinical improvement.

In patients with resistant disease despite corticosteroids and methotrexate or azathioprine, successful treatment has been reported with the B cell–depleting drug rituximab. An alternative regimen includes IVIG infusions in addition to corticosteroid therapy. In patients with refractory PM or DM with interstitial lung disease, tacrolimus or cyclosporine can be used. Other alternative therapies for resistant disease include mycophenolate mofetil or cyclophosphamide.[43]

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Vasculitis

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Vasculitis is defined by the presence of blood vessel inflammation. It can be observed in a wide variety of settings, which can be broadly grouped as secondary vasculitides, which occur in association with an underlying disease or trigger, or primary vasculitides, in which vasculitis is occurring for as-yet unknown causes. The primary systemic vasculitides comprise a range of disease entities that are uniquely identified by their clinical, histopathologic, and therapeutic characteristics. Individual diseases predominantly affect blood vessels of a particular size, which influences their clinical manifestations and has been used in their classification. The vasculitides can also differ in their severity, extending from self-limited illnesses to those that can be life-threatening in the absence of prompt initiation of treatment. Immunosuppressive agents are used to treat many vasculitic diseases. Although such approaches can be effective, the patient's long-term course can be influenced by organ damage from their initial presentation, disease relapses, and medication toxicity. Recent investigations have focused on understanding disease pathophysiology and the exploration of novel therapeutic approaches. (J Allergy Clin Immunol 2010;125:S216-25.)

Key words: *Vasculitis, arteritis, antineutrophil cytoplasmic antibody, granuloma, glucocorticoid, cyclophosphamide*

Abbreviations used

ANCA:	Antineutrophil cytoplasmic antibodies
AZA:	Azathioprine
CHCC:	Chapel Hill Consensus Conference
CNS:	Central nervous system
CSS:	Churg-Strauss syndrome
CYC:	Cyclophosphamide
GACNS:	Granulomatous angiitis of the central nervous system
GCA:	Giant cell arteritis
HCV:	Hepatitis C virus
HSP:	Henoch-Schönlein purpura
MPA:	Microscopic polyangiitis
MPO:	Myeloperoxidase
MTX:	Methotrexate
PACNS:	Primary angiitis of the central nervous system
PAN:	Polyarteritis nodosa
PMR:	Polymyalgia rheumatica
PR3:	Proteinase 3
TAK:	Takayasu arteritis
WG:	Wegener granulomatosis

Vasculitis is characterized by histologic evidence of blood vessel inflammation. When vasculitis occurs, it can lead to blood vessel stenosis/occlusion, causing organ ischemia or thinning of the blood vessel and resulting in aneurysm formation or hemorrhage. Vasculitis can be thought of in 2 broad categories: secondary vasculitides, in which blood vessel inflammation occurs in association with an underlying disease or exposure, or primary vasculitides, which are entities of unknown cause in which vasculitis is the pathologic basis of tissue injury. This review will focus on the clinical features, diagnosis, and treatment of the primary vasculitic diseases.

CLASSIFICATION

The first account of a patient who had a noninfectious vasculitis was made in 1866, when Kussmaul and Maier published a detailed report of a disorder characterized by nodular inflammation of the muscular arteries. They named this disease periarteritis nodosa, which later also became referred to as polyarteritis nodosa (PAN). The description of other necrotizing vasculitides followed, and in 1952, Zeek proposed the first classification system. The nomenclature and classification of the vasculitides has remained an evolving process as our knowledge about these diseases has grown. In 1990, the American College of Rheumatology introduced classification criteria for 7 forms of vasculitis to provide a standard way to describe groups of patients in therapeutic, epidemiologic, or other studies.[1] This was followed in 1994 by a proposal of uniform terms and definitions for the most common forms of vasculitis at the Chapel Hill Consensus Conference (CHCC; Table I).[2] Although these both represented advancements in standardization for the vasculitic diseases, they were not intended and should not be used for the purposes of diagnosing the individual patient.

PATHOPHYSIOLOGY AND ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

The pathophysiology of the vasculitides remains poorly understood and can vary between different diseases.[3,4] Clinical and laboratory-based evidence has supported the hypothesis that immunologic mechanisms appear to play an active role in mediating the necrotizing inflammation of blood vessels. Although the primary events that initiate this process remain largely unknown, recent investigators have brought us closer to understanding some of the critical pathways involved in disease and provided a rationale for the study of novel therapeutic agents (Table II).

Antineutrophil cytoplasmic antibodies (ANCA) have been a prominent focus of study in the vasculitides, not only for their possible influence in disease pathogenesis but also for their clinical applications. Two types of ANCA have been identified in patients with vasculitis: ANCA directed against the neutrophil serine protease proteinase 3 (PR3), which cause a

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TABLE I. Names and definitions of vasculitides adopted by the CHCC on the Nomenclature of Systemic Vasculitis

Large-vessel vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches with a predilection for the extracranial branches of the carotid artery: often involves the temporal artery, usually occurs in patients older than 50 y, and often is associated with PMR.
TAK	Granulomatous inflammation of the aorta and its major branches: usually occurs in patients younger than 50 y.
Medium-sized vessel vasculitis	
PAN	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or (classic PAN) vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large, medium, and small arteries, and associated with mucocutaneous lymph node syndrome: coronary arteries are often involved, aorta and veins might be involved, and usually occurs in children.
Small-vessel vasculitis	
WG	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries): necrotizing glomerulonephritis is common.
CSS	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels often associated with asthma and eosinophilia.
MPA	Necrotizing vasculitis with few or no immune deposits affecting small vessels (ie, capillaries, [microscopic polyarteritis] venules, or arterioles): necrotizing arteritis involving small- and medium-sized arteries might be present, necrotizing glomerulonephritis is very common, and pulmonary capillaritis often occurs.
HSP	Vasculitis with IgA-dominant immune deposits affecting small vessels (ie, capillaries, venules, or arterioles): typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis.
Essential cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (ie, capillaries, venules, or arterioles) and associated with cryoglobulins in serum: skin and glomeruli are often involved.
Cutaneous leukocytoclastic vasculitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Adapted from Jennette et al.[2]

cytoplasmic immunofluorescence pattern (cANCA) on ethanol-fixed neutrophils, and ANCA directed against the neutrophil enzyme myeloperoxidase (MPO), which result in a perinuclear immunofluorescence pattern (pANCA).[5] Because the methodology of testing can influence the interpretation, ANCA positivity determined by means of indirect immunofluorescence should be corroborated with antigen-specific testing for PR3 and MPO.

The strongest association of a disease with ANCA has been that between Wegener granulomatosis (WG) and PR3-cANCA. Although ANCA have also been described with variable frequency in other vasculitic diseases, in particular microscopic polyangiitis (MPA) and, to a lesser degree, Churg-Strauss syndrome (CSS) (Table III), many forms of vasculitis are not associated with circulating ANCA. ANCA can also be seen in association with other entities, including infection, inflammatory bowel disease, and other connective tissue diseases. In these settings ANCA are typically positive, as determined by means of indirect immunofluorescence, but negative for PR3, MPO, or both, as determined by means of antigen-specific testing, which emphasizes the importance of testing with both methodologies.

In patients with WG, the sensitivity of PR3-cANCA has been reported to be 28% to 92%, whereas specificity has been reproducibly high, ranging from 80% to 100%.[5] This raised the question as to whether ANCA measurement can be used in place of tissue biopsy for diagnosing WG. In patients with sinusitis, an active urine sediment, and pulmonary disease in which infection has been excluded, the predictive value of PR3-cANCA for WG can exceed 90%.[6] However, for other clinical presentations in which the prevalence of WG would be low, the predictive value of ANCAs is insufficient to justify the initiation of toxic therapy in the absence of a tissue diagnosis.

ANCA levels will vary during the course of WG, and from cohort studies, it was observed that patients with active disease had higher levels of ANCA compared with those who were in remission. However, changes in sequential ANCA measurements in an individual patient have not been found to be a reliable disease biomarker. In the largest prospective study published to date, increases in ANCA levels were not associated with relapse, and only 43% relapsed within 1 year of an increase in ANCA levels.[7] Given the toxicity of therapy, an increasing ANCA titer should not be used as the sole basis to start or increase immunosuppressive therapy.

TABLE II. Potential mechanisms of vessel damage in selected primary vasculitis syndromes

Immune complex formation
PAN-like vasculitis associated with hepatitis B
HSP
Cryoglobulinemic vasculitis
Production of ANCA
WG
MPA
CSS
Pathogenic T-lymphocyte responses and granuloma formation
GCA
TAK
WG
CSS

INDIVIDUAL VASCULITIC DISEASES

Giant cell arteritis

Giant cell arteritis (GCA), which has also been known as *temporal arteritis*, is a granulomatous, large-vessel vasculitis that preferentially affects the extracranial branches of the carotid artery.[8] It is the most common form of systemic vasculitis that

TABLE III. Clinical comparison of 4 forms of systemic vasculitis affecting small-sized vessels, medium-sized vessels, or both

Characteristic	WG	MPA	PAN	CSS
Upper airways disease	95%	No	No	50% to 60%
Pulmonary disease				
Asthma	No	No	No	90% to 100%
Radiographic nodule/infiltrates	70% to 85%	15% to 70%	No	40% to 70%
Alveolar hemorrhage	5% to 15%	10% to 50%	No	<5%
Glomerulonephritis	70% to 80%	75% to 90%	No	10% to 40%
Gastrointestinal	<5%	30%	14% to 53%	30% to 50%
Nervous system				
Peripheral	40% to 50%	60% to 70%	38% to 72%	70% to 80%
Central	5% to 10%	10% to 15%	3% to 30%	5% to 30%
Cardiac	10% to 25%	10% to 15%	5% to 30%	10% to 40%
Ocular	50% to 60%	<5%	<5%	<5%
Arthralgia/arthritis	60% to 70%	40% to 60%	50% to 75%	40% to 50%
Genitourinary	<2%	<5%	5% to 10%	<2%
Skin	40% to 50%	50% to 65%	28% to 60%	50% to 55%
ANCA				
PR3-cANCA	75% to 90%	10% to 50%	Rare	3% to 35%
MPO-pANCA	5% to 20%	50% to 80%	Rare	2% to 50%

affects human subjects, with an incidence of 18.8 cases per 100,000 persons in Olmsted County, Minnesota. GCA occurs almost exclusively in persons older than 50 years at a female/male ratio of up to 2:1 and is observed predominantly in persons of European ancestry.

GCA can be thought of as having 4 phenotypes that can occur alone, together, or sequentially and include cranial disease, polymyalgia rheumatica (PMR), systemic inflammatory disease, and large-vessel involvement. The most common presenting symptoms of GCA include headache, jaw or tongue claudication, scalp tenderness, weight loss, or fever (Table IV).[9] PMR, which is characterized by aching and morning stiffness in the proximal muscles of the shoulder and hip girdles, can occur in isolation but is also seen in 40% to 60% of patients with GCA. Cranial ischemic complications can occur as a result of vascular occlusion causing tissue infarction. Of these, the most dreaded complication is vision loss, which can occur in 14% of patients and is caused by optic nerve ischemia from arteritis involving vessels of the ocular circulation. Large-vessel involvement of the aorta or its primary branches occurs in 27% of cases and can present with limb claudication or complications related to an aortic aneurysm.[10]

TABLE IV. Clinical manifestations of GCA

Manifestation	Patients affected (%)
Headache	68
Weight loss/anorexia	50
Jaw claudication	45
Fever	42
Malaise/fatigue/weakness	40
PMR	39
Other musculoskeletal pain	30
Transient visual symptoms	16
Synovitis	15
CNS abnormalities	15
Fixed visual symptoms	14
Sore throat	9
Swallowing claudication/dysphagia	8
Tongue claudication	6

Adapted from Calamia and Hunder.[9]

The suspicion of GCA is raised by clinical features together with an increased erythrocyte sedimentation rate, which occurs in more than 80% of patients. The diagnosis is confirmed by means of temporal artery biopsy, which demonstrates a panmural mononuclear cell infiltration that can be granulomatous with histiocytes and giant cells. To increase yield, the length of the biopsy specimen should be at least 3 to 5 cm and sampled at multiple levels. Temporal artery biopsy specimens are positive in 50% to 80% of cases, and if the first biopsy specimen is negative, consideration should be given to a biopsy of the contralateral artery. In patients strongly suspected of having GCA, treatment should be instituted immediately to protect vision while a prompt temporal artery biopsy is being arranged. Although histologic changes can persist, a temporal artery biopsy should be performed as soon as possible after starting prednisone to obtain the best possible yield.

Glucocorticoids bring about a rapid improvement in cranial and systemic symptoms and prevent visual complications in patients with GCA. In one study the probability of loss of vision was only 1% after starting glucocorticoids.[11] Prednisone is usually initiated at a dose of 40 to 60 mg/d. After an initial dose of 60 mg/d, this can usually be reduced to 50 mg/d after 2 weeks and to 40 mg/d after 4 weeks. After that time, the dose is decreased by approximately 10% of the total daily dose every 1 to 2 weeks.[8] In patients with acute visual loss, 1 g/d methylprednisolone sodium succinate for 3 to 5 days is frequently given to protect remaining vision.[11] Isolated PMR can be effectively treated with 10 to 20 mg/d prednisone, with a rapid response to glucocorticoids being one of the diagnostic hallmarks of this disease.

The desire to identify effective treatment beyond prednisone has come from the recognition that 36% to 85% of patients have 1 or more side effects from this therapy.[12] Aspirin, 81 mg/d, has been found to reduce the risk of cranial ischemic complications and should be given together with prednisone in all patients who do not have a contraindication.[13,14] The ability of methotrexate (MTX) to decrease relapses and lessen glucocorticoids was examined in 2 randomized studies that yielded conflicting results.[15-17] At this time, neither the addition of MTX nor any other cytotoxic agent has been found to be uniformly effective in

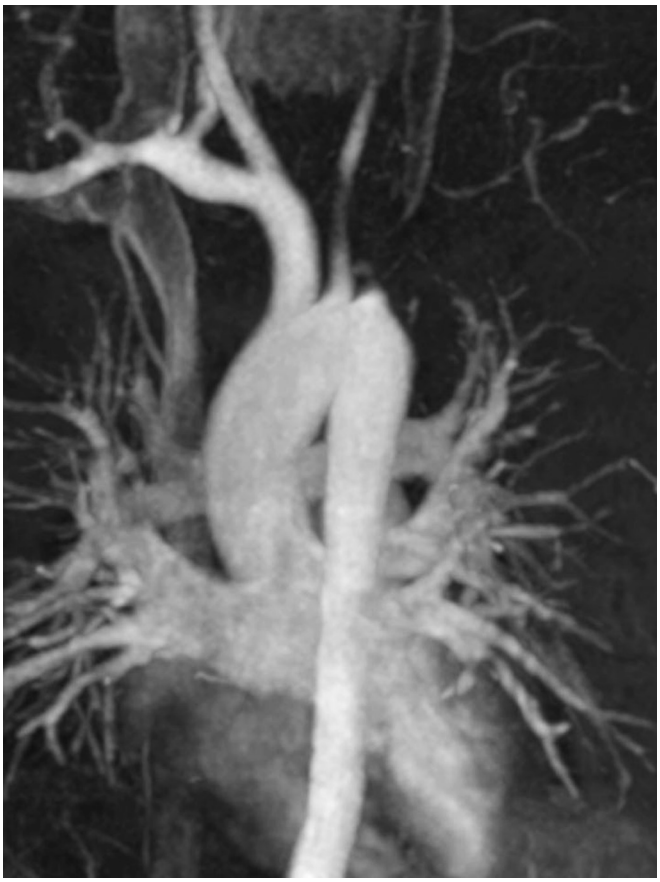

FIG 1. Magnetic resonance arteriogram in a patient with Takayasu arteritis demonstrating occlusion of the left subclavian artery coming off the aortic arch and severe stenosis of the left common carotid shortly after its origin from the arch.

reducing the use of prednisone sufficiently to decrease its risk of side effects. Randomized trials in patients with GCA and PMR did not find infliximab to provide benefit, and it is not recommended for use in these diseases.[18,19]

Acute mortality from GCA caused by stroke or myocardial infarction is uncommon, and overall, patients with GCA have a survival rate similar to that of the general population. However, thoracic aortic aneurysms might occur as a late complication of disease and can be associated with rupture and death.[10] Symptomatic relapses requiring increase or reinstitution of prednisone occur in at least 75% of patients.[16] Most patients require glucocorticoids for more than 2 years, with many receiving more than 4 years of treatment.

Takayasu arteritis

Takayasu arteritis (TAK) is a disease that affects the aorta, its main branches, and the pulmonary arteries in which granulomatous vasculitis results in stenosis, occlusion, or aneurysms of affected vessels.[20,21] Although it has been characterized as a disease affecting young women of eastern ethnicity, TAK has been observed throughout the world and can have varying clinical spectrums in different populations.

Patients with TAK can have systemic symptoms, features, or both of vascular injury. Systemic symptoms might be absent in 13% to 80% of patients and include fatigue, malaise, weight loss, night sweats, fever, arthralgias, or myalgias. Vascular symptoms are related to the location and nature of the lesion or lesions and the collateral blood flow. Hypertension occurs in 32% to 93% of patients and contributes to renal, cardiac, and cerebral injury.

A complete aortic arteriogram with visualization of all major branches is important in all patients in whom TAK is being considered as a means of diagnosis and determination of disease extent (Fig 1). The noninvasive nature of magnetic resonance and computed tomographic arteriography has made these modalities useful for serial vascular monitoring in patients with TAK, although catheter-directed dye arteriography remains valuable in providing central blood pressure measurements and precise assessment of luminal dimensions.

Disease activity is typically assessed based on clinical symptoms and signs, the erythrocyte sedimentation rate, and the presence of new arteriographic changes. However, these are not always reliable, and in one surgical series active arteritis was observed in 44% of patients who had been judged quiescent.[20]

Initial treatment of TAK usually consists of 1 mg/kg per day prednisone given for the first 1 to 3 months and then tapered to discontinuation over a 6- to 12-month period. Glucocorticoids relieve systemic symptoms in 25% to 100% of patients and might bring about an improvement in blood flow. Cytotoxic therapy is primarily used in patients who have persistent disease activity despite glucocorticoid treatment or in whom glucocorticoids cannot be tapered. MTX at 15 to 25 mg/wk in combination with glucocorticoids has been found to induce remission and minimize

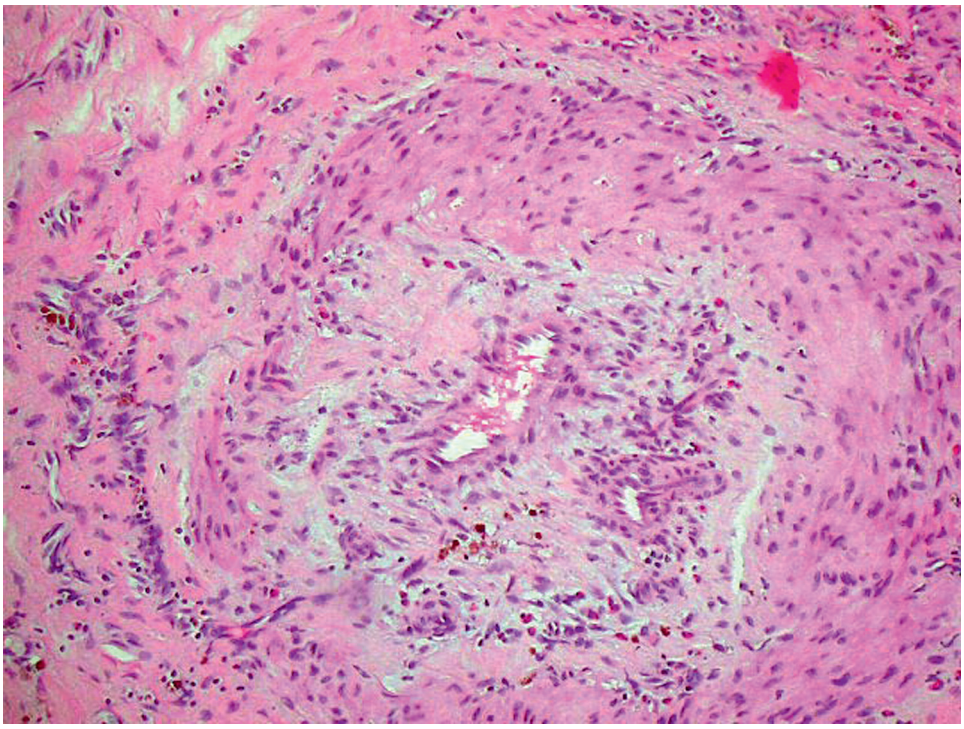

FIG 2. Medium-vessel vasculitis in a patient with PAN.

glucocorticoid therapy and toxicity.[22] Cyclophosphamide (CYC) should be reserved for patients with severe disease who cannot taper glucocorticoids and are unresponsive, intolerant, or unable to take MTX. Pilot studies have demonstrated favorable results with infliximab, but the efficacy of this therapy has not been proved from randomized trials.[23]

Nonmedical interventions have an important role in TAK in treating fixed vascular lesions that produce significant ischemia or aneurysms. The most frequent indications for surgical intervention include cerebral hypoperfusion, renovascular hypertension, limb claudication, repair of aneurysms, or valvular insufficiency. Surgical bypass has had the highest long-term patency rate, with vascular stents and angioplasty often occluding over time.[21] Nonmedical interventions should be performed in the setting of quiescent disease when possible to optimize outcome.

Patients with TAK have a low frequency of acute mortality, with the estimated 15-year survival rate being 83%. Relapses have been observed in 70% to 96% of patients, with sustained remission seen in only 28% of patients.[21]

PAN

Although PAN was the first described form of systemic vasculitis, changes in nomenclature have affected our interpretation of past literature, which included many patients who would now be considered to have MPA under the definitions of the CHCC. PAN, as it is currently defined, is estimated to be an extremely uncommon disease.

The most common clinical manifestations of PAN include hypertension, fever, musculoskeletal symptoms, and vasculitis involving the nerves, gastrointestinal tract, skin, heart, and nonglomerular renal vessels (Table III).[24] PAN is diagnosed by means of biopsy or arteriography. Biopsy specimens reveal necrotizing inflammation involving the medium-sized or small arteries, with abundant neutrophils, fibrinoid changes, and disruption of the internal elastic lamina (Fig 2). Dye arteriography is most often performed to examine the visceral and renal circulation, in which PAN would be suggested by the presence of microaneurysms, stenoses, or a beaded pattern brought about by sequential areas of arterial narrowing and dilation.

Patients with immediately life-threatening PAN affecting the gastrointestinal system, heart, or central nervous system (CNS) should be treated with 2 mg/kg per day CYC and glucocorticoids.[25] In patients in whom the disease manifestations do not pose an immediate threat to life or major organ function, glucocorticoids alone can be considered as initial therapy, with CYC being added in patients who continue to have evidence of active disease or who are unable to taper prednisone. The estimated 5-year survival rate of treated patients with PAN is 80%, with death being influenced by disease severity.[25] Relapses occur in 10% to 20% of patients.[25]

A PAN-like vasculitis can also be seen in patients infected with hepatitis B, hepatitis C, or HIV.[26] In the setting of hepatitis B or C, an antiviral agent should be part of the treatment regimen, with the goal being to contain viral replication and favor seroconversion. Patients might require glucocorticoids, alone or combined with CYC, together with plasmapheresis to initially gain control of the active vasculitis.[26]

WG

WG is a multisystem disease characterized by clinical disease involving the upper and lower respiratory tracts and kidneys with histologic evidence of granulomatous inflammation, vasculitis of the small- to medium-sized vessels, and a

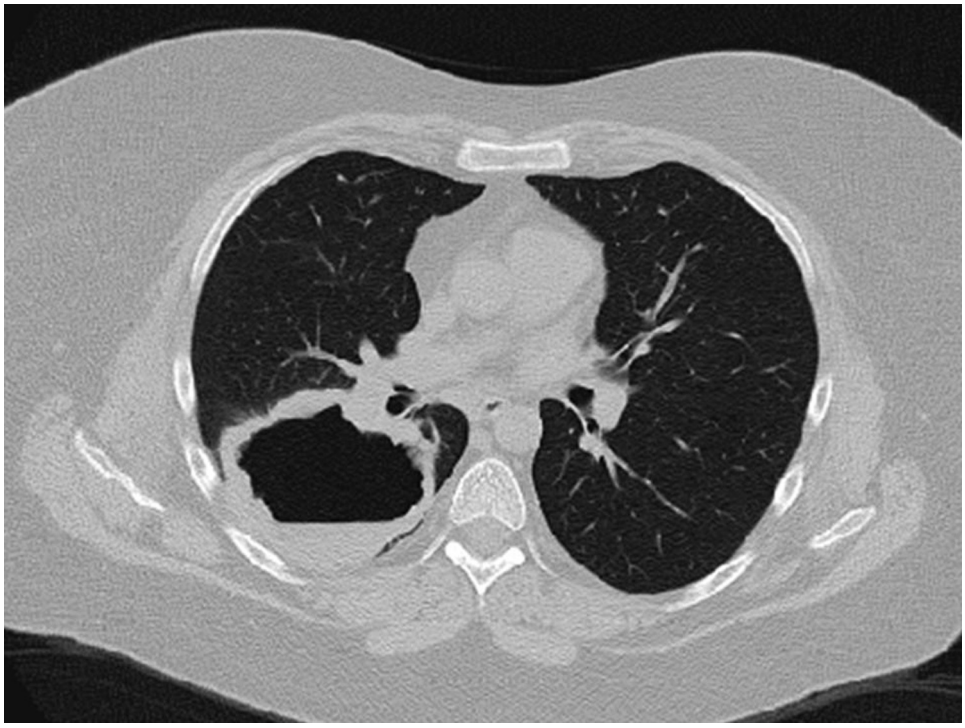

FIG 3. A large cavitary lung nodule seen on a computed tomographic scan in a patient with WG.

pauci-immune glomerulonephritis (Table III).[27] The disease can occur at any age and appears to affect men and women in equal proportions.

More than 90% of patients with WG first seek medical attention for upper airways symptoms, lower airways symptoms, or both. Nasal and sinus mucosal inflammation might result in cartilaginous ischemia with perforation of the nasal septum, saddlenose deformity, or both. Pulmonary radiographic abnormalities can include single or multiple nodules or infiltrates, cavities (Fig 3), and ground-glass infiltrates (Fig 4). Glomerulonephritis is present in 20% of patients at the time of diagnosis but develops in 80% at some point during the disease course. Renal involvement has the potential to be rapidly progressive but is asymptomatic, being detected by the presence of an active urine sediment with dysmorphic red blood cells and red blood cell casts.

The diagnosis of WG is usually based on biopsy results, with nonrenal tissues demonstrating the presence of granulomatous inflammation and necrosis, with necrotizing or granulomatous vasculitis.[27] Surgically obtained biopsy specimens of abnormal pulmonary parenchyma demonstrate diagnostic changes in 91% of cases. Biopsy of the upper airways is less invasive but demonstrates diagnostic features only 21% of the time. The characteristic renal histology is that of a focal, segmental, necrotizing, crescentic glomerulonephritis with few to no immune complexes. The clinical utility of ANCA in patients with WG is discussed in a separate section of this review.

Active WG is potentially life-threatening, and initial treatment requires glucocorticoids combined with a cytotoxic agent. Patients who have active severe WG should initially be treated with 2 mg/kg per day CYC in combination with prednisone at 1 mg/kg per day. After 4 weeks of treatment, if there is improvement, the prednisone is tapered and discontinued by 6 to 12 months. CYC is given for 3 to 6 months, after which time it is stopped and switched to a less toxic medication for remission maintenance. The 2 maintenance agents with which there has been the greatest body of data have been 20 to 25 mg/wk MTX[28] or 2 mg/kg per day azathioprine (AZA),[29,30] with a smaller experience existing with mycophenolate mofetil. In patients who have active but nonsevere disease, prednisone given together with 20 to 25 mg/wk MTX has been found to be effective at inducing and then maintaining remission.[31] In the absence of side effects, maintenance therapy is continued for at least 2 years, after which, if patients remain in remission, consideration can be made on an individual basis for tapering and discontinuation of therapy. In the setting of fulminant disease immediately threatening to life, 1 g/d methylprednisolone sodium succinate can be given in divided doses over a period of 3 days in combination with 3 to 4 mg/kg per day CYC for 3 days, after which time it is reduced to 2 mg/kg per day. Plasmapheresis has also been found to offer benefit in patients with rapidly progressive glomerulonephritis.[32]

Recognition of medication toxicity with strategies for monitoring and prevention play an important role in patient care (Table V).[33] CYC is associated with substantial toxicity, including bone marrow suppression, bladder injury, infertility, myeloproliferative disease, and transitional cell carcinoma of the bladder. Daily CYC should be taken all at once in the morning with a large amount of fluid, with monitoring of complete blood counts every 1 to 2 weeks. MTX should not be given to patients with impaired renal function (creatinine clearance, <35 mL/min) or chronic liver disease. Screening for the thiopurine methyltransferase genotype to detect patients at risk of severe neutropenia has become widely used before AZA initiation.

Recent investigations have explored the role of biologic agents. A randomized trial did not find etanercept to have any beneficial role in the induction or maintenance of WG.[34] A promising preliminary experience has been seen with rituximab (anti-CD20)

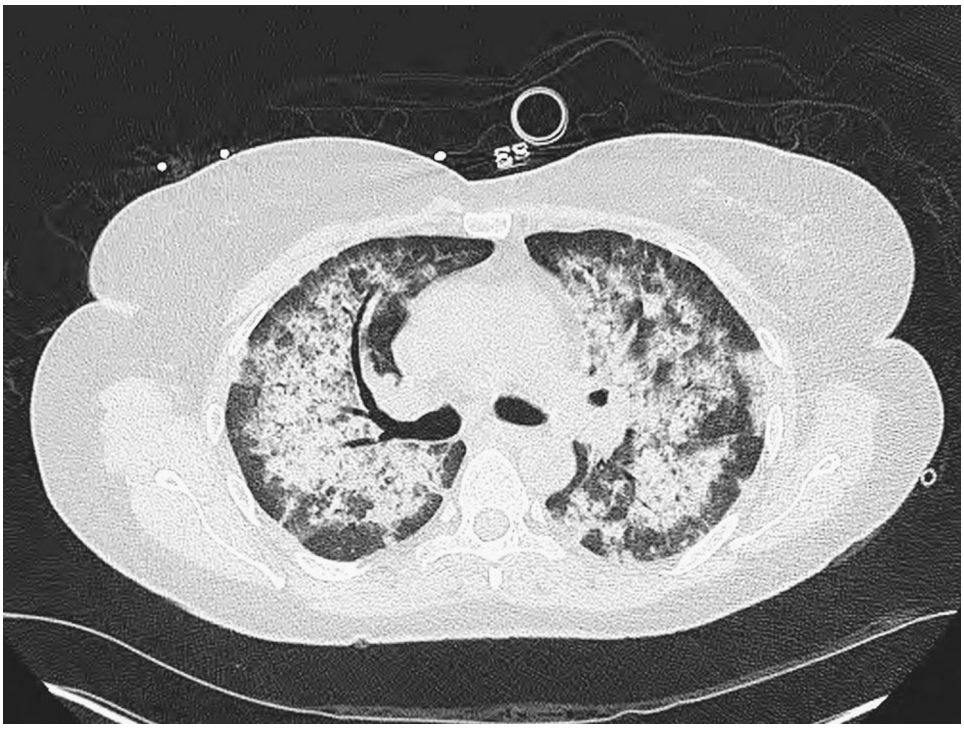

FIG 4. Computed tomographic scan demonstrating bilateral ground-glass infiltrates from alveolar hemorrhage as can occur in WG or MPA.

in patients with active severe WG or MPA.[35] This agent is currently being compared against CYC in a randomized, double-blind, placebo-controlled trial.

Before the development of treatment, patients with WG had a mean survival time of 5 months, with death occurring from pulmonary or renal failure. Current treatment regimens induce remission in 75% to 100% of patients with WG and result in the potential for long-term survival. However, relapse occurs in 50% to 70% of patients,[27] and disease-related organ damage is common.

MPA

As defined by the CHCC, MPA is characterized by necrotizing vasculitis with few or no immune deposits affecting small vessels. MPA has many similarities to WG, which has provided useful insights regarding diagnosis and management.

The cardinal features of MPA include glomerulonephritis, pulmonary hemorrhage (Fig 4), mononeuritis multiplex, and fever (Table III).[36] Approximately 75% to 85% of patients with MPA have circulating MPO-pANCA. The diagnosis of MPA is made by means of biopsy demonstration of necrotizing vasculitis of the small vessels or small- to medium-sized arteries in which granulomatous inflammation is absent. Biopsy specimens of lung tissue in the setting of pulmonary hemorrhage reveal capillaritis, hemorrhage into the alveolar space, and the absence of linear immunofluorescence, as would be seen in antiglomerular basement membrane antibody disease (Goodpasture syndrome). The renal histology is similar to that observed in WG in being a focal segmental necrotizing glomerulonephritis with few to no immune complexes.

Patients with life-threatening disease involving the lung, kidney, or nerve should initially be treated with 2 mg/kg per day CYC and 1 mg/kg per day prednisone, according to the schedule outlined for WG, followed by AZA or MTX for remission maintenance.[29,30] Patients with active nonsevere disease can be treated with MTX for remission and maintenance.[31]

In one series the estimated 5-year survival rate of MPA was 74%.[36] Like WG, MPA is a relapsing disease, with recurrences developing in at least 38% of patients.

CSS

CSS is a rare disease characterized by asthma, fever, hypereosinophilia, and systemic vasculitis.[37,38] It has been estimated to affect about 3 persons per million and has been observed in all ages equally between sexes.

CSS has been thought of as having 3 phases: a prodromal phase with allergic rhinitis and asthma, a phase characterized by peripheral eosinophilia and eosinophilic tissue infiltrates, and, ultimately, vasculitic disease that can involve the nerve, lung, heart, gastrointestinal tract, and kidney (Table III).[37] Although these phases are conceptually helpful, they might not be clinically identifiable in all patients, and they often do not occur in sequence. The histologic features of CSS include eosinophilic tissue infiltrates, extravascular "allergic" granuloma, and small-vessel necrotizing vasculitis. Vasculitis can be difficult to definitively establish, making clinical manifestations of particular importance in the diagnosis of CSS.

Prednisone, 1 mg/kg per day, is effective for many manifestations of CSS.[39] Asthma often persists after remission of the vasculitis and might limit the ability for pred to be tapered to complete discontinuation. Patients with life-threatening disease should be treated with glucocorticoids and 2 mg/kg per day CYC, as would be given for WG.[25]

Prognosis is influenced by the presence of severe disease involving sites such as the heart, gastrointestinal tract, CNS, and kidney.[37] CSS is characterized by frequent exacerbations of asthma, and relapses of vasculitic disease occur in at least 26%.[37]

Cutaneous vasculitis

Cutaneous vasculitis is the most commonly encountered vasculitic manifestation in clinical practice. Lesions most commonly consist of palpable purpura, although nodules and ulcerative lesions are also seen. Cutaneous vasculitis is histologically characterized by the presence of small-vessel inflammation within the dermis, often with leukocytoclasis.[40,41] Involvement of medium-sized vessels might be seen in cutaneous PAN.

In more than 70% of cases, cutaneous vasculitis occurs in the setting of an underlying process, such as a medication exposure, infection, malignancy, or connective tissue disease, or as a manifestation of a primary systemic vasculitis. A diagnosis of idiopathic cutaneous vasculitis should only be made after other causes have been ruled out. The course of idiopathic cutaneous vasculitis ranges from a single episode to multiple protracted recurrences. Progression to systemic vasculitis occurs infrequently.

If an underlying disease or exposure is identified, management of this process forms the primary basis for treating the cutaneous vasculitis. The therapeutic principle for idiopathic cutaneous vasculitis should be to use the least toxic yet effective regimen because there have been no standardized trials in this disease setting. Glucocorticoids are frequently used, but there remains no optimal dosage schedule. Other agents with which there has been anecdotal experience include nonsteroidal anti-inflammatory agents, antihistamines, dapsone, hydroxychloroquine, and colchicine. Cytotoxic agents should be reserved for select cases in which patients have severe disease that is unresponsive to other measures or when glucocorticoids cannot be tapered. CYC should rarely, if ever, be used to treat isolated cutaneous vasculitis.

Cryoglobulinemic vasculitis

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins that can occur in conjunction with a variety of diseases, including plasma cell or lymphoid neoplasms, chronic infection, and inflammatory diseases.[42] With the discovery of the hepatitis C virus (HCV), it became established that the majority of cases of cryoglobulinemia are related to HCV infection.[43] Cryoglobulinemia can be associated with a vasculitic illness characterized by palpable purpura, arthritis, weakness, neuropathy, and glomerulonephritis.[42] Although the presence of glomerulonephritis is associated with an overall poor prognosis, progression to end-stage renal failure is uncommon.

Combined therapy with IFN-α and ribavirin provide the best opportunity for improvement of HCV-associated cryoglobulinemic vasculitis, but long-term resolution is confined to patients who have a sustained virologic response.[44] Plasmapheresis has been used with brief responses but is not practical for long-term management. Glucocorticoids, CYC, AZA, and MTX have been applied, particularly in the case of severe disease.[44,45] Treatment with immunosuppressive drugs might transiently improve the inflammatory manifestations of cryoglobulinemic vasculitis but might also lead to an increase in HCV viremia. Although favorable results have been seen in case series with the use of rituximab, randomized controlled trials are needed to determine its efficacy.

TABLE V. Suggested toxicity laboratory monitoring schedule for prominent medications that are used in the treatment of certain vasculitides

Agent	Frequency	Investigation
Cyclophosphamide	Every 1-2 wk	CBC with differential Serum creatinine ESR Urinalysis
	Every 6-12 mo (even after treatment has been discontinued)	Urine cytology
Methotrexate	Every week during dose escalation and every 4 wk thereafter	CBC with differential Serum creatinine LFTs ESR Urinalysis
Azathioprine or mycophenolate mofetil	Every week for the first month, every 2 wk for the second month, and every 4 wk thereafter	CBC with differential Serum creatinine LFTs ESR Urinalysis

CBC, Complete blood count; *ESR*, erythrocyte sedimentation rate; *LFTs*, liver function tests.

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is a small-vessel vasculitis that predominantly affects children.[46] Although adults can have HSP, 75% of cases occur before the age of 8 years. Two thirds of patients report an antecedent upper respiratory tract infection, although no predominant organism has been identified.

The 4 cardinal features of HSP are palpable purpura, arthritis, gastrointestinal involvement, and glomerulonephritis. Gastrointestinal manifestations include colicky abdominal pain, vomiting, and potentially intussusception. Renal disease, most often characterized by hematuria and proteinuria, is seen in 20% to 50% of affected children, with 2% to 5% progressing to end-stage renal failure. Less is known about HSP in adults, although several studies suggest that glomerulonephritis might be more severe and lead to renal insufficiency in up to 13% of cases.

The diagnosis of HSP is established by the pattern of clinical manifestations but can be less certain when other features precede the skin lesions. Skin biopsy reveals leukocytoclastic vasculitis with IgA deposition in blood vessel walls but is not required in most instances. Renal biopsy is rarely necessary for diagnosis but might have prognostic utility.

HSP is typically a self-limited condition that often does not require treatment. Glucocorticoids can lessen tissue edema, arthritis, and abdominal discomfort and decrease the rate of intussusception. However, they are of no proved benefit in skin or renal disease and do not appear to shorten the duration or lessen the likelihood of relapse.[47] Uncontrolled studies suggest that glucocorticoids in combination with a cytotoxic agent might be beneficial in patients with active glomerulonephritis and progressive renal insufficiency.

Outcome in patients with HSP is excellent, with disease-related death occurring in 1% to 3% of cases. Relapse occurs in up to 40% of cases, often within the first 3 months after the initial episode.

Kawasaki disease

Kawasaki disease is an acute vasculitis of childhood and represents the primary cause of acquired heart disease in children from the United States and Japan.[48] Eighty percent of children with Kawasaki disease are less than 5 years old, and boys are affected 1.5 times more often than girls.

Kawasaki disease begins as an acute febrile illness that is followed within 1 to 3 days by rash, conjunctival injection, and oral mucosal changes. Extremity changes characterized by brawny induration occur early in the disease, and 50% to 75% have cervical adenopathy. Together with fever, these 5 features constitute the criteria on which the diagnosis is based. Coronary artery lesions are responsible for most of the disease-related morbidity and mortality that occurs in patients with Kawasaki disease. Aneurysms appear 1 to 4 weeks after the onset of fever and develop in up to 25% of affected children who do not receive intravenous immunoglobulin.

Intravenous immunoglobulin, 2 g/kg, has been shown to prevent coronary aneurysm formation, lessen fever, and reduce myocardial inflammation.[49] Aspirin, 80 to 100 mg/kg per day, is given concurrently. An echocardiogram should be obtained at diagnosis and then at 2, 6, and 8 weeks to monitor for the development of coronary aneurysms. Children with multiple aneurysms, giant aneurysms, or coronary artery obstruction require close follow-up with serial ultrasonographic monitoring into adulthood and possible long-term anticoagulation.

Kawasaki disease has been reported to have a 3% mortality rate. Recurrences can develop in 1% to 3% of patients.

Behçet disease

Behçet disease is a multisystem inflammatory disease with manifestations that can affect arteries and veins of all sizes.[50,51] It occurs most commonly in 20- to 35-year-old persons of Asian and Eastern Mediterranean descent, with a male predominance in some ethnic populations.

Behçet disease is characterized by recurrent aphthous oral ulcers and at least 2 or more of the following: recurrent genital ulceration, eye lesions, cutaneous lesions, or a positive pathergy test result.[52] Among the most severe manifestations are gastrointestinal inflammation and ulceration, ocular inflammation that can lead to blindness, CNS disease with meningoencephalitis, and vascular involvement. Large venous or arterial lesions occur in 7% to 38% of patients and might include vessel thrombosis and occlusion, as well as pulmonary or peripheral artery aneurysms.

Treatment of Behçet disease is based on the disease manifestations. Aphthous lesions and mucocutaneous disease can be treated with topical or intralesional glucocorticoids, dapsone, or colchicine. Ocular and CNS disease require aggressive immunosuppression, with cyclosporine, AZA, and chlorambucil being the most commonly used agents. Preliminary studies have suggested favorable results with anti-TNF agents in patients with severe ocular inflammation.

Death occurs in 4% of patients with Behçet disease, generally as the result of gastrointestinal perforation, vascular rupture, and CNS disease. Behçet disease has the ability to remit and relapse frequently.

Primary angiitis of the CNS

Primary angiitis of the CNS (PACNS) is an uncommon disease in which patients have vasculitis isolated to the CNS without evidence of systemic vasculitis.[53,54] Granulomatous angiitis of the CNS (GACNS) represents about 50% of cases of PACNS and is a progressive disease that clinically presents with focal neurological deficits, chronic headache, or alterations in higher cortical function. More than 90% of patients with GACNS will have abnormal cerebrospinal fluid with mononuclear pleocytosis and increased protein with normal glucose levels. Results of magnetic resonance imaging are almost always abnormal, reflecting multifocal vascular insults of different ages. A cerebral arteriogram can reveal stenoses and ectasia in up to 40% of patients. Biopsy of tissue from the CNS is the diagnostic modality of choice, but results can be falsely negative in up to one fifth of patients. The diagnostic yield might be increased by taking biopsy specimens of both the leptomeninges and the underlying cortex.

In all instances a careful search must be made for processes of similar appearance, including atherosclerosis, infection, neoplasms, and drug-induced changes. An important diagnosis to distinguish from PACNS is reversible cerebral vasoconstrictive syndrome, which is characterized by a sudden onset of severe headache (thunderclap headache) with arteriographic cerebrovascular changes that have a similar appearance to vasculitis but that normalize within 12 months.[55]

GANCS is characteristically a fatal and progressive disorder but can respond to 1 mg/kg per day prednisone and 2 mg/kg per day CYC. For the 50% of patients with PACNS who do not have GACNS, treatment is based on the severity of disease manifestations and the rate of progression.

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Immunologic endocrine disorders

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Autoimmunity affects multiple glands in the endocrine system. Animal models and human studies highlight the importance of alleles in HLA-like molecules determining tissue-specific targeting that, with the loss of tolerance, leads to organ-specific autoimmunity. Disorders such as type 1A diabetes, Graves disease, Hashimoto thyroiditis, Addison disease, and many others result from autoimmune-mediated tissue destruction. Each of these disorders can be divided into stages beginning with genetic susceptibility, environmental triggers, active autoimmunity, and finally metabolic derangements with overt symptoms of disease. With an increased understanding of the immunogenetics and immunopathogenesis of endocrine autoimmune disorders, immunotherapies are becoming prevalent, especially in patients with type 1A diabetes. Immunotherapies are being used more in multiple subspecialty fields to halt disease progression. Although therapies for autoimmune disorders stop the progress of an immune response, immunomodulatory therapies for cancer and chronic infections can also provoke an unwanted immune response. As a result, there are now iatrogenic autoimmune disorders arising from the treatment of chronic viral infections and malignancies. (J Allergy Clin Immunol 2010;125:S226-37.)

Key words: *Type 1 diabetes, HLA, autoantibodies, immunotherapy, Addison disease, autoimmune polyendocrine syndrome type 1, autoimmune polyendocrine syndrome type 2, Graves disease, polyendocrine autoimmunity, iatrogenic autoimmunity*

Multiple endocrine diseases are immune mediated and now predictable. Autoimmune disorders can cluster in individuals and their relatives. A family history of autoimmunity and screening for autoantibodies can identify at-risk subjects. Knowledge of these disorders and their disease associations can lead to earlier diagnosis and management, resulting in less morbidity and, in some cases, mortality. We will review endocrine organ-specific autoimmune diseases, autoimmune polyendocrine syndromes, and iatrogenic endocrine autoimmune disorders with an emphasis on immunopathogenesis, hopefully leading to immunotherapy for standard and experimental clinical care.

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Abbreviations used

ACTH:	Adrenocorticotropic hormone
AIRE:	Autoimmune regulator gene
APS-1:	Autoimmune polyendocrine syndrome type 1
APS-2:	Autoimmune polyendocrine syndrome type 2
CGMS:	Continuous glucose monitoring system
CTLA:	Cytotoxic T lymphocyte–associated antigen
FOXP3:	Forkhead box protein 3 gene
GAD:	Glutamic acid decarboxylase
GO:	Graves ophthalmopathy
HT:	Hashimoto thyroiditis
IA-2:	Islet-associated antigen (ICA512)
IPEX:	Immune dysfunction, polyendocrinopathy, enteropathy, X-linked
NOD:	Nonobese diabetic
POEMS:	Polyneuropathy, organomegaly, endocrinopathy, serum monoclonal protein, and skin changes
POF:	Premature ovarian failure
PTPN22:	Protein tyrosine phosphatase nonreceptor 22
TGA:	Tissue transglutaminase
TPO:	Thyroid peroxidase
TSH:	Thyroid-stimulating hormone
TSHR:	Thyroid-stimulating hormone receptor
TSI:	Thyroid-stimulating immunoglobulin
ZnT8:	Zinc T8 transporter

DIABETES MELLITUS

Background

Based on the American Diabetes Association classification, type 1A diabetes is the immune-mediated form of diabetes, whereas type 1B represents non–immune-mediated forms of diabetes with β-cell destruction, leading to absolute insulin deficiency.[1] There are additional forms of insulin-dependent diabetes with defined causes. Type 2 diabetes is overall the most common form of diabetes and is characterized by insulin resistance and less β-cell loss. In the United States, with a population of approximately 300 million, there are about 1.5 million persons with type 1A diabetes, and of these, approximately 170,000 are less than 20 years of age. The incidence of type 1A diabetes, similar to that of other immune-mediated diseases, such as asthma, is doubling approximately every 20 years.[2] Diabetes almost always develops in the setting of genetic susceptibility best defined by polymorphisms of HLA alleles.[3] Currently, there is no known cure for type 1A diabetes, and treatment for the disease consists of lifelong insulin administration. Immunotherapies aimed at preventing β-cell destruction at the time of clinical onset are actively being studied.

Genetic susceptibility

There are monogenic and polygenic forms of both immune-mediated and non–immune-mediated diabetes. Monogenic non-immune diabetes includes permanent neonatal diabetes mellitus, transient neonatal diabetes, and maturity-onset diabetes of the

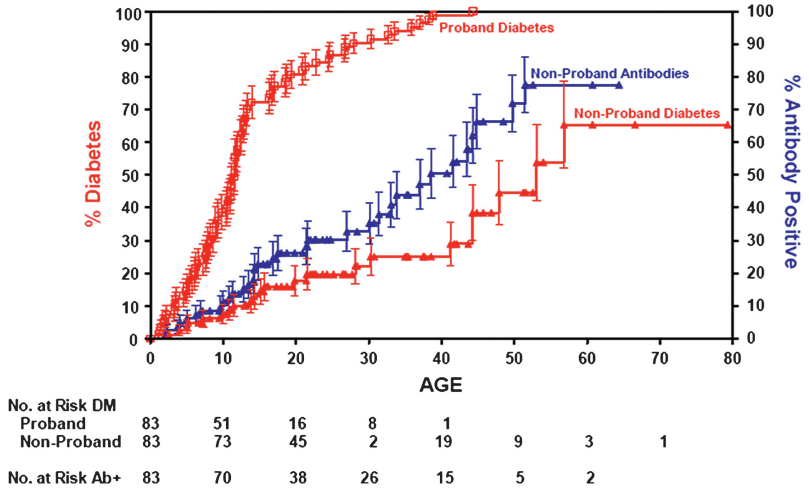

FIG 1. Progression to diabetes of initially discordant monozygotic twin siblings of patients with type 1 diabetes showing progressive conversion to diabetes. Approximately 80% become concordant for expression of anti-islet autoantibodies. *Ab*, antibody; *DM*, diabetes mellitus. Used with permission from Redondo et al.[5]

young. In general, children with these disorders lack all anti-islet autoantibodies, and therefore autoantibody assays can aid in identifying children to consider for genetic analysis. It is important to identify those who do not have type 1A diabetes, with estimates showing that approximately 1.5% of children presenting with diabetes have monogenic forms of diabetes. Several monogenic forms of diabetes are reported to be better treated with sulfonylurea therapy than with insulin (eg, mutations of the ATP-sensitive β cell–selective potassium channels and hepatocyte nuclear factor 1 alpha mutations),[4] and diabetes caused by glucokinase mutations requires no therapy at all. Approximately one half of permanent neonatal diabetes is due to mutations of the proinsulin gene that leads to β-cell loss. Two monogenic syndromes with immune-mediated diabetes are autoimmune polyendocrine syndrome type 1 (APS-1) and the immune dysfunction, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which will be discussed subsequently. The rest of this section will focus on the more common polygenic form of diabetes, type 1A diabetes.

Approximately 1 in 300 persons from the general population will have type 1A diabetes compared with 1 of 20 siblings of patients with type 1A diabetes. The concordance rate for monozygotic twins with type 1A diabetes is greater than 60% (Fig 1),[5] and a recent analysis of long-term twin data indicates that there is no age that an initially discordant monozygotic twin is no longer at risk.[5] Compared with monozygotic twins, initially discordant dizygotic twins are less often positive for anti-islet autoantibodies than nontwin siblings.[6] Offspring of a father with type 1A diabetes have a greater risk compared with offspring of a mother.[7]

The major determinant of genetic susceptibility to type 1A diabetes is conferred by genes in the HLA complex, which is divided into 3 regions: classes I, II, and III. Alleles of the class II genes, DQ and DR (and to a lesser extent DP), are the most important determinants of type 1A diabetes. These class II molecules are expressed on antigen-presenting cells (macrophages, dendritic cells, and B cells) and present antigens to $CD4^+$ T lymphocytes. DR3 and DR4 haplotypes are strongly associated with type 1A diabetes, with more than 90% of patients with type 1A diabetes possessing 1 or both of these haplotypes versus 40% of the US population.[8] Each unique amino acid sequence of DR and DQ is given a number. Because DRA does not vary, haplotypes can be defined by specific DRB, DQA, and DQB alleles. The highest-risk DR4 haplotypes vary at both DR (DRB1*0401, DRB1*0402, or DRB1*0405) and DQ (DQA1*0301 or DQA1*0302). DR3 haplotypes are almost always conserved with DRB1*03 combined with DQA1*0501 or DQB1*0201. The highest-risk genotype has both DR3 DQB1*0201/DR4 DQB1*0302. This genotype occurs in 30% to 50% of children with type 1A diabetes; approximately 50% of children with type 1A diabetes before the age of 5 years are DR3/4 heterozygotes versus 30% of young adults presenting with type 1A diabetes and 2.4% of the general population in Denver, Colorado. The excess risk for heterozygous haplotypes might be related to the transencoded DQ molecule (DQA and DQB encoded by different chromosomes) that can form in DR3/4 heterozygous individuals, namely DQA1*0501/DQB1*0302.[3]

In addition to HLA genes, many genetic loci contributing to diabetes risk have been implicated through genome-wide association studies (Fig 2),[9] which involves analyzing thousands of single nucleotide polymorphisms from large populations to find alleles associated with a particular disease. These alleles can increase risk (ie, high-risk alleles) or protect against a certain disease. Although HLA alleles confer the highest risk, multiple non-HLA genetic polymorphisms modify disease risk. The group of longer variable number of tandem nucleotide repeats 5′ of the insulin gene protects against diabetes. The decreased diabetes risk is associated with greater insulin message and resultant deletion of autoreactive T cells in the thymus.[10] Alleles of other identified genes primarily influence immune function, such as the protein tyrosine phosphatase nonreceptor 22, which regulates T-cell receptor signaling. The R620 W single amino acid change of protein tyrosine phosphatase nonreceptor 22 decreases T-cell receptor signaling (gain of function) and increases the risk of many autoimmune disorders, including type 1A diabetes, Addison disease, Graves disease, rheumatoid arthritis, and others.[11] Recently, a further genome-wide association study analysis identified 2 additional loci, *UBASH3A* and *BACH2*, associated with type 1A diabetes, loci having odds ratios of 1.16 and 1.13, respectively. Both of these loci were

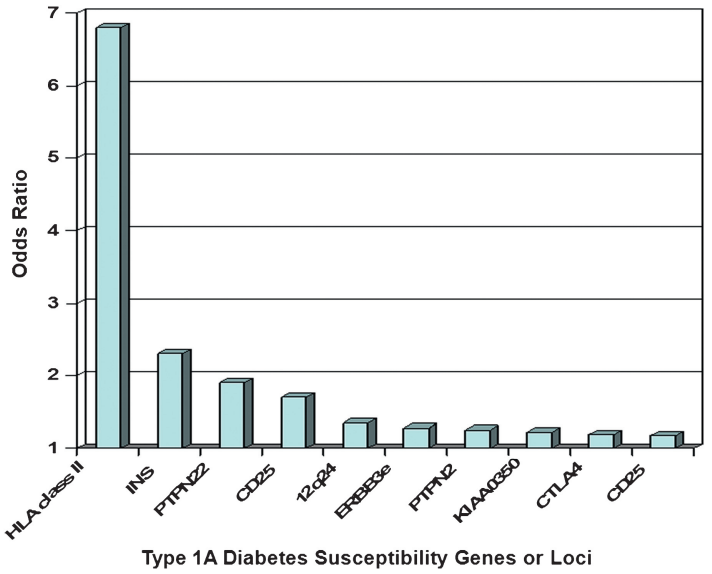

FIG 2. Summary of subsets of confirmed loci from whole-genome screens associated with type 1A diabetes and their odds ratios (from Teaching Slides at www.barbaradaviscenter.org). *CD25,* Also known as IL-2 receptor α chain; *ERBB3e,* an unidentified gene at 12q; *INS,* insulin; *KIAA 0350,* a lectin-like gene; *PTPN2,* protein tyrosine phosphatase nonreceptor 2; *PTPN22,* protein tyrosine phosphatase nonreceptor 22. Modified from Todd et al.[9]

validated from 2 separate populations, the Wellcome Trust Case-Control Consortium and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort.[12]

Environmental factors

The incidence of type 1A diabetes has been increasing dramatically at a rate of 3% to 5% per year for the last 50 years, and this rapid increase cannot be explained by genetics. There is no evidence that the epidemic of type 1A diabetes has leveled off in Finland, one of the countries with the highest incidence. The increase in the incidence of diabetes is most marked in children less than 5 years of age.[13] These observations suggest that environmental factors increasing diabetes risk have been introduced or factors decreasing risk have been removed. The Diabetes Autoimmunity Study of the Young found no evidence that bovine milk products, vaccinations, or enteroviral infections contribute to diabetes risk but has implicated decreased omega-3 fatty acid intake[14] and early cereal introduction. There appears to be a window from the ages of 4 to 6 months during which initial cereal introduction is not associated with an increased risk of islet autoimmunity because children who received initial cereal exposure at less than 3 months or after 7 months of age had a higher risk for having islet autoantibodies.[15] Omega-3 fatty acid supplementation in children with an increased genetic risk of diabetes was associated with a reduced risk of islet autoimmunity.[16] There have been several studies showing an association between vitamin D supplementation during the first year of life and a reduced risk of diabetes. A large prospective study of islet autoimmunity failed to confirm an association between type 1A diabetes risk and serum α- and γ-tocopherol concentrations, the principal forms of vitamin E in the diet and in human tissues.[17] Epigenetic influences are likely to be evaluated in future studies for diabetes risk. Hypermethylation has been associated with dietary supplements,[18] and there is discordance of methylation between monozygotic twins that increases with age.[19]

Pathogenesis

Type 1A diabetes is a T cell–mediated disease in which T cells infiltrate the islets, causing insulitis and ultimately β-cell death, decreased insulin production, and insulin-dependent diabetes. In a genetically susceptible subject, the development of diabetes occurs in stages (Fig 3). The presence of autoantibodies against islet cell antigens is the first indication for the development of diabetes, and patients retain sufficient β-cell mass initially for euglycemia. There are currently 4 autoantibodies used to predict the development of type 1A diabetes: antibodies against glutamic acid decarboxylase (GAD65), a tyrosine phosphatase–like protein (ICA512 also termed islet-associated antigen [IA-2]), insulin, and the recently discovered zinc T8 transporter (ZnT8).[20] After autoantibody development, there is progressive loss of insulin release as the autoimmune response progresses. During later stages, patients progressively experience subclinical hyperglycemia. In the final stages of development, decreased C-peptide levels cause patients to present with overt signs of diabetes.

Much of what we know about the autoimmune process in patients with diabetes comes from the study of animal models. The nonobese diabetic (NOD) mouse is a model in which type 1A diabetes and sialitis develop spontaneously, and the biobreeding rat has both diabetes and thyroiditis. As in human subjects, both models have alleles of genes within the MHC complex that influence antigen presentation to T lymphocytes and development of autoimmunity. One self-epitope in NOD mice has been shown to be a peptide of the insulin B chain, amino acids 9 to 23, that is recognized by autoreactive T lymphocytes.[21] During disease progression, activated T cells invade the pancreas and destroy β cells, resulting in insulin deficiency. Once β-cell destruction is initiated,

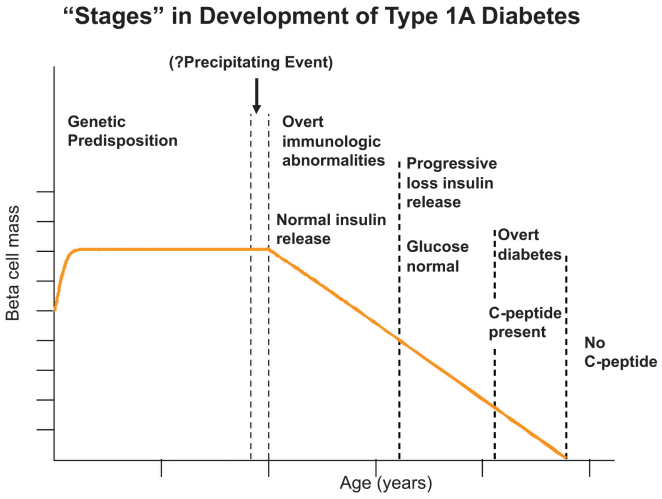

FIG 3. Hypothetic stages and loss of β cells in a patient progressing to type 1A diabetes (from Teaching Slides at www.barbaradaviscenter.org). Reproduced with permission from Eisenbarth GS.

other antigens become targets for the immune response, including islet glucose-related phosphatase, which is β cell specific.[22] Adoptive transfer of T cells from a diabetic mouse to an unaffected mouse results in diabetes. These animal models highlight the importance of having a genetic predisposition resulting in impaired immune regulation for autoimmunity to develop.

In human subjects a recent study examining postmortem pancreas specimens from patients with recent-onset type 1A diabetes showed a temporal pattern of immune cell infiltration. Initially, the inflammatory infiltrate consisted of $CD8^+$ cytotoxic T cells and macrophages.[23] $CD20^+$ B cells were not present in early insulitis but appeared in larger numbers as β-cell death progressed. $CD4^+$ T_H cells were present throughout insulitis but were not as prevalent as cytotoxic T cells and macrophages. The exact mechanism of β-cell death remains to be elucidated but likely involves cytokines, Fas/Fas ligand–induced cell death, and $CD8^+$ T cell–mediated cytotoxicity.

Diagnosis and prediction

The hallmark of type 1A diabetes is the autoimmune destruction of the pancreatic β cells by T cells. However, diagnosis is not made with T-cell assays because they are not as well developed or standardized compared with autoantibody assays. The lack of dependable assays for autoreactive T cells leads to the reliance on autoantibodies as the initial laboratory evaluation to detect an immune response against pancreatic β cells and distinguishing type 1 from type 2 diabetes.

There are several clinical scenarios in which the determination of autoantibodies is relevant. Children with transient hyperglycemia and adults presenting with hyperglycemia can present diagnostic dilemmas. Most children with transient hyperglycemia will remain healthy, but a subset will have type 1A diabetes; those with autoantibodies almost always progress to diabetes. Adults are much more likely to have type 2 diabetes, but 5% to 10% express islet autoantibodies, and these subjects progress more rapidly to insulin dependence. Independent of autoantibodies, routine monitoring of blood glucose levels is important to prevent the metabolic decompensation that can occur with many forms of diabetes.

Type 1A diabetes is a predictable disease. Autoantibodies against GAD65, insulin, IA-2, and the recently identified ZnT8 are current markers for type 1A diabetes. Relatives of patients with type 1A diabetes have been studied in detail. Expression of 2 or more autoantibodies (insulin, GAD65, or IA-2) has a positive predictive value of greater than 90% among relatives of a patient with type 1 diabetes (Fig 4)[25]; this holds true for the general population as well.[24] A single autoantibody carries a risk of approximately 20%.[25,26] With the addition of a fourth autoantibody, ZnT8, prediction will only improve because 26% of patients with autoantibody-negative type 1A diabetes in the Diabetes Autoimmunity Study in the Young study were found to have the ZnT8 autoantibodies.[27]

Treatment

The mainstay of type 1A diabetes treatment is insulin therapy. Over the last several years, multiple advances in insulin preparation, insulin delivery, and glucose monitoring have considerably improved treatment. Multiple analog insulins provide either a faster onset of action or longer duration and decrease the variability of insulin absorption. Insulin pumps allow for a more physiologic administration of insulin throughout the day. Continuous glucose monitoring systems (CGMSs) have been developed and measure interstitial fluid glucose levels. CGMSs assess blood glucose trends and provide alarms for high and low blood glucose levels. There is still a need to both calibrate the monitors and confirm low blood glucose values with fingerstick glucose determination. There is research underway with CGMS monitors controlling insulin delivery from insulin pumps.

Despite treatment with insulin therapy, long-term complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease, can result. Although the progress to complete insulin dependence occurs quickly after clinical onset, initially after diagnosis, the pancreas is able to produce a significant amount of insulin[28]; at this time, immunologic intervention can save β-cell function and reduce reliance on insulin. Two international networks conducting immunotherapy trials, the Immune Tolerance Network and TrialNet, have been established. Immunotherapies in patients with type 1A diabetes are aimed at altering the underlying immune process that results in β-cell loss. These therapies consist of agents that are non–antigen specific and those that are antigen specific. Non–antigen-specific therapies target various components of the immune system and include those directed against T cells (anti-CD3 mAbs, anti-thymocyte globulin, and cyclosporine), B cells (anti-CD20 mAbs), and other components of the immune system (Table I).[29-33] Antigen-based therapies are believed to mediate immune tolerance to antigens that result in autoimmunity to β cells. These therapies include vaccines with GAD, the B chain of insulin, and other insulin peptides (Table II).[34] Many of these therapies have reversed hyperglycemia in the NOD mouse, and several therapies show promise in altering the underlying immune process in human subjects.[35]

INSULIN AUTOIMMUNE SYNDROME

The insulin autoimmune syndrome, also known as Hirata disease, results from autoantibodies reacting with insulin. The diagnostic criteria include fasting hypoglycemia without evidence of exogenous insulin administration, high levels of serum immunoreactive insulin, and the presence of high-titer insulin

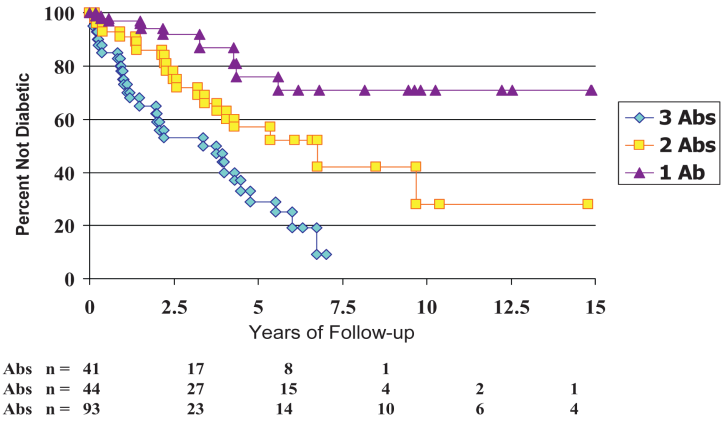

FIG 4. Progression to diabetes versus number of autoantibodies (GAD, ICA5112, and insulin). *Abs*, Antibodies. Used with permission from Verge et al.[25]

TABLE I. Non–antigen-specific immunotherapy trials for new-onset type 1A diabetes

Agent	Stage of development	Comments	References and links
Anti-CD3 mAbs	Phase II/III	Reduced insulin requirements out to 18 mo	Herold et al[85] and Keymeulen et al[86]
Anti-CD20 mAb (rituximab)	Phase II	Ongoing	www.clinicaltrials.gov/ct2/show/NCT00279305
Anti-thymocyte globulin	Phase I/II	Ongoing	www.clinicaltrials.gov/ct2/show/NCT00515099
Cyclosporine	Multiple trials	Successful remission but unacceptable side effects	Jenner et al[87]
Nicotinamide	Pilot	No effect	Elliott and Chase[88]
BCG	Pilot	No effect	Allen et al[89]
Anti-CD52 (Campath-1H)	Phase I	Withdrawn secondary to adverse events	www.clinicaltrials.gov/ct2/show/NCT00214214
CTLA-4 immunoglobulin (abatacept)	Phase I	Ongoing	www.clinicaltrials.gov/ct2/show/NCT00505375
Mycophenolate and daclizumab	Phase I	No effect	www.clinicaltrials.gov/ct2/show/NCT00100178

autoantibodies. Patients have recurrent and spontaneous hypoglycemia. The insulin autoantibodies can be monoclonal, from a B-cell lymphoma, or polyclonal. The polyclonal disorder is strongly associated with the DRB1*0406 haplotype and usually follows therapy with a sulfhydryl-containing medication, such as methimazole (an antithyroid drug used to treat Graves disease).[36]

AUTOIMMUNE THYROID DISEASE

Background

Autoimmune thyroid disease consists of Graves disease and Hashimoto thyroiditis (HT). It is very common, with a prevalence of 5% to 10% in the general population. Autoantibodies to various enzymes and proteins in the thyroid gland, thyroid peroxidase (TPO) and thyroglobulin, are the hallmark of autoimmune thyroid disease.

Graves disease

Background. Graves disease was first described by Robert Graves in 1835 as being associated with a goiter, palpitations, and exophthalmos. It is now know that the thyroid-stimulating hormone receptor (TSHR) is stimulated by autoantibodies, thyroid-stimulating immunoglobulins (TSIs), and that thyroid cells are activated, resulting in signs and symptoms of hyperthyroidism. The clinical manifestations of hyperthyroidism include a constellation of symptoms comprised of palpitations, tremor, heat intolerance, sweating, anxiety, emotional lability, and weight loss despite a normal to increased appetite. Extrathyroidal manifestations of Graves disease include Graves ophthalmopathy (GO) and dermatopathy (pretibial myxedema) with little understanding of the cause of these disease components.

Pathogenesis. Graves disease occurs in genetically susceptible individuals, with the HLA alleles contributing the greatest increase in risk, which is similar to type 1A diabetes. In white subjects HLA DR3 (HLA DRB1*03) and DQA1*0501 confer the highest risk,[37] whereas HLA DRB1*0701 is protective.[38] For monozygotic twins, the concordance rate is 20%; the rate is much lower for dizygotic twins, indicating other susceptibility factors for disease development. Female sex is the main risk factor, with smoking, lithium treatment, and low iodine consumption also associated with the disease.

Patients with Graves disease have diffuse lymphocytic infiltration of the thyroid gland and lose tolerance to multiple thyroid antigens, TSHR, thyroglobulin, TPO, and the sodium-iodine cotransporter. Autoantibodies develop when T cells recognize multiple epitopes of the TSHR.[39] The autoantibodies can either stimulate or inhibit thyroid hormone secretion. It is a balance of these autoantibodies toward thyroid cell activation that results in hyperthyroidism. Because of these various autoantibodies with differing functions, autoantibody concentrations cannot be correlated to thyroid hormone levels in patients with Graves disease. Fluctuating antibody titers can result in a thyroid yo-yo syndrome with alternating hyperthyroidism and hypothyroidism.[40] Although TSIs cause Graves disease, the serum antibody

TABLE II. Selected antigen-specific immunotherapy trials for type 1A diabetes

Agent	Stage of development	Comments	References and links
GAD65	Phase II/III	C peptide preserved at 18 mo	Ludvigsson et al[90]
Insulin B chain in incomplete Freund adjuvant	Phase I	Ongoing	www.clinicaltrials.gov/ct2/show/NCT00057499
Proinsulin-based DNA vaccine (BHT-3021)	Phase I	C peptide preserved at 12 mo	www.bayhilltx.com
Oral insulin	Prevention trial	Subset with insulin autoantibodies having a potential response	www.clinicaltrials.gov/ct2/show/NCT00419562

concentration can be low or undetectable in some patients. This could be due to assay insensitivity, misdiagnosis of the cause of hyperthyroidism, or intrathyroidal production of autoantibodies.[41]

GO is associated with Graves hyperthyroidism, but the 2 diseases can exist independently of one another. GO is clinically evident in 25% to 50% of patients with hyperthyroidism, and of these patients, 3% to 5% experience severe symptoms. GO results from increased orbital fat and muscle volume within the orbit. Histologic analysis of orbital tissue reveals lymphocytic infiltration and the inflammatory cytokines IL-4 and IL-10. Smoking is a strong risk factor for GO and worsens the symptoms of eye disease.

The association between Graves hyperthyroidism and GO suggests that the 2 disorders result from an autoimmune process to 1 or more antigens from the thyroid and orbit. Orbital fibroblasts are thought to be the antigenic target in GO. TSHR mRNA and protein expression in orbital fibroblasts has been documented in both healthy subjects and patients with GO.[42] It is possible that a form of TSHR or similar protein is expressed in the orbit and might serve as a cross-reactive target for TSIs.

Diagnosis. Graves disease is the most common cause of hyperthyroidism. Diagnosis is made with clinical and biochemical manifestations of hyperthyroidism. Thyroid function tests show low to suppressed thyroid-stimulating hormone (TSH) levels and increased thyroxine and triiodothyronine levels. Diagnosis is confirmed with a radioactive iodine uptake and scan (only tested in nonpregnant, non–breast-feeding patients) showing increased homogenous uptake. TSI levels aid in the diagnosis but are not confirmatory because patients can have Graves disease without autoantibodies present. TSI autoantibodies measured in the third trimester of pregnancy are a good predictor of neonatal Graves disease. During pregnancy, thyroid autoantibodies generally decrease, presumably because of secretion of trophoblast factors that are immunosuppressive.

Treatment. Treatment of Graves disease has changed little over the last 50 years. Treatment options include antithyroid drugs, radioactive iodine, and surgery. Antithyroid drugs block thyroid hormone synthesis, but the majority of patients experience relapses with discontinuation of therapy. Radioactive iodine ablation is the preferred treatment method in the United States. Ablation generally results in iatrogenic hypothyroidism, requiring lifelong thyroid hormone replacement. Anti-CD20 mAb has been tried in a small number of patients with Graves disease. Twenty patients received methimazole for Graves disease and were rendered euthyroid. Ten patients received anti-CD20 mAb infusions during the final 3 weeks of methimazole treatment. Fewer patients receiving anti-CD20 antibody treatment relapsed at 1 month (6/10) than those who did not (8/10).[43]

Immunotherapy trials for GO show more promise than for Graves disease alone. Agents such as anti-CD20 mAbs and anti–TNF-α mAbs have been used. In a pilot study anti-CD20 mAbs improved proptosis, soft tissue changes, and eye motility in 7 patients with moderate-to-severe GO. None of the treated patients followed to 1 year had a relapse. This was compared with 15 of 20 patients responding to methylprednisolone therapy; 10% had experienced relapses at the conclusion of the study.[44] Larger randomized controlled trials are needed to confirm these results.

HT

Background. HT is the most common endocrine autoimmune condition, affecting up to 10% of the general population. It is characterized by a gradual loss of thyroid function, goiter, and T-cell infiltration on histology. HT affects women more frequently than men, with a sex ratio of 7:1.

Pathogenesis. HT occurs in genetically susceptible populations but lacks a strong association with HLA. Mutations in the thyroglobulin gene[45] and cytotoxic T lymphocyte–associated antigen (CTLA) 4 are associated with disease.[46] T cells play a crucial role in disease pathogenesis by reacting with thyroid antigens and secreting inflammatory cytokines. Autoantibodies develop in patients with HT to TPO, thyroglobulin, and the TSHR. It is believed that these autoantibodies are secondary to thyroid follicular cell damage induced by T cells. TPO is the major autoantigen, and autoantibodies to TPO are closely associated with disease activity.

Diagnosis and treatment. The diagnosis and treatment of HT has changed very little over the last several decades. Diagnosis is made based on clinical (fatigue, weakness, cold intolerance, weight gain, constipation, dry skin, depression, and growth failure or delayed puberty in children) and biochemical manifestations of hypothyroidism. Thyroid function tests show an increased TSH level and a low thyroxine and triiodothyronine levels. Other causes of thyroiditis (postpartum, acute, subacute, and silent) need to be excluded. Treatment is with lifelong thyroxine replacement with a goal of normalizing the TSH level. Continuous monitoring of thyroid function is needed to avoid overreplacement, which can lead to premature osteoporosis and cardiac arrhythmias. Fine-needle aspiration of thyroid nodules is recommended to rule out thyroid cancer because differentiated thyroid cancer is associated with a favorable prognosis and low recurrence once detected.

ADDISON DISEASE

Background

Thomas Addison described a group of patients affected with anemia and diseased adrenal glands in 1849. Addison disease is a chronic disorder of the adrenal cortex resulting in decreased production of glucocorticoids, mineralocorticoids, and

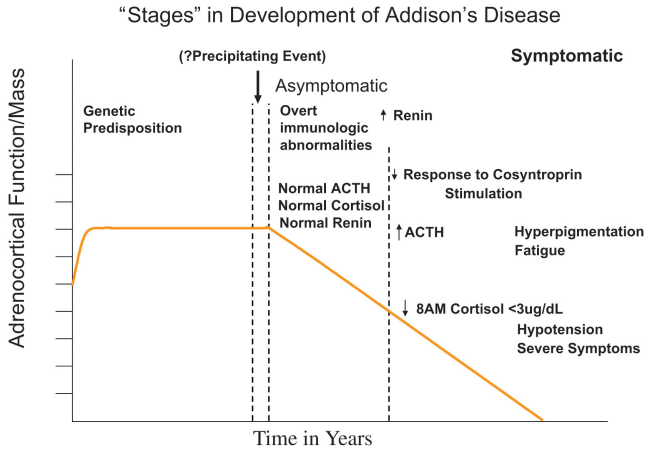

FIG 5. Stages in the development of Addison disease.[42] Adrenocortical function is lost over a period of years. In the first stage genetic predisposition is conferred by a patient's HLA genotype. In the second stage events that precipitate anti-adrenal autoimmunity occur but are currently unknown. In the third stage, which involves presymptomatic disease, 21-hydroxylase autoantibodies predict future disease. Finally, in the fourth stage overt Addison disease develops. An increased plasma renin level is one of the first metabolic abnormalities to occur and is followed by the sequential development of other metabolic abnormalities (a decreased cortisol level after cosyntropin stimulation, an increased corticotropin level, and a decreased basal cortisol level). Finally, there are severe symptoms of adrenal insufficiency, such as hypotension.

androgens. There is increased secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. Histologic examination of adrenal glands from patients with autoimmune adrenal insufficiency reveals fibrosis with a mononuclear cell infiltrate, plasma cells, and rare germinal centers.[47] The most common cause of primary adrenal insufficiency in developed countries is autoimmunity (70% to 90%), with tuberculosis the second most common cause (10% to 20%). Addison disease can be present in 3 clinical forms: part of syndromes termed APS-1 and autoimmune polyendocrine syndrome type 2 (APS-2) and as an isolated disease.

Pathogenesis and genetics

Similar to type 1A diabetes, Addison disease also can be divided into stages of disease progression. Genetically predisposed individuals have autoantibodies to the 21-hydroxylase enzyme and eventually lose the ability to produce cortisol (Fig 5).[48] Autoantibodies against 21-hydroxylase are present in more than 90% of patients with recent-onset disease. Susceptibility is conferred through the genes encoding the class II MHC, and as is the case with type 1A diabetes, there is a strong association with the DR3 haplotype. The highest-risk genotype, occurring in 30% of patients with Addison disease, consists of DR3/4, DQ2/DQ8,[49] and in this case the DRB1*0404 DR4 subtype confers highest risk on DR4 haplotypes. The MHC class I–related molecule A 5.1 allele, an atypical HLA molecule (MHC class I–related gene A), is also associated with genetic risk.[50] Polymorphisms of the MHC class I–related molecule A gene are based on the number of triplicate GCT repeats in exon 5. The translated protein interacts with the NKG2D receptor, which is important for thymic maturation of T cells.[51] NKG2D can also regulate the priming of human naive $CD8^+$ T cells.[52] The allele, designated 5.1, is associated with the insertion of a base pair, which results in a premature stop codon and loss of the membrane-binding region of the protein.

Diagnosis and treatment

The diagnosis of Addison disease is made in symptomatic patients with high levels of ACTH and a deficiency of cortisol or when serum cortisol levels do not increase after an ACTH stimulation test in the presence of increased basal ACTH levels; 21-hydroxylase autoantibodies are usually (>90%) present. The clinical manifestations are subtle (weakness, fatigue, anorexia, orthostasis, nausea, myalgias, and salt craving), and a high index of suspicion is necessary to diagnose adrenal insufficiency before an adrenal crisis. We recommend screening patients with type 1A diabetes, hypoparathyroidism, and polyendocrine autoimmunity for 21-hydroxylase autoantibodies. If present, yearly monitoring with an ACTH stimulation test is performed to allow early diagnosis and prevent an adrenal crisis. Treatment is with lifelong glucocorticoids and mineralocorticoids, with counseling about the need for stress-dose steroids for illnesses and before surgical procedures. Forty percent to 50% of patients with Addison disease will have another autoimmune disease, necessitating lifelong monitoring for associated autoimmune conditions.

IDIOPATHIC HYPOPARATHYROIDISM

Background

Idiopathic hypoparathyroidism results from a deficiency of parathyroid hormone, which regulates the serum calcium concentration and does not have an identifiable cause. This disease is a common component of APS-1 in infants and young children. It also occurs sporadically in adults, most often affecting female subjects with HT. An autoimmune basis for idiopathic hypoparathyroidism has been suggested because of its association with other autoimmune conditions.

Pathogenesis

Hypocalcemia results from parathyroid hormone deficiency. Recent work by Alimohammadi et al[53] identified a parathyroid autoantigen, NACHT leucine-rich repeat protein 5, in patients with APS-1. NACHT leucine-rich repeat protein 5 autoantibodies were identified in patients with APS-1 with hypoparathyroidism and not in healthy subjects or subjects with other autoimmune disorders. Autoantibodies to the calcium-sensing receptor on parathyroid glands have been described as well and can activate the receptor, thereby causing decreased production of parathyroid hormone.[54]

Diagnosis and treatment

Idiopathic hypoparathyroidism is diagnosed when no other causes of hypocalcemia and hypoparathyroidism can be identified. Treatment is with calcium and magnesium supplementation. To absorb calcium, active 1,25 dihydroxyvitamin D needs to be administered with calcium, and frequent monitoring of serum calcium levels is required.

PREMATURE OVARIAN FAILURE

Background

Premature ovarian failure (POF) is defined as amenorrhea, increased gonadotropin levels, and hypoestrogenism before age

40 years. POF can occur before or after puberty. Girls should begin puberty by age 13 years and menstruate within 5 years after the onset of puberty. Two distinct clinical scenarios have been identified.

Idiopathic POF with adrenal autoimmunity. Approximately 10% of female subjects with Addison disease will have POF. Steroid cell autoantibodies, directed against the enzymes 21-hydroxylase or 17-hydroxylase, cross-react with theca interna/granulosa layers of ovarian follicles. The presence of these autoantibodies correlates with the histologic diagnosis of autoimmune oophoritis.[55] MHC class II is expressed on granulosa cells of patients with POF and might potentiate a local T-cell autoimmune response.[56]

Idiopathic POF with exclusive manifestations of ovarian autoimmunity. The vast majority (>90%) of women with POF do not have Addison disease or steroid cell autoantibodies, calling into question the autoimmune component of the disease. Thyroid autoimmunity is present in about 14% of these patients. Approximately 10% of patients with isolated POF and without Addison disease will have numerous ovarian follicles intact. These patients are categorized as having resistant ovary syndrome that is insensitive to ovulation induction with exogenous gonadotropins.

Treatment

Currently, there is no treatment available to induce ovarian function or stop progression of autoimmune ovarian destruction. Treatment is focused on treating symptoms of estrogen deficiency and maintaining bone health to prevent osteoporosis. Infertility can be treated with *in vitro* fertilization with donor eggs. However, there is a relapsing and remitting component to the underlying autoimmunity, and occasionally, conceptions can be achieved. Screening for associated autoimmune conditions (type 1A diabetes, Addison disease, and thyroid autoimmunity) should be considered in patients with idiopathic POF.

LYMPHOCYTIC HYPOPHYSITIS

Background

Lymphocytic hypophysitis is a rare inflammatory lesion of the pituitary gland. Approximately 500 cases have been reported in the literature since the initial report in 1962.[57] This condition is more common in female subjects and affects women during later pregnancy and the postpartum period (eg, postpartum hypophysitis). It is strongly associated with other autoimmune disorders. Of note, ipilimumab, an mAb that blocks CTLA-4, is an immunologic therapy used in oncologic clinical trials and has induced hypophysitis.[58]

Pathogenesis

The morphologic features of hypophysitis resemble those of other autoimmune endocrinopathies. The absence of granulomas on histology distinguishes this condition from the granulomatous hypophysitis seen in association with sarcoidosis, tuberculosis, and syphilis. Anti-pituitary antibodies have been isolated in a minority of patients with disease.

Diagnosis and treatment

Presenting symptoms include fatigue, headache, and visual field deficits. Diagnosis is confirmed by means of histologic examination of a pituitary biopsy specimen. Anterior pituitary hormone deficits are common, and hormone replacement is indicated. High-dose glucocorticoid pulse therapy has been used for treatment.[59]

AUTOIMMUNE POLYENDOCRINE SYNDROMES

Background

The autoimmune polyendocrine syndromes are a constellation of disorders characterized by multiple autoimmune disorders, including endocrine gland failure or hyperactivity (Graves disease). Some of the components of the syndromes have been described previously in the review. The syndromes include APS-1; APS-2; IPEX syndrome; polyneuropathy, organomegaly, endocrinopathy, serum monoclonal protein, and skin changes (POEMS) syndrome; non–organ-specific autoimmunity (eg, lupus erythematosus) associated with anti-insulin receptor antibodies; thymic tumors with associated endocrinopathy; and Graves disease associated with insulin autoimmune syndrome. APS-1–, APS-2–, IPEX-, POEMS syndrome–, and diabetes-associated autoimmune disorders will be discussed in further detail.

APS-1

Background. APS-1/APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) is a rare disorder generally seen in infants, and the diagnosis is made when a child has 2 or 3 of the following: mucocutaneous candidiasis, hypoparathyroidism, or Addison disease. Mucocutaneous candidiasis involving the mouth and nails is usually the first manifestation followed by the development of hypotension or fatigue from Addison disease or hypocalcemia from hypoparathyroidism. APS-1 is associated with other autoimmune disorders (type 1A diabetes, vitiligo, alopecia, hepatitis, pernicious anemia, and primary hypothyroidism) and asplenism.

Pathogenesis/genetics. APS-1 is due to a mutation in the autoimmune regulator gene *(AIRE)*, which is transmitted in an autosomal recessive manner. The *AIRE* gene encodes a transcription factor needed for the expression and presentation of self-antigens to developing lymphocytes in the thymus.[60] More than 40 mutations in *AIRE* have been described,[61] and when mutations are present, tolerance is lost to multiple self-antigens. The resulting autoreactive T cells that escape deletion in the thymus have the ability to destroy multiple specific tissues, producing a phenotype of multiple autoimmune disorders. Animal models with a knockout of the *AIRE* gene result in widespread autoimmunity, although the phenotype is mild with lymphocytic infiltration of the liver and atrophy of the adrenal and thyroid glands. The majority of mice also exhibit autoantibodies to the pancreas, adrenal glands, testes, and liver.[62] Human studies of isolated autoimmune disorders, such as Addison disease occurring without evidence of APS-1, have not found mutations in the *AIRE* gene.[63]

Diagnosis. Diagnosis is based on the presence of specific autoimmune disorders and mucocutaneous candidiasis. The known *AIRE* gene mutations can now be screened. Meager et al[64] recently reported that patients with APS-1 have multiple anti-interferon antibodies, with IFN-ω–reactive autoantibodies present in 100% of patients; assays for such autoantibodies might aid in rapid diagnosis.

Treatment. Hormone replacement is the mainstay of treatment for the endocrinopathies present in patients with APS-1.

Mucocutaneous candidiasis needs to be treated aggressively and monitored for recurrence because it can occur anywhere along the gastrointestinal tract. Untreated disease can lead to the development of epithelial cancers. Asplenism needs to be identified, and vaccinations against pneumococcus, meningococcus, and *Haemophilus influenzae* need to be administered.

A high clinical suspicion for other autoimmune disease needs to be maintained in patients with APS-1 and their relatives. Patients with APS-1 need to be followed at a center with experience monitoring and caring for these patients. Siblings need to be followed closely, and consideration should be given to screening for anti–IFN-ω autoantibodies. Recommendations are to see these patients at 6-month intervals and screen for autoantibodies.[65] If autoantibodies are present without the associated disease, functional testing is indicated. Patients with 21-hydroxylase antibodies are often followed with annual ACTH levels, 8 AM cortisol levels, and cosyntropin stimulation testing unless symptoms or signs warrant more frequent monitoring. The presence of islet cell autoantibodies warrants glucose tolerance testing to detect disease before overt clinical symptoms and education related to the symptoms of diabetes along with home glucose monitoring.

APS-2

Background. APS-2, also known as Schmidt syndrome, is the most common autoimmune polyendocrine syndrome. APS-2 has Addison disease as its defining component with either autoimmune thyroid disease or type 1A diabetes in conjunction. Women are typically affected at a higher rate than male subjects. Other diseases less commonly associated with APS-2 include celiac disease, vitiligo, pernicious anemia, myasthenia gravis, stiff man syndrome, and alopecia. Familial aggregation was demonstrated by a study looking at 10 families with APS-2, and one in 7 relatives had an undiagnosed autoimmune disease, the most common being thyroid disease.[66] Diseases can develop years to decades apart, making knowledge of the syndromes necessary to detect disease and provide treatment before morbidity and mortality. Table III compares APS-1 and APS-2.[67]

Pathogenesis/genetics. The genetics of APS-2 are governed by the HLA haplotypes, which confer disease risk to multiple autoimmune disorders. The DR3, DQA1*0501, DQB1*0201 haplotype increases the risk for type 1A diabetes, Addison disease, and celiac disease. The DR4 haplotype of patients with all 3 of these diseases is associated with DQA1*0301, DQB1*0302. If a patient with type 1A diabetes has the DRB1*0404 allele and express 21-hydroxylase antibodies, there is a 100-fold increase in the risk of Addison disease.[68] Autoimmune diseases result from a failure to develop or maintain tolerance along with a genetic predisposition, MHC alleles, controlling specific disease development. Multiple autoimmune disorders develop when tolerance is lost to a number of self-antigens.

Diagnosis and treatment. Similar to APS-1, treatment of APS-2 focuses on identifying and treating the underlying autoimmune conditions. Autoimmune thyroid disease is very common. It is prudent to screen patients with type 1A diabetes and those with Addison disease with a yearly TSH. We recommend screening patients with type 1A diabetes for 21-hyroxylase and tissue transglutaminase (TGA) autoantibodies. The optimal screening interval is not defined; however, autoantibodies can develop at any age, and repeat testing is necessary in the case of a negative test result. Relatives of patients with APS-2 need to be monitored closely.

TABLE III. Comparison of APS-1 and APS-2

APS-1	APS-2
Onset infancy	Older onset
Siblings	Multiple generations
AIRE gene mutated	
Not HLA associated	DR3/4 associated
Immunodeficiency	No defined immunodeficiency
Asplenism	
Mucocutaneous candidiasis	
18% Type 1A diabetes	20% Type 1A diabetes
100% Anti-interferon antibodies	

Available from the Teaching Slides at www.barbaradaviscenter.org.

IPEX syndrome

Background. The rare IPEX syndrome is caused by mutations in the forkhead box protein 3 gene *(FOXP3)*, resulting in absent or dysfunctional regulatory T cells.[69] Clinically, it presents during the first few months of life with dermatitis, growth retardation, multiple endocrinopathies, and recurrent infections. Affected neonates have overwhelming autoimmunity, including type 1A diabetes, developing as early as 2 days of age.

Pathogenesis/genetics. To date, 20 mutations in *FOXP3* have been identified in patients with IPEX syndrome.[70,71] Most of these mutations occur in the forkhead (winged-helix) domain and leucine zipper region, resulting in impaired DNA binding. The inability of FOXP3 protein to bind DNA in regulatory T cells impairs immune-suppressor function. Dysregulated T-cell function leads to overwhelming autoimmunity and recurrent infections. The scurfy mouse had a disease very similar to IPEX and has a homologous gene, scurfin, to the human *FOXP3*. The scurfy mouse model allows for understanding disease pathogenesis and provides a model to evaluate treatment modalities.[72,73] Neonatal thymectomy in male scurfy mice ameliorates disease and increases lifespan. Transfer of peripheral $CD4^+$ T cells, but not $CD8^+$ T cells, from affected mice to homologous wild-type mice results in disease, whereas bone marrow transplantation does not induce disease. Peripheral $CD4^+$ T cells appear to be hyperresponsive to antigens and have a decreased requirement for costimulation with CD28.[74] The inability of $CD4^+$ T cells to regulate the immune response from mutations in scurfin or *FOXP3* results in the IPEX syndrome.

Treatment. Children affected with IPEX usually die in the first 2 years of life of sepsis or failure to thrive. Supportive care and treatment of underlying disorders is necessary. Immunosuppressive medications have been tried in case reports or small case series. High-dose glucocorticoids, tacrolimus, cyclosporine, methotrexate, sirolimus, infliximab, and rituximab have been tried with varying degrees of success. The toxicity and infectious complications limit their dosing and use. In the scurfy mouse the disease can be cured with partial T-cell chimerism, and the same appears to be true in human subjects with normal T lymphocytes able to regulate the abnormal immune system in a dominant fashion.[75] Bone marrow transplantation can reduce symptoms and prolong survival.[76] Transplantation should be considered early in the disease to limit the autoimmune destruction to endocrine organs and possibly reduce the infectious complications from chronic immune suppression.

POEMS syndrome

POEMS syndrome has polyneuropathy, organomegaly, endocrinopathies, M-protein, and skin manifestations (hyperpigmentation and hypertrichosis) as clinical features. The causative factors of this constellation of diseases are not well defined. The syndrome is associated with plasmacytomas and osteosclerotic lesions, with radiation therapy to localized lesions being beneficial. Autologous hematopoietic stem cell transplantation has improved symptoms.[77]

Diabetes-associated autoimmune disorders

Multiple autoimmune disorders are associated with type 1A diabetes. Many of the disorders have been discussed previously in this review, and this section will focus on their relationship to type 1A diabetes.

Celiac disease is an autoimmune disorder that results in T-cell infiltration of the mucosa of the small intestine. Gliadin, a protein of wheat gluten, has been identified as the antigen responsible for inducing the autoimmune process. Like type 1A diabetes, a genetic predisposition is conferred through the HLA alleles DQ2 and DQ8. Symptoms of celiac disease can be mild but can also include diarrhea, abdominal pain, iron deficiency anemia, pubertal delay, growth failure, decreased bone mineralization, and vitamin D deficiency. TGA IgA autoantibodies are a sensitive and specific marker for the autoimmune process, more so than the older antiendomysial antibody assay. TGA autoantibodies are present in up to 16% of patients with type 1 diabetes.[78] A definitive diagnosis is made with a small-intestine biopsy showing flattened villi and intraepithelial lymphocytic infiltrates. Treatment is with a gluten-free diet, which results in reversal of the autoimmune process and normalization of the intestinal villi.[79] We recommend screening with TGA autoantibodies yearly in patients with type 1 diabetes and performing a small-intestine biopsy if the results of a repeat TGA autoantibody are positive. The biopsy specimen should be obtained close to the time of antibody measurement because the half-life of IgA antibodies are short and the titer of TGA autoantibody fluctuates with the amount of gluten in the diet. Those with a positive biopsy result are counseled on a gluten-free diet. These recommendations are based on the known risks of symptomatic celiac disease (osteoporosis, anemia, and gastrointestinal malignancy) and the rationale that the intestinal pathology is reversible with gluten avoidance.

Addison disease is present in 1 in 10,000 subjects in the general population compared with 1 in 200 in the type 1 diabetic population. One percent to 2% of patients with type 1 diabetes have 21-hydroxylase autoantibodies.[80] Many patients with Addison disease are adrenally insufficient for years before diagnosis. It is advisable to screen patients with type 1 diabetes for 21-hydroxylase autoantibodies and monitor those with positive cosyntropin (ACTH) stimulation test results.

Autoimmune thyroid disease is common in patients with type 1 diabetes. Twenty percent to 30% of patients with type 1 diabetes express TPO, thyroglobulin autoantibodies, or both, twice that of the general population. Long-term follow-up has shown 30% of patients with type 1 diabetes will have autoimmune thyroid disease.[81] It is recommend that patients with type 1 diabetes be screened for thyroid dysfunction annually with a serum TSH level.[82]

Pernicious anemia results in a macrocytic anemia from autoimmune destruction of parietal cells in the fundus and body of the stomach. The frequency of pernicious anemia in patients with type 1 diabetes has been reported to be up to 4%, with a rate of 0.12% in the general population.[83]

Vitiligo, the loss of melanocytes in the skin, is associated with many autoimmune conditions, including type 1A diabetes.

IATROGENIC ENDOCRINE AUTOIMMUNE DISORDERS

Background

Drug-induced autoimmune diseases have been recognized for years and span multiple disciplines. Iatrogenic autoimmunity is increasing in frequency as more therapies are designed to alter immune mechanisms in autoimmune conditions and cancer.

Pharmaceutical agents

IFN-α. The interferons are a group of proteins characterized by antiviral activity, growth-regulatory properties, and a variety of immunomodulatory activities. IFN-α is currently used to treat patients with the hepatitis C virus. IFN-α has been reported to cause HT and Graves disease. It is also associated with nonautoimmune thyroiditis. Approximately 5% to 10% of patients treated with IFN-α have thyroid autoimmunity, whereas another 15% have thyroid autoantibodies without clinical disease.[84] The drug also induces both islet autoantibodies and rapid progression to diabetes in a subset of patients with islet autoantibodies.[85] At a minimum, glucose levels should be monitored in patients. If these levels are abnormal, the patient should be evaluated for islet autoantibodies and monitored for diabetes, and the risks/benefits of therapy should be carefully considered.

IL-2. IL-2 induces T-cell proliferation, B-cell growth, and natural killer cell and monocyte activation. IL-2 has antitumor activity and has been used in the treatment of metastatic melanoma, renal cell carcinoma, and HIV. Thyroiditis and HT have been described with IL-2 treatment either alone or in conjunction with IFN-α in up to 16% of patients.[86]

Ipilimumab. Ipilimumab is an mAb that blocks CTLA-4, a receptor on T cells; blockade of CTLA-4 results in T-cell activation, proliferation, and differentiation. Ipilimumab has been used to treat patients with metastatic renal cell cancer and melanoma. Endocrinopathies, hypophysitis, and hypothyroidism, as well as nonendocrine autoimmune disorders, have been reported.[87] Up to 59% of participants in the National Institutes of Health studies treated with anti–CTLA-4 mAbs have presented with autoimmune toxicities. Many of the autoimmune events are transient, and some can be successfully treated with high-dose glucocorticoids. Five percent (8/163) of patients treated with anti–CTLA-4 mAbs at the National Institutes of Health have hypophysitis.[88] In the case of hypophysitis, anterior pituitary hormone deficiencies have been reported to be present for up to 2 years, despite discontinuation of therapy with ipilimumab.

Campath-1H. Campath-1H is a humanized anti-CD52 mAb that suppresses T_H1 lymphocytes. Graves disease has been associated with treatment in patients with multiple sclerosis and new-onset type 1A diabetes. In a study of 29 patients with multiple sclerosis treated with Campath-1H, 9 had Graves disease after 6 to 31 months of treatment.[89]

Highly active antiretroviral therapy. Highly active antiretroviral therapy, which is used to treat HIV infection, has been associated with Graves disease. The prevalence is rare, and it

occurs 16 to 19 months after initiation of therapy. After highly active antiretroviral therapy, there is immune reconstitution, and this is when autoimmunity develops, likely resulting from changes to $CD4^+$ T cells.[90]

CONCLUSIONS

Improved understanding of the immune pathogenesis of endocrine diseases has led to the initial development of therapies that target the underlying autoimmunity. Type 1A diabetes, one of the best-studied organ-specific autoimmune diseases, is now predictable in human subjects, and therapies are emerging to augment the underlying autoimmune destruction of β cells. With continued basic understanding of the immunologic mechanisms causing autoimmunity, better therapies can be designed to improve the quality of life for patients and their families afflicted with these disorders.

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Diagnostic testing and interpretation of tests for autoimmunity

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Laboratory testing is of great value when evaluating a patient with a suspected autoimmune disease. The results can confirm a diagnosis, estimate disease severity, aid in assessing prognosis and are useful for following disease activity. Components of the laboratory examination include a complete blood count with differential, a comprehensive metabolic panel, measurement of inflammatory markers and autoantibodies, and flow cytometry. This chapter discusses these components and includes a discussion about organ-specific immunologic diseases for which immunologic laboratory testing is used. Comprehensive laboratory evaluation of a suspected autoimmune illness in conjunction with a thorough clinical evaluation provides a better understanding of a patient's immunologic disease.
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Autoimmunity involves the loss of normal immune homeostasis such that the organism produces an abnormal response to its own tissue. The hallmark of autoimmune diseases generally involves the presence of self-reactive T cells, autoantibodies, and inflammation. An area of intense research is determining why the immune system turns against its host. Over the past decade, research has greatly advanced our understanding of autoimmunity, and the scientific findings from these investigations are assisting in the creation of new clinical laboratory studies of patients to aid in diagnoses.

Examining patients for potential autoimmune diseases is fraught with difficulty because no one laboratory test establishes such a diagnosis. Typically, multiple laboratory tests are needed and include basic studies like a complete blood count (CBC), comprehensive metabolic panel, measurement of acute-phase reactants, immunologic studies, serology, flow cytometry, cytokine analysis, and HLA typing. Although some tests might be nonspecific, such as the erythrocyte sedimentation rate (ESR), they are useful for assessing disease activity. These tests can be useful in the diagnosis and management of patients with autoimmune diseases and help in providing a prognosis or indicating the severity of organ involvement or damage.

Abbreviations used

ACE:	Angiotensin-converting enzyme
AIHA:	Autoimmune hemolytic anemia
ALT:	Alanine transaminase
ANA:	Antinuclear antibody
ANCA:	Antineutrophil cytoplasmic antibody
Anti-GBM:	Anti–glomerular basement membrane
aPL:	Antiphospholipid
APS:	Anti–phospholipid antibody syndrome
AST:	Aspartate aminotransferase
cANCA:	Cytoplasmic antineutrophil cytoplasmic antibody
CBC:	Complete blood count
CCP:	Cyclic citrullinated peptide
CH50:	Plasma total hemolytic complement assay
CK:	Creatinine kinase
CRP:	C-reactive protein
CSS:	Churg-Strauss syndrome
DM:	Dermatomyositis
dsDNA:	Double-stranded DNA
ESR:	Erythrocyte sedimentation rate
IBM:	Inclusion body myositis
IIM:	Idiopathic inflammatory myopathy
JIA:	Juvenile idiopathic arthritis
LDH:	Lactate dehydrogenase
MPA:	Microscopic polyangiitis
MPO:	Myeloperoxidase
pANCA:	Perinuclear antineutrophil cytoplasmic antibody
PM:	Polymyositis
PR3:	Proteinase 3
RA:	Rheumatoid arthritis
RBC:	Red blood cell
RF:	Rheumatoid factor
RIA:	Radioimmunoassay
RNP:	Ribonucleoprotein
SLE:	Systemic lupus erythematosus
SRP:	Signal recognition particle
WBC:	White blood cell
WG:	Wegener granulomatosis

INITIAL LABORATORY EVALUATION

Inflammatory diseases will cause abnormalities in routine laboratory studies. Characteristic findings can include a normochromic normocytic anemia indicating the chronicity or severity of disease. Common hematologic parameters also include an increased or decreased platelet count, white blood cell (WBC) count, or both. Leukopenia and thrombocytopenia are common in patients with systemic lupus erythematosus (SLE).

Testing will find aberrations in serum levels of specific organ enzymes or abnormalities in metabolic processes that are reflected in the comprehensive metabolic panel. For example, autoimmune hepatitis can be manifested by increases in transaminase, bilirubin, and serum protein levels. One should be aware that these abnormalities can also be associated with drug toxicity.

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Coagulation studies, such as a prolongation of the activated partial thromboplastin time, the prothrombin time, or both that do not correct with mixing studies, suggest an inhibitor of the clotting process is present, as seen in the antiphospholipid (aPL) syndrome. Hypercalcemia can be observed in approximately 30% of patients with sarcoidosis. An increase in muscle enzyme levels (creatinine kinase [CK], alanine transaminase [ALT], and aspartate aminotransferase [AST]) can be seen in autoimmune inflammatory myopathies (dermatomyositis [DM], polymyositis [PM], and inclusion body myositis [IBM]). Serum protein levels are helpful to screen for abnormal increases of immunoglobulin levels.

Urinalysis is commonly used to assess renal injury (glomerulonephritis and interstitial nephritis) and will show proteinuria, hematuria, or active sediment (WBC casts or red blood cell [RBC] casts). Many other illnesses, such as diabetic nephropathy, poorly controlled hypertension, or infections, can be tested similarly, but when autoimmune disease is suspected, the common laboratory evaluation will serve as an initial red flag to pursue further testing.[1]

INFLAMMATORY MARKERS

Serum proteins that are produced in response to inflammation can be referred to as inflammatory markers. These proteins are mainly produced by the liver in response to stress and can also be called acute-phase reactants. Proinflammatory cytokines, such as IL-1, IL-6, and TNF-α, induce synthesis of some acute-phase reactants that include C-reactive protein (CRP), fibrinogen, and haptoglobin. Other proteins, like albumin, are not sensitive to inflammatory cytokines for increased synthesis; instead, chronic stress (inflammation) results in a lower synthesis rate and resultant decreased serum concentrations. The inflammatory markers are not diagnostic of inflammation but reflect abnormalities that are seen in autoimmune diseases, infections, malignancies, and other illnesses.[11]

ESR

The ESR is the measure of the quantity of RBCs that precipitate in a tube in a defined time and is based on serum protein concentrations and RBC interactions with these proteins. Inflammation causes an increase in the ESR. Multiple factors influence the ESR and include the patient's age, sex, RBC morphology, hemoglobin concentration, and serum level of immunoglobulin. The sample must be handled appropriately and processed within a few hours to ensure test accuracy. Although the ESR is not a diagnostic test, it can be used to monitor disease activity and treatment response and signal that inflammatory or infectious stress is present. For example, in patients with rheumatoid arthritis (RA), the ESR correlates well with disease activity; however, normalization of the ESR often lags behind successful treatment that causes resolution of the inflammatory state.[2,3]

CRP

CRP/CRP high sensitivity was discovered and named for its reactivity to the C polysaccharide in the cell wall of *Streptococcus pneumoniae*. CRP, an innate immune protein, helps opsonize pathogens for phagocytosis and activates the complement system. CRP production is under the control of IL-1, IL-6, and TNF-α. Serum CRP concentrations change more quickly than those in the ESR, and therefore CRP might be a better reflection of current inflammation. Unlike the ESR, CRP is a fairly stable serum protein with measurement that is not time sensitive and not affected by other serum components. The magnitude of inflammation directly relates to the concentration of CRP. Levels of less than 0.2 mg/dL are considered normal, whereas those greater than 1.0 mg/dL are suggestive of inflammation, infection, or both. More recently, high-sensitivity CRP has been used. This test might better quantify lower levels of inflammation and has been important in evaluating cardiac disease and other inflammatory states.[2,3]

Ferritin

Serum ferritin is a storage protein for iron, and its synthesis is regulated by intracellular iron, cytokines (TNF-α, IL-1, and IL-6), products of oxidative stress, and growth factors. Increased levels can indicate acute or chronic sepsis, inflammation, or malignancy. Diseases such as adult Still disease, systemic-onset juvenile idiopathic arthritis (JIA), hemophagocytic lymphohistiocytosis, and iron-overload diseases, including hemochromatosis or hemosiderosis, should be considered with increased ferritin levels.[4,5]

Less common indicators of inflammatory states

Ceruloplasmin is the major copper-containing protein in the blood that plays a role in iron metabolism, and its concentration is increased in patients with acute and chronic inflammatory states, pregnancy, lymphoma, RA, and Alzheimer disease.[6,7]

Fibrinogen is a hemostatic coagulation factor produced in response to tissue injury. Fibrinogen synthesis is controlled at the transcriptional level and is increased in the presence of inflammation and stress that is mediated by IL-6.

Haptoglobin is produced in response to tissue injury. Increased levels of haptoglobin can be seen during inflammation, malignancy, surgery, trauma, peptic ulcer disease, and ulcerative colitis. Decreased levels might indicate chronic liver disease or anemia.

Albumin is a serum protein synthesized by the liver that aids body tissues in maintaining the oncotic pressure necessary for proper body fluid distribution. The average amount of albumin in the plasma is approximately 300 to 400 g, and about 15 g is produced by the liver per day. Although the rate of synthesis can double in situations of rapid albumin loss, as seen in glomerulonephritis or inflammatory bowel disease, serum levels will decrease.

AUTOANTIBODIES AND IMMUNOLOGIC STUDIES

The presence of an autoantibody in a patient does not ensure a diagnosis of an autoimmune disease. Rather, a positive serologic test result in the company of appropriate signs and symptoms helps to support a diagnosis. Serologic testing is flawed by the presence of autoantibodies in healthy subjects and other patients with nonautoimmune diseases and imperfect testing systems. Historically, many different methods were used to test for the presence of an autoantibody. Today, testing is principally done with enzyme immunosorbent assays because of cost-saving measures with mechanization.

ELISA

The ELISA is an immunometric method for detecting and measuring specific antibodies. The basic components of this laboratory method include a substrate in which an antigen is fixed (typically a 96-well microwell plate), the patient's sera, washing solutions, and a detection method in which an enzyme is linked to

an antibody that detects the antigen. In a typical double-antibody sandwich ELISA, an antibody that is attached to the bottom of a well provides both antigen capture and immune specificity while another antibody linked to an enzyme provides detection and acts as an amplification factor. This allows for accurate and sensitive detection of the antigen of interest. However, performance is largely dependent on antibody quantity, the kit's manufacturer, and the operator's skill and experience. ELISAs permit measurement of only 1 antigen at a time for a given aliquot of sample. Furthermore, ELISAs have a limited dynamic range (ie, the range over which there is a linear relationship between antigen concentration and absorbance reading); the range is narrow relative to the range for other technologies, such as multiplex assays.[8]

Rheumatoid factor and anti–cyclic citrullinated peptide antibody

Rheumatoid factor (RF) is an autoantibody that reacts to the Fc portion of polyclonal IgG, although it can be any class of immunoglobulin. Most assays detect the IgM RF. RF is helpful when evaluating patients who might have RA because the sensitivity is approximately 70%, with a specificity of approximately 70%. RF is absent in approximately 15% of patients with RA. However, approximately 15% of the healthy population might have a low titer of RF. RF-positive patients are more likely to have progressive erosive arthritis with loss of joint mobility and also have extra-articular manifestations, including rheumatoid nodules, vasculitis, Felty syndrome, and secondary Sjögren syndrome. In addition, the presence of RF is seen in other autoimmune disorders, including Sjögren syndrome, SLE, and cryoglobulinemia; in pulmonary diseases, such as interstitial fibrosis and silicosis; and in various infectious diseases.

Recently, a new biomarker for RA has been described: autoantibodies to cyclic citrullinated peptide (CCP). Inflammation activates the enzyme peptidylarginine deiminase, which incorporates citrulline into certain proteins. In patients with RA, autoantibodies are formed against the citrullinated protein (anti-CCP). The presence of serum anti-CCP antibodies is approximately 95% specific for the diagnosis of RA, with a sensitivity similar to that of RF. Testing for both anti-CCP and RF is beneficial when excluding the diagnosis of RA rather than testing for either antibody alone. In patients with early undifferentiated disease, anti-CCP–positive patients tend to go on to have more severe, erosive, and aggressive disease. Anti-CCP can also be present in other disease states, such as some cases of JIA, psoriatic arthritis, lupus, Sjögren syndrome, inflammatory myopathies, and active tuberculosis.[2,3]

Antinuclear antibody

Autoantibodies to nuclear antigens are a diverse group of antibodies that react against nuclear, nucleolar, or perinuclear antigens. These antigens represent cellular components, such as nucleic acid, histone, chromatin, and nuclear and ribonuclear proteins. Classically, the antinuclear antibody (ANA) hallmarks the serologic diagnosis of SLE, but finding an ANA is common to most other autoimmune diseases. Methods used for detection use immunofluorescence testing of the patient's serum at various dilutions with a cell substrate. Typically, screening the patient's serum for the detection of an ANA with an ELISA provides high sensitivity but lacks specificity. Results are reported as either the dilution of serum that evokes a positive test response or the degree of positivity measured by using the testing procedure. Historically, HEp2 cells (a human laryngeal epithelioma cancer cell line) have been used as the cell substrate because the result offers the advantage of detecting a nuclear fluorescent pattern. The fluorescent patterns (homogenous, diffuse, speckled, peripheral, and rim) suggest clinical associations with certain autoimmune diseases. However, because of the time and expense for testing with HEp2 cells, the assay procedures are largely done with ELISA methods.[2,3]

TABLE I. Sensitivity and specificity of specific anti-nuclear antibodies

	ANA	dsDNA	Histone	Nucleoprotein	Smith (ribonuclear)
SLE					
Sensitivity	>95%	70%	~50%	60%	25%
Specificity	60	95	50	Medium	99
RA					
Sensitivity	45	1	Low	25	1
Specificity	60			Low	
Scleroderma					
Sensitivity	60	<1	<1	<1	<1
Specificity	50				
PM/DM					
Sensitivity	60	<1	<1	<1	<1
Specificity	60				
Sjögren syndrome					
Sensitivity	50	<5	Low	Medium	<5
Specificity	50		Low	Medium	

Immunofluorescence is particularly useful as an initial screening test for those individuals suspected of having an autoimmune disease, such as SLE, Sjögren syndrome, RA, mixed connective tissue disease, scleroderma, and PM/DM. However, one must use caution when interpreting the presence of ANA because this autoantibody is found in nonrheumatic diseases, such as Hashimoto thyroiditis, Graves disease, autoimmune hepatitis, primary autoimmune cholangitis, primary pulmonary hypertension, and various infections and malignancies. Furthermore, the presence of low-titer ANA occurs more frequently in elderly populations.

Table I details the sensitivity and specificity of the various ANAs in several autoimmune diseases. Values are reported as approximate percentages, as seen in several published reviews. Table II lists specific autoantibodies and clinical disease associations.

Anti–double-stranded DNA

Autoantibodies to double-stranded DNA (dsDNA) are an important marker used in the diagnosis and monitoring of SLE. Antibodies to dsDNA are highly specific for SLE. However, some patients with other rheumatic diseases or chronic active hepatitis might have mildly or moderately increased serum titers. Previously, anti-dsDNA was typically measured by using an RIA (particularly the Farr assay). The more common current tests use an immunofluorescence assay or ELISA. The immunofluorescence assay uses a target antigen, *Crithidia luciliae*, a flagellated protozoa containing a dsDNA-containing small organelle called a kinetoplast. Antibodies to dsDNA are detected semiquantitatively by demonstrating IgG bound to the kinetoplast. In contrast, with ELISA testing, the dsDNA is bound to the solid phase of the microwell plate. The serum is incubated, and then the bound IgG is detected.[2,3]

TABLE II. Specific autoantibodies with their antigenic determinant and clinical disease associations

Autoantibody	Antigenic determinant	Clinical associations
Anti-dsDNA	dsDNA	High specificity for SLE; often correlates with active severe disease
Anti–extractable nuclear antigens Anti-Sm Anti-RNP	Smith Proteins containing U1-RNA	High specificity for SLE MCTD, SLE, RA, scleroderma, Sjögren syndrome
Anti-SSA (Ro)	RNPs	Sjögren syndrome, SLE (subacute cutaneous lupus), neonatal lupus
Anti-SSB (La)	RNPs	Sjögren syndrome, SLE, neonatal SLE
Anticentromere	Centromere/kinetochore region of chromosome	Limited scleroderma, pulmonary hypertension, primary biliary cirrhosis
Anti–Scl 70	DNA topoisomerase I	Diffuse scleroderma
Anti–Jo-1 (anti-synthetase antibodies)	Histidyl tRNA synthetase (other tRNA synthetases)	Inflammatory myopathies with interstitial lung disease, fever and arthritis
Anti-SRP	Antibody to signal recognition protein	Inflammatory myopathies with poor prognosis
Anti-PM/Scl	Antibody to nucleolar granular component	PM/scleroderma overlap syndrome
Anti–Mi-2	Antibodies to a nucleolar antigen of unknown function	DM

MCTD, Mixed connective tissue disease.

Anti–extractable nuclear antigen

The extractable nuclear antigens consist of the Smith antigen, ribonucleoprotein (RNP) or U1RNP, anti-SSA (Ro), and anti-SSB (La). They are called extractable because they are readily soluble or extractable in neutral buffers. The Smith antigen is highly specific for SLE, but it is found in only approximately 25% of patients with SLE. The U1RNP antigen is seen in patients with SLE plus systemic sclerosis and in patients with mixed connective tissue disease. The SSA (Ro) and SSB (La) nuclear antigens are often found together in patients with Sjögren syndrome. Anti-SSA and anti-SSB are also seen in some subsets of patients with SLE. This group includes those patients with subcutaneous lupus erythematosus (prominent photosensitive rashes and sometimes vasculitis) but without severe renal disease. The presence of anti-SSA and anti-SSB is associated with neonatal lupus, in which transplacental transfer of these antibodies (maternal IgG) can cause transient photosensitive rash, congenital heart block, or both.[2,3]

Anti–signal recognition particle, anti–Jo-1, anti-Mi-2 and anti-PM/Scl

Anti–signal recognition particle (anti-SRP), anti–Jo-1, anti–Mi-2 and anti-PM/Scl are termed myositis-specific antibodies because of the high specificity to the autoimmune idiopathic inflammatory myopathies (IIMs). Anti-SRP antibodies are directed toward an RNA–protein complex consisting of 6 proteins and a 300-nucleotide RNA molecule (7SL RNA). Patients with this antibody have a distinct type of IIM that is characterized by acute onset of muscle weakness, a muscle biopsy specimen that lacks inflammation, and a poor response to therapy. Anti–Jo-1 autoantibodies are the most common autoantibodies found in the group of inflammatory myopathies called the antisynthetase syndrome.

Anti–Jo-1 autoantibodies are directed against histidyl–tRNA synthetase (an enzyme that attaches histidine to growing polypeptide chains). Other less well-understood antisynthetase autoantibodies include anti-PL12, anti-EJ, anti-OJ, anti-PL7, and anti-KS. These antibodies are reportedly more common in patients with PM than in patients with DM and are rare in children. Patients with antisynthetase syndrome have disease characteristic that are very different than those of patients with anti-SRP and often present with muscle weakness, interstitial lung disease, arthritis, and fevers. The anti–Jo-1 response appears to be self-antigen driven, with isotype switching and affinity maturation.

Anti-Mi-2 antibodies recognize a major protein of a nuclear complex formed by about 7 proteins involved in transcription. Autoantibodies to Mi-2 are specific for DM and associated with acute onset, a better prognosis, and good response to therapy.

Anti-PM/Scl is an autoantibody to the nucleolar granular component. This is often seen with myositis and scleroderma overlap. Detection of such autoantibodies is done mostly through commercial blot assays using immunoblotting or dot immunoblotting methodologies in addition to traditional ELISA.[8]

Antineutrophil cytoplasmic antibody (myeloperoxidase and proteinase 3)

Antineutrophil cytoplasmic antibodies (ANCAs) react with cytoplasmic granules of neutrophils. Initial ANCA testing screens sera for the presence of ANCA, and 2 general immunofluorescent staining patterns are observed: cytoplasmic (cANCA) and perinuclear (pANCA). The immunofluorescence pattern is helpful to distinguish various ANCA-associated vasculitis syndromes. cANCA is most often seen in patients with Wegener granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS). pANCA patterns were initially described in patients with MPA, but pANCA has now been observed in a variety of diseases, including other types of vasculitis, inflammatory bowel disease, SLE, RA, and JIA. Antigenic determinants of the ANCAs that are important to detect in vasculitis are proteinase 3 (PR3) and myeloperoxidase (MPO). Vasculitic states with positive test results are named PR3-ANCA positive or MPO-ANCA positive. The presence of PR3 or MPO can help the clinician to determine the type of vasculitis and activity of disease.

Antibodies to PR3 or MPO are predictive of the various vasculitis syndromes. cANCA plus PR3 has increased positive predictive value for ANCA-associated vasculitis, particularly WG. pANCA plus MPO has an increased positive predictive value for MPA and less often for CSS. ANCA plus MPO more than PR3 often leads toward a diagnosis of CSS. With increased disease activity, there is a greater likelihood that ANCA results

will be positive. ANCA titers might normalize with treatment, although persistent ANCA positivity or increasing ANCA titers do not reliably predict disease exacerbation or flare. Therefore one should not use ANCA titers to determine treatment efficacy. Furthermore, one should also be wary of ANCA positivity because this can be seen in other disease states that include infection, drug use (eg, thyroid medication, particularly propylthiouracil), and other autoimmune disease. If the suspicion for vasculitis remains, tissue biopsy should be considered.[2-4,9]

Complement

The complement cascade is a complex, tightly regulated series of proteolytic enzymes, regulatory proteins, and cell-surface receptors that mediate and augment both the complement, humoral, and cellular immune response. The classical pathway is initiated by immune complexes binding to C1q and involves C4 and C2. The alternative pathway involves factors B and D and properdin. The mannose-binding lectin pathway and classical and alternative pathways all involve cleavage of C3. This release product induces the formation of the terminal membrane attack complex (C5-C9).

Individual components, such as C3, C4, and factor B, are measured by means of nephelometry and ELISA. The plasma total hemolytic complement assay (CH50) uses a functional assay to assess the functional integrity of the classical pathway. To measure these values, diluted serum is added to sheep antibody–coated erythrocytes, and the subsequent value is the reciprocal of the highest dilution able to lyse 50% of the RBCs. CH50 is a useful screening tool to detect deficiencies of the classical pathway.

Serum levels of complement components can serve as markers of disease activity. In patients with immune complex deposition disease, serum complement proteins are consumed. and serum levels decrease. Immune complex disease results from the deposition of antigen–antibody complexes in involved organ tissues. Immune complex glomerulonephritis in patients with SLE, decreased C3 and C4 levels indicate increased consumption and disease activity. In contrast, increases of C3 and C4 levels indicate inflammatory disorders because these proteins are also acute-phase reactants. Hypocomplementemia is generally not specific for any disease and might be secondary to nonrheumatic diseases, such as subacute bacterial endocarditis or poststreptococcal glomerulonephritis. If C4 levels are low compared with C3 levels, this can indicate the presence of cryoglobulins or the genotype C4-null allele. If CH50 levels are low or undetectable, it might indicate a deficiency of 1 or more complement components. Genetic or congenital deficiencies of early complement components (C1-C4) might increase the risk for development of immune complex diseases. For example, congenital C1q deficiency, although rare in the general population, is associated with persons who have lupus.[2-4,8]

Immunoglobulins (quantitative and qualitative)

Measuring total quantitative immunoglobulin levels is a key component to any immunologic evaluation. The immunoglobulin levels reflect B-cell function (humoral production and T-cell interaction), and serum immunoglobulin levels aid in disease detection. Quantitative measurements of serum immunoglobulin levels, mainly IgG, IgA, and IgM, are done with nephelometry.

TABLE III. Differential diagnosis for immunoglobulin levels

Immunoglobulin	Increased	Decreased
IgG	Infection, inflammation, hyperimmunization, IgG multiple myeloma, liver disease, rheumatic fever, systemic rheumatic disease	Agammaglobulinemia, amyloidosis, leukemia, myeloma, preeclampsia
IgM	Early HIV infection, infectious mononucleosis, lymphoma, macroglobulinemia, myeloma, RA	Rarely agammaglobulinemia, amyloidosis, leukemia, myeloma
IgA	Chronic infections (especially of gastrointestinal tract), inflammatory bowel disease, myeloma, rheumatic fever	Agammaglobulinemia, hereditary IgA deficiency, myeloma or protein-losing enteropathy

Table III lists diseases that are associated with increased or decreased serum immunoglobulin levels.

Simple qualitative measurements of serum immunoglobulin levels reflect a subject's ability to mount a humoral immune response. Titers to tetanus, *Haemophilus influenzae* type B, and pneumococcus can easily be tested to evaluate the quality of the immune response. These levels assess the function of B cells and also detect defects that might indicate immunodeficiency. Responses to protein and polysaccharide antigens should be evaluated to assess antibody production. B-cell testing is done primarily by using *in vivo* (vaccination) studies. Protein vaccinations, such as tetanus toxoid, measure T cell–dependent responses. Polysaccharide vaccines, like Pneumovax (Merck, Whitehouse Station, NJ), measure T cell–independent responses.

Testing of specific antibody titers (eg, to influenza immunization) are reported relative to protective values. These values are based on epidemiologic data regarding protection in larger populations. For randomly acquired antibody levels, an initial comparison with protective values can be used to decide whether a proper immune response was achieved. A 4-fold increase in titers to protein vaccination indicates a normal response. A 2-fold increase in titers to a polysaccharide antigen indicates a normal response. Failure to mount an appropriate response to antigen is a clue to the physician to pursue B- and T-cell function further.[2-4,8]

Cryoglobulins

Cryoglobulins are immunoglobulins that precipitate reversibly in cold temperatures. In disease states these antibodies can bind with complement proteins and other peptides to form immune complexes and cause tissue damage. Three types of cryoglobulins exist. Type I cryoglobulins are monoclonal immunoglobulins often of the IgM isotype. Type II cryoglobulins are a mixture of polyclonal IgG and monoclonal IgM. Type III cryoglobulins are a combination of polyclonal IgG and polyclonal IgM.

At phlebotomy, whole blood is obtained, placed in prewarmed tubes without anticoagulant, and maintained at body temperature until coagulation occurs (about 1 hour). The sample is then centrifuged, and the clot is removed. The remaining serum is kept

at 4°C up to several days. The specimen is then examined daily to determine whether proteins have precipitated. Once a precipitate is present, the sample is spun again, and a cryocrit value is measured in a calibrated tube. Confirmation of the cryocrit value is seen if the precipitate redissolves when placed in a 37°C water bath.

Cryoglobulins are nonspecific indicators of disease states. Type I monoclonal cryoglobulins are associated with multiple myeloma, Waldenstrom macroglobulinemia, and lymphoproliferative disorders. Type II and III cryoglobulins can bind complement, unlike type I cryoglobulins, and are associated with hepatitis C and small-vessel vasculitis. The presence of multiple immunoglobulin components within the cryoglobulin is known as mixed cryoglobulin. Symptoms generally associated with cryoglobulins include purpura, ulcerations, Raynaud phenomenon, arthralgias, proteinuria, and renal failure. Cryoglobulins are rarely found in children.[2-4,8]

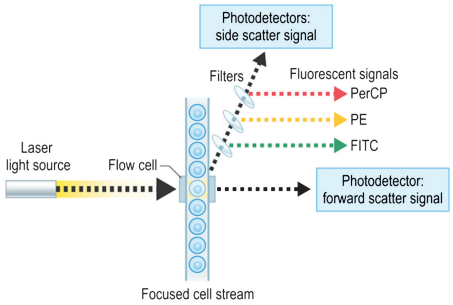

FIG 1. Flow chamber. *PerCP*, Peridinin chlorophyll protein; *PE*, phycoerythrin; *FITC*, fluorescein isothiocyanate. Reprinted with permission from Fleisher TA from Fleisher T, de Oliveira JB (2008). Flow cytometry (Ed. 3), Clinical Immunology: Principles and Practice (p. 1436). Philadelphia, PA: Elsevier Limited.

Lupus anticoagulant/anticardiolipin/aPL autoantibodies

In patients with autoimmune disease, serum antibodies that inhibit or prolong *in vitro* clinical laboratory coagulation tests are termed aPL antibodies (also called anti-cardiolipin antibodies, anti-phospholipid antibodies or lupus anticoagulant) because they are directed against phospholipids and phospholipid-binding proteins. The existence of these antibodies is associated with the anti–phospholipid antibody syndrome (APS). APS is suspected in subjects who have venous thromboses, arterial thromboses, or both; recurrent fetal loss; or thrombocytopenia. APS can occur independently of or with systemic rheumatic diseases. aPL antibodies can also be found in healthy subjects and in patients with various infections who do not have features of aPL antibody syndrome. The term anticoagulant is paradoxic in that the presence of aPL is associated with thromboses in patients. The presence of aPL can be directly measured by using enzyme-linked assays. IgG anticardiolipin has a higher predictive value than IgM or IgA of a thrombosis. β_2-Glycoprotein I has been identified as one of the major antigenic determinants of aPL antibodies.[12-15]

FLOW CYTOMETRY

Flow cytometry is a technique in which particles or tagged cells flow through laser light so that populations of particles/cells can be counted and phenotyped by using cell characteristics and surface proteins. Initial applications of flow cytometry pertained to the interest in certain cell populations, such as the numbers of lymphocytes in patients infected with HIV. The number of T cells that are $CD4^+$ is an important gauge of severity of HIV infection. However, the methodology has greatly expanded its role such that cell-cycle analysis, quantification of malignant cells, and activation status of lymphocyte subpopulations can be determined. When evaluating a patient with a suspected immunodeficiency, flow cytometry is crucial to determine the quantitative number of immune cells (typically T, B, and natural killer cells). Remember, flow cytometric testing reveals numbers of cells and does not indicate cellular function. Testing for cellular functioning involves other laboratory methods, such as measurement of quantitative immunoglobulin levels to indicate proper B-cell function.[16,17]

The markers commonly used to assess lymphocyte subsets by means of flow cytometry are listed in Table III.

The flow cytometric device consists of an illumination source, an optical bench, a fluidic system, electronic monitoring, and a computer. Cells that will flow through the cytometer are first prepared by tagging cell-surface molecules with fluorescently labeled mAbs. Illumination of the cell occurs by using air-cooled lasers that provide a monochromatic light source (argon at 488 nm or blue and helium neon at 633 nm or red). The point of illumination occurs within the flow cell. The optical bench contains lenses that shape and focus the illumination beam. Nonfluorescent and fluorescent signals generated by the labeled cell are collected and measured by using a detection system consisting of filters linked to a photodetector. Cells are injected into a moving fluid sheath to establish a focused single-file flow of cells that move through the analysis point. Differences in the magnitude of emission signal generated from each cell reflect biologic differences between the cells. Software collects data that can be used to analyze cell subpopulations based on the presence or absence of labeled antibody binding. Data are then presented as fluorescence intensity versus cell number.[8]Figures 1 and 2 illustrate the flow chamber and the presentation of data using dot plot and contour plot.

CYTOKINE STUDIES

Cytokines are molecules secreted by a variety of cells that function in cellular communication. Immunologists are keenly interested in cytokines, particularly those that influence immune function and inflammation. Commercial testing laboratories do not routinely assay most serum cytokine levels because this testing is largely done in research laboratories. Testing is laborious because of the labile nature of these small molecules. After phlebotomy, the serum needs to be quickly removed from the cellular components and frozen as quickly as possible, and testing should not be delayed. Laboratory methods commonly used to assay cytokine levels include flow cytometry and ELISA.[15,16]

Cytokines that influence inflammation include IL-1, IL-6, and TNF-α. There is extensive evidence that these cytokines promote inflammation and therefore have become targets for therapy. RA is the best example of an autoimmune illness in which anti-TNF therapy has revolutionized the natural history of the disease. Targeting TNF with proteins (fusion produced or mAbs) that antagonize TNF action results in dramatic improvement of disease activity. In fact, RA is the prototypic autoimmune disease in which the efficacy of anticytokine therapy is best demonstrated. Currently, anti-TNF, anti–IL-1, and anti–IL-6 therapies have all proved to be effective in treating RA.

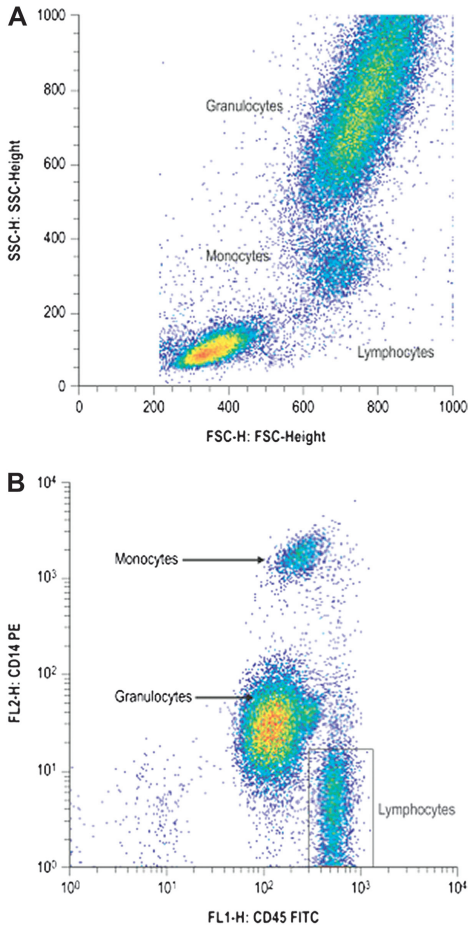

FIG 2. Presentation of data for CD8/CD4 as dot plot (A) and contour plot (B). *SSC*, Side scatter; *FSC*, forward scatter; *PE*, phycoerythrin; *FITC*, fluorescein isothiocyanate. Reprinted with permission from Fleisher TA from Fleisher T, de Oliveira JB (2008). Flow cytometry (Ed. 3), Clinical Immunology: Principles and Practice (p. 1436). Philadelphia, PA: Elsevier Limited.

MHC (HLA)

HLA is synonymous with MHC. MHC class I and II genes are the major genetic determinants of susceptibility to many autoimmune diseases. MHC class I molecules include HLA-A, HLA-B, and HLA–C. MHC class II molecules include HLA-DR, HLA-DQ, and HLA-DP. Detection of HLA type can be done routinely and can be assayed by using several methods that include gel electrophoresis, PCR, ELISA, and newer methods using high-throughput detection of nucleic acid. Many antigens of the MHC, especially of HLA class I and II, have been associated with rheumatic disorders. HLA-B27 is present in approximately 90% to 95% of white patients with ankylosing spondylitis and only 7% to 8% of the general population. HLA-DR1 and HLA-DR4 increase the risk of polyarticular JIA in many populations. HLA-DR3 and HLA-DR2 are associated with lupus in white populations, whereas much of the risk attributable to MHC is associated with variation at HLA-DRB1 in patients with RA.[3,18,19]

SPECIFIC IMMUNOLOGIC DISEASE ENTITIES

Immunologic lung disease

Sarcoidosis. Sarcoidosis is a systemic granulomatous disease characterized by noncaseating granulomas affecting multiple organ systems. The cause of sarcoidosis is not known but is believed to involve chronic inflammation with a T_H1 cellular contribution, and immunosuppressive therapy is beneficial. The organ systems most frequently involved, in decreasing order, include the lungs, skin, sinus and upper respiratory tract, eye, and musculoskeletal, abdominal, hematologic, salivary/parotid, cardiac, and neurologic organs. Biopsy of the affected tissue is vital for diagnosis, and histologic findings should show noncaseating granulomas. Imaging studies, particularly chest radiography or chest computed tomography, show bilateral hilar lymphadenopathy, interstitial infiltrates, or both. Chest computed tomography reveals nodular infiltrates that tend to be distributed along the bronchoalveolar structures.

Laboratory investigations helpful in the diagnosis of sarcoidosis include measurement of serum angiotensin-converting enzyme (ACE) and vitamin D levels. ACE levels are generally increased; however, ACE levels lack disease specificity and therefore have limited diagnostic and therapeutic utility.[4] High serum levels of 1, 25(OH)2D3 vitamin D are commonly seen in patients with granulomatous disease and are believed to induce hypercalcemia. IFN-γ produced by T_H1 cells is possibly a stimulus for 25(OH)2D3 synthesis by macrophages.

CSS. CSS is a necrotizing vasculitis affecting small and medium blood vessels characterized by eosinophilic infiltration, eosinophilic granulomas, nasal polyps, allergic rhinitis, conductive hearing loss, eye disease (scleritis, episcleritis, and uveitis), asthma, fleeting infiltrates, alveolar hemorrhage, segmental necrotizing glomerulonephritis, heart failure, and vasculitic neuropathy. Initial symptoms typically suggest a reactive airway process similar to that seen in patients with asthma. Immunologic studies that aid in the diagnosis of CSS include a CBC that reveals a peripheral eosinophilia and the serologic presence of an ANA and a pANCA directed against MPO. As is the case with any suspected vasculitis, a biopsy specimen of the involved organ showing an inflammatory destruction of the blood vessels with eosinophilic infiltrates and granuloma formation is vital for diagnosis. Characteristic of all inflammatory vasculitidies are a significantly increased ESR and CRP level.

WG and MPA. WG is characterized by systemic granulomatous vasculitic lesions of the upper and lower respiratory tract and the kidney. MPA is characterized by nongranulomatous vasculitic lesions of the lower respiratory tract, kidney, skin, and nerve. Both of these diseases can be manifested by acute renal failure, with the urinalysis showing RBCs, RBC casts, and proteinuria. Renal biopsy reveals a segmental necrotizing glomerulonephritis with a characteristic lack of immune complexes. WG can be a chronic undiagnosed illness in which a patient complains of chronic sinusitis that might cause nasal septal perforation. The auditory nerve can be inflamed, causing a conductive or sensorineural hearing loss. Cartilage inflammation will cause subglottic stenosis, saddle-nose deformity, or both; ocular inflammation leads to orbital pseudotumor, scleritis, episcleritis, or uveitis; and lung disease with nodules, infiltrates, and/or cavitary lesions, alveolar hemorrhage, or both can occur. Characteristic of vasculitis, the ESR and CRP levels will be increased. Other laboratory evaluations for WG and MPA include a serologic finding of cANCA/PR3 generally associated with WG and pANCA/MPO generally associated with MPA. Important HLA associations with WG are HLA-DR4 and HLA-DR13.

Goodpasture syndrome. Anti–glomerular basement membrane (anti-GBM) disease or Goodpasture syndrome is characterized by pulmonary hemorrhage, glomerulonephritis, or both.

Pathognomonic to Goodpasture syndrome are autoantibodies to the renal glomerular and lung alveolar basement membrane. The specific autoantigen is the 235 amino acid carboxy-terminal noncollagenous domain of type IV collagen. Urinalysis of affected subjects reveals proteinuria, dysmorphic RBCs, WBCs, and RBC cellular and granular casts. Diagnostic testing includes the detection of anti–GBM antibodies. In cases in which only the presence of diffuse alveolar hemorrhage occurs, antibodies might not be present. In those cases the diagnosis is established by demonstrating linear immunofluorescence in lung tissue.

Other autoimmune diseases with pulmonary manifestations. Many autoimmune diseases have pulmonary complications. For example, extra-articular manifestations of RA include parenchymal lung disease with nodules, diffuse interstitial lung disease, or both; obliterative bronchiolitis; or bronchiectasis. Pleural effusions and pleurisy can be bilateral in up to one quarter of cases of RA. Pleurisy is very common in patients with SLE. Other pulmonary diseases in patients with SLE include pneumonitis, pulmonary hemorrhage, and shrinking lung syndrome. These pulmonary processes can cause cough with hemoptysis and dyspnea. The aPL syndrome's pulmonary manifestations consist of pulmonary thromboembolism and pulmonary hypertension. Scleroderma pulmonary manifestations of interstitial lung disease and pulmonary hypertension are the leading cause of death in systemic sclerosis. Lastly, cases of idiopathic inflammatory myositis (PM, DB, and IBM) have varying lung disease, primarily that of interstitial lung disease.

The astute physician will be aware of the patient's symptoms so that he or she can pursue further investigations into the cause of pulmonary disease. Remembering that chronic lung disease can be associated with spurious RF autoantibodies, one must test for serum autoantibodies that are specific to a disease state. Anti-CCP antibodies help in the diagnosis of RA if accompanied by radiographic evidence demonstrating erosive disease and clinical evidence of joint involvement. High-titer ANA with anti-DNA anti–extractable nuclear antigen autoantibodies are helpful in the diagnosis of SLE, particularly if hypocomplementemia exists and the urine shows hematuria, proteinuria, and cellular elements. The presence of aPL antibodies can be confirmed with a positive lupus anticoagulant test result, anti-cardiolipin antibody, or β_2-glycoprotein antibody. The diagnosis of scleroderma is assisted with anti–SCL-70 antibodies or anti-centromere antibodies. For suspected lung disease associated with a myopathy, increased CK, AST, ALT, or aldolase levels in conjunction with the presence of a myositis-specific autoantibody are very helpful.[8]

Inflammatory or immune-mediated renal disease

Amyloidosis. Amyloidosis describes a group of disorders characterized by the extracellular tissue deposition of a variety of low-molecular-weight proteins called amyloid. Currently, there are more than 25 types of amyloid. The most frequent is type AL, which is found in primary amyloidosis, as well as in myeloma-associated amyloidosis. Type AA is found in secondary amyloidosis and is associated with chronic infections or inflammatory disease and some periodic fever syndromes, such as familial Mediterranean fever. Deposition of AL and AA occurs primarily in the kidneys (causing asymptomatic proteinuria, nephrotic syndrome, renal failure, and end-stage renal disease), heart (cardiomyopathy, systolic or diastolic dysfunction, heart block, and angina or infarct), liver (hepatomegaly), and gastrointestinal tract (gastroparesis, constipation, bacterial overgrowth, malabsorption, and intestinal pseudo-obstruction).

Amyloidosis from chronic inflammation will reveal an increased ESR and CRP level, clues to suggest inflammation is present and amyloid should be considered as a cause of organ dysfunction. Testing serum levels of type A amyloid is possible in research laboratories. Diagnosis is confirmed by means of tissue or aspiration biopsy of the affected organ, looking for birefringent material on Congo red stain.

Henoch-Schönlein purpura and IgA nephropathy. Henoch-Schönlein purpura is an immune-mediated vasculitis associated with IgA deposition and is the most common form of systemic vasculitis in children. Signs and symptoms include palpable purpura, arthritis, arthralgias, abdominal pain, and renal disease. Adults with Henoch-Schönlein purpura have presentations similar to those of children and are at increased risk for developing significant renal disease. Renal disease presents similarly to IgA nephropathy and is characterized by deposition of IgA immune complexes causing glomerulonephritis.

Diagnosis by using laboratory tests can include increased levels of serum IgA, an increased ESR and CRP level, normochromic normocytic anemia, and urinalysis showing RBCs or WBCs, cellular casts, and proteinuria. Renal biopsy discloses IgA deposition in the mesangium.

SLE. SLE is an autoimmune disease that can affect most organs. Renal involvement occurs with a high incidence, and clinical features include hematuria; proteinuria; nephrotic syndrome, nephritic syndrome, or both; acute renal failure; and chronic renal failure. Analysis of urine can show various casts (ie, RBC, WBC, granular, and waxy) in addition to oval fat bodies. In patients with active disease, both the classic and alternative complement cascades are activated, resulting in decreased serum levels of complement components (C3 and C4 are typically tested). Most patients with lupus nephritis will have high titers of anti-dsDNA autoantibodies.[20]

Anti-GBM disease. As described previously in the immunologic lung disease section of this chapter, anti-GBM disease or Goodpasture syndrome is characterized by anti-GBM autoantibodies. Patients presenting with renal involvement often have abrupt onset of oliguria or anuria, hematuria, and anemia. Renal biopsy can reveal crescents in more than 50% of the glomeruli on light microscopy (LM). Immunofluorescence demonstrates linear deposition of IgG along the glomerular capillaries and occasionally the distal tubules. Rarely, IgA or IgM can be present. Anti-GBM antibodies are also detected in the serum by means of immunofluorescence or ELISA. Many patients are also found to have positive results for ANCAs, particularly pANCA/MPO.

WG and MPA. As discussed previously, this small- to medium-sized vasculitis is able to cause inflammation in several tissues. Vasculitis often involves the kidney, causing proteinuria, hematuria, cellular casts, hypoalbuminemia, and renal failure. Serologic testing shows WG and MPA to be ANCA-associated diseases with specificity of the ANCA to PR3 in WG and the ANCA to MPO in MPA.

Other autoimmune diseases with renal manifestations. In a similar fashion discussed previously in which autoimmune diseases cause pulmonary disease, the same scenario is seen with autoimmune disease and renal involvement. RA, aPL antibody syndrome, scleroderma, and Sjögren syndrome all have known renal complications. Proteinuria might be the first clue that the kidney is involved from the result of chronic inflammation or immune complex deposition. Persistent inflammation seen in patients with

TABLE IV. Common cell markers

Marker	Cell type	Comment
CD3	T cells	Expressed on all T cells
CD4	T-cell subset	Helper/inducer T cells
CD8	T-cell subset	Cytotoxic T cells: expressed by up to one third of NK cells
CD19 or CD20	B cells	
CD16	NK cells	Some NK cells might not express CD16
CD56	NK cells	Expressed on majority of NK cells

NK, Natural killer.

RA can cause a membranous nephropathy, which is the result of reactive amyloid deposition. One must also remember that therapies to treat inflammatory disease, as seen in patients with RA, such as medications like gold or penicillamine, can cause proteinuria. Vasculitis lesions can also occur in patients with severe RA. Therefore a vigilant watch of renal function with frequent urinalysis is critically important in monitoring the autoimmune patient.[21]

Immunologic neuromuscular disease

PM, DM, and IBM constitute the IIMs. Although the cause is not well defined, muscles become inflamed as the result of both humoral and cellular immune dysfunction, causing lymphocytic infiltration and muscle damage. These myopathies differ in their cause, clinical presentation, and histology.

PM is defined by symmetric proximal muscle weakness, increases in muscle enzyme levels, characteristic electromyographic findings, and a muscle biopsy specimen that shows inflammation. The illness is progressive, with clinical symptoms that can include myalgias, dysphagia, and dyspnea. DM mimics PM with the addition of skin rashes, such as a heliotrope rash and Gottron papules. The rate of malignancy is increased in patients with IIM and more so in patients with DM and can precede, coincide with, or postdate the diagnosis. Therefore screening for malignancy is very important. IBM is the most common form of IIM in patients older than 50 years. Features that set IBM apart from other forms of myositis are asymmetry and distal involvement, particularly affecting the foot extensors and finger flexors. The disease tends to be indolent in its progression and resistant to therapy.

Diagnostic testing for myositis includes common laboratory tests (CBC and complete metabolic panel), serologies, imaging studies, and muscle biopsy. Levels of serum muscle enzyme are increased, such as CK and what are most often thought of as the subject of liver function tests: AST, ALT, and lactate dehydrogenase (LDH). The AST, ALT, and LDH actually reflect muscle disease, as well as liver disease. CK levels usually increase to 10- to 100-fold of normal values, and transaminase levels can increase to 10-fold of the normal value. Myositis-specific antibodies are found in approximately 50% of affected patients. These antibodies are listed in Table IV and are helpful in predicting the future course, prognosis, or both of disease. For example, anti-tRNA synthetase antibodies (eg, anti–Jo-1 antibodies) are strong predictors of interstitial lung disease. Genetic risk factors for the development of myositis include the alleles HLA-DRB1*0301 and HLA-DQA1*0501. Muscle biopsy is helpful to distinguish PM, DM, and IBM. PM typically demonstrates a lymphocytic infiltration seen mostly within the fascicles (endomysial inflammation), some fiber necrosis, and degenerative and regenerative fibers. MHC class I antigens on fibers identified by means of immunohistochemistry can also be seen. In patients with DM, perifascicular atrophy is common. The main features of IBM include endomysial inflammation, vacuolization ("red-rimmed vacuoles" on Gomori trichrome stain), and loss of muscle fibers. Large, atrophic, or angulated fibers are also present.[8,10,21-23]

Hematologic disease

Autoimmune hemolytic anemia. Autoimmune hemolytic anemia (AIHA) is characterized by increased erythrocyte destruction, decreased red cell survival, or both caused by autoantibodies directed against self-antigens on red cells. Two major types of AIHA exist: warm and cold. AIHA caused by the presence of warm agglutinins is almost always due to IgG antibodies that react with protein antigens on the erythrocyte surface at body temperature (37°C). The cause of warm AIHA includes infections (often in children), autoimmune disease (SLE), malignancies of the immune system (non-Hodgkin lymphoma and chronic lymphocytic leukemia), prior allogenic blood transfusion, and certain drugs (cephalosporins, hydralazine, isoniazid, sulfonamides, tetracycline, and triamterene). Signs and symptoms of mild warm AIHA include anemia, occasional jaundice, and mild-to-moderate splenomegaly, with severe cases also involving fever, tachypnea, tachycardia, angina, or heart failure. Peripheral blood examination can show leukopenia, neutropenia, or thrombocytopenia, but often patients have a normal platelet count, neutrophilia, and mild leukocytosis. Peripheral blood smear reveals polychromasia, spherocytosis, fragmented and nucleated erythrocytes, and sometimes erythrophagocytosis by monocytes in severe cases. Reticulocytosis is commonly present. Serum haptoglobin levels are decreased, and LDH levels are increased. Diagnosis depends on the demonstration of immunoglobulin, complement proteins, or both bound to the patient's erythrocytes through the direct antiglobulin test.[24-27]

The other major form of AIHA is due to cold-reactive antibodies and includes the cold agglutinin syndrome and paroxysmal cold hemoglobinuria. In patients with cold-reactive AIHA, the antibodies exhibit a greater affinity for erythrocytes at temperatures of less than 37°C and cause RBC membrane injury by activating complement. The majority of cold-reactive autoantibodies are cold agglutinins.[28]

Cold agglutinin syndrome usually occurs in middle-aged and elderly persons, with IgM the responsible immunoglobulin. Signs and symptoms are chronic anemia, dark urine, acrocyanosis, pallor, and jaundice. Laboratory testing includes mild-to-moderate anemia with prominent autoagglutination, abnormal erythrocyte morphology, reticulocytosis, jaundice, hemoglobinuria, and erythroid hyperplasia in the bone marrow.

Paroxysmal cold hemoglobinuria frequently occurs in children, often after an upper respiratory tract infection, and IgG is typically the causative immunoglobulin. Acute attacks are often severe, but the illness usually resolves spontaneously within a few days to several weeks. Signs and symptoms consist of fever, malaise, abdominal pain, dark-colored urine, jaundice, and pallor. Laboratory findings show anemia (often severe), reticulocytosis, abnormal RBC morphology, hemoglobinuria, usually erythroid hyperplasia, leukocytosis, and a platelet count that is normal or slightly increased.

Vascular thrombotic disorders. aPL syndrome is a thrombophilic disease defined by 2 major components: the presence of at least 1 type of autoantibody (aPL antibody, as mentioned earlier in this chapter), which is directed against phospholipid-binding plasma proteins, and the occurrence of at least 2 of several clinical features (recurrent fetal loss, arterial thromboses, or thrombocytopenia). Primary aPL antibody syndrome is diagnosed in the absence of other underlying diseases, and secondary aPL antibody syndrome is diagnosed if another illness (eg, SLE) is identified. Therapy consists of anticoagulation and treatment of any coexisting illness that might give rise to aPL antibodies.

Thrombocytopenia (idiopathic thrombocytopenia and posttransfusion purpura). Immune or idiopathic thrombocytopenic purpura is an acquired disorder without a clear cause. Both acute and chronic forms occur. The pathogenesis is thought to occur through a combination of increased platelet destruction and inhibition of megakaryocyte platelet production by specific IgG autoantibodies. Clinical manifestations are variable, can be abrupt or acute, and often are insidious. Symptoms include bleeding, ranging from petechiae and easy bruising to severe bleeding diathesis. Intracranial hemorrhage is quite rare. Children often exhibit symptoms after a viral or bacterial infection. Thrombocytopenia is noted on laboratory work. Bone marrow cellularity is normal, with normal erythropoiesis and myelopoiesis. Megakaryocytes are present in normal to increased numbers. However, bone marrow examination is not usually required unless another disease is suspected or if the patient is greater than 60 years of age because of concern for myelodysplasia.

Posttransfusion purpura is a rare condition that usually develops 7 to 10 days after an RBC transfusion. The syndrome is characterized by severe thrombocytopenia and bleeding caused by alloimmunization to human platelet-specific antigens after a blood component transfusion. Patients are usually middle-aged multiparous women, although posttransfusion purpura has also been reported in male subjects. Most cases occur with the formation of human platelet antigen 1a antibodies. These antibodies destroy transfused HPA-$1a^+$ cells and the negative recipient's cells through a poorly understood antiplatelet mechanism.[29]

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