Allergic and Pseudoallergic Drug Reactions

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KEY CONCEPTS

1. Hypersensitivity reactions are responsible for 6% to 10% of adverse reactions to medications. Although some reactions are relatively well defined, the majority are due to mechanisms that are either unknown or poorly understood.

2. The following criteria suggest that a drug reaction may be immunologically mediated: (a) the reaction occurs in a small percentage of patients receiving the drug, (b) the observed reaction does not resemble the drug's pharmacologic effect, (c) the type of manifestation is similar to that seen with other allergic reactions (anaphylaxis, urticaria, serum sickness), (d) there is a lag time between first exposure of the drug and reaction, (e) the reaction is reproduced even by minute doses of the drug, (f) the reaction is reproduced by agents with similar chemical structures, (g) eosinophilia is present, or (h) the reaction resolves after the drug has been discontinued. Exceptions to each of these criteria are observed commonly.

3. Anaphylaxis is an acute, life-threatening allergic reaction involving multiple organ systems that generally begins within 30 minutes but almost always within 2 hours after exposure to the inciting allergen. Anaphylaxis requires prompt treatment to restore respiratory and cardiovascular function. Epinephrine is the drug of choice to counteract bronchoconstriction and peripheral vasodilation. IV fluids should be administered aggressively to restore intravascular volume.

4. Factors that influence the likelihood of allergic drug reactions are the chemical composition of the drug, whether the drug contains proteins of nonhuman origin, the route of drug administration, and the sensitivity of the individual as determined by genetics or environmental factors. For some drugs, genetic predisposition to specific human leukocyte antigen alleles has been identified as a risk factor for allergic-mediated skin reactions.

5. Patients with a history of an immediate reaction to penicillin are advised not to receive cephalosporins if they can be avoided. Patients who have negative penicillin skin test results or experienced only mild cutaneous reactions, such as maculopapular rashes, have a low risk of serious reactions to cephalosporins. Similarities in the R1 side chain of the agents should be considered when assessing the risk of cross-reactivity.

6. Fewer than 1% of patients receiving nonionic radiocontrast agents experience some type of adverse reaction. Of the variety of reactions reported, about 90% are allergic-like, mostly urticarial, with severe reactions occurring as infrequently as 0.02%.

7. Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) can produce two general types of reactions, urticaria/angioedema and rhinosinusitis/asthma, in susceptible patients. About 20% of individuals with asthma are sensitive to aspirin and other NSAIDs.

8. Cross-reactivity between sulfonamide antibiotics and nonantibiotics is low. The low cross-reactive rate may be explained by differences in the chemical structures and reactive metabolites of the sulfonamide antibiotics and nonantibiotics.

9. The basic principles of management of allergic reactions to drugs or biologic agents include (a) discontinuation of the medication or agent when possible; (b) treatment of the adverse clinical signs and symptoms; and (c) substitution, if necessary, of another agent.

10. One of the most helpful tests to evaluate risk of penicillin allergy is the skin test. Skin testing can demonstrate the presence of penicillin-specific immunoglobulin E and predict a relatively high risk of immediate hypersensitivity reactions. Skin testing does not predict the risk of delayed reactions or most dermatologic reactions.

11. When an allergenic drug is considered medically necessary, no adequate therapeutic alternative exists, and there is no reliable skin testing method, two options are available to the clinician: induction of drug tolerance (previously known as desensitization) and graded challenge.

INTRODUCTION

1. Allergic drug reactions, also known as hypersensitivity reactions, result from an overresponse of the immune system to the standard dose of a drug. The hyperresponse of the immune system to the antigenic drug leads to host tissue damage manifesting as an organ-specific or generalized systemic reaction. Adverse drug effects not proven to be immune mediated but resembling allergic reactions in their clinical presentation are referred to as allergic-like or pseudoallergic reactions. Immunologically mediated adverse drug reactions account for 6% to 10% of all adverse drug reactions and even up to 15% by some estimates. Examples of allergic drug reactions are anaphylaxis from β-lactam antibiotics, halothane hepatitis, Stevens–Johnson’s syndrome (SJS) from sulfonamides, allopurinol hypersensitivity syndrome, and serum sickness from phenytoin. Examples of pseudoallergic reactions are isolated urticaria after radiocontrast media, aspirin-induced asthma, opiate-related urticaria, and flushing after vancomycin infusion.
The true frequency of allergic drug reactions is difficult to determine because many reactions may not be reported, and others may be difficult to distinguish from nonallergic adverse events. Dermatologic reactions represent the most frequently recognized and reported form of allergic drug reaction.²

**MECHANISMS OF ALLERGIC DRUG REACTIONS**

Drugs can cause hypersensitivity reactions by a variety of immunologic mechanisms. Although some reactions are relatively well defined, most are due to mechanisms that are either unknown or poorly understood.² ³

The following criteria suggest that a drug reaction may be immunologically mediated: (a) the observed reaction does not resemble the drug’s pharmacologic effect; (b) there is a lag time between first exposure of the drug and reaction unless the recipient has been sensitized by prior exposure to the drug, which can lead to immediate reactions; (c) the reaction may occur even by minute doses of the drug; (d) the symptoms are characteristic of an allergic reaction (e.g., anaphylaxis, urticaria, serum sickness); (e) the reaction resolves after the drug has been discontinued; and (f) the reaction may be reproduced by agents with similar chemical structures.²

Exceptions to each of these criteria are observed commonly. Many allergic reactions can be classified into one of four immunologic categories: type I, II, III, or IV (eTable 22-1 and eFig. 22-1).² ³ ⁵

**EFFEKTORS OF ALLERGIC DRUG REACTIONS**

Allergic drug reactions can involve most of the major components of the innate and adaptive immune systems, including the cellular elements, immunoglobulins, complement, and cytokines. Most immunoglobulin isotypes have been implicated in immunologically mediated drug reactions. Immunoglobulin E (IgE) bound to basophils or mast cells mediates immediate (anaphylactic-type) reactions. IgG or IgM antibodies also may be involved in allergic reactions, resulting in destruction of cells and tissues. T lymphocytes have a major role in hypersensitivity reactions and are involved in all four types (I–IV) of the drug hypersensitivity reactions described by Coombs and Gell.² ³ ⁵

**Cellular Elements**

A variety of cells are involved in drug hypersensitivity. Antigen-presenting cells (APCs) include macrophages, dendritic cells, and cutaneous Langerhans cells. APCs process the antigenic drug for subsequent recognition by T and B lymphocytes. Basophils and mast cells are instrumental in the development of immediate hypersensitivity reactions, whereas eosinophils are recruited in both immediate and nonimmediate reactions. Platelets and vascular endothelial cells are important because they also can release a number of inflammatory mediators.² Most cells of the body, including nerve cells, can become involved directly or indirectly in allergic drug reactions.

**Mediators of Allergic Reactions**

The release of a number of preformed, pharmacologically active chemical mediators (e.g., histamine, heparin, proteases such as tryptase and chymase, and a variety of other enzymes) is triggered when antigens cross-link IgE molecules on the surface of circulating basophils and tissue mast cells. Newly formed mediators include platelet-activating factor (PAF) and arachidonic acid metabolites (e.g., prostaglandins [PGs], thromboxanes, and leukotrienes [LTs]).

Histamine is a low-molecular-weight amine compound formed by decarboxylation of histidine and is stored in basophil and mast cell granules.³ Release of histamine from these cells is triggered by antigen cross-linking IgE bound to specific receptors on the surface membranes of mast cells and basophils. The tissue effects of histamine are evident within 1 to 2 minutes, but it is rapidly metabolized within 10 to 15 minutes. The major effects of histamine on target tissues include increased capillary permeability, contraction of bronchial and vascular smooth muscle, and hypersecretion of mucous glands. Four classes of histamine receptors (H₁–H₄) are present in varying degrees in organs and tissues. H₁ receptors are most prominent in blood vessels and bronchial and intestinal smooth muscle.

Platelet-activating factor is a glyceride-derived substance that is released by mast cells, alveolar macrophages, neutrophils, platelets, and other cells but not by basophils. It has potent bronchoconstrictor effects and causes platelet aggregation and lysis. It attracts neutrophils and causes their activation. PAF enhances vascular permeability and can cause pain, pruritus, and erythema.

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eTable 22-1  Classification of Allergic Drug Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Descriptor</th>
<th>Characteristics</th>
<th>Typical Onset</th>
<th>Drug Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anaphylactic (IgE mediated)</td>
<td>Allergen binds to IgE on basophils or mast cells, resulting in release of inflammatory mediators.</td>
<td>Within 30 min to &lt;2 hours</td>
<td>Penicillin immediate reaction Blood products Polypeptide hormones Vaccines Dextran</td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic</td>
<td>Cell destruction occurs because of cell-associated antigen that initiates cytolysis by antigen-specific antibody (IgG or IgM). Most often involves blood elements.</td>
<td>Typically &gt;72 h to weeks</td>
<td>Penicillin, quinidine, heparin, phenylbutazone, thiouracils, sulfonamides, methyldopa</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex</td>
<td>Antigen–antibody complexes form and deposit on blood vessel walls and activate complement. Result is a serum sickness-like syndrome.</td>
<td>&gt;72 h to weeks May be caused by penicillins, sulfonamides, minocycline, hydantoin</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated (delayed)</td>
<td>Antigens cause activation of T lymphocytes, which release cytokines and recruit effector cells (e.g., macrophages, eosinophils).</td>
<td>&gt;72 h Tuberculin reaction Maculopapular rashes to a variety of drugs; Contact dermatitis Bullous exanthems Pustular exanthems</td>
<td></td>
</tr>
</tbody>
</table>

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The LTs are metabolites of arachidonic acid produced through the 5-lipoxygenase pathway that have potent effects on bronchial and vascular smooth muscle. Three important LTs, LTC₄, LTD₄, and LTE₄, are produced by basophils or mast cells. These three substances are also referred to as cysteinyl LTs and were previously referred to as slow-reacting substances of anaphylaxis. The LTs have more potent and longer-lasting bronchoconstrictor effects than histamine and can increase vascular permeability and cause arteriolar vasoconstriction followed by vasodilation. Their effects are slower in onset but longer lasting than those of histamine. Another product, LTB₄, is a potent chemoattractant, particularly for neutrophils. It is also produced by neutrophils, macrophages, and monocytes.

Prostaglandins and thromboxanes are metabolites of arachidonic acid produced through the cyclooxygenase (COX) pathway. Some PGSs have vasodilatory or bronchodilatory properties, whereas others are vasodilatory or bronchoconstrictive. PGD₂ is the major PG product of mast cells. It is a potent inhibitor of platelet aggregation and is a bronchoconstrictor. Thromboxanes cause platelet aggregation and are important regulators of coagulation.

The complement system consists of about 30 plasma proteins and is involved in hypersensitivity through a variety of immunologic responses, including enhancement of phagocytosis (opsonization of target cells), cell lysis, and generation of anaphylatoxins C₃a, C₄a, and C₅a, which can cause non–IgE-mediated activation of mast cells and release of inflammatory mediators.

### CLASSIFICATION OF IMMUNOPATHOLOGIC DRUG REACTIONS

Immunologic mechanisms have been identified for some drug reactions, and many can be classified into one of four immunopathologic reactions, first described by Coombs and Gell. Small-molecular-weight molecules (<10 kDa) do not have the ability to serve as antigens on their own. With the exception of polypeptide compounds, most drugs are smaller than 1,000 Da. To become immunogenic, these small compounds must first covalently bind to carrier proteins in plasma or tissue. The combination of the drug bound to a carrier protein can be recognized as foreign by APCs and T lymphocytes, culminating in an immune response. The more likely that the carrier protein can be recognized as foreign by APCs and T lymphocytes, the greater the risk of producing an allergic reaction. Penicillin G (356 Da) is an example of a drug that binds covalently to serum proteins through amide or disulfide linkages. For drugs such as the sulfonamides, the parent compound must be converted to a metabolite before it can combine with the macromolecule. The species that combines with the carrier macromolecule is referred to as a hapten or an incomplete antigen. Some macromolecular drugs such as insulin are referred to as complete antigens because they are large enough to initiate an immune response without binding to another
Type I
Type I reactions require the presence of IgE specific for the drug or the portion of the drug that becomes a hapten. IgE specific for the drug allergen is produced on initial exposure to the drug. It then binds to basophils and mast cells through high-affinity receptors. On repeat exposure to the drug, two or more IgE molecules on the basophil or mast cell surface may bind to one multivalent antigen molecule (referred to as cross-linking; see eFig. 22-1), initiating cellular activation. Activation causes the extracellular release of granules with preformed inflammatory mediators, including histamine, heparin, and proteases (tryptase in the mast cell), as well as generation of newly formed mediators, as previously discussed, such as LTs, PGs, thromboxanes, and PAF, among others.

Generation of a type I reaction can be evident as an immediate hypersensitivity reaction, or anaphylaxis. Immediate reactions may be limited to single organs, typically in the nasal mucosa (rhinitis), respiratory tract (acute asthma), skin, or gastrointestinal tract, or they can involve multiple organs simultaneously, termed anaphylaxis.

Type II
Type II immunopathologic reactions involve destruction of host cells (usually blood cells) through cytotoxic antibodies by one of two mechanisms (see eFig. 22-1). First, the drug binds to the cell as a hapten (e.g., the platelet or red blood cell). Antibodies (IgG or IgM) specific for the bound drug or to a component of the cell surface that has been altered by the drug then bind, initiating a cytolytic reaction. Cell death may be mediated by complement or by phagocytic cells that have antibody Fc receptors on their surfaces. Activation of complement near the cell surface can result in loss of cell membrane integrity and cell death. Alternatively, neutrophils, monocytes, or macrophages may bind to an antibody-coated cell through IgG Fc receptors on their cell surfaces, resulting in phagocytosis of the target cell. The process of enhancement of phagocytosis by antibody binding to cell surfaces or other particles is referred to as opsonization. In addition, cell-bound IgG may direct the nonphagocytic action of T cells or natural killer cells, which results in cell destruction by a process called antibody-dependent cellular cytotoxicity. This process can proceed in a nonspecific fashion as T cells bind to the target cell through IgG Fc receptors on the T-cell surface. Contact between the target and effector cells is necessary.

Cells commonly affected by these types of reactions include erythrocytes, leukocytes, and platelets, resulting in hemolytic anemia, agranulocytosis, and thrombocytopenia, respectively. This process may be initiated by drugs such as penicillin, quinidine, quinine, phenacetin, cephalosporins, and sulfonamides.

Another type of reaction that may affect the formed elements in blood is the “innocent bystander” reaction. With this type of reaction, antigen–antibody complexes formed in blood adhere nonspecifically to cells. Complement is then activated, resulting in cell lysis.

Type III
Type III immunologic reactions are caused by antigen–antibody complexes that are formed in blood. The complexes form with drug allergen and antibody in varying ratios and may deposit in tissues, resulting in local or disseminated inflammatory reactions. Antigen–antibody complex formation can result in platelet aggregation, complement activation, or macrophage activation. Chemotactic substances such as C4a also are produced. These substances cause the influx of neutrophils and result in the release of a number of toxic substances from the neutrophil (e.g., proteinases, collagenases, kinin-generating enzymes, and reactive oxygen and nitrogen substances), which can cause local tissue destruction.

Platelet aggregation may occur as a result of immune-complex formation, resulting in the formation of microthrombi and the release of vasoactive mediators. Also, insoluble complexes may be phagocytized by macrophages and activate these cells.

The formation of antigen–antibody complexes can lead to clinical syndromes such as the Arthus reaction. In this model, a high level of preformed specific IgG antibody combines with antigen to produce a localized edematous, erythematous reaction within 5 to 8 hours. The reaction involves local formation of insoluble antigen–antibody complexes, complement activation with release of C3a and C5a collectively referred to as anaphylatoxins, mast cell degranulation, and influx of polymorphonuclear cells.

Type IV
Type IV reactions are delayed hypersensitivity reactions that typically are demonstrated as dermatologic events mediated by T cells (CD4+ or CD8+). The Coombs and Gell classification of allergic drug reactions was developed before our understanding of the varied roles of T cells in the immune response. Four subclasses of type IV reactions (Ivα–Ivδ) have been described based on the responding T cell (e.g., T helper type 1 cell, T helper type 2 cell, cytotoxic T cell), effector mechanism (e.g., recruitment of macrophages, eosinophils, or neutrophils), and clinical manifestations (e.g., contact dermatitis, bullous exanthems, maculopapular eruptions, pustular exanthems) (eFig. 22-1). Type IV reactions require memory T cells specific for the antigen in question. On exposure to the antigen, the immune response is mediated by a specific subtype of T cell that orchestrates an inflammatory response through the secretion of cytokines and the recruitment of effector cells. These reactions are associated with a wide variety of adverse effects (e.g., contact dermatitis, maculopapular exanthems, bullous exanthems, eczema, or pustular exanthems), and they also may be useful for diagnostic purposes. Examples of the latter include the purified protein derivative (PPD) antigen from Mycobacterium tuberculosis used in the tuberculin skin test and other recall skin test antigens, such as mumps. After intradermal injection, these antigens produce a local reaction (erythema and induration) within 48 to 72 hours. Delayed contact hypersensitivity also can be caused by a wide variety of chemicals and drugs.

Other Allergic Reactions
The precise mechanism of many drug reactions is not known, although the reactions are believed to be immune mediated. Perhaps most common are the delayed dermatologic reactions that occur with a variety of drugs (especially penicillins and sulfonamides). These reactions may be evident as fixed drug eruptions; macropapular, morbilliform, or erythematous rashes; exfoliative dermatitis; photosensitivity reactions; or eczema. These reactions also may be manifest as late onset pruritus, urticaria, and angioedema.

A number of serious cutaneous adverse reactions, known as SCARs, may be the result of immunologic reactions. SCARs include drug rash with eosinophilia and systemic symptoms (DRESS) and the mucocutaneous disorders, SJS and toxic epidermal necrolysis (TEN). Drug-induced fever also may involve immunologic mechanisms. Other general types of reactions
believed to be immune mediated in some cases include hepatic drug reactions (cholestatic or hepatocellular) and pulmonary reactions (e.g., interstitial pneumonitis, which has been associated with nitrofurantoin).

Anaphylactoid Reactions

Various drugs can produce reactions that are similar to anaphylaxis in clinical signs and symptoms but are not mediated by immune mechanisms. The drugs causing these reactions can cause release of mast cell- and basophil-derived mediators by a pharmacologic or physical effect rather than through cell-bound IgE. These reactions are described as anaphylactoid (anaphylaxis-like) reactions or non–immune-mediated anaphylaxis, the most severe form of pseudoallergy. Pseudoallergy refers to a wide array of reactions ranging from localized hives to life-threatening angioedema, hypotension, and anaphylaxis, all of which are explained by the nonimmunologic release or activation of inflammatory mediators. Drugs that can produce anaphylactoid reactions include vancomycin, opiates, iodinated radiocounter agents, angiotensin-converting enzyme (ACE) inhibitors, amphotericin B, and D-tubocurarine. The “red man syndrome” is a common example of a pseudoallergic reaction from vancomycin. If vancomycin is infused too rapidly, it can cause the direct release of histamine and other mediators from cutaneous mast cells, producing a typical clinical picture of itching, flushing, and hives, first around the neck and face and then progressing to the chest and other parts of the body usually beginning shortly after the infusion has begun. In some cases, the cutaneous manifestations of “red man syndrome” may be accompanied by hypotension, thereby constituting an anaphylactoid event. Most patients who have had “red man syndrome” will tolerate vancomycin if the rate of infusion is slowed. In rare cases, the severity of the reaction may preclude continued therapy with vancomycin. A number of other agents (including aspirin) may produce anaphylactoid reactions by altering the metabolism of inflammatory mediators such as PGs or kinins. Angioedema from ACE inhibitors is a classic example of an anaphylactoid reaction. Although the mechanism by which this anaphylactlike event occurs is not fully understood, inhibition of the breakdown of bradykinin and substance P by the ACE inhibitor may explain the inflammation, increased vascular permeability, and vasodilation.

CLINICAL MANIFESTATIONS OF ALLERGIC AND ALLERGIC-LIKE REACTIONS

Anaphylaxis

Anaphylaxis is an acute, life-threatening reaction, usually mediated by an immune mechanism, that involves multiple systems and occurs in 10 to 20 per 100,000 population per year. About 1,500 deaths from anaphylaxis occur annually in the United States. From 1.2% to 15% of the United States population may be at risk for anaphylactic reactions. Recently reported data suggest that the prevalence is rising, most notably in the younger age group. Although many drugs may cause anaphylaxis (or anaphylactoid) reactions, the most commonly reported are penicillins, aspirin and other NSAIDs, and insulin. In most patients, the initial signs and symptoms occur in the skin (flushing, pruritus, urticaria, angioedema). The second most common symptoms are respiratory (tightness of the throat and chest, dysphagia, dysphonia and hoarseness, cough, stridor, shortness of breath, dyspnea, congestion, rhinorrhea, sneezing) followed by dizziness and gastrointestinal tract symptoms (nausea, crampy abdominal pain, vomiting, diarrhea). About 10% to 30% of patients develop hypotension. Additional cardiovascular effects include syncope, altered mental status, chest pain, and dysrhythmia. In 2010, a consensus panel reconvened to update the definition and management of anaphylaxis. Anaphylaxis is highly likely when one of the following three scenarios is present:

1. Acute onset of a reaction (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives; pruritus or flushing; swollen lips, tongue, uvula) and at least one of the following:
   - Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen (minutes to several hours):
   - Involvement of skin or mucosal tissue (as above)
   - Respiratory compromise (as above)
   - Reduced blood pressure or associated symptoms
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen (minutes to several hours)

The panel indicated that other presentations may indicate anaphylaxis, such as acute chest pain or arrhythmia without dermatologic manifestations, and that the potential exists for false-positive results.

Anaphylaxis generally begins within 30 minutes but almost always within 2 hours of exposure to the inciting allergen. The risk of fatal anaphylaxis is greatest within the first few hours. Late phase or “biphasic reactions” can occur 1 hour to 72 hours after the initial presentation with most occurring within 10 hours. Because of the possibility of a biphasic reaction, patients should be observed for at least 12 hours after an anaphylactic reaction. Fatal anaphylaxis most often results from asphyxia caused by airway obstruction either at the larynx or within the lungs. Cardiovascular collapse may occur as a result of asphyxia in some cases; in other cases, cardiovascular collapse may be the dominant manifestation from the release of mediators within the heart muscles and coronary blood vessels.

Newer clinical markers may aid in the diagnosis of anaphylaxis. Serum levels of tryptase or mature tryptase (also known as β-tryptase) peak in the serum within 0.5 to 2 hours after the onset of anaphylaxis. Tryptase levels are most helpful in making the diagnosis if they are drawn no more than 6 hours after the onset of symptoms. Plasma histamine levels remain elevated for only 30 to 60 minutes; thus, they are not clinically useful in patients who present 1 hour or later after the onset of anaphylaxis.

Serum Sickness and Serum Sickness–Like Disease

Serum sickness is a clinical syndrome resulting from the effects of soluble circulating immune complexes that form under conditions of antigen excess. The reaction commonly results from the use of antiserum containing foreign (donor) antigens such as equine serum in the form of antitoxins or antivenoms. The onset of serum sickness is usually 7 to 14 days after antigen administration. The onset may be more rapid with reexposure to the same agent in an individual with prior serum sickness. Fever, malaise, and lymphadenopathy are the most common clinical manifestations. Arthralgias, urticaria, and morbilliform skin eruption also may...
be present. A milder and more transient form of serum sickness is serum sickness–like disease (SSLD). The predominant feature of SSLD is a cutaneous eruption, either urticarial or maculopapular, that occurs within 5 to 21 days of drug administration. As with serum sickness, the rash is usually preceded by a prodromal phase consisting of fever, malaise, lymphadenopathy, and arthralgias. SSLD has been associated with the administration of ciprofloxacin, hydralazine, quinidine, sulfonamides, penicillins, and cephalosporins (especially cefaclor). SSLD is usually self-limiting after discontinuation of the causative agent, but it can sometimes progress to include vasculitis.

### Drug Rash with Eosinophilia and Systemic Symptoms

Previously known by the term drug hypersensitivity syndrome, the triad of rash, eosinophilia, and internal organ involvement is currently referred to as drug rash with eosinophilia and systemic symptoms (DRESS). Bocquet and colleagues described the following criteria for a diagnosis of DRESS: (a) cutaneous drug eruption (usually a diffuse maculopapular rash accompanied by facial and neck edema); (b) hematologic abnormalities including eosinophilia greater than 1,500 cells/mm³ (1.5 x 10⁹/L) or the presence of atypical lymphocytes; and (c) systemic involvement including adenopathy greater than 2 cm in diameter, hepatitis, interstitial nephritis, interstitial pneumonia, or carditis. Both the allopurinol hypersensitivity syndrome and anticonvulsant hypersensitivity syndrome are examples of DRESS. Other drugs associated with DRESS include minocycline, dapsone, lamotrigine, and the sulfonamides. The onset of DRESS is typically delayed ranging from 3 to 8 weeks after drug initiation, and there is a high degree of interpatient variability in the targeted organs and the severity of organ involvement.

### Drug Fever

Fever may occur in response to an inflammatory process or develop as a manifestation of a drug reaction. Drug fever has been estimated to occur in as many as 10% of hospital inpatients. Many drugs have been reported to cause fever with the most frequently implicated classes being the antimicrobials (e.g., acyclovir, amphotericin B, β-lactams, minocycline, rifampin, sulfonamides, tetracycline), anticonvulsants (e.g., carbamazepine, phenytoin), antiarrhythmics (e.g., procainamide, quinidine), and other cardiac medications (e.g., clofibrate, diltiazem, dobutamine, furosemide, heparin, methyl dopa, procainamide). These drugs may affect the central nervous system (CNS) directly to alter temperature regulation or stimulate the release of endogenous pyrogens (e.g., interleukin-1 and tumor necrosis factor), PGs, or nervous system monamines that alter the thermoregulatory set point. Drugs also may cause fever as a result of their pharmacologic effects on tissues (e.g., fever resulting from massive cell destruction caused by chemotherapy).

The temperature pattern of drug-induced fever is quite variable and therefore of little help in the diagnosis. Four patterns of drug fever have been described: continuous, remittent, intermittent, and hectic. A combination of intermittent and remittent, hectic fever is the most common pattern with temperatures of 102° F interrupting normal temperatures throughout the day. Drug fever may occur at any time during the course of therapy with a median reported time of 7 to 10 days after drug initiation. Antimicrobials and antineoplastic drugs have been associated with the shortest time to onset (median, 6 and 0.5 days, respectively), whereas CNS agents and cardiovascular drugs have longer times to onset (median, 10 and 16 days, respectively). Laboratory findings such as leukocytosis, eosinophilia, elevated lactic dehydrogenase, and elevated erythrocyte sedimentation rate may aid in the diagnosis. Generally, withdrawal of the causative agent results in prompt defervescence as soon as the drug is eliminated completely. Fever usually recurs on readministration of the causative agent.

### Drug-Induced Autoimmunity

Autoimmune diseases have been associated with drugs and may involve a variety of tissues and organs. A commonly recognized drug-related autoimmune disorder is systemic lupus erythematosus (SLE) induced by infliximab, etanercept, procainamide, hydralazine, quinidine, or isoniazid. Exposure of susceptible persons to these agents appears to alter normal body proteins, RNA, or DNA in such a way as to make these components antigenic, leading to the formation of autoreactive antibodies and cells. Most patients treated with infliximab develop antinuclear antibodies, but only 2% of patients present with SLE symptoms. The most common clinical manifestations include arthralgias, myalgias, and polyarthritis. Facial rash, ulcers, and alopecia occur less frequently. Renal or pulmonary involvement also may occur. These reactions typically develop several months after beginning the drug and generally resolve soon after the drug is discontinued.

Other syndromes believed to involve autoimmune mechanisms include drug-induced hemolytic anemia attributed to methyldopa, interstitial nephritis produced by methicillin, and hepatitis caused by phenytoin and halothane. Interstitial nephritis is characterized by fever, rash, and eosinophilia associated with proteinuria and hematuria. Hepatic damage due to drugs generally is manifested as either hepatocellular necrosis or cholestatic hepatitis. Drug-induced hepatitis has been associated with phenothiazines, sulfonamides, halothane, phenytoin, and isoniazid (see eChap. 17). Hepatocellular destruction is evidenced by elevations in serum transaminases. Hepatomegaly and jaundice sometimes may be evident. Cholestasis may be manifested by jaundice and elevations in serum alkaline phosphatase and sometimes by rash, fever, and eosinophilia.

### Vasculitis

Vasculitis is a clinicopathologic process characterized by inflammation and necrosis of blood vessel walls. The vasculitic process may be limited to the skin, or it may involve multiple organs, including the liver or kidney, joints, or CNS. Characteristically, cutaneous vasculitis is manifested by purpuric lesions that vary in size and number. Vasculitis also may be manifested as papules, nodules, ulcers, or vesiculobullous lesions, generally occurring on the lower extremities but sometimes involving the upper extremities, including the hands. Drugs associated with vasculitis include allopurinol, β-lactam antibiotics, sulfonamides, thiazide diuretics, phenytoin, and vancomycin.

### Dermatologic Reactions

A wide variety of dermatologic drug reactions have been reported to have an immunologic basis. Cutaneous reactions are the most common manifestations of allergic drug reactions. Although most dermatologic reactions are mild and resolve promptly after discontinuing the drug, some such as SJS and TEN are serious.
or even life-threatening reactions. Both SJS and TEN are classified as progressive bullous or “blistering” disorders that constitute dermatologic emergencies.23 They are considered severe variants of erythema multiforme. Similar to erythema multiforme, SJS and TEN are associated with the widespread development of a variety of skin lesions, including macules, purpuric lesions, and the target iris lesion. The target lesion is discrete and round and identified by an area of central clearing surrounded by two concentric rings of edema and erythema. Unlike erythema multiforme, SJS and TEN are most commonly drug induced rather than associated with recurrent herpes simplex viral infection, and they progress to include mucous membrane erosion and epidermal detachment.24 Mucosal membranes in the mouth, lips, nasal cavity, and conjunctivae are usually involved. As these syndromes progress, the erythematous lesions become more widespread on the face, trunk, and extremities, and many evolve into blisters. Within days after the onset of the lesions, full-thickness epidermal detachment occurs. SJS and TEN are often considered as a continuous spectrum of a disease, with TEN being the most severe form. The extent of epidermal detachment is used to distinguish between SJS and TEN (i.e., <10% detachment of body surface area with SJS; greater than 30% detachment of body surface area with TEN). The term SJS-TEN overlap is used to describe cases in which epidermal detachment occurs on 10% to 30% of the body surface area.23-24 Both SJS and TEN are associated with a number of long-term sequelae, including permanent visual impairment, temporary nail loss, cutaneous scarring, and irregular pigmentation. Being the more severe form, TEN is also more likely to be complicated by systemic organ involvement, including acute kidney failure, neutropenia, and respiratory failure. A severity-of-illness scoring system known as SCORTEN has been developed to predict prognosis in patients with TEN.25 SCORTEN uses seven independent risk factors based on an assessment within 24 hours of clinical presentation.

Cutaneous adverse reactions were reported to occur in 2.7% of hospitalized patients.26 TEN is estimated to occur in 0.4 to 1.3 cases per 1 million people per year, and SJS has been reported in 1 to 6 cases per 1 million people per year.27-28 The mortality rates associated with SJS and TEN range from 1% to 5% and 10% to 70%, respectively.26 eTable 22-2 lists drugs and agents associated most commonly with cutaneous reactions.26 In general, antimicrobials are implicated most frequently as the cause of cutaneous events with reaction rates ranging from 1% to 8%. The most likely offenders of SJS and TEN, determined in case-control studies, are the sulfonamides, particularly trimethoprim–sulfamethoxazole.29 Other major offenders of SJS and TEN identified in these studies are allopurinol, the aminopenicillins, carbamazepine, chloromazanone, cephalosporins, the imidazole antifungals, lamotrigine, nevirapine, the oxicam NSAIDs, phenytoin, quinolones, and the tetracyclines.29

**Respiratory Reactions**

Drugs may produce upper or lower respiratory tract reactions, including rhinitis and asthma. Respiratory tract manifestations may result from direct injury to the airways or may occur as a component of a systemic reaction (e.g., anaphylaxis). Asthma may be induced by aspirin and other NSAIDs or by sulfites used as preservatives in foods and medications. Other pulmonary drug reactions believed to be immunologic include acute infiltrative and chronic fibrotic pulmonary reactions. The latter is often caused by antineoplastic agents such as bleomycin. For a more detailed discussion of drug-induced pulmonary disease, see eChapter 15.

**Hematologic Reactions**

Most formed elements and soluble components of the hematopoietic system may be affected by immunologic drug reactions. Eosinophilia is a common manifestation of drug hypersensitivity and may be the only presenting sign. Hemolytic anemia may result from hypersensitivity to drugs. Other hematologic reactions include thrombocytopenia, granulocytopenia, and agranulocytosis. For a detailed discussion of hematologic drug reactions, see eChapter 24.

**FACTORS RELATED TO THE OCCURRENCE OR SEVERITY OF ALLERGIC DRUG REACTIONS**

Among the factors that influence the likelihood of allergic drug reactions are the degree to which the drug and its metabolites bind covalently to human proteins, how the drug is metabolized, whether the drug contains proteins of nonhuman origin (e.g., chimeric monoclonal antibodies, streptokinase) or antigenic excipients (e.g., peanut oil, FD&C dyes, sulfites, soybean emulsion), the route of exposure, and the sensitivity of the individual as determined by genetics and environmental factors. Hypersensitivity can occur with any dose of a drug, but sensitization is more likely to occur with continuous dosing rather than single dosing. After a patient has become sensitized, the severity of a reaction is often determined by the dose and the duration of exposure. The route of administration may also influence drug sensitivity. The topical route of drug administration appears to be the most likely to sensitize and predispose to drug reactions. The oral route is the safest, and the parenteral route is the most hazardous for administration of drugs in sensitive individuals. Relatively few cases of immediate hypersensitivity-associated deaths with oral β-lactam antimicrobials have been reported.

The presence of genetically determined human leukocyte antigen (HLA) alleles increases susceptibility to a number of drug hypersensitivity syndromes. In patients infected with the human immunodeficiency virus (HIV), hypersensitivity to abacavir has been associated with the presence of HLA-B*5701.30 Severe immune-mediated cutaneous reactions to allopurinol, including SJS and TEN, have been associated with the presence of HLA-B*5801 in Han Chinese.31 In this same patient population, the presence of HLA-B*1502 increases the risk of SJS and TEN with carbamazepine, phenytoin, and fosphenytoin.32 Associations between HLA alleles and drug reactivity have been described for aminopenicillins, aspirin, iodinated contrast media, gold, lamotrigine, and trimethoprim–sulfamethoxazole.33 Genetic factors can also influence the metabolic deactivation of drugs via phase 1 and 2 metabolism. For example, slow acetylators of procainamide and hydralazine are at increased risk for SLE. Genes also encode for the type of T-cell receptor and the specific cytokines involved in the signaling of allergic drug reactions.
Drug allergies appear to develop with equal frequency in atopic and nonatopic individuals. In addition, patients with a history of drug allergy appear to be at increased risk for adverse reactions to other pharmacologic agents. Age seems to be related to the risk of allergic reactions because they occur less frequently in children. This may be related to immaturity of the immune system or decreased exposure. The presence of some concurrent diseases, particularly viral infections, predisposes to drug reactions. Examples include the higher rate of morbilliform rash when ampicillin is administered to patients with infectious mononucleosis, the higher rate of reactions to trimethoprim–sulfamethoxazole in HIV-infected patients, and the relationship between infection with human herpes virus 6 (HHV-6) and the development of DRESS.

**DRUGS COMMONLY CAUSING ALLERGIC OR ALLERGIC-LIKE DRUG REACTIONS**

### β-Lactam Antimicrobials

Allergy to β-lactam antibiotics is commonly reported by patients in healthcare settings. Allergic reactions to penicillin occur in 0.7% to 8% of treatment courses but was as high as 15% in one retrospective report of hospitalized patients treated with penicillin. Although most patients reporting penicillin allergy do not have allergy, a reported history is associated with a higher likelihood of positive skin test reactivity. Only 10% to 20% of patients reporting penicillin allergy are found to be allergic by skin testing. Patients with a history of immediate penicillin allergy who have a negative penicillin skin test result are unlikely to react on subsequent courses of penicillin.

The most common reactions to penicillin include urticaria, pruritus, and angioedema. All four of the major types of hypersensitivity reactions have been reported with penicillin, as well as some reactions that do not fit into these categories. A wide variety of idiopathic reactions occur, such as maculopapular eruptions, drug-induced eosinophilia, SJS, and exfoliative dermatitis. Cutaneous reactions can occur in up to 4.4% of treatment courses of penicillin and in up to 8% of those of aminopenicillins. The incidence of ampicillin rash is close to 100% in patients with viral infections such as infectious mononucleosis.

Some aspects of the mechanism of penicillin immunogenicity have been determined. Because benzylpenicillin is a relatively small molecule (356 Da), it must combine with macromolecules (presumably proteins) to elicit an immune response. Penicillin is rapidly hydrolyzed to a number of reactive metabolites that have the ability to covalently link to proteins. Of these metabolites, 95% is in the form of benzylpenilloyl that binds covalently to the lysine residues of proteins such as albumin through an amide linkage involving the β-lactam ring. This penicilloyl–protein conjugate is referred to as the major antigenic determinant. The other penicillin metabolites such as penilloate and penicilloate bind in lesser quantities to proteins. These are referred to as minor antigenic determinants. The terms major and minor refer to the relative proportions of these conjugates that are formed and not to the clinical severity of the reactions generated. Immediate hypersensitivity reactions may be mediated by IgE for both minor and major determinants. In fact, the minor antigenic determinants are more likely to cause life-threatening anaphylactic reactions.

In addition to the major and minor determinants, unique side-chain determinants may mediate allergy to some penicillins. Both the aminopenicillins and piperacillin may cause hypersensitivity reactions via unique side-chains on their structures. Therefore, a patient may exhibit hypersensitivity to amoxicillin or piperacillin via a side chain determinant while exhibiting no reactivity to other penicillins. Reports of selective allergy to amoxicillin have become relatively common. The R-group side chain of amoxicillin is believed to be the primary epitope, but selective reactivity to clavulanic acid has been postulated and explored in those experiencing a reaction to amoxicillin clavulanate. Careful history taking is needed to identify patients with high likelihood of side-chain–specific reactions. Skin testing with dilute concentrations of amoxicillin, ampicillin, and piperacillin has been used to aid in the determination of side-chain–specific reactions.

**Figure 22-2** Formation of a benzylpenicilloyl hapten–protein complex.
Patients who are allergic to penicillins also may be sensitive to other β-lactams. The exact incidence of cross-reactivity between cephalosporins and penicillins is not known but is believed to be low. The risk was originally reported as 10% to 15% in the 1970s when cephalosporins were contaminated with trace amounts of penicillin. Current estimates of the cross-reactive risk between penicillin and the first- and second-generation cephalosporins are 5% to 7.5% and as low as 1% between penicillin and the third- and fourth-generation cephalosporins. One percent to 8% of patients with penicillin-specific IgE may develop an immediate-type hypersensitivity reaction to cephalosporins. In contrast, patients with reported penicillin allergy and negative skin test results are at no greater risk. Ideally, cephalosporins should be avoided in patients with history of an immediate hypersensitivity reaction to penicillin, although most studies suggest there is little risk of an allergic response to a cephalosporin even in a person with a positive skin test result to penicillin. Based on the results of one meta-analysis, patients with penicillin allergy have the highest risk of cross-reactivity with the first-generation cephalosporins (odds ratio [OR], 4.79; 95% confidence interval [CI], 3.71–6.17). The odds of reacting to a second- and third-generation cephalosporin were 1.13 (95% CI, 0.61–2.12) and 0.45 (95% CI, 0.18–1.13), respectively. The R1 side chain is connected to the opened β-lactam ring, thereby influencing the antigenicity of these agents. When assessing the potential for cross-reactivity between penicillins and cephalosporins, clinicians should evaluate the similarities in the R1 side chains of the agents. Beta-lactams having an R1 substitution chemically similar to that of penicillin G are cephaloridine, cephalothin, and cefoxitin. In the R1 position, amoxicillin is chemically similar to ampicillin, cefaclor, cephalaxin, and cephradine. Cefotaxime, ceftriaxone, cefpodoxime, and cefepime have chemically similar substitutions in the R1 position that may influence the risk of cross-reactivity.

Cephalosporins may induce immune responses mediated by the core β-lactam structure; however, they are more likely to do so via unique R-group side-chain determinants. In a patient with a cephalosporin allergy, skin testing with the major and minor determinants of penicillin can be used to identify the likelihood of reactivity to the core β-lactam ring. The risk of cross-reactivity between cephalosporins is considered to be higher than that between the penicillins and cephalosporins. Cross-reactions may occur through identical R1 side chains. Of note, ceftriaxone shares a common side chain with aztreonam.

The actual risk of a cross-reaction between the penicillins and the carbapenems appears to be much lower than originally described. The initial estimate of the cross-reactive risk was 47.4%, but current estimates range from 0.9% to 11%. The initial estimate was based on the results of skin testing with penicillin and nonstandardized carbapenem reagents. A number of retrospective studies reporting variable rates of cross-reactivity relied on self-reported histories as confirmation of penicillin allergy. Three recently published prospective studies used both skin testing methods and carbapenem challenge dosing to assess cross-reactive risk. In one of these studies, only one of 112 patients with skin test–confirmed penicillin allergy demonstrated a positive skin test result for imipenem. Challenge dosing with imipenem to a final dose of 500 mg was subsequently performed in 110 patients with negative imipenem skin test results; none of the 110 patients had a reaction. Results of two additional prospective studies, one of which was performed in children ages 3 to 14 years, suggest a low risk of cross-reactivity between penicillin and meropenem. Graded challenge dosing with meropenem was tolerated in 100% of the skin test–negative patients in both studies. It is important to note that none of the skin test–negative patients were subsequently treated with full therapeutic regimens of the carbapenem. However, the high level of tolerability to challenge dosing suggests a low rate of cross-reactivity in skin test–negative patients. Based on these results, the routine practice of avoiding carbapenem use in patients with history of penicillin allergy should be reconsidered.

Of the monobactams, aztreonam only weakly cross-reacts with penicillin and can be administered safely to most patients who are penicillin allergic.

Radiocontrast Media

Radiocontrast agents frequently cause reactions categorized as immediate (in ≤1 hour) or nonimmediate (in 1–10 days) via both IgE-mediated and non-IgE–mediated mechanisms. The frequency and severity of these reactions are influenced by the type of radiocontrast agent (ionic vs. nonionic), and patient-specific factors such as history of atopy, asthma, or prior reaction to a radiocontrast agent. Current reported estimates of the frequency of anaphylactoid reactions with ionic and nonionic agents are 1% to 3% and less than 0.5%, respectively. Delayed skin reactions, usually presenting as maculopapular exanthems, occur in 1% to 3% of patients over 5 to 7 days. Severe, immediate anaphylactic reactions occur in 0.01% to 0.04% of patients. In addition, radiocontrast agents may cause dose-dependent toxic reactions that can produce renal impairment, cardiovascular effects, and arrhythmias. The mechanism of reactions to radiocontrast agents is not clearly understood. Histamine release and mast cell triggering have been documented in severe immediate reactions, suggesting an IgE-mediated mechanism. The older, high-osmolar radiocontrast agents can activate mast cells, basophils, and the complement system directly (IgE-independent mechanism), resulting in the release of inflammatory mediators. The delayed-onset maculopapular rash appears to be T-cell mediated. The low-osmolar nonionic contrast agents appear to cause fewer anaphylactoid reactions.

The risk of anaphylactoid reactions to radiocontrast media is greater in women and in patients with a history of atopy or asthma. Other recognized risk factors include a history of previous reaction, severe drug allergies, cardiac disease, and treatment with β-blockers. Despite a common misconception, seafood allergy or iodine allergy does not predispose to radiocontrast media reactions. Neither skin tests nor oral tests are useful for predicting reactions to these agents. Although some regimens have been recommended to prevent the recurrence of immediate events in patients who have experienced reactions previously, the value of these preventive regimens has not been proven, and their use remains controversial.
A commonly recommended regimen in high-risk patients is oral prednisone (50 mg) 13, 7, and 1 hours before exposure with 50 mg of diphenhydramine given orally or intramuscularly 1 hour before exposure to prevent immediate reactions.62 Ephedrine 25 mg orally has also been recommended 1 hour before the radiodiagnostic study as a component of the pretreatment regimen; however, ephedrine should not be used if the patient has history of unstable angina, hypertension, or arrhythmia.10,14 Other studies have examined the use of H₁- and H₂-antihistamines, clemastine, or cimetidine, respectively,10,14

Anaphylactoid reactions to gadolinium, a noniodinated contrast agent, have been reported at frequencies of 0.07% in adults and 0.04% in children.60 Most reactions have been mild, requiring either no medical management or treatment with antihistamines. Moderate and severe reactions, although rare, have also been reported. Pretreatment regimens similar to those used with iodinated contrast studies are usually effective but have been associated with breakthrough reactions, particularly in patients with a history of reactions to gadolinium or iodinated contrast agents.61

**Insulin**

Insulin is capable of producing allergic reactions through a variety of immunologic mechanisms. A protein molecule, insulin is a complete antigen. Allergic reactions have been reported with beef, pork, and recombinant human insulin, although the frequency of reactions with human insulin appears low. Reactions to insulin may involve the insulin molecule itself or other substances that have been added to insulin (e.g., protamine). Most patients have anti-insulin IgG antibodies after a few months of therapy.

Insulin reactions may be limited to the site of injection, or they may produce systemic reactions. Local reactions present most often as a wheal and flare at the injection site and may occur immediately after injection or up to 8 to 12 hours later. These reactions are generally mild, do not require treatment, and resolve with continued insulin administration. If a patient does not tolerate the local reaction well, antihistamines may be given, or a different insulin source (or product of higher purity) may be substituted. Rarely, systemic reactions to insulin (e.g., urticaria or anaphylaxis) occur. IgE-mediated reactions to insulin allergy appear to be declining with greater use of human insulins.62 Skin testing with various products can aid in selecting the type of insulin least likely to cause a systemic reaction. Human insulin appears to be least allergenic but occasionally may cause reactions. In some patients, insulin desensitization may be indicated.

**Aspirin and Nonsteroidal Antinflammatory Drugs**

Aspirin and other NSAIDs can produce eight general types of reactions, four of which are related to COX inhibition.85,64 These reactions can involve asthma and rhinitis, urticaria/angioedema, anaphylaxis and anaphylactoid reactions, aseptic meningitis, or pneumonitis. The two most prevalent aspirin sensitivity reactions are respiratory (asthma, rhinorrhea) and urticaria/angioedema. About 9% to 20% of people with asthma are sensitive to aspirin and other NSAIDs.85,65

The rhinosinusitis/asthma syndrome typically develops in middle-aged patients who are nonatopic and have no history of aspirin intolerance. Women are 2.5 times more likely to develop aspirin-induced asthma than men.66 It usually progresses from rhinitis to sinusitis with nasal polyps and steroid-dependent asthma. It is uncommon in children and young adults. However, children with asthma may be aspirin sensitive. Aspirin-sensitive asthma appears to be an inherited disorder characterized by overexpression of LTC₄ synthase in airways.67 In aspirin-sensitive people with asthma, administration of aspirin and NSAIDs may provoke severe and sometimes fatal asthmatic attacks. The mechanism of aspirin sensitivity is not completely understood.

One suspected mechanism of aspirin and NSAID sensitivity is COX-1 blockade, which may facilitate depletion of prostaglandin E₂ (PGE₂) and production of alternative arachidonic acid metabolites (e.g., LTs).68 Whereas PGE₂ protects mast cell degranulation, LTs cause bronchoconstriction and increased mucus production. Increased LT production may also explain the development of angioedema and urticaria. This proposed mechanism is supported by the observed correlation between the degree of COX-1 blockade and the risk of a sensitivity reaction. Therefore, agents such as acetaminophen, which minimally block COX-1, rarely cause reactions. Additional support is found in the clinical observation that LT-modifying drugs can reduce the severity of aspirin-induced asthma and urticaria.69 It is also possible that aspirin and NSAIDs stimulate mast cells directly to release inflammatory mediators. Subjects with aspirin-induced asthma also have a marked increase in airway responsiveness to LTs. Aspirin and the COX-2–selective inhibitors celecoxib and rofecoxib do not appear to be cross-reactive.68–70

In patients with aspirin sensitivity (asthma or urticaria), an oral challenge or provocation test can be performed to diagnose the condition. A number of different protocols to detect aspirin or NSAID sensitivity have been recommended, but the risk for anaphylaxis cannot be reliably predicted.63,66 The challenge should be performed with great caution in a hospital setting with resuscitation equipment at hand. For patients with aspirin-induced asthma, induction of drug tolerance (desensitization) is recommended. A number of aspirin desensitization protocols have been described, ranging from 2- to 4-day protocols for patients with history of asthma to rapid (2- to 5-hour) protocols.80 Rapid desensitization protocols have been limitedly studied, primarily in patients with history of cutaneous reactions (urticaria or angioedema) who require aspirin for acute coronary syndromes or before stent placement.71 Aspirin desensitization has been shown to improve asthma symptom scores and lead to reductions in maintenance steroid doses. If desensitization is not performed, patients with aspirin sensitivity must avoid aspirin and the nonselective NSAIDs as the major preventive measure.

Aspirin and individual NSAIDs (e.g., ibuprofen, sulindac) can also cause IgE-mediated hypersensitivity. These reactions occur on reexposure to the drug and may present as urticaria, bronchospasm, or anaphylaxis with or without hypotension. A careful and complete allergy history may suggest true hypersensitivity to aspirin or an isolated NSAID. Such patients should be advised to avoid the specific NSAID and any structurally similar NSAIDs (e.g., all propionic acid derivatives, all indole acetic acid derivatives) because of the risk of cross-reactivity.

NSAIDs have been associated with pulmonary infiltrates and eosinophilia syndrome. Pulmonary infiltrates and eosinophilia syndrome are associated with fever, cough, dyspnea, infiltrates on chest radiography, and a peripheral eosinophilia that develops 2 to 6 weeks after initiating treatment. Pulmonary infiltrates and eosinophilia syndrome occurs more frequently for naproxen compared with other NSAIDs and is noted to resolve rapidly after discontinuation of the offending agent.72

**Sulfonamides**

Sulfonamide drugs containing the sulfa (SO₂NH₂) moiety include antibiotics, thiazide and loop diuretics, oral hypoglycemics, and carbonic anhydrase inhibitors. Allergic reactions have been reported in 4.8% of 20,226 patients who received a sulfonamide antibiotic and in 2% of patients who received a nonantibiotic sulfonamide.73 Although immediate IgE-mediated reactions such as anaphylaxis can occur, sulfonamides typically cause delayed cutaneous reactions, often beginning with fever and then followed by a rash (e.g., maculopapular or morbilliform eruptions). Infrequently, a seemingly
benign maculopapular rash may progress to a mucocutaneous syndrome (e.g., SJS or TEN). Other reactions to sulfonamides may include hepatic, renal, or hematologic complications, which may be fatal. Immune-mediated sulfonamide reactions depend on the production of reactive metabolites in the liver. Trimethoprim–sulfamethoxazole, considered the most highly reactive sulfonamide, contains an arylamine in the N4 position of its chemical structure, allowing for the drug’s metabolism to two highly reactive metabolites, a hydroxylamine and a nitroso-sulfonamide. Structural differences between the sulfonamides antibiotics and nonantibiotics may influence the metabolic conversion and resultant reactivity of these compounds. Slow acetylator phenotype may also increase the risk for these reactions.

8 Cross-reactivity between sulfonamide antibiotics and nonantibiotics appears to be minimal, with cross-reactivity characterized as “highly unlikely.” In one study, about 10% of patients with a history of allergy to an antibiotic sulfonamide subsequently reacted to a nonantibiotic sulfonamide (e.g., acetazolamide, loop diuretic, sulfonylurea, thiazide). This low rate of cross-reactivity has been attributed in part to differences in the chemical structures of the antibiotic and nonantibiotic sulfonamides. The occurrence of allergic reactions after receipt of nonantibiotic sulfonamides has also been attributed to a predisposition to allergic reactions in the affected individuals rather than cross-reactivity with sulfonamide antibiotics. In fact, in one study, cross-reactivity between sulfonamide antibiotics and penicillin was higher than that between the antibiotic and nonantibiotic sulfonamides.

Trimethoprim–sulfamethoxazole is used frequently for preventive or active treatment of Pneumocystis jiroveci pneumonia in patients with AIDS. Adverse reactions to trimethoprim–sulfamethoxazole occur much more frequently in HIV-positive patients. Adverse effects to trimethoprim–sulfamethoxazole occur in 50% to 80% of AIDS patients compared with 10% of other immunocompromised patients. Trimethoprim–sulfamethoxazole was associated with an adverse event rate of 26.3 per 100 person-years and hypersensitivity events at 22 per 100 person-years. Although reactions may include angioedema, SJS, and thrombocytopenia, most reactions to trimethoprim–sulfamethoxazole in HIV-infected patients are delayed and present as diffuse maculopapular rash with or without fever. The mechanism by which these allergic or allergic-like reactions occur in HIV-infected patients is unclear. It is unlikely that these reactions are IgG or IgE mediated. Proposed mechanisms include alterations in drug metabolism caused by glutathione deficiency, a direct toxic or immunologic effect of the sulfonamide metabolites on body tissues, and increased expression of major histocompatibility complex proteins with increased recognition of the drug antigen by CD4 and CD8 cells. The adverse event rate has been related to higher CD4+ T-cell count greater than 20 cells/mm³ (>20 × 10⁹/L), CD4-to-CD8 ratio less than 0.10, and treatment for fewer than 14 days.

**Pharmaceutical Excipients and Additives**

Pharmaceutical products contain a number of “inert” additives (e.g., dyes, fillers, buffers, and stabilizers) in addition to the therapeutic ingredients. These additives are not always inert and may cause adverse effects, including allergic reactions.

The azo dye tartrazine (FD&C Yellow No. 5) is associated with anaphylactoid reactions, acute bronchospasm, urticaria, rhinitis, and contact dermatitis. Although the immunologic mechanisms are unclear, about 10% of aspirin-sensitive people with asthma are also intolerant to tartrazine, suggesting a role for tartrazine as a COX inhibitor. As little as 0.85 mcg or as much as 25 mg tartrazine has provoked positive responses.

Sulfites (including sulfur dioxide, sodium sulfate, sodium and potassium bisulfite, and sodium and potassium metabisulfite) are used commonly as antioxidants in pharmaceutical products and some foods. Many cases of adverse reactions associated with ingestion of sulfites (usually in foods) have been reported to the U.S. Food and Drug Administration (FDA), including wheezing, dyspnea, chest tightness, urticaria, angioedema, flushing, weakness, nausea, anaphylaxis, and death.

IgE-mediated and nonimmunologic sulfite hypersensitivity has been demonstrated in children with a history of chronic asthma. Adverse reactions to sulfite-preserved injectables, such as gentamicin, metoclopramide, lidocaine, and doxycycline, have been reported. In contrast to reactions caused by foods, these reactions do not occur more frequently in steroid-dependent people with asthma and do not always coincide with a positive oral sulfite challenge. Blunted bronchodilatation may be observed in individuals with asthma after inhalation of sulfite-containing nebuleur solutions. Although many nebuleur solutions contain sulfites, metered-dose inhalers do not. Many aqueous epinephrine products also contain sulfites. The FDA labeling states that in emergency situations when sulfite-free preparations are not available, sulfite-containing epinephrine should not be withheld from a sulfite-intolerant individual because small subcutaneous doses of sulfites usually are well tolerated. However, an increased risk of anaphylaxis exists after subcutaneous injection in rare patients with a positive oral challenge to 5 to 10 mg of sulfite.

Parabens (including methyl-, ethyl-, propyl-, and butylparaben) are used widely in pharmaceutical products as a biocidal agent. Most allergic reactions to parabens are observed after topical exposure. Delayed hypersensitivity contact dermatitis occurs more often in individuals with preexisting dermatitis. Immediate hypersensitivity after parenteral administration is rare. Although these agents are chemically related to benzoic acid and p-aminobenzoic acid, the evidence for cross-sensitivity is lacking.

**Cancer Chemotherapy Agents**

Chemotherapy agents are implicated in hypersensitivity reactions in 5% to 15% of patients who receive them. Up to 65% of patients receiving 1-asparaginase experience immediate hypersensitivity reactions such as urticaria and anaphylaxis.

The combination regimen of paclitaxel (or docetaxel) and carboplatin is frequently responsible for producing hypersensitivity reactions. Each agent precipitates a distinct reaction, allowing for differentiation between causative factors. Hypersensitivity or allergy-like reactions have been observed with paclitaxel and docetaxel in as many as 34% of patients. The reaction typically occurs within minutes after initiation of the first or second dose, suggesting a non–IgE-mediated mechanism. Both the vehicles of the taxanes (polyoxyethylated castor oil for paclitaxel; polysorbate 80 for docetaxel) and the taxanes themselves have been implicated as the cause of the reactions. A cross-reactive risk of 90% (nine of 10 patients) between paclitaxel and docetaxel provides further evidence that the reaction is most likely attributed to the taxane moiety. Severe reactions are characterized by dyspnea, bronchospasm, urticaria, and hypo- or hypertension. Minor reactions include flushing and rashes. In patients receiving a 3-hour infusion, the incidence of severe reactions is reduced to 1.3%, and the incidence of minor reactions is 42%. To reduce the risk of hypersensitivity reaction, patients are routinely premedicated with corticosteroids and H₂ and H₁-receptor antagonists. A protein-bound formulation of paclitaxel (Abraxane®) devoid of the castor oil vehicle is available, avoiding some but not all reactions.

Hypersensitivity to platinum-containing agents is delayed, developing after six or more courses of carboplatin, cisplatin, or oxaliplatin. The reaction rates differ depending on the platinum agent with reported frequencies of 5% to 20% with cisplatin, 9% to 27% with carboplatin, and 10% to 19% with oxaliplatin. Reactions
Biologics

Biologic agents (e.g., monoclonal antibodies, fusion proteins, recombinant proteins) are derived from living sources such as yeast, bacteria, animal cells, or mammalian cells. Unlike nonbiologic agents, these large proteins can serve as complete antigens. Examples include recombinant insulin, erythropoietin, interferon-β, human growth hormone, infliximab, cetuximab, rituximab, and omalizumab. Immunoologic reactions to these agents range from minor infusion or injection-site reactions to anaphylaxis. Depending on the agent, reactions can occur on first or subsequent exposure, and the timing may be within 4 hours of drug administration or up to 14 days after an infusion.

Factors influencing the antigenicity of biologic agents are patient specific (e.g., atopy, congenital protein deficiency), production related (e.g., presence of contaminants or stabilizing agents, degree of protein glycosylation, presence of nonhuman protein sequences, storage temperature), and administration related (e.g., route of administration, frequency of use, concurrent immunosuppressant use). Of the monoclonal antibodies, reactions are most frequently observed with the murine-derived agents (0% human) and chimeric agents (75% human) as opposed to the humanized (>90% human) and human (100% human) agents. Some immune reactions to biologic agents result from the development of neutralizing antibodies that can prevent the protein from exerting its intended effect. Neutralizing antibodies have been shown to mediate reactions to interferon-β and β, infliximab, natalizumab, recombinant factor VIII, and recombinant factor IX. Anti-infliximab antibodies, which occur in up to 60% of treated patients, are associated with higher frequency of infusion reactions and decreased therapeutic effect. Concomitant administration of immunosuppressive agents such as prednisone or low-dose methotrexate has been shown to decrease the incidence of antibody formation to infliximab.

Delayed onset anaphylaxis, ranging from minutes to days postinjection, has been reported with omalizumab, a humanized monoclonal antibody targeted against IgE. Omalizumab-treated patients require observation for 2 hours after the first 3 injections and for 30 minutes after subsequent injections. Patients are advised to carry an epinephrine autoinjector during and for 24 hours after drug administration. Risk factors for this adverse event have not been identified. Inclusion of polysorbate 80 as a stabilizing agent in the formulation, and an alteration in the protein sequence via glycosylation, may influence the immunogenicity of omalizumab.

Management of allergic or allergic-like reactions to biologic agents varies based on the culprit agent and the severity and nature of the reaction. Immediate management with epinephrine and permanent discontinuation of the drug may be warranted (e.g., omalizumab-induced anaphylaxis). Depending on the biologic agent, reactions may be managed by decreasing the infusion rate or lessened by pretreating with antihistamines or corticosteroids or administering concomitant steroid therapy. Desensitization protocols for infliximab, cetuximab, rituximab, and transtuzumab have also been described.

Anaphylaxis

Anaphylaxis requires prompt treatment to minimize the risk of serious morbidity or death. On presentation, attention should be given first to stopping the likely offending agent, if possible, and restoring respiratory and cardiovascular function. A protocol developed by the Joint Task Force on Practice Parameters for Allergy and Immunology for treatment of anaphylaxis is presented in eTable 22-3. Epinephrine is the drug of first choice, although it is underused and often dosed suboptimally for this indication. It should be administered as primary treatment to counteract bronchoconstriction and peripheral vasodilation leading to hypotension. At recommended doses, epinephrine also enhances coronary blood flow. The recommended administration technique is intramuscularly in the lateral aspect of the thigh. If blood pressure is not restored by epinephrine, crystalloid IV fluids should be administered to restore intravascular volume. Typically, 1 L of 0.9% sodium chloride is administered over 5 to 10 minutes. This can be repeated if the patient is still believed to be volume depleted. A maintenance IV fluid then is initiated. IV fluids should be given early in the course of treatment in an attempt to prevent shock. An immediate priority is to establish and maintain an airway by the use of endotracheal intubation if necessary. When a patient with anaphylaxis is hypotensive, vasopressors may be needed in addition to crystalloids. Norepinephrine is the vasoconstrictor agent of choice for treatment of anaphylactic shock, although dopamine also may be useful. Patients in shock should remain supine with raised legs.

Other agents may be required for treatment of anaphylactic reactions. Corticosteroids (hydrocortisone sodium succinate IV) should never be given in place of or before epinephrine. Their onset of action is delayed, and their role is to reduce the risk of late-phase “biphasic” reactions. In patients treated chronically with...
Skin Testing and Drug Provocation Testing

Identification of patients at high risk for allergic drug reactions requires careful history taking with attention to the specific agent to which the patient reacted, a complete description of the reaction, and the time since last exposure to the culprit drug. The importance of accurate and complete history taking cannot be overstated. Although skin and oral provocation testing are used to assess reactive risk to some drugs, many of the testing procedures have not been validated. A drug provocation test (DPT) involves the controlled administration of a drug for the purpose of diagnosing an immune response. DPTs can be used to evaluate sensitivity to aspirin. When available, skin testing should be performed before a DPT because of the lesser risks incurred to the patient. For some drugs, skin testing can reliably demonstrate the presence of drug-specific IgE and predict a relatively high risk of immediate hypersensitivity reactions. Reliable skin test reagents are not available for most culprit drugs. Moreover, skin testing should not be performed in patients with history of severe mucocutaneous reactions (e.g., SJS, TEN) or other nonimmediate reactions (e.g., serum sickness, vasculitis, hepatitis).

Skin testing can reduce the uncertainty of penicillin sensitivity and should be performed in all patients who have a history of an immediate allergy and require treatment with a β-lactam antibiotic. Penicillin skin testing in advance of need for penicillin treatment in patients with a history of penicillin allergy does not appear to induce sensitization. Testing for the major penicillin determinant is accomplished with penicilloyl-polylysine (PPL; Pre-Pen), a product recently reintroduced in the United States. Ideally, skin testing should be performed with both the major and minor determinants. Of the minor determinants, only penicillin G is commercially available in the United States, and it should be used at a concentration of 10,000 units/mL with PPL in skin testing. If left in solution to “age,” penicillin G will not spontaneously degrade to form the other minor determinants, penilloate and penicilloate. Similar reaction rates to oral penicillin challenges have been shown in patients with skin test negativity to PPL plus penicillin G compared with those with skin test negativity to the full set of major and minor determinants. Skin testing with the major and minor determinants has been shown to facilitate the safe use of penicillin in up to 90% of patients with a history of immediate penicillin allergy. Fewer than 1% of patients with a negative history and up to 72% of patients with a convincing positive history of penicillin allergy have skin test positive reactivity. In patients who report a history of penicillin allergy but are skin test negative, the risk of resensitization (i.e., conversion to a positive skin test result) after a course of penicillin ranges from 1% to 28%. The procedure for performing penicillin skin testing is given in eTable 22-4. In Europe, skin testing can be accomplished with a kit containing both the major and minor determinant mixture (Diater Labs, Madrid, Spain).

A negative penicillin skin test result indicates that the risk of life-threatening immediate reactions is extremely low with administration of penicillin or other β-lactams. Such patients are candidates for treatment with full therapeutic doses of a penicillin or a related β-lactam. Certain types of patients (e.g., those with dermatographism, taking antihistamines) may be unsuitable for skin testing because a false-positive or false-negative test may result. To prevent interference with skin testing, antihistamines should be discontinued at least 1 week before skin testing. Penicillin is the only drug for which the predictive value of skin testing has been well established. Although the negative predictive value is high, penicillin skin testing with the major and minor determinants does not identify patients who are at risk for unique side chain–mediated reactions to β-lactams (e.g., third-generation cephalosporins, piperacillin). Dilute concentrations of amoxicillin and piperacillin have been used to skin test for side chain–mediated reactions. The value of skin testing to predict the risk of allergic reactions to other antibiotics (e.g., sulfonamides, tetracyclines, fluoroquinolones) is largely unknown.

Skin testing is used to identify patients at risk for hypersensitivity reactions to carboplatin. The negative predictive value of intradermal skin testing with carboplatin has been shown to be 98% to 99% in patients who have received a number of treatment courses.

Induction of Drug Tolerance and Desensitization

For some patients with history of an immediate reaction to a drug, no reasonable alternatives exist, and the inciting drug or a related compound may be necessary for treatment of an underlying condition (e.g., infection). In this situation, the temporary...
induction of drug tolerance is indicated. In the past, the term “desensitization” was used to describe the procedure of temporarily acquiring drug tolerance, whether the underlying mechanism of intolerance was immunologically mediated or not. Experts in drug allergy currently recommend that the phrase “induction of drug tolerance” be used in place of “desensitization” to globally describe procedures used to modify a patient’s response to a drug and temporarily allow safe drug therapy. Induction of drug tolerance can involve a variety of drug mechanisms, including IgE-mediated immune mechanisms, non-IgE mechanisms, pharmacologic mechanisms, and undefined mechanisms (eTable 22-5). Regardless of the underlying mechanism, all procedures used to induce drug tolerance involve a stepwise process of incremental dosing of the inciting drug or a related compound. Desensitization, a form of inducing drug tolerance specifically refers to the process in which the mast cells are rendered less responsive to degranulation. This term should be used when the underlying mechanism of drug intolerance is believed to be IgE mediated (i.e., anaphylaxis to penicillin). Immediate reactions most amenable to desensitization include dermatologic (e.g., flushing, pruritus, urticaria, angioedema), upper and lower respiratory tract (e.g., sneezing, dyspnea, wheezing), gastrointestinal (e.g., abdominal pain, nausea and vomiting), and cardiovascular (e.g., hypotension). Procedures to induce drug tolerance should not be used in patients with history of severe non–IgE reactions to a drug such as DRESS, SJS, TEN, exfoliative dermatitis, hemolytic anemia, or hepatitis.

All procedures to induce drug tolerance should be performed by a physician experienced in the risks and management of severe allergic reactions in a hospital setting with resuscitation equipment available. The potential risks and benefits should be discussed with the patient. The procedures differ in starting dose, number of steps in the dosing process, and frequency of drug dosing. The specific procedure should be chosen based on an analysis of the patient’s history of the reaction and with consideration to the specific inciting drug and the suspected underlying mechanism of drug intolerance (i.e., IgE mechanism versus non-IgE mechanism vs. pharmacologic mechanism). The starting dose for a desensitization procedure is typically one in 10,000 of the final therapeutic dose and the procedure can be completed within 4 to 12 hours. A rapid 12-step desensitization protocol has been described and tested in patients with both IgE- and non-IgE-mediated reactions to antibiotics, platinum-containing chemotherapeutic agents, taxane chemotherapy agents, and monoclonal antibodies. The 12-step method starts with a 1:1,000 dilution of the final dose of the inciting drug. Incrementally increased doses are administered every 15 minutes using three-10-fold diluted solutions. This method has been tested in nearly 800 patients, including patients with cystic fibrosis and allergy to antibiotics. In high-risk patients, desensitization is achieved with either a 16- or a 20-step protocol.

In the case of penicillin or β-lactam allergy, desensitization should be performed with the specific β-lactam antibiotic that will

eTable 22-4

Procedure for Performing Penicillin Skin Testing

A. Percutaneous (Prick) Skin Testing (Using a 22- to 28-Gauge Needle)

<table>
<thead>
<tr>
<th>Materials</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Pen 6 × 10⁶ M</td>
<td>1 drop</td>
</tr>
<tr>
<td>Penicillin G 10,000 units/mL</td>
<td>1 drop</td>
</tr>
<tr>
<td>β-Lactam drug (amoxicillin) 2 mg/mL</td>
<td>1 drop</td>
</tr>
<tr>
<td>Saline control</td>
<td>1 drop</td>
</tr>
<tr>
<td>Histamine control (1 mg/mL)</td>
<td>1 drop</td>
</tr>
</tbody>
</table>

1. Place a drop of each test material on the volar surface of the forearm.
2. Prick the skin with the needle to make a single shallow puncture of the epidermis through the drop.
3. Interpret skin responses during the next 15 minutes. Observe for a wheal or erythema and the occurrence of itching.
4. A wheal in diameter of 5 mm or greater surrounding the puncture site is considered a positive test result.
5. Wipe off the solution near the puncture site.
6. If the prick test result is negative or equivocal (wheal <5 mm in diameter with no itching or erythema), proceed to the intradermal test.
7. If the histamine control is nonreactive, the test is considered uninterpretable. Ensure no interference by antihistamines.

B. Intradermal Skin Testing

<table>
<thead>
<tr>
<th>Materials</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Pen 6 × 10⁶ M</td>
<td>0.02 mL</td>
</tr>
<tr>
<td>Penicillin G 10,000 units/mL</td>
<td>0.02 mL</td>
</tr>
<tr>
<td>β-Lactam drug (amoxicillin) 2 mg/mL</td>
<td>0.02 mL</td>
</tr>
<tr>
<td>Saline control</td>
<td>0.02 mL</td>
</tr>
<tr>
<td>Histamine control (0.1 mg/mL)</td>
<td>0.02 mL</td>
</tr>
</tbody>
</table>

1. Inject 0.02–0.03 mL of Pre-Pen intradermally (amount sufficient to produce a small bleb of approximately 3 mm in diameter) in duplicate at least 2 cm apart.
2. Inject 0.02–0.03 mL of the other materials at least 5 cm from the Pre-Pen sites.
3. Interpret skin responses after 20 minutes.
4. A wheal in diameter of 5 mm or greater surrounding the puncture site is considered a positive test result. An ambiguous response is a wheal only slightly larger than the original bleb or discordance between the duplicates. The control site should show no increase in the original bleb.
5. If the histamine control is nonreactive, the test is considered uninterpretable. Antihistamines may blunt the response and cause false-negative results.

Using a 0.5- to 1-cc syringe with a 3/8- to 5/8-inch long, 26- to 30-gauge short-bevel needle


**Table 22-5**

<table>
<thead>
<tr>
<th>Underlying Mechanism</th>
<th>Initial Dose</th>
<th>Duration of Protocol</th>
<th>Potential Outcome of Process</th>
<th>Duration of Induced Tolerance</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic IgE (desensitization)</td>
<td>Micrograms</td>
<td>Hours</td>
<td>Desensitization; render mast cells less responsive to degranulation</td>
<td>Temporary</td>
<td>β-Lactam antibiotics; taxanes</td>
</tr>
<tr>
<td>Immunologic non-IgE</td>
<td>Milligrams</td>
<td>Hours to days (e.g., 6 hours to 10 days)</td>
<td>Not known</td>
<td>Temporary</td>
<td>Delayed cutaneous reactions to trimethoprim–sulfamethoxazole in HIV-infected individuals</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Milligrams</td>
<td>Hours to days (e.g., 2 hours to 5 days)</td>
<td>Cautious induction of a reaction followed by a shift in a metabolic process</td>
<td>Temporary</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Undefined</td>
<td>Micrograms to milligrams</td>
<td>Prolonged; days to weeks</td>
<td>Not known</td>
<td>Temporary</td>
<td>Isolated cutaneous reactions to allopurinol</td>
</tr>
</tbody>
</table>

be administered for treatment of the patient’s infection. Before initiating the protocol, the patient should be stabilized and fluid, pulmonary, and cardiovascular function optimized. Premedications (antihistamines or corticosteroids) have not been routinely advised because these agents may mask the early signs of acute reactions and do not reliably reduce the severity of acute reactions. However, some recently described desensitization regimens include premedication with single doses of diphenhydramine and famotidine. About one third of patients who have undergone desensitization to a penicillin will experience mild, transient allergic reactions either during the desensitization procedure or during penicillin therapy. Patients who can take oral medication should undergo desensitization with oral drug. After the desensitization protocol is begun, it should not be interrupted except for severe reactions. Antihistamines or epinephrine can be administered to treat reactions. In addition, if the patient completes the desensitization regimen and then undergoes full-dose treatment, a lapse between doses of as few as 24 hours can allow for reemergence of sensitivity. Protocols for oral penicillin and IV cephalosporin desensitization are listed in eTables 22-6 and 22-7, respectively. Protocols for desensitization with other β-lactam antibiotics are also available. Most reactions to trimethoprim–sulfamethoxazole in HIV-infected patients are considered to be non–IgE-mediated, and a number of protocols to induce tolerance to trimethoprim–sulfamethoxazole have been described. These regimens have not been compared in controlled clinical trials; thus, there is no alternative drug is equally effective, and a reliable skin testing method is not available. A classic example is the slow introduction of a cephalosporin in a patient with a history of reacting to another cephalosporin with a dissimilar R1 side chain. Aspirin desensitization protocols have been described for the slow introduction of furosemide in a patient with heart failure and history of sulfonamide allergy. Challenge dosing is not recommended when there is history of a severe drug allergy (e.g., anaphylaxis, SJS, TEN). Premedications should not be used because they may mask signs of an early breakthrough allergic reaction. Compared with drug tolerance should not be attempted in any patient with history of an exfoliative reaction to trimethoprim–sulfamethoxazole.

Both rapid (over less than 4 hours) and traditional desensitization protocols are available for aspirin and clopidogrel. Aspirin desensitization is more effective in patients with history of aspirin-induced asthma as compared with those with angioedema/urticarial presentation.66

### Graded Challenge

Also known as test dosing, a graded drug challenge involves the cautious introduction of a drug when the risk of a reaction is deemed to be low. A graded drug challenge is an alternative to the induction of drug tolerance, and it does not modify the immune or nonimmune response to the drug. Instead, graded challenge is used when the risk of a severe reaction to a drug on reexposure is low, no alternative drug is equally effective, and a reliable skin testing method is not available. A classic example is the slow introduction of a cephalosporin in a patient with a history of reacting to another cephalosporin with a dissimilar R1 side chain. Graded challenge protocols have been described for the slow introduction of furosemide in a patient with heart failure and history of sulfonamide allergy. Challenge dosing is not recommended when there is history of a severe drug allergy (e.g., anaphylaxis, SJS, TEN). Premedications should not be used because they may mask signs of an early breakthrough allergic reaction. Compared with drug tolerance procedures, graded challenges involve higher starting doses and fewer steps in the dosing process. The starting dose is typically 1/10th to 1/100th of the final treatment dose, and the oral route of drug administration is preferred to limit the risk of a severe reaction. If no reaction occurs to the initial dose, the dose may be increased in two- to fivefold increments and administered every 30 to 60 minutes until the full therapeutic dose is achieved. There is no standard protocol for graded challenge dosing; a therapeutic dose may be achieved over a matter of hours or days. Because of the risk of breakthrough allergic reactions, graded challenges should be performed in monitored settings.
ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>antigen-presenting cell</td>
</tr>
<tr>
<td>DRESS</td>
<td>drug rash with eosinophilia and systemic symptoms</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>IgE</td>
<td>immunoglobulin E</td>
</tr>
<tr>
<td>LT</td>
<td>leukotriene</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal antiinflammatory drug</td>
</tr>
<tr>
<td>PAF</td>
<td>platelet-activating factor</td>
</tr>
<tr>
<td>PG</td>
<td>prostaglandin</td>
</tr>
<tr>
<td>PPD</td>
<td>purified protein derivative</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens Johnson syndrome</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>TEN</td>
<td>toxic epidermal necrolysis</td>
</tr>
</tbody>
</table>

REFERENCES


