Chapter e108: Drug Allergy

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 4, Drug Allergy.

KEY CONCEPTS

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1. Drug allergy accounts for 6% to 10% of adverse drug reactions to medications. Most of these immune events are mediated by IgE or activated T cells.

2. Three theories—the prohapten/hapten concept, the p-i concept, and the altered repertoire model—have been proposed to explain how drugs stimulate an immune response.

3. Anaphylaxis is an acute, life-threatening allergic reaction involving multiple organ systems that generally begins within 1 hour but almost always within 2 hours after exposure to the inciting allergen. Anaphylaxis requires prompt treatment to restore respiratory and cardiovascular functions. Epinephrine is the drug of first choice and should be administered to counteract bronchoconstriction and peripheral vasodilation. Intravenous fluids should be administered aggressively to restore intravascular volume.

4. Factors that influence the likelihood of drug allergy are the drug's chemical composition, whether the drug contains proteins of nonhuman origin, the route of drug administration, and the individual's sensitivity as determined by genetics or environmental factors. For some drugs, the presence of specific human leukocyte antigen alleles is a risk factor for allergic skin reactions.

5. Ideally, cephalosporins should be avoided in patients with a history of an immediate penicillin allergy, but the risk of an allergic cross-response to a cephalosporin, even in a person with a positive penicillin skin test result, is low. Similarities in the R1 side chain of the agents should be considered when assessing the risk of β-lactam cross-reactivity.

6. 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 sulfonamide antibiotics and nonantibiotics.

7. In susceptible patients, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can produce two general types of reactions, urticaria/angioedema and rhinosinusitis/asthma. Most patients with aspirin sensitivity who require aspirin for the prevention of cardiovascular disease can safely undergo and complete a graded challenge or induction of drug tolerance (previously known as desensitization).

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

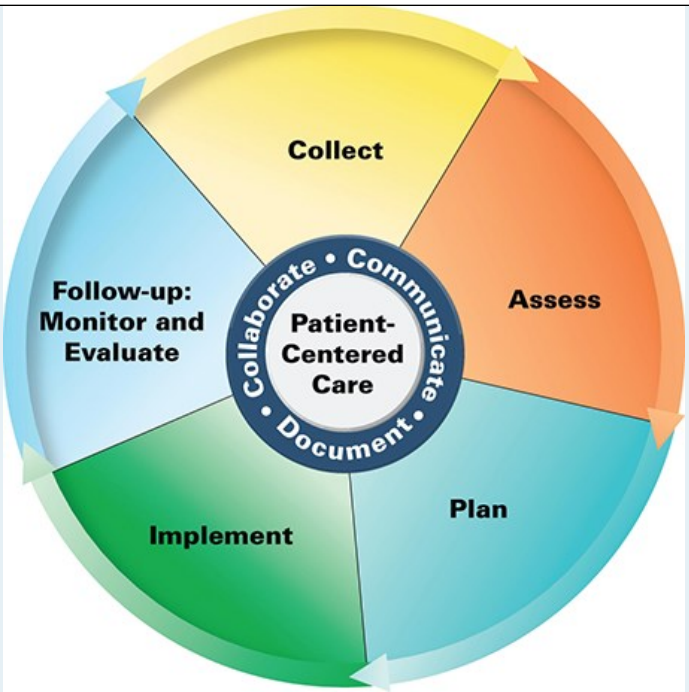
9. The basic principles of management of allergic reactions to drugs or biologic agents include (a) discontinuation of the medication or offending agent when possible; (b) treatment of the adverse clinical signs and symptoms; and (c) substitution, if necessary, of another agent.

10. The penicillin skin test is the reference standard for evaluating the risk of immediate hypersensitivity to penicillin. Skin testing can demonstrate the presence of penicillin-specific immunoglobulin E, if present, and predict immediate reactions. Skin testing is not indicated for non-IgE-mediated reactions.

11. When an allergenic drug is considered medically necessary and no therapeutic alternative or reliable skin testing method exists, three options are available to the clinician: induction of drug tolerance, graded dose challenge, or rechallenge.

PATIENT CARE PROCESS

Patient Care Process for Drug Allergy



Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Medication history (eg, prescription, OTC, and complementary medications such as herbals)
- Allergy history (eg, medications, foods, environmental exposures with descriptions of each reaction)
- Subjective findings of the allergic reaction (eg, shortness of breath, itching, feeling of flushing, lip-tingling, nausea, lightheadedness)
- Objective data
  - BP, HR, RR
  - Labs (eg, serum electrolytes, serum tryptase, Scr, BUN, LFTs)
  - Observation of the rash, if applicable (eg, type of lesion(s), distribution of lesions, presence or absence of oral or genital ulcerations, presence or absence of bullae)

Assess

- Timing of the reaction relative to the initiation of each of the patient's current medications
- Likelihood of cross-reactivity relative to documented allergy history (eg, previously documented allergy to penicillin in a patient receiving a non-penicillin beta-lactam antibiotic)
- Presence of risk factors (see the "Factors Related to the Risk or Severity of Allergic Drug Reactions" section)
- Coadministration of medications that may increase the risk of an allergic reaction when used in combination (eg, lamotrigine and valproate)
- Severity of the reaction (eg, localized rash vs a systemic reaction involving one or more organs)
- Medications that may interfere with the identification or treatment of the allergic reaction (eg, chronic use of antihistamines when skin testing may be warranted; chronic beta-blocker use in a patient with anaphylaxis)

- Need for drug desensitization or induction of drug tolerance (see Table e108-4)

Plan*

- Management of the allergic reaction (see Table e108-2 if patient presents with anaphylaxis)
- Management of the condition for which the allergic medication was indicated (eg, treatment of the underlying infection for which the allergenic antibiotic was indicated)
- Patient education (eg, recognition of likely allergenic medication, risk of cross-reactivity with related agents, use of epinephrine self-injectors, if applicable)
- Referrals to other providers when appropriate (eg, allergist)

Implement*

- Provide education to the patient and healthcare providers on an effective management plan
- Drug desensitization or graded challenge protocols, if appropriate
- Drug skin testing, if appropriate

Follow-up: Monitor and Evaluate

- Assess responsiveness to the management plan and revise the plan, if applicable
- Identify most likely causative medication based on responsiveness to drug discontinuation and treatment
- Document allergic reaction and update drug allergy information in medical record
- Reinforce patient education on allergic medication, type of reaction, potential cross-reactive medications, and self-management of reaction (if applicable)

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Listen to the podcast series entitled “The Itch: An SIDP Podcast Miniseries on Penicillin Allergy” (broadcast on June 26, 2019): https://sidp.org/podcasts/ (or https://sidp.pinecast.co/ and click “Back in time“). These podcasts led by drug allergy experts in the pharmacy field discuss various topics including myth-busting with regards to penicillin allergies (#1), how to successfully implement penicillin skin testing (#2), and finally “lessons learned from the front-line” (#3) to help those interested in developing a comprehensive penicillin allergy assessment and skin test program.

INTRODUCTION

Drug allergy is defined by the World Health Organization as an immunologically mediated hypersensitivity reaction to a drug in a sensitized person. This can be further classified as immediate or delayed based on the time of onset in symptoms and the probable immunologic mechanism.[1] The hyper-response of the immune system to the antigenic drug leads to host tissue damage manifesting as an organ-specific or generalized systemic reaction. The International CONsensus (ICON) on Drug Allergy has proposed that the term *drug allergy* be used for drug reactions in which a definite immune

mechanism (either antibody- or T-cell-mediated) has been proven. *Drug hypersensitivity reaction (DHR)* is the term that should be used for more heterogeneous reactions that clinically resemble an allergy but may or may not be mediated via an immune response.[2] Examples of drug allergies are anaphylaxis from β-lactam antibiotics, halothane hepatitis, Stevens–Johnson syndrome (SJS) from carbamazepine, heparin-induced thrombocytopenia, allopurinol hypersensitivity syndrome, and serum sickness from phenytoin. Examples of DHRs are isolated urticaria after radiocontrast media, aspirin-induced asthma, opiate-related pruritus, and flushing after vancomycin infusion.[3]

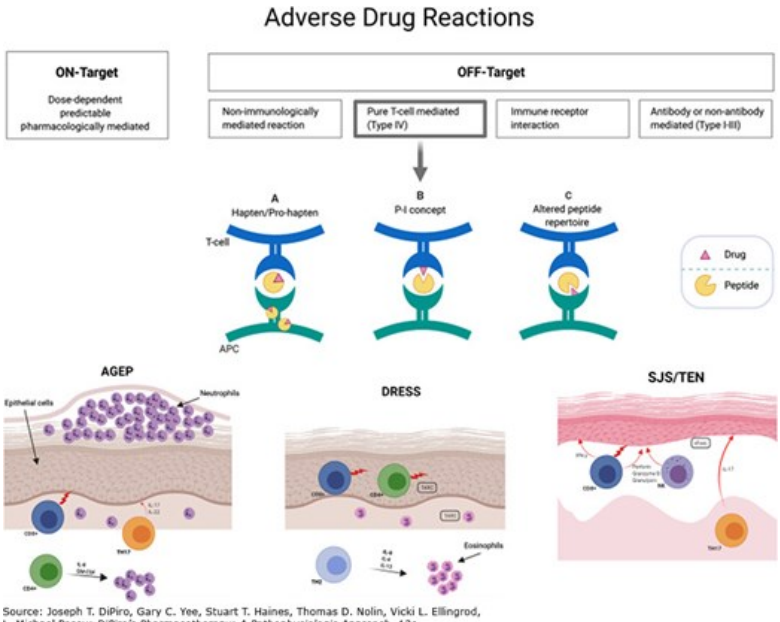
Immune-mediated reactions account for 6% to 10% of all adverse drug reactions and up to 15% when the more heterogenous DHRs are included.[4,5] The true frequency of drug allergies is difficult to determine because many reactions may not be reported, and others may be difficult to distinguish from nonimmune DHRs. Dermatologic reactions represent the most frequently recognized and reported form of drug allergy.

MECHANISMS OF ALLERGIC DRUG REACTIONS

Drugs can cause allergic 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.[5] Several theories or concepts have been proposed to describe the initiation of an immune response to a drug (see Fig. e108-1).

FIGURE e108-1

T-cell-mediated delayed hypersensitivity mechanistic hypotheses. Three non-mutually exclusive hypotheses have been described to clarify drug-triggered T-cell activation: (**A**) The hapten/prohapten model describes how an antigen (drug) that covalently binds to a self-peptide is intracellularly processed and then presented by MHC to T cells. Alt Text: The illustration shows an antigen presenting cell accepting a protein-bound antigen from a T cell. (**B**) The p-i concept (pharmacological interaction with an immune receptor) is based upon non-covalent binding of antigens to HLA or TCR without immune processing. Alt Text: The illustration shows an antigen bound directly to a T cell which is then being presented to an antigen presenting cell. (**C**) The altered repertoire model indicates that drugs can occupy positions in the peptide-binding groove of the MHC, altering the binding cleft and the specificity of MHC binding. Alt Text: The illustration shows an antigen detected by the antigen presenting cell... HLA, human leukocyte antigens; MHC, major histocompatibility complex; TCR, T-cell receptor. *(Reprinted, with permission, from Copaescu A, Gibson A, Li Y, et al. An updated review of the diagnostic methods in delayed drug hypersensitivity. Front Pharmacol, 2021;11:573–573.)*



Prohapten/Hapten Concept

This concept is based on the assumption that small-molecular-weight molecules (less than 10 kDa) cannot serve as antigens on their own. Except for

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 is recognized as foreign by antigen presenting cells (APCs) such as macrophages and dendritic cells. The drug's *antigenic determinant*, the drug portion that is immunogenic, is subsequently processed by antigen presenting cells and presented on major histocompatibility complex (MHC) molecules for recognition by T cells, thereby initiating the immune response. Drugs of low molecular weight that combine with a carrier macromolecule for processing by antigen presenting cells are referred to as *haptens* or *incomplete antigens*.[2,7,8] Penicillin G (356 Da) is an example of a drug that binds covalently to serum proteins through amide or disulfide linkages thereby forming a complete antigen. For some drugs, such as sulfonamides, the parent compound must be converted to a metabolite before it can combine with the macromolecule. Drugs that are chemically inert and rely on conversion to a metabolite with an antigenic determinant are referred to as *prohaptens*.[2,7,8] Some macromolecular drugs such as insulin are *complete antigens* because they are large enough to initiate an immune response without binding to another protein.

p-i Concept

Some small-molecular-weight drugs may cause an immune response through a nonhapten pathway.[7–9] Known as the p-i concept, this pathway involves a direct pharmacologic interaction of drugs with immune receptors that do not require the initial binding of the drug to a carrier protein or processing by antigen presenting cells.[7–9] Based on this theory, drugs can bind to T-cell receptors in a reversible manner, similar to the binding of a ligand to a receptor.[7] It is unknown if the drug binds initially to the T-cell receptor or whether the drug binds first to the MHC molecule on the antigen presenting cell, thereby signaling T-cell activation. The p-i concept is most applicable to the initiation of delayed T-cell-mediated reactions as compared to hapten-initiated immediate immunoglobulin E (IgE) reactions.[7–9]

Altered Repertoire Model

Human leukocyte antigens (HLA) are a set of genetically linked proteins that present antigenic peptides to T cells during an immune response.[10] In the altered repertoire model, a drug positions itself within the HLA peptide-binding groove, thus altering the repertoire and specificity of self-peptide ligands that are bound and presented.[11] Changes in the HLA peptide composition are perceived as foreign which consequently triggers an immune response. This model has been established for abacavir hypersensitivity associated with *HLA-B*5701* polymorphisms and may provide an alternative mechanistic explanation for other HLA-associated drug toxicities.[6,10,11]

EFFECTORS 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. Although most immunoglobulin isotypes have been implicated in drug allergy, reactions are usually mediated by IgE and activated T cells. IgE bound to basophils or mast cells mediates immediate reactions. Antibodies to other immunoglobulins, such as IgG or IgM, also may be involved in drug allergy, 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 DHRs described by Gell and Coombs (see Table e108-1).[2,5,12]

TABLE e108-1

Classification of Allergic Drug Reactions

Type	Descriptor	Characteristics	Typical Onset	Clinical Manifestations
I	Immediate (IgE mediated)	Allergen binds to IgE on basophils or mast cells, resulting in release of inflammatory mediators	Within 1 hour (may be within 1-6 hours)	Anaphylaxis, angioedema, hives, itching, wheezing, hypotension
II	Delayed; cytotoxic	Cell destruction occurs because of cell-associated antigen that initiates cytolysis by antigen-specific antibody (IgG) and complement. Most often involves blood elements	Typically >72 hours to weeks	Hemolytic anemia, thrombocytopenia
III	Delayed; immune complex	Antigen–antibody (IgG or IgM) complexes form and deposit on blood vessel walls and activate complement, which results in a serum sickness-like syndrome or vasculitis	>72 hours to weeks	Serum sickness, fever, rash, lymphadenopathy, joint pain
IV	Delayed; T cell–mediated	Antigens cause activation of T lymphocytes, which release cytokines and recruit effector cells	>72 hours	
	IVa	Th1 cells and interferon-γ, monocytes, and eosinophils respond to the antigen	1-21 days	Tuberculin reaction, contact dermatitis
	IVb	Th2 cells, interleukin-4, and interleukin-5 respond to the antigen	1-6 weeks	Maculopapular rashes with eosinophilia
	IVc	Cytotoxic T cells, perforin, granzyme B, FasL respond to the antigen	4-28 days	Bullous exanthems; fixed drug eruptions
	IVd	T cells and interleukin-8 respond to the antigen	>72 hours	Acute generalized exanthematous pustulosis

Cellular Elements

A variety of cells are involved in drug allergies. The antigen presenting cells, which include macrophages, dendritic cells, and cutaneous Langerhans cells, process the antigenic drug for subsequent recognition by T and B lymphocytes. Basophils and mast cells are instrumental in the development of immediate reactions, whereas eosinophils are recruited in both immediate and nonimmediate reactions. Platelets and vascular endothelial cells are important because they also can release several inflammatory mediators.[13] Most cells of the body, including nerve cells, can become involved directly or indirectly in drug allergy.

Mediators of Allergic Reactions

The release of several preformed, pharmacologically active chemical mediators (eg, 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 (eg, 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.[14] After the release of these granules following antigen cross linking, 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 muscles, and hypersecretion of mucous glands. Four classes of histamine receptors (H_1-H_4) are present in varying degrees in organs and tissues. H_1 receptors are most prominent in blood vessels and bronchial and intestinal smooth muscles.

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. Platelet-activating factor enhances vascular permeability and can cause pain, pruritus, and erythema.

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, LTC_4, LTD_4, and LTE_4, 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, LTB_4, is a potent chemoattractant, particularly for neutrophils. It is also produced by neutrophils, macrophages, and monocytes.

PGs and thromboxanes are metabolites of arachidonic acid produced through the cyclooxygenase (COX) pathway. Some PGs have vasoconstrictive or bronchodilatory properties, while others are vasodilatory or bronchoconstrictive. The major PG product of mast cells is PGD_2. It is a potent inhibitor of platelet aggregation and 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 allergy 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 ALLERGIC DRUG REACTIONS

Immunologic drug reactions are most commonly classified by the system described by Gell and Coombs in 1968.[2,5,12] This system classifies the varied reactions based on the effector cells involved and the timing and clinical presentation of the immune event. The Gell and Coombs classification was developed before our understanding of the varied roles of T cells in the immune response. The original classification system has been adapted to better represent our current understanding of drug allergy (see Table e108-1).[2,5,12]

The ICON expert panel on drug allergy has recommended that drug allergies be classified as *immediate* or *nonimmediate* based on the onset of the reaction. *Immediate* reactions are those culminating in the production of an IgE-mediated response. Immediate reactions typically occur within 1 hour of reexposure to an immunogenic drug and manifest as angioedema, bronchospasm, anaphylaxis, or anaphylactic shock. *Nonimmediate* or delayed drug allergies include a broader category of events; they may occur at least 1 hour after initial drug exposure and up to weeks or months after initial exposure. Nonimmediate reactions are typically mediated by activated T cells and manifest as maculopapular exanthems or delayed urticaria. As noted by the expert panel, this classification system has limitations because the route of drug administration and the presence of immune cofactors (eg, viruses, drug interactions affecting drug metabolism) can influence the onset or progression of the immune reaction.[2]

Immediate (Type I) Reaction

Type I immediate reactions require the presence of IgE specific for the drug's (or drug metabolite's) antigenic determinant. After presentation on MHC molecules and recognition by T cells, the drug immunogen stimulates plasma cells to produce IgE on initial exposure. IgE then binds to basophils and mast cells through high-affinity FcεRI receptors. On repeat exposure to the drug, memory B cells allow for early recognition of the immunogen. Two or more IgE molecules on the basophil or mast cell surface bind to one multivalent antigen molecule (referred to as *cross-linking*), 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 results in an immediate reaction that may be limited to single organs, typically in the nasal mucosa (rhinitis), respiratory tract (acute asthma), skin (urticaria), or gastrointestinal tract, or they can involve multiple organs simultaneously, termed *anaphylaxis*.

Delayed Type II Reaction

Type II allergic reactions are relatively uncommon and involve the destruction of host cells (usually blood cells) through cytotoxic antibodies by one of two mechanisms. First, the drug binds to the cell (eg, platelet or red blood cell) as a hapten. Antibodies (IgG or IgM) are produced that are specific for the bound drug or a component of the cell surface altered by the drug. The antigen-antibody binding initiates a cytolytic reaction. Cell destruction 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 type II 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, cephalosporins, and sulfonamides.

Delayed Type III Reactions

Type III allergic reactions occur uncommonly and are caused by antigen–antibody complexes that are formed in the blood. The complexes form with drug immunogen 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 may be produced. These substances cause the influx of neutrophils and result in the release of several toxic substances from the neutrophil (eg, 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 the local formation of insoluble antigen–antibody complexes, complement activation with the release of C3a and C5a collectively referred to as *anaphylatoxins,* mast cell degranulation, and influx of polymorphonuclear cells. Both vasculitis and serum sickness are often the result of Type III reactions.

Delayed Type IV Reactions

Type IV reactions typically manifest as dermatologic events mediated by activated T cells (T helper cell or $CD4^+$; cytotoxic T cell or $CD8^+$).[7,9] Four subclasses of type IV reactions (IVa-IVd) have been described based on the responding T cell (eg, T helper type 1 cell, T helper type 2 cell, cytotoxic T cell), effector mechanism (eg, recruitment of macrophages, eosinophils, or neutrophils), and clinical manifestations (eg, contact dermatitis, bullous exanthems, maculopapular eruptions, pustular exanthems) (see Table e108-1).[2,7,9] 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, 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 and maculopapular rashes frequently result from a Type IV reaction.

Other Allergic Reactions

Not all drug allergies can be classified with the system described by Gell and Coombs because the precise immune drug mechanism may not be known.

In some cases, hepatic drug reactions (cholestatic or hepatocellular) and pulmonary reactions (eg, nitrofurantoin-associated interstitial pneumonitis) have been described as immune events. 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; maculopapular, morbilliform, or erythematous rashes; exfoliative dermatitis; photosensitivity reactions; or eczema. These reactions also may manifest as late-onset pruritus, urticaria, and angioedema.

Some serious cutaneous adverse reactions (SCARs) may be the result of immunologic reactions. SCARs include drug rash with eosinophilia and systemic symptoms (DRESS) and mucocutaneous disorders, SJS and toxic epidermal necrolysis (TEN) (see Fig. e108-1). Both SJS and TEN are purported to result from a T cell response leading to keratinocyte apoptosis. Cytotoxic T cells stimulated in response to the drug immunogen activate caspases, intracellular proteases that can cleave a key intracellular protein in the keratinocyte resulting in apoptosis.[15] The caspase cascade may be activated by two T-cell-mediated pathways: the Fas-FasL pathway and the perforin-granzyme pathway.[16] The blister fluid of patients with SJS/TEN has contained concentrations of FasL, perforin, and granzyme B that correlated with the severity of the events. Overexpression of tumor necrosis factor-β, IL-2, and IL-5 has also been seen in skin lesions of patients with SJS and TEN.

Drug Hypersensitivity Reactions

Based on the new terminology, DHRs include adverse drug reactions that clinically resemble drug allergy but have not yet been proven to be associated with an immune response. Various drugs can produce reactions that are clinically similar to drug allergy, both immediate and delayed in onset, but are not mediated by immune mechanisms. Drugs can cause the release of mast cell–derived and basophil-derived mediators by a pharmacologic or physical effect rather than through cell-bound IgE. Nonimmune DHRs refer 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.[2] Drugs that can produce a nonimmune DHR include vancomycin, opiates, iodinated radiocontrast agents, angiotensin-converting enzyme (ACE) inhibitors, amphotericin B, and D-tubocurarine. A vancomycin infusion reaction is a common example of a DHR. If vancomycin is infused too rapidly, it can cause the direct release of histamine and other mediators from cutaneous mast cells, producing a 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 vancomycin infusion reactions may be accompanied by hypotension, thereby constituting an immediate DHR. Most patients who have had infusion-related reactions will tolerate vancomycin if the rate of infusion is slowed. In rare cases, the severity of the reaction may preclude continued therapy with vancomycin. Some agents (including aspirin) may produce nonimmune DHRs by altering the metabolism of inflammatory mediators such as PGs or kinins. Angioedema from ACE inhibitors or sacubitril, a neprilysin inhibitor, are classic examples of nonimmune DHRs. With these agents, angioedema results from pharmacologic inhibition of the breakdown of bradykinin, leading to inflammation, increased vascular permeability, and vasodilation.

CLINICAL MANIFESTATIONS OF ALLERGIC DRUG REACTIONS

Anaphylaxis

Anaphylaxis is an acute, life-threatening reaction, usually mediated by an immune mechanism, that involves multiple organ systems and occurs in 10 to 20 per 100,000 population per year.[17] About 1,500 deaths from anaphylaxis occur annually in the United States.[18] The lifetime prevalence of anaphylaxis (estimated at 1.6%-5.1%) is rising, most notably in association with the increased use of biologic agents and in the younger age group due to food allergies. Although many drugs may cause anaphylaxis, the most commonly reported are penicillins, aspirin and other NSAIDs, and insulins.[3,19] In most patients, the initial signs and symptoms occur in the skin (flushing, pruritus, urticaria, and 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, and sneezing) followed by dizziness, hypotension, and gastrointestinal symptoms (nausea, cramping abdominal pain, vomiting, and diarrhea).[19] About 10% to 30% of patients develop hypotension. Additional cardiovascular effects include syncope, altered mental status, chest pain, and dysrhythmia.[17]

A consensus panel on allergy has defined anaphylaxis as highly likely when one of the following three scenarios is present[19]:

1. Acute onset of a reaction (minutes to several hours) that involves the skin (mucosal tissue) and the respiratory tract and/or a decrease in blood pressure.

2. The rapid onset of a reaction after exposure to a likely allergen that involves two organ systems (respiratory tract, skin, cardiovascular, and/or gastrointestinal).

3. A decrease in blood pressure alone after exposure to a known allergen.

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

Anaphylaxis generally begins within 1 hour 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 to 72 hours after the initial presentation with most occurring within 6 hours. Because of the possibility of a biphasic reaction, for patients with a severe initial presentation of anaphylaxis (hypotension, multiple doses of epinephrine, or other markers of severity), extended observation should be considered (≥ 6 hours).[19] 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 other cases, cardiovascular collapse may be the dominant manifestation from the release of mediators within the heart muscles and coronary blood vessels.

Clinical markers may aid in the diagnosis of anaphylaxis. Serum concentrations of tryptase or mature tryptase (also known as β-tryptase) peak within 0.5 to 2 hours after the onset of anaphylaxis.[19] Tryptase concentrations are most helpful in making the diagnosis if they are drawn no more than 6 hours after the onset of symptoms. Since plasma histamine concentrations remain elevated for only 30 to 60 minutes, they are not clinically useful in patients who present 1 hour or later after the onset of anaphylaxis.[19]

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 antisera 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, bupropion, hydantoins, minocycline, sulfonamides, penicillins, and cephalosporins (especially cefaclor). SSLD is usually self-limiting after discontinuation of the causative agent, but it can sometimes progress to 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 referred to as DRESS (see Fig. e108-1). The criteria for a diagnosis of DRESS are as follows: (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/mm^3 (1.5×10^9/L) or the presence of atypical lymphocytes; and (c) systemic involvement including adenopathies 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.[20] Other drugs associated with DRESS include vancomycin, minocycline, dapsone, lamotrigine, and sulfonamides.[21] The onset of DRESS is typically delayed ranging from 3 to 8 weeks after drug initiation and the clinical manifestations (targeted organs and the severity of organ involvement) can vary between patients.[21] The mortality rate associated with DRESS is 10%, and it is largely attributed to the systemic involvement of the liver, kidneys, or lungs.[20] After discontinuation of the causative drug, the skin rash resolves and laboratory abnormalities normalize over 4 to 8 weeks. Systemic corticosteroids (0.5-1 mg/kg/day prednisone or steroid equivalent) have been used in the treatment of DRESS based on the severity of organ involvement.

Drug Fever

Fever may occur in response to an inflammatory process or develop as a manifestation of an adverse drug reaction. Drug fever has been estimated to occur in as many as 10% of hospital inpatients and is a diagnosis made after excluding other known causes of fever.[22] Many drugs have been reported

to cause fever with the most frequently implicated classes being antimicrobials (eg, acyclovir, amphotericin B, β-lactams, minocycline, rifampin, sulfonamides, and tetracycline), anticonvulsants (eg, carbamazepine and phenytoin), antiarrhythmics (eg, procainamide and quinidine), and other cardiac medications (eg, clofibrate, diltiazem, dobutamine, furosemide, heparin, methyldopa, and procainamide).[22] These drugs may affect the central nervous system (CNS) directly to alter temperature regulation or stimulate the release of endogenous pyrogens (eg, interleukin-1 and tumor necrosis factor), PGs, or nervous system monoamines that alter the thermoregulatory set point.[22] Drugs also may cause fever as a result of their pharmacologic effects on tissues (eg, fever resulting from massive tumor 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 to 104°F (38.9°C–40.0°C) interrupting normal temperatures throughout the day.[22] Drug fever may occur at any time during 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).[22] Laboratory findings such as leukocytosis, eosinophilia, elevated lactic dehydrogenase, and elevated erythrocyte sedimentation rate may aid in the diagnosis. Withdrawal of the causative agent usually results in prompt defervescence. Fever usually recurs upon 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 (see Chapter 107).[23] Exposure of susceptible persons to these agents alters 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 nafcillin/oxacillin, and hepatitis caused by phenytoin and halothane. Interstitial nephritis is characterized by fever, rash, and eosinophilia associated with proteinuria and hematuria. The presence of urine eosinophils helps make the diagnosis, but their absence does not rule out interstitial nephritis. 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 Chapter e56). 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. Cutaneous vasculitis is usually manifested by purpuric lesions that vary in size and number. Vasculitis also may be manifested as papules, nodules, ulcerations, or vesiculobullous lesions, generally occurring on the lower extremities but sometimes on the upper extremities, including the hands. Drugs associated with vasculitis include allopurinol, β-lactam antibiotics, sulfonamides, thiazide diuretics, phenytoin, and vancomycin.

Serious Cutaneous Reactions

Although most dermatologic reactions are mild and resolve promptly after drug discontinuation, SJS and TEN are serious or even life-threatening reactions (see Fig. e108-1). Both SJS and TEN are classified as progressive bullous or “blistering” disorders that constitute dermatologic emergencies.[24] 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 often 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 (eg, less than 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.[24] Both SJS and TEN are associated with long-term sequelae, including permanent visual impairment, temporary nail loss, cutaneous scarring, and irregular pigmentation. As 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.

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.[26,27] The mortality rates associated with SJS and TEN range from 1% to 5% and 10% to 70%, respectively.[27] 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 are the sulfonamides, particularly trimethoprim–sulfamethoxazole.[28] Other major offenders of SJS and TEN identified in these studies are allopurinol, aminopenicillins, carbamazepine, cephalosporins, imidazole antifungals, lamotrigine, nevirapine, oxicam NSAIDs, phenytoin, quinolones, and tetracyclines.[28] Cutaneous manifestations of SJS or TEN are often preceded several days by fever with or without flu-like symptoms. Therefore, early discontinuation of the offending medication in patients who have these early signs and symptoms before cutaneous manifestations may prevent disease progression.

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 (eg, 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. See Chapter e48 for a more detailed discussion of drug-induced pulmonary disease.

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 (see Chapter e125).

FACTORS RELATED TO THE RISK OR SEVERITY OF ALLERGIC DRUG REACTIONS

4 Among the factors that influence the likelihood of drug allergy 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 (eg, chimeric monoclonal antibodies, and streptokinase) or antigenic excipients (eg, peanut oil, FD&C dyes, sulfites, and 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 is the most likely to sensitize and predispose to drug reactions. The oral route is the safest, and the parenteral route is most hazardous for the 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 HLA alleles increases susceptibility to several 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*.[29] Severe immune-mediated cutaneous reactions to allopurinol, including SJS and TEN, have been associated with the presence of *HLA-B*5801* in Han Chinese.[30] In this same patient population, the presence of *HLA-B*1502* increases the risk of SJS and TEN with carbamazepine, phenytoin, and fosphenytoin.[31] *HLA-A*3101*

has been related to the development of nonblistering DHRs such as DRESS to carbamazepine in European and North Asian populations.[32] Associations between HLA alleles and drug reactivity have been described for aminopenicillins, aspirin, iodinated contrast media, gold, lamotrigine, and trimethoprim–sulfamethoxazole.[33] In patients with a history of immediate reactions to β-lactam antibiotics, a single nucleotide polymorphism of HLA-*DRA*, an MHC Class II gene, was a predictor of skin test positivity to amoxicillin and other penicillins but not cephalosporins.[34] Genetic factors can also influence the metabolic deactivation of drugs via phase 1 and 2 metabolisms. For example, slow acetylators of procainamide and hydralazine are at increased risk for SLE. A genetic variant in *CYP2C*, notably *CYP2C9*3*, was associated with phenytoin-induced SCARs.[35] Genes also encode for the type of T cell receptor and the specific cytokines involved in allergic drug reactions.

Drug allergies develop with equal frequency in atopic and nonatopic individuals. In addition, patients with a history of drug allergy are 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 and elderly adults. This may be related to immaturity of the immune system or naturally waning of the immune system over time, also referred to as *immunosenescence*. 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 herpesvirus 6 (HHV-6) and the development of DRESS.

DRUGS COMMONLY ASSOCIATED WITH ALLERGIC DRUG REACTIONS

Antimicrobials

β-Lactams

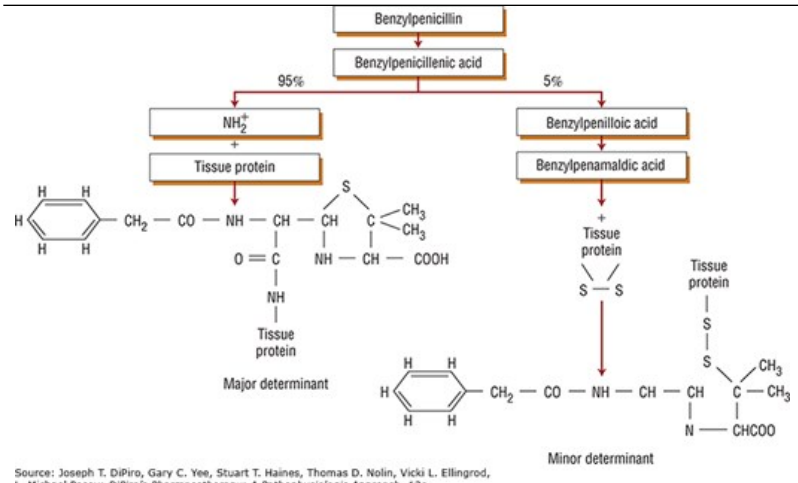
About 8% of individuals in the United States healthcare system report an allergy to penicillin and 1% have a noted cephalosporin allergy.[36] Avoidance of penicillins in patients with self-reported allergy is a growing health concern. The use of alternative antibiotics in these patients is associated with increased medical costs and an increased frequency of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile*.[37] Only 10% to 20% of patients reporting penicillin allergy have a positive skin test.[3,38] Patients with a history of immediate penicillin allergy who have a negative penicillin skin test (PST) result are unlikely to react on subsequent courses of penicillins.[3,38]

The most common reactions to penicillin include urticaria, pruritus, and angioedema. All four of the major types of allergic reactions described in the Gell and Coombs classification scheme 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, eosinophilia, SJS, and exfoliative dermatitis. Cutaneous reactions can occur in up to 4.4% of treatment courses of penicillin and up to 8% of those of aminopenicillins.[39] The incidence of a rash is close to 100% in patients receiving ampicillin with viral infections such as infectious mononucleosis.

Some aspects of the mechanism of penicillin immunogenicity have been determined. As a relatively small molecule (356 Da), benzylpenicillin must combine with macromolecules (presumably proteins) to elicit an immune response. Penicillin is rapidly hydrolyzed to several reactive metabolites that can covalently link to proteins. Of these metabolites, 95% is in the form of benzylpenicilloyl that binds covalently to the lysine residues of proteins such as albumin through an amide linkage involving the β-lactam ring (see Fig. e108-2). 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. The minor antigenic determinants are more likely to cause life-threatening anaphylactic reactions.

FIGURE e108-2

Formation of a benzylpenicilloyl hapten–protein complex. Alt Text: Penicillin is rapidly hydrolyzed to several reactive metabolites that can covalently link to proteins. Of these metabolites, 95% is in the form of benzylpenicilloyl that binds covalently to the lysine residues of proteins 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.



In addition to the major and minor determinants, unique side-chain determinants may mediate allergy to some penicillins. The frequency of reactions to the β-lactam core of penicillin, as determined via skin testing, is decreasing while reactions to the R-group side chains of the penicillins are increasing.[40] Both the aminopenicillins and piperacillin may cause hypersensitivity reactions via their unique side chains.[41] 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 evaluated in those experiencing a reaction to amoxicillin/clavulanate.[42,43] Careful history taking is needed to identify patients with a 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.[44–46]

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.[36,47] 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.[3] One percent to 8% of patients with penicillin-specific IgE may develop an immediate-type hypersensitivity reaction to cephalosporins.[48] In contrast, patients with reported penicillin allergy and negative skin test results are at no greater risk than the general population.[3]

5 Ideally, cephalosporins should be avoided in patients with a history of a severe, immediate hypersensitivity reaction to penicillin, although most studies report a low risk of an allergic response to a cephalosporin even in a person with a positive skin test result to penicillin. 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).[49] 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.[49] The higher rate of cross-reactivity between penicillin and the first-generation cephalosporins has been attributed to similarities in the R1 side chains of these agents.[3,46] 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.[46,49,50] β-lactam antibiotics with an R1 substitution chemically similar to that of penicillin G are cephalothin and cefoxitin. In the R1 position, amoxicillin is chemically similar to ampicillin, cefaclor, cephalexin, and cefadroxil.

Cephalosporins rarely induce immune responses mediated by the core β-lactam structure, but they are more likely to do so via unique R-group side-chain determinants.[49] 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 higher than that between the penicillins and cephalosporins. Cross-reactions may occur through identical R1 side chains. Of note, ceftazidime and cefiderocol share a common side chain with aztreonam.

The actual risk of a cross-reaction between the penicillins and the carbapenems is 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%.[47] The initial estimate was based on the results of skin testing with

penicillin and nonstandardized carbapenem reagents. Several retrospective studies reporting variable rates of cross-reactivity relied on self-reported histories as confirmation of penicillin allergy. In four published prospective studies, both skin testing methods and carbapenem challenge dosing were used to assess cross-reactive risk. In one of these studies, only one of 112 patients with skin test–confirmed penicillin allergy had a positive skin test result for imipenem.[51] 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 aged 3 to 14 years, suggest a low risk of cross-reactivity between penicillin and meropenem.[52,53] In both studies, only one patient with skin test-positivity to penicillin had a positive skin test result for meropenem. Graded challenge dosing with meropenem was tolerated in 100% of the skin test–negative patients in both studies. In another study, 212 patients with a skin test positive to penicillin underwent skin testing with ertapenem, meropenem, and imipenem.[54] None of the 212 patients had skin test positivity to a carbapenem. Graded challenge to a full therapeutic dose of each carbapenem was subsequently performed in 211 subjects.[54] No patient exhibited a reaction during challenge dosing. Based on these results, the routine practice of avoiding carbapenem use in patients with a 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.[3,47] In 211 patients with a positive skin test to a penicillin, graded challenge dosing to a full therapeutic dose of aztreonam was uneventful in all patients.[54]

Sulfonamides

Sulfonamide drugs containing the sulfa (SO_2NH_2) moiety include antibiotics, thiazide and loop diuretics, oral hypoglycemics, COX-2 inhibitors, and carbonic anhydrase inhibitors. Other less commonly recognized sulfonamides include antivirals (amprenavir, fosamprenavir, and darunavir), probenecid, tamsulosin, triptans, and zonisamide. 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 sulfonamide nonantibiotic.[55] 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 (eg, maculopapular or morbilliform eruptions). Infrequently, a seemingly benign maculopapular rash may progress to a mucocutaneous syndrome (eg, SJS or TEN).[4] Other potentially life-threatening reactions to sulfonamides may include hepatic, renal, or hematologic complications.

Immune-mediated sulfonamide reactions depend on reactive metabolites produced in the liver.[56] 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.[56,57] Structural differences between the sulfonamide antibiotics and nonantibiotics may influence the metabolic conversion and resultant reactivity of these compounds. Slow acetylator phenotypes may also increase the risk for these reactions. When assessing the potential for allergy to a sulfonamide, the clinician should consider the chemical structure of the agent. Attention should be given to the presence of an arylamine group in the N4 position and/or an N-containing ring attached to the N1 nitrogen of the sulfonamide group.[57]

6 Cross-reactivity between sulfonamide antibiotics and nonantibiotics is minimal, with cross-reactivity characterized as "highly unlikely."[58] In one study, about 10% of patients with a history of allergy to a sulfonamide antibiotic subsequently reacted to a sulfonamide nonantibiotic (eg, acetazolamide, loop diuretic, sulfonylurea, and thiazide).[55] This low rate of cross-reactivity has been attributed in part to differences in the chemical structures, and therefore metabolites, of sulfonamide antibiotics and nonantibiotics. The occurrence of allergic reactions after the receipt of sulfonamide nonantibiotics has also been attributed to a predisposition to allergic reactions in the affected individuals rather than cross-reactivity with sulfonamide antibiotics.[55] In one study, cross-reactivity between sulfonamide antibiotics and penicillin was higher than that between the sulfonamide antibiotics and nonantibiotics.[55]

Trimethoprim–sulfamethoxazole is used frequently to prevent or treat *Pneumocystis jirovecii* pneumonia in patients with AIDS or hematologic malignancies. Adverse drug reactions to trimethoprim–sulfamethoxazole occur much more frequently in HIV-positive patients.[59,60] Adverse drug reactions to trimethoprim–sulfamethoxazole occur in 50% to 80% of AIDS patients compared with 10% of other immunocompromised patients.[60] Trimethoprim–sulfamethoxazole was associated with an adverse event rate of 26.3 per 100 person-years and a hypersensitivity event rate of 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 a 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.[61] 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 MHC proteins with increased recognition of the drug antigen by $CD4^+$ and $CD8^+$ cells.[61] The adverse drug reaction rate has been associated with a higher $CD4^+$ T cell count greater than 20 cells/mm^3 (0.020×10^9/L), CD4 to CD8 ratio less than 0.10, and treatment for fewer than 14 days.[60]

Antiretrovirals

Antiretrovirals are commonly implicated in drug hypersensitivity. Early studies suggest HIV-positive patients are one hundred times more susceptible to adverse drug reactions than the general population. The pathophysiology of antiretroviral hypersensitivity in HIV-infected individuals is multifactorial and thought to be related to various drug-disease interactions. Although *in vitro* data supports T-cell-mediated mechanisms, other factors occurring simultaneously, such as the presence of an underlying opportunistic infection, immune reconstitution inflammatory syndrome, and/or initiation of prophylactic antimicrobials with overlapping adverse drug reactions (eg, trimethoprim-sulfamethoxazole), may complicate the clinical diagnosis. A comprehensive history with strong consideration of temporal drug exposure is critical when evaluating antiretroviral hypersensitivity.

A wide range of hypersensitivity reactions has been described with nearly all classes of antiretrovirals. Delayed cutaneous reactions, ranging from self-limiting, mild exanthems to SCAR, are the most common manifestation.[3,62] Systemic features such as fever, rigors, and myalgias are also frequently present. Immediate reactions are rarely reported.

Genetic predisposition may increase the risk of antiretroviral hypersensitivity. For example, the presence of MHC class I allele *HLA-B*5701* significantly increases the risk of abacavir hypersensitivity.[62] Abacavir hypersensitivity syndrome occurs in up to 9% of patients and clinically manifests as fever, constitutional symptoms, and gastrointestinal disturbances with delayed rash occurring in up to 70% of patients. Symptoms generally present within 6 weeks of therapy initiation and resolve within days of therapy cessation.[63] Given these clinical implications, preemptive *HLA-B*5701* screening is recommended before starting therapy.[63] Initiation or continuation of therapy is contraindicated if identified since subsequent reactions may occur more rapidly and may be more severe in nature.[63]

Similar to abacavir, genetic variants of the HLA allele and cytochrome P450 polymorphisms are associated with nevirapine hypersensitivity reactions. Skin rash is observed in 17% to 32% of patients and occurs within 3 months of treatment initiation.[64] Genetic analyses in various patient populations have demonstrated a strong association between the *HLA-B*3505* allele and nevirapine-induced cutaneous reactions, although these data are from small, preliminary analyses.[65] Metabolic variations have also been implicated in nevirapine hypersensitivity reactions. Alterations in cytochrome P450 2B6 (CYP2B6) are associated with higher plasma concentrations of nevirapine which may predispose patients to hepatotoxicity and SCAR.[63,66,67] Irrespective of mechanism, nevirapine hepatotoxicity occurs in 17% to 32% of patients.[64]

Management of antiretroviral hypersensitivities depends on the type and severity of presenting symptoms with special consideration of genetic associations. For mild reactions without systemic organ involvement, symptomatic support with close monitoring may allow for therapy continuation.[62] For patients presenting with more severe phenotypes where alternative options are limited, drug provocation testing, patch testing, and/or desensitization procedures may be considered in a monitored setting, although data supporting these approaches are limited.[62] Desensitization protocols have been described for numerous antiretrovirals including darunavir and efavirenz.[64] Re-exposure to a culprit antiretroviral in patients who experience SCAR or severe drug-induced liver injury is contraindicated. In the case of abacavir, *HLA-B*5701* genetic testing is recommended by guidelines and should be completed before therapy initiation. As previously mentioned, abacavir administration, including via patch testing and desensitization protocols, is contraindicated for patients who are carriers of this HLA allele. Immediate hypersensitivity reactions to antiretrovirals occur rarely. Therefore, standardized approaches in this subgroup of patients have not been established.

Chemotherapeutic Agents

Chemotherapeutic agents are implicated in hypersensitivity reactions in 5% to 15% of patients who receive them. Up to 65% of patients receiving L-asparaginase experience immediate hypersensitivity reactions such as urticaria and anaphylaxis.[68]

The combination of paclitaxel (or docetaxel) and carboplatin is frequently responsible for 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.[4,68,69] The reaction typically occurs within minutes after initiation of the first or second dose, suggesting a non-IgE-mediated mechanism. Non-immediate skin reactions can occur from 12 hours to 15 days after exposure. Both of 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% between paclitaxel and docetaxel provides further evidence that the reaction is most likely attributed to the taxane moiety.[70] 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 reactions, patients are routinely premedicated with corticosteroids and both H_1- and H_2-receptor antagonists. A protein-bound formulation of paclitaxel (Abraxane®) devoid of the castor oil vehicle avoids some but not all reactions. Skin testing may determine the safest management approach for patients who experience an immediate taxane-induced hypersensitivity reaction.[71]

Hypersensitivity to platinum-containing agents is delayed, developing after six or more courses of carboplatin, cisplatin, or oxaliplatin, with rates peaking around the eighth or ninth dose.[72–74] 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.[75] Reactions typically develop shortly after completing the infusion or up to 3 days after therapy. Symptoms of severe reactions include tachycardia, dyspnea, facial swelling, rigors, and hypotension. Mild reactions include itching, erythema, and facial flushing. An association between reactivity and the duration of the platinum-free interval has been described for carboplatin.[76] The risk of a severe reaction was 47% if the platinum-free interval was greater than 24 months versus only 6.5% with intervals less than 12 months.[76] Management strategies include decreasing the rate of infusion and administration of corticosteroids and H_1- and H_2-receptor antagonists.[74] Skin testing can assist in the diagnosis of carboplatin hypersensitivity.[72,75] Given the potential for false-negative skin tests, however, repeat skin testing is recommended for patients with severe or life-threatening histories who have a negative initial skin test result. Desensitization to carboplatin[72,73] and oxaliplatin[77,78] is well tolerated. Antihistamine premedication is recommended before the use of these desensitization protocols to minimize the risk and/or severity of breakthrough reactions.[79]

Biologics

Biologic agents (eg, monoclonal antibodies, fusion proteins, and recombinant proteins) are derived from living sources such as yeast, bacteria, animal cells, or mammalian cells.[80] 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. Immunologic 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.[80] Both cutaneous and systemic allergic reactions have been reported.

Factors influencing the antigenicity of biologic agents are patient-specific (eg, atopy, congenital protein deficiency), product-specific (eg, presence of contaminants or stabilizing agents, degree of protein glycosylation, presence of nonhuman protein sequences, and storage temperature), and administration related (eg, route of administration, frequency of use, concurrent immunosuppressant use).[80] Of the monoclonal antibodies, reactions are most frequently observed with the murine-derived agents (0% human) and chimeric agents (75% human) as compared to the humanized (greater than 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 can mediate reactions to interferon-β_{1b} and β_{1a}, infliximab, natalizumab, recombinant factor VIII, and recombinant factor IX.[80] Anti-infliximab antibodies, which occur in up to 60% of treated patients, are associated with a higher frequency of infusion reactions and decreased therapeutic effect.[81] Concomitant administration of immunosuppressive agents such as prednisone or low-dose methotrexate can decrease the risk of antibody formation to infliximab.[80,81]

Rituximab, a chimeric human-murine IgG_1 monoclonal antibody directed against the CD20 antigen on surface B cells, is commonly associated with hypersensitivity reactions. More than 75% of patients experience infusion-associated reactions within 24 hours of the first dose. Symptoms reported are consistent with immediate-type reactions, such as urticaria, pruritus, bronchospasms, angioedema, and hypotension.[63,82] Since most infusion reactions only occur upon first exposure, standard administration of subsequent doses is recommended for patients with non-life-threatening

reaction histories. Skin testing has also been described and may identify patients with suspected IgE-mediated rituximab hypersensitivity, although the negative predictive value is unknown.

Cetuximab, a human-murine IgG_1 monoclonal antibody directed against epidermal growth factors, presents a unique situation as an allergen.[83] Cetuximab carries a black box warning regarding serious infusion reactions that usually occurred on first dose administration in 3% of patients in pre-marketing studies. Following the approval of the drug, infusion reaction rates as high as 20% were noted in specific regions of the southern United States.[84] These reactions (eg, difficulty breathing, hypotension, shock, loss of consciousness, and/or heart attack) also occurred with the first infusion, but many were severe enough to warrant total discontinuation of therapy. Further investigation of these regional cases revealed a common link: the presence of preexisting IgE antibodies against the oligosaccharide, galactose-α-1,3-galactose (alpha-gal) secondary to lone star tick bites.[85] This oligosaccharide present in the tick is also found on the Fab portion of the heavy chain of cetuximab, resulting in IgE cross-reactions on first drug exposure. Alpha-gal is also present in the serum of nonprimate mammals and may be responsible for delayed hypersensitivity reactions secondary to the ingestion of certain meats.[85] Experience with cetuximab as an immunogen has raised awareness of potential drug-food-environment cross-reactions.

Delayed onset anaphylaxis, ranging from minutes to days post-injection, has been reported with omalizumab, a humanized monoclonal antibody targeted against IgE for the treatment of moderate-to-severe asthma or chronic idiopathic urticaria.[86,87] Although uncommon, occurring in 0.1% to 0.2% of patients, omalizumab carries a black box warning for anaphylaxis. Risk factors include a history of anaphylaxis, regardless of the cause, which increases the risk of an anaphylactic event to 0.6%. Omalizumab-treated patients require observation for 2 hours after the first three injections and 30 minutes after subsequent injections.[88] Patients are advised to carry an epinephrine autoinjector during and for 24 hours after drug administration.[88,89] 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.[87] For select, low-risk patients (eg, no prior history of anaphylaxis; received at least three doses uneventfully; and patient or caregiver is educated and able to recognize and manage signs and symptoms of a severe hypersensitivity reaction), self-administration using a pre-filled auto-injector is now FDA approved.[90]

Management of allergic or DHRs 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 (eg, omalizumab-induced anaphylaxis). Depending on the biologic agent, reactions may be managed by decreasing the infusion rate (if given intravenously) or by pretreating with antihistamines or corticosteroids. Graded challenge and desensitization protocols for adult and pediatric patient populations to numerous biologic agents have also been described.[75,91,92]

Aspirin and Nonsteroidal Anti-inflammatory Drugs

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can cause eight general types of DHRs, four of which are related to COX inhibition.[93,94] These DHRs can involve asthma and rhinitis, urticarial/angioedema, anaphylaxis, or pneumonitis. The two most common aspirin sensitivity reactions are respiratory (asthma and rhinorrhea) and urticaria/angioedema in patients without chronic urticaria. Urticaria and angioedema can be IgE- or non-IgE-mediated due to COX-1 inhibition. About 5% of children and 7.2% of adults with asthma are sensitive to aspirin and other NSAIDs.[93–96]

NSAID-exacerbated respiratory disease (NERD), formerly known as aspirin-exacerbated respiratory disease (AERD) and Samter's Triad, refers to a triad of characteristics consisting of asthma, rhinosinusitis with nasal polyps, and acute respiratory tract symptoms upon exposure to aspirin or NSAIDs. This syndrome typically develops in middle-aged patients who are nonatopic and have no history of aspirin or NSAID intolerance. Women are 2.5 times more likely to develop NERD than men.[97] Symptoms usually progress from rhinitis to sinusitis with nasal polyps and moderate-to-severe asthma. It is uncommon in children and young adults. The mechanism of NERD is not completely understood, but it is characterized by overexpression of LTC_4 synthase in the airways.[98,99] In patients with NERD, administration of aspirin and NSAIDs may provoke severe and sometimes fatal asthmatic attacks.

One proposed mechanism of aspirin and NSAID sensitivity is COX-1 blockade, which may facilitate depletion of prostaglandin E_2 (PGE_2) and production of alternative arachidonic acid metabolites (eg, LTs).[93] PGE_2 prevents mast cell degranulation, while LTs cause bronchoconstriction and increased mucus production. Increased LT production may also explain the development of angioedema and urticaria, based on 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. This mechanism is also supported by the clinical observation that LT-modifying drugs can reduce the severity of aspirin-induced asthma and urticaria.[93] It is also possible that aspirin and NSAIDs stimulate mast cells directly to release inflammatory mediators. Patients with NERD may tolerate the selective COX-2–selective inhibitors celecoxib and rofecoxib, as they do not cross-react with aspirin.[100,101]

In patients with aspirin sensitivity (asthma or urticaria) in which aspirin is medically indicated, oral graded challenge dosing and/or desensitization may be tried depending on the clinical history.[102] Several different protocols have been described, and the risk for anaphylaxis cannot be reliably predicted.[93,97,102] Graded challenges should be performed when there is a low clinical suspicion of ongoing aspirin or NSAID sensitivity, while desensitizations are recommended in patients requiring aspirin or NSAIDs, but with a high risk of a repeat reaction. Both graded challenge and desensitization should be performed with caution in a monitored setting with resuscitation equipment at hand. For patients with a history of cutaneous reactions to aspirin, a two-dose challenge of 40.5 mg (one-half of an 81-mg tablet) given 90 minutes apart with no pretreatment has shown promising results.[102] If no reaction occurs after administration of the second dose, the patient may receive 81 mg of aspirin per day for the cardioprotective therapy.[102] In patients with higher risk histories suggestive of a severe IgE-mediated reaction, desensitization protocols have been administered successfully.[63] Management for patients with NERD focuses on treating asthma and nasal polyps with usual therapy and avoidance of aspirin and NSAIDs. However, aspirin desensitization may be indicated, as it improves asthma and nasal polyp burden. These protocols differ from protocols developed for IgE-mediated aspirin allergy. Several oral, bronchial, and nasal aspirin desensitization protocols have been described, ranging from 2- to 4-day protocols for patients with a history of asthma to rapid (2-5 hours) protocols.[3,102,103] For any hypersensitivity reaction, if the oral challenge is not successful and desensitization is not performed, patients with aspirin sensitivity must avoid aspirin and the nonselective NSAIDs.

Individual NSAIDs (eg, ibuprofen, sulindac) and aspirin can cause IgE-mediated allergic reactions. These reactions occur upon re-exposure to the drug and may present as urticarial/angioedema-bronchospasm or anaphylaxis with or without hypotension. A careful and complete allergy history may suggest true allergy to an isolated NSAID. Such patients should be advised to avoid the specific NSAID and any structurally similar NSAIDs (eg, all propionic acid derivatives, all indole acetic acid derivatives) because of the risk of cross-reactivity. Graded challenges can be performed to clarify with NSAIDs are safe to administer. Patients with a history of reacting to a specific NSAID other than aspirin can safely receive aspirin.[102]

NSAIDs have been associated with pulmonary infiltrates and eosinophilia syndrome. Pulmonary infiltrates and eosinophilia syndrome is associated with fever, cough, dyspnea, infiltrates on chest radiography, and 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 resolves rapidly after the offending agent is discontinued.

Insulin

Insulin can produce an IgE-mediated reaction, an immune complex reaction and delayed T-cell-mediated allergy. The reported prevalence of insulin allergy is 0.1% to 3% and the most common manifestation is an IgE-mediated local reaction at the injection site.[104] Allergic reactions have been reported with bovine and porcine insulin and more rarely with the recombinant human insulin. Insulin's antigenicity may be explained by alterations in protein unfolding during the manufacturing process.[104] Hypersensitivity reactions to insulin have also been associated with additives, such as zinc or protamine, and injection or infusion-related equipment. Development of anti-insulin IgG antibodies occurs commonly after a few months of therapy, but these antibodies remain inactive in most patients.

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. Before labeling the patient as allergic to insulin, consideration should be given to the patient's insulin administration technique. Systemic antihistamines may be administered in patients who continue to have local reactions, and a different insulin source may be substituted. Systemic reactions to insulin (eg, urticaria or anaphylaxis) rarely occur. For immediate-type reactions, skin testing for insulin preparations used, alternative preparations, and additives is recommended to identify the type of insulin least likely to cause a systemic reaction.[104] For sensitized patients requiring insulin, continuous subcutaneous insulin infusion induction protocols have been administered successfully.[89,105]

Other Agents

Radiocontrast Media

Radiocontrast agents frequently cause reactions categorized as immediate (within 1 hour) or nonimmediate (more than 1 hour and up to 10 days) via both IgE-mediated and non-IgE-mediated mechanisms.[88] 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. The incidence of immediate reactions with ionic and nonionic agents are 1% to 3% and less than 0.5%, respectively.[3,19] Delayed skin reactions, usually presenting as maculopapular exanthems, occur in 1% to 3% of patients over 5 to 7 days.[88] Severe, immediate anaphylactic reactions occur in 0.01% to 0.04% of patients.[88] In addition, radiocontrast agents may cause dose-dependent toxic reactions that can produce renal impairment, cardiovascular effects, and arrhythmias.[106] The mechanism of reactions to radiocontrast agents is not clearly understood. Histamine release and mast cell triggering have been observed 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 cause fewer acute reactions.

The risk of immediate reactions to radiocontrast media is greater in women and patients with a history of atopy or asthma.[88] Other recognized risk factors include a history of previous reaction, severe drug allergies, cardiac disease, and treatment with β-blockers.[3,19] Despite a common misconception, seafood allergy or iodine allergy does not predispose to radiocontrast media reactions. Although not recommended in current guidelines, patients with prior immediate reactivity to a radiocontrast agent often undergo skin testing. Skin testing with a panel of different radiocontrast agents may identify a product with low reactive risk.[88] 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.[88,107] A commonly recommended regimen in high-risk patients is prednisone 50 mg orally 13, 7, and 1 hours before exposure with diphenhydramine 50 mg orally or intramuscularly 1 hour before exposure to prevent immediate reactions.[19] Ephedrine 25 mg orally has also been recommended 1 hour before the radiocontrast study as a component of the pretreatment regimen, but ephedrine should not be used if the patient has a history of unstable angina, hypertension, or arrhythmia.[3,19] Other studies have examined the use of H_1- and H_2-antihistamines, clemastine, or cimetidine, respectively.[3,19]

Immediate reactions to gadolinium, a noniodinated contrast agent, have been reported at frequencies of 0.07% in adults and 0.04% in children.[108] Most reactions have been mild, requiring either no medical management or treatment with antihistamines. Moderate and severe reactions have also been rarely reported. Pretreatment regimens similar to those used with iodinated contrast studies are usually effective, but they have been associated with breakthrough reactions, particularly in patients with a history of reactions to gadolinium or iodinated contrast agents.[109]

Pharmaceutical Excipients and Additives

Pharmaceutical products contain many “inert” additives (eg, 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. Excipients that may cause allergic reactions include benzyl alcohol, carboxymethylcellulose, povidone, dyes, sodium benzoate, sulfites, and polyethoxylated surfactants.[110] Identification of additives and excipients as causes of allergic reactions are typically performed by the process of elimination.

Anticonvulsants

Many anticonvulsant drugs produce a variety of DHRs. Drugs such as phenytoin, phenobarbital, carbamazepine, and lamotrigine can cause an “anticonvulsant hypersensitivity syndrome” characterized by a triad of symptoms including fever, rash, and internal organ involvement. Lymphadenopathy and eosinophilia are frequently present and many reactions meet the definition of DRESS. The onset usually occurs several weeks into therapy.[32] In some cases, morbilliform rash develops into exfoliative dermatitis. The risk of cross-reactivity between the aromatic anticonvulsants (eg, carbamazepine, phenobarbital, and phenytoin) ranges from 40% to 80% and is associated with specific genetic predispositions.[32] A genetic marker for severe reactions to carbamazepine, phenytoin, fosphenytoin, and lamotrigine is the presence of the *HLA-B*1502* allele.[31] This allele is found in 10% to 15% of patients from China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan. In a population of patients from Taiwan, Japan, and Malaysia, genetic variation in the *CYP2C* gene, notably *CYP2C9*3*, was associated with phenytoin-induced SCARs (OR 11; 95% CI 6.2-11.8).[35]

Oxcarbazepine, the 10-keto derivative of carbamazepine, has exhibited both in vitro and in vivo cross-reactivity with carbamazepine. The concomitant use of valproate with lamotrigine significantly increases the risk of DHRs because of reduced lamotrigine metabolism, leading to a prolonged elimination half-life.

ACE Inhibitors and Angiotensin-Receptor Blockers

ACE inhibitor-associated angioedema occurs in 0.2% to 1% of treated patients.[111] It usually involves the face, tongue, lips, and pharynx but may also extend to the lower gastrointestinal tract. ACE is a nonspecific dipeptidase that not only inhibits the conversion of angiotensin I to angiotensin II but is also involved in the inactivation of bradykinin, substance P, and neurokinin A. High levels of bradykinin and substance P have been associated with vasodilation, increased vascular permeability, and inflammation resulting in angioedema in susceptible patients. The prevalence of ACE inhibitor–induced angioedema is highest in women and African American patients.[111] An added risk factor is the concomitant use of medications that inhibit bradykinin metabolism, such as the neprilysin inhibitor, sacubitril. Current labeling for the sacubitril/valsartan combination product provides a cautionary recommendation for a 36-hour washout period when converting to or from an ACE inhibitor.[112]

Angioedema secondary to angiotensin-receptor blockers (ARBs) has been reported; the weighted incidence was 0.11% in a meta-analysis of 35,000 patients treated with an ARB.[113] The mechanism by which ARBs cause angioedema is poorly understood. The risk of a “cross-reaction” between ACE inhibitors and ARBs is not clear. ARBs may cause repeat events through an independent mechanism or through a common pathway not yet determined. Based on a systematic review of 71 patients, the risk of subsequent angioedema after switching to an ARB was 9.4% for possible cases and 3.5% for confirmed cases.[114] None of the events were fatal. Before switching to an ARB in patients with a history of ACE inhibitor–related angioedema, consideration must be given to the severity of the initial event (eg, isolated nondiffuse facial swelling vs diffuse angioedema with laryngeal inflammation, esophageal or intestinal involvement), the prior responsiveness to treatment for angioedema and the benefit to risk ratio of ARB use in the patient.

Chlorhexidine

The prevalence of allergy or DHRs to chlorhexidine is not known, but cases ranging from anaphylaxis to contact dermatitis have been increasingly reported over the past 10 years.[115] Chlorhexidine is one of the most frequently used antiseptics. Having both bacteriostatic and bactericidal activities, chlorhexidine is used as a skin antiseptic before surgery, for urethral catheterization as a lubricant gel, and as a coating in central venous catheters.[116] It is also an ingredient in toothpaste, mouthwashes, and mouth rinses. Sensitization is most commonly associated with application to mucous membranes.[116] When applied to the skin as a hand-washing solution, low sensitization rates are attributed to poor transdermal absorption of chlorhexidine. Most allergic reactions are confined to the skin and manifest as urticaria with itching or contact dermatitis. However, anaphylaxis has been reported perioperatively after skin antisepsis, following insertion of a chlorhexidine-coated central venous catheter, and during tooth brushing. Both skin prick and intradermal testing have been used to identify high-risk patients before surgery. In a case series of six severe, immediate reactions to chlorhexidine that occurred during surgery, the onset of reactivity was within 10 to 20 minutes of chlorhexidine exposure.[115] When assessed 6 weeks after surgery, five of the six patients had self-reported prior histories of reactivity to chlorhexidine and four of the six demonstrated reactivity to skin prick testing.[115] The results of skin testing, the rapid onset and the increased intensity of reactivity observed upon reexposure to chlorhexidine support an IgE-mediated mechanism. Based on the widespread use of this antiseptic, chlorhexidine should be considered as a potential cause of any unexplained allergy. Once recognized as sensitized, patients must be educated to avoid subsequent exposures in both healthcare settings (eg, handwashing solutions and skin antiseptics) and in the private home (eg, personal hygiene products containing chlorhexidine).

TREATMENT

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

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. In 2020, the Joint Task Force on Practice Parameters for

Allergy and Immunology updated the treatment guidelines for anaphylaxis (see Table e108-2).[19] Epinephrine remains the drug of first choice, although it is underused and often dosed suboptimally for this indication.[117] Underuse and delays in its administration have been associated with poor outcomes. Epinephrine should be administered as a primary treatment to counteract bronchoconstriction and peripheral vasodilation leading to hypotension.[19,117] At recommended doses, epinephrine also enhances coronary blood flow. The recommended administration technique is intramuscularly in the lateral aspect of the thigh.[19,118] 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 volume depleted. A maintenance IV fluid then is initiated. IV fluids should be given early in the treatment course in an attempt to prevent shock. An immediate priority is to establish and maintain an airway with 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 and the use of a continuous IV infusion of epinephrine has also been described.[19,119] Patients in shock should remain supine.[19]

TABLE e108-2

Treatment of Anaphylaxis

- Remove the inciting allergen, if possible.
- Assess airway, breathing, circulation, and orientation. Support the airway.
- Cardiopulmonary resuscitation: Start chest compressions (100/min) if cardiovascular arrest occurs at any time.
- Administer epinephrine 1:1,000 (in a dose of 0.01 mg/kg to a maximum of 0.5 mg in adults and 0.3 mg in children) IM in the lateral aspect of the thigh.
- Place the patient in a recumbent position.
- Administer oxygen 8-10 L/min through facemask or up to 100% oxygen as needed; monitor by pulse oximetry, if available.
- Repeat IM epinephrine every 5-15 minutes for up to three injections if the patient is not responding.
- Establish IV line for venous access. Keep line open with 0.9% saline solution. For hypotension or failure to respond to epinephrine, administer 1-2 L at a rate of 5-10 mL/kg in the first 5-10 minutes. Children should receive up to 30 mL/kg in the first hour.
- Consider nebulized albuterol 2.5-5 mg in 3 mL of saline for lower airway obstruction; repeat as necessary.
- In cases of refractory bronchospasm or hypotension not responding to epinephrine because a β-adrenergic blocker is complicating management, glucagon 1-5 mg IV (20-30 µg/kg; maximum, 1 mg in children) given IV over 5 minutes.
- Give norepinephrine or epinephrine by continuous IV infusion for patients with inadequate response to IM epinephrine and IV saline. For epinephrine, add 1 mg (1 mL of 1:1,000) to 1,000 mL of 0.9% saline solution; start infusion at 2 µg/min and increase up to 10 µg/min based on blood pressure, heart rate, and cardiac function.
- Consider intraosseous access for either adults or children if attempts at IV access are unsuccessful.
- Consider diphenhydramine (adults 25-50 mg; children 1 mg/kg, up to 50 mg) IM or by slow IV infusion.
- Consider ranitidine 50 mg in adults and 12.5-50 mg (1 mg/kg) in children. The dose may be diluted in 5% dextrose in water to a volume of 20 mL and injected over 5 minutes.
- Consider methylprednisolone 1-2 mg/kg/dose up to 125 mg (or an equivalent steroid) to reduce the risk of recurring or protracted anaphylaxis. Prednisone 20 mg orally can be given in mild cases. These doses can be repeated every 6 hours as required.

IM, intramuscular.

Adapted from Shaker MS, Wallace DV, Golden DB, et al. Anaphylaxis: A 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1082-1123.

Other agents may be required for the treatment of anaphylactic reactions. Corticosteroids (hydrocortisone sodium succinate IV) should never be given in place of or before epinephrine.[19] Their onset of action is delayed, and their role is to reduce the risk of late-phase "biphasic" reactions. In patients treated chronically with β-blockers, glucagon should be considered because it has inotropic and chronotropic effects that do not rely on β-receptor responsiveness.[19] Histamine (H_1)–receptor blockers (eg, diphenhydramine) can be administered to reduce some of the symptoms associated with anaphylaxis, but these agents are not effective as primary therapy. The combination of diphenhydramine and an H_2-receptor blocker (eg, ranitidine) is

superior to diphenhydramine alone in the treatment of cutaneous manifestations of anaphylaxis.[19] Intraosseous access should be considered for adult and pediatric patients in whom attempts at IV access are unsuccessful.[19,119]

Following the treatment of anaphylaxis, patients should be assessed for possible recurrence. Patients who may reencounter the allergic trigger (eg, peanuts, shellfish, and medications) should be prescribed auto-injectable epinephrine.[120] Adults should receive the 0.3 mg dose and children should receive the auto-injector that delivers 0.15 mg per dose.[120] Patients should be instructed to carry two auto-injectors at all times.[19] Optimal dosing has not been described for obese patients. Both adequate needle length for intramuscular delivery of the drug and weight-based dosing are concerns in the obese population.[120] Patient education is crucial to prevent fatalities due to underuse and incorrect administration of epinephrine.

Delayed Allergic Reactions

Except for anaphylaxis, the treatment of other drug allergies or DHRs is less defined and standardized. Questions most often arise regarding the preferred treatment of SCARs. After the offending agent is discontinued, treatment of SJS/TEN is directed at supportive care including wound care, nutritional support, fluid and electrolyte balance, temperature regulation, pain management and the prevention of infectious complications.[15] Affected patients, particularly those with extensive epidermal involvement, should be managed in a burn center or ICU. Wounds should be treated similar to that of burn injuries, but topical use of silver sulfadiazine is typically avoided because of a high risk of cross-reactivity with sulfamethoxazole, a major offender in SJS/TEN. To prevent blindness or conjunctival scarring, ocular therapy involves the use of antiseptics, lubricants, antibiotics, and steroid eye drops or ointments. The use of systemic steroids remains controversial. In a systematic review of published studies, only one of six retrospective cohort studies demonstrated a significant impact of steroids on mortality.[121] The appropriate dose, time of initiation of therapy, and duration of steroid therapy are not known. Additional therapies used in the treatment of SJS/TEN include intravenous immunoglobulin (IVIG) and cyclosporine. A proposed mechanism of IVIG is inhibition of dermal cell apoptosis triggered by the Fas-FasL pathway. Both low-dose (0.2-0.5 g/kg) and high-dose (2-3 g/kg) IVIG regimens have been described with most studies supporting the use of mean total IVIG doses not less than 2 g/kg.[122] Cyclosporine (3-5 mg/kg/day for 7 days) was associated with a greater mortality benefit as compared to IVIG (total of 1 g/kg for 3 days).[123] Similar to corticosteroids, treatment protocols of these agents substantially differ, and the optimal doses, time of initiation, and duration of therapy are yet to be determined.

Antibiotic Allergy Evaluation

10 Patients presenting with a subjective allergy, especially to antibiotics, should be evaluated for specifics of the reaction and offending agent that likely caused the response. Identification of patients at high risk for drug allergy 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 an accurate and complete history cannot be overstated. The end goal should be to de-label patients who are not truly allergic. Options that are available to the patient include skin testing, desensitization, graded dose challenge, or rechallenge.[124,125] Patients with negative tests should be educated on the importance of not continuing to identify as having an allergy.

Skin Testing

Skin testing followed by an optional oral challenge can be used to assess reactive risk to some drugs, but many of the testing procedures have not been validated and are not available for most culprit drugs. PST is the only available commercial product in the United States used to determine true allergenicity. PST should not be performed in patients with a history of severe mucocutaneous reactions (eg, SJS, TEN) or other nonimmediate reactions (eg, serum sickness, vasculitis, and hepatitis).

10 PST 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. PST in advance of the need for penicillin treatment in patients with a history of penicillin allergy does not induce sensitization.[126] Testing for the major penicillin determinant is accomplished with penicilloyl-polylysine (PPL; Pre-Pen), a product reintroduced in the United States in 2009. 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.[36,127] If left in solution to "age," penicillin G will not spontaneously degrade to form the other minor determinants, penilloate and penicilloate.[3] 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.[36,38] Skin testing with the major and minor determinants facilitates the safe use of penicillin in up to 90% of patients with a history of immediate penicillin allergy.[36] In patients who report a history of penicillin allergy but are skin test negative, the risk of resensitization (eg, conversion to a positive skin test result) after a course of penicillin ranges from 1% to 28%.[128] The procedure for performing PST is described in Table e108-3. In Europe, skin testing can be accomplished with a kit containing both the major and minor determinant mixture (Diater Labs, Madrid, Spain).[75]

TABLE e108-3

Procedure for Performing Penicillin Skin Testing

Step 1: Prick Test

This will be performed first on the patient, before proceeding to intradermal testing.

1. Clean the volar surface of either forearm with an alcohol swab.
2. Using an ink pen, draw 3 vertical lines approximately 1 in. (2.5 cm) apart on the designated testing site of the arm.
3. Draw up 0.1 mL of the four solutions (Pre-pen, diluted Penicillin G, histamine positive control, and saline negative control) in four separate allergy syringes.
4. Apply a small drop of each solution to the separate pre-marked sites on the testing arm.
5. The histamine test site should be the most distal site from the elbow, followed up the arm by saline, Pre-Pen, and Pen G
6. Puncture the epidermis using a twisting motion with a sterile 22-28 gauge needle at each drop site. Do not draw blood. Little pressure is required.
7. Read the test in 15-20 minutes: (document test results below)

   Test is **negative:** change in diameter of the wheal is **less than** 3 mm than that observed with the negative control. **Proceed to intradermal test.**

   Test is **positive:** change in diameter of the wheal is **greater than** 3 mm than that observed with the negative control. As soon as a positive response is observed, the solution should be wiped off the skin. **Do not proceed to intradermal test.**

   The positive control (histamine skin test) should be positive to ensure the results are not falsely negative.

   The negative control (saline skin test) should be negative. If a wheal >2-3 mm develops after 20 minutes, repeat prick skin test. Upon retesting, if control still creates a wheal >2-3 mm after 20 minutes, discontinue test and notify the appropriate clinician (eg, ID physician, ID stewardship pharmacist, Allergist).

Step 2: Intradermal Test

Only conduct this test if the patient produced a negative result with the prick test in step 1.

1. Select five sites on the volar surface on the forearm. These sites should be on the opposite arm from the prick test if possible.
2. Using a 26-30 gauge, short bevel needle, intradermally inject 0.02 mL of Pre-Pen solution **twice** (separate at least 2 cm apart). Mark the margins of the initial blebs with an ink pen.
3. Using separate needles and syringes, intradermally inject diluted Pen G (0.02 mL = 200 units of penicillin) **twice** (separate at least 2 cm apart) and 0.02 mL of saline (separate at least 5 cm apart from other sites).
4. Read in 20 minutes: (document test results below)

   Test is **negative**: there is no increase in the original bleb and no greater reaction than the negative control site.

   Test is **positive**: bleb or wheal increases >2 mm from its original size or is >2 mm larger than the negative control. **Patient is NOT to receive penicillin.**

Step 3: (Optional) Oral Penicillin Challenge

1. If deemed necessary by ordering clinician

   Oral penicillin (eg, amoxicillin 250 mg) challenge or graded challenge of target drug in a monitored setting for 30-45 minutes.

Data from Reference 134.

A negative PST result indicates that the risk of life-threatening immediate reactions is extremely low with the 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 antibiotic. Certain patients (eg, those with dermatographism, taking H_1 antihistamines) may be unsuitable for PST because a false-positive or false-negative test may result. To

prevent interference with skin testing, drugs with antihistaminic properties should be discontinued 48 to 72 hours before skin testing, especially H_1 antagonists. Penicillin is the only drug for which the predictive value of skin testing has been well established. Although the negative predictive value is high, PST with the major and minor determinants does not identify patients who are at risk for unique side-chain–mediated reactions to β-lactams (eg, third-generation cephalosporins, piperacillin). Dilute concentrations of amoxicillin and piperacillin have been used to skin test for side chain–mediated reactions.[44–46] The value of skin testing to predict the risk of allergic reactions to other antibiotics (eg, sulfonamides, tetracyclines, and fluoroquinolones) is largely unknown.[127]

Skin testing is also used to identify patients at risk for hypersensitivity reactions to carboplatin. The negative predictive value of intradermal skin testing with carboplatin is 98% to 99% in patients who have received several treatment courses.[72]

Temporary Induction of Drug Tolerance and Desensitization

11 For some patients with a 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 (eg, neurosyphilis requiring penicillin). 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 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.[14] Induction of drug tolerance can involve a variety of drug mechanisms, including IgE-mediated immune mechanisms, non-IgE mechanisms, pharmacologic mechanisms, and undefined mechanisms (see Table e108-4).[3] 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 method to induce drug tolerance, specifically refers to the process in which 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 (eg, anaphylaxis to penicillin).[3] Immediate reactions most amenable to desensitization include dermatologic (eg, flushing, pruritus, urticaria, and angioedema), upper and lower respiratory tract (eg, sneezing, dyspnea, and wheezing), gastrointestinal (eg, abdominal pain, nausea and vomiting), and cardiovascular (eg, hypotension).[75] Procedures to induce drug tolerance should not be used in patients with a history of severe non-IgE reactions to a drug such as DRESS, SJS, TEN, exfoliative dermatitis, hemolytic anemia, or hepatitis.

TABLE e108-4

Characteristics of Drug Tolerance Protocols

Underlying Mechanism	Initial Dose	Duration of Protocol	Potential Outcome of Process	Example
Immunologic IgE (desensitization)	Micrograms	Hours	Desensitization; renders mast cells less responsive to degranulation	Anaphylaxis to β-Lactam antibiotics; taxanes
Immunologic non-IgE	Milligrams	Hours to days (eg, 6 hours-10 days)	Not known	Delayed cutaneous reactions to trimethoprim–sulfamethoxazole
Pharmacologic	Milligrams	Hours to days (eg, 2 hours-5 days)	Cautious induction of a reaction followed by a shift in a metabolic process	NSAID-exacerbated respiratory disease
Undefined	Micrograms to milligrams	Prolonged; days to weeks	Not known	Isolated cutaneous reactions to allopurinol

Adapted from Solensky R, Khan DA. Drug allergy: An updated Practice Parameter. Ann Allergy Clin Immunol. 2010;105:259-273.

All procedures to induce drug tolerance should be performed by a physician experienced in the risks and management of severe allergic reactions in a

monitored 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 evaluation of the patient's history of the reaction with consideration to the specific inciting drug and the suspected underlying mechanism of drug intolerance (eg, IgE mechanism vs non-IgE mechanism vs pharmacologic mechanism). The starting dose for a desensitization procedure is typically 1/1,000th of the final therapeutic dose, and the procedure can be completed within 4 to 12 hours.[3,38] 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.[73,75] 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 with three 10-fold diluted solutions. This method has been tested in nearly 800 patients, including patients with cystic fibrosis and allergy to antibiotics.[75] In high-risk patients, desensitization is achieved with either a 16- or a 20-step protocol.[73,75]

In the case of penicillin or β-lactam allergy, desensitization should be performed with the specific β-lactam antibiotic that will 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) are not routinely advised because these agents may mask the early signs of acute reactions and do not reliably reduce the severity of acute reactions. 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 medications should undergo desensitization with oral drugs. 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. A protocol for IV cephalosporin desensitization is listed in Table e108-5. Protocols for desensitization with other β-lactam antibiotics are also available.[129] The use of standardized antibiotic desensitization protocols is recommended to reduce the potential for medication error and better achieve the goals of antimicrobial stewardship.[130] It is important to note that unlike a negative PST, successful desensitization does not remove the allergy long-term from the medical record, but only allows for administration of the agent at that time.

TABLE e108-5

Induction of Drug Tolerance Protocol for IV Cephalosporin[a]

Preparation of Solutions					
	Volume of Diluents (eg, 0.9% NSS)			Total to be Injected in Each Bottle	Final Concentration (mg/mL)
Solution 1	250 mL			10 mg	0.04
Solution 2	250 mL			100 mg	0.4
Solution 3	250 mL			1,000 mg	4
Induction of Drug Tolerance Protocol					
Step	**Solution**	**Rate (mL/hr)**	**Time (min)**	**Administered Dose (mg)**	**Cumulative Dose (mg)**
1	1	2	15	0.02	0.02
2	1	5	15	0.05	0.07
3	1	10	15	0.1	0.17
4	1	20	15	0.2	0.37
5	2	5	15	0.5	0.87
6	2	10	15	1	1.87
7	2	20	15	2	3.87
8	2	40	15	4	7.87
9	3	10	15	10	17.87
10	3	20	15	20	37.87
11	3	40	15	40	77.87
12	3	75	184.4	922.13	1,000

NSS, normal saline solution.

[a]Full dose equals 1,000 mg. Total time was 349.4 minutes.

Adapted from Solensky R, Khan DA. Drug allergy: An updated Practice Parameter. Ann Allergy Clin Immunol. 2010;105:259-273.

Most reactions to trimethoprim–sulfamethoxazole in HIV-infected patients are non-IgE-mediated, and several protocols to induce tolerance to trimethoprim–sulfamethoxazole have been described. The preferred regimen is not known because the regimens have not been compared in controlled clinical trials. Tolerance to trimethoprim–sulfamethoxazole can be achieved within 2 days in most HIV-infected patients.[3] This can be accomplished with the following schedule of oral doses (milligrams of sulfamethoxazole–trimethoprim): day 1: 9 am, 4 and 0.8 mg; 11 am, 8 and 1.6 mg;

1 pm, 20 and 4 mg; 5 pm, 40 and 8 mg; day 2: 9 am, 80 and 16 mg; 3 pm, 160 and 32 mg; 9 pm, 200 and 40 mg; day 3: 9 am, 400 and 80 mg, and 400 and 80 mg daily thereafter. With this regimen, the failure rate was associated with higher relative and absolute $CD4^+$ cell counts. Other investigators have described a 6-hour oral regimen in HIV-infected patients and a more gradual 9-day oral regimen. Induction of drug tolerance should not be attempted in any patient with a 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.[103,131] Nearly all patients with aspirin-induced asthma and urticaria/angioedema can be effectively desensitized to subsequently receive aspirin for the treatment of cardiovascular disease.[102]

Graded Challenge and Rechallenge

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. Unlike desensitization, a graded drug challenge does not modify the immune or nonimmune response to the drug.[3,120] 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.[129] Graded challenge protocols have been described for the slow introduction of furosemide in a patient with heart failure and a history of sulfonamide allergy.[132,133] Challenge dosing is not recommended in patients with a history of a severe drug allergy (eg, anaphylaxis, SJS, and 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.[129] If no reaction occurs to the initial dose, the dose may be increased in two- to five-fold increments and administered every 30 to 60 minutes until the full therapeutic dose is achieved.[46,129] There is no standard protocol for graded challenge dosing but two- and three-step protocols are described. Although the risk of breakthrough infections is low, graded challenges should be performed in monitored settings.

Low-risk individuals who have a remote allergy to penicillin or other antibiotics that is unlikely to be IgE-mediated can be safely challenged with a therapeutic dose to confirm tolerance.

CONCLUSION

The approach to the evaluation and management of drug allergy has evolved over the past several decades from prohibitive to proactive. The discovery of a drug allergy previously eliminated certain preferred pharmacotherapeutic options. More current evidence-based approaches based on an understanding of the immunologic mechanisms of drug allergy now allow the use of first-line medications in many patients. As a result, clinical and organizational outcomes improve when drug allergy optimization practices are incorporated into routine clinical care.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
APC	antigen presenting cell
ARBs	angiotensin-receptor blockers
CI	confidence interval
CNS	central nervous system
COX	cyclooxygenase
CYP	cytochrome P-450

DHR	drug hypersensitivity reaction
DRESS	drug rash with eosinophilia and systemic symptoms
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICON	International CONsensus
IgE	immunoglobulin E
IVIG	intravenous immunoglobulin
LT	leukotriene
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PAF	platelet-activating factor
PG	prostaglandin
PPD	purified protein derivative
PST	penicillin skin testing
SCAR	serious cutaneous adverse reaction
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SSLD	serum sickness–like disease
TEN	toxic epidermal necrolysis

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SELF-ASSESSMENT QUESTIONS

1. In a patient with a history of anaphylaxis to penicillin G, which of the following statements is correct?

   A. The risk of a cross-reaction to an antipseudomonal penicillin is low, averaging 10%.

   B. The risk of a cross-reaction to a first-generation cephalosporin is <7.5%.

   C. The risk of a cross-reaction to a third-generation cephalosporin is 5% to 7.5%.

   D. The risk of a cross-reaction to imipenem or meropenem is about 50%.

2. An anaphylactoid reaction differs from an anaphylactic reaction in which of the following ways?

   A. An anaphylactoid reaction does not involve an IgE-mediated mechanism.

   B. An anaphylactoid reaction only occurs on first exposure to a drug and does not recur on subsequent drug exposure.

   C. An anaphylactoid reaction does not cause bronchospasm.

   D. An anaphylactoid reaction is not responsive to treatment with epinephrine and/or corticosteroids.

3. Which of the following statements is false regarding reactions to aspirin?

   A. About 20% of patients with asthma are sensitive to aspirin.

   B. Patients who develop aspirin-induced asthma are generally sensitive to other COX-1 NSAIDs.

   C. Aspirin is believed to cause allergic-like reactions by blocking cyclooxygenase which facilitates the production of alternative arachidonic acid metabolites.

   D. Aspirin desensitization has not been shown to improve asthma scores and symptoms in aspirin-sensitive patients.

4. Which of the following statements is correct regarding the risk of hypersensitivity to the sulfonamide class of agents?

   A. The risk is less with the sulfonamide antibiotics as compared with the sulfonamide nonantibiotics (eg, thiazides, sulfonylureas).

   B. Cross-reactivity between the sulfonamide antibiotics and nonantibiotics is about 50%.

   C. Trimethoprim–sulfamethoxazole is considered the least allergenic sulfonamide agent.

   D. The risk of allergic or allergic-like reactions to sulfonamides is increased in HIV-infected patients and those with other immunocompromised states.

5. Which of the following statements is true regarding a type III (immune complex) allergic drug reaction?

   A. Occurs within 24 hours of initial drug exposure

   B. Involves complement activation in response to the antigen–antibody complex

   C. Typically manifests as an allergic blood disorder

   D. Is synonymous with a delayed hypersensitivity reaction

6. Which antibody is involved in a type I allergic drug reaction?

   A. IgE

   B. IgG

   C. IgM

   D. IgA

7. Which of the following is false regarding allergic or allergic-like reactions with radiocontrast agents?

   A. The risk is greater in women and patients with a history of atopy or asthma.

   B. An allergy to seafood predisposes to radiocontrast reactions.

C. Reactions to radiocontrast media can largely be prevented by appropriate screening mechanisms and pretreatment with prednisone and diphenhydramine.

D. Skin testing with different radiocontrast agents may help identify a product with a low reactive risk

8. Which of the following patients is an appropriate candidate for skin testing for penicillin allergy?

A. A patient with a history of Stevens-Johnson syndrome associated with piperacillin

B. A patient with a history of drug rash with eosinophilia and systemic symptoms (DRESS) associated with amoxicillin

C. A patient with a history of a diffuse maculopapular rash with ampicillin–sulbactam

D. A patient with a history of bronchospasm and urticaria with penicillin G

9. Is the following statement true or false? The low-osmolar (nonionic) radiocontrast agents have a greater frequency of allergic-like reactions compared with the high-osmolar agents.

A. True

B. False

10. The subtypes of type IV allergic drug reactions are differentiated based on which of the following features?

A. The type of responding antibody (eg, IgG, IgA, IgM, and IgE)

B. The presence or absence of pruritus as a manifestation of the reaction

C. The responding T cell (eg, T helper type I cell, T helper type II cell, and cytotoxic T cell)

D. The onset of the reaction (eg, less than 24 hours vs greater than 24 hours after drug exposure)

11. Which of the following statements reflects the primary differentiating feature between graded challenge dosing and desensitization?

A. Graded challenge allows for more rapid modification of the immune response and a faster time to desensitization.

B. Graded challenge is used when the risk of a severe reaction to a drug on reexposure is considered to be low.

C. Desensitization is effective in patients with a wider range of allergic reactions including severe skin reactions (eg, Stevens–Johnson syndrome, toxic epidermal necrolysis).

D. Graded challenge is only performed using oral doses of the offending allergenic drug.

12. A negative penicillin skin test is unable to predict if the patient will have side-chain–mediated reactions to beta-lactams.

A. True

B. False

13. Which of the following is the correct dose of epinephrine for anaphylactic reactions in an adult?

A. 0.01-0.03 mg

B. 0.3-0.5 mg

C. 0.5-1 mg

D. 1-2 mg

14. Which of the following allergic drug reactions may be IgM-mediated?

    A. Type I

    B. Type II

    C. Type III

    D. Type IV

15. In type I allergic reactions, allergens bind to which immune cells resulting in the release of inflammatory mediators?

    A. T cells

    B. Basophils

    C. Cytokines

    D. Eosinophils

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** The risk of cross-reaction to a first- and second-generation cephalosporin in a patient with a history of anaphylaxis to penicillin G is 7.5%. The rate drops to 1% for third- and fourth-generation cephalosporins.

2. **A.** Anaphylactoid reactions are non-IgE-mediated while anaphylactic reactions are IgE-mediated.

3. **D.** Aspirin desensitization can be effective for patients with aspirin-induced asthma and symptoms (urticaria, angioedema)—especially if they have a cardiac indication for asthma.

4. **D.** Adverse reactions to trimethoprim-sulfamethoxazole occur in about 50% to 80% of AIDS patients and 10% of other immunocompromised patients. A is incorrect as the risk of hypersensitivity is greater with sulfonamide antibiotics. B is incorrect as cross-reactivity between sulfonamide antibiotics and nonantibiotics is highly unlikely. C is incorrect as trimethoprim-sulfamethoxazole is considered the most allergenic sulfonamide agent.

5. **B.** Type III reactions are in response to antigen-antibody complexes in the blood that cause complement activation. A is incorrect because type III reactions are delayed and manifest >72 hours to weeks from exposure. C is incorrect as it manifests as vasculitis or serum sickness disorder. D is incorrect as type III is not the only delayed reaction type.

6. **A.** Type I reactions are IgE-mediated.

7. **B.** Seafood or iodine allergies do not predispose a patient to radiocontrast reactions.

8. **D.** Patients with a history of an IgE-mediated hypersensitivity reaction to a penicillin are appropriate candidates for penicillin skin testing. A and B are incorrect because skin testing should not be conducted in patients with severe non-IgE mediated reactions. C is incorrect as maculopapular rash is not an IgE-mediated reaction.

9. **B.** The low-osmolar agents cause fewer allergic-like reactions.

10. **C.** The subtypes of type IV allergic drug reactions are differentiated between the type of responding T cell and not the manifestation or timing of reaction—making choices B and D incorrect. Type IV reactions are not antibody mediated so answer A is incorrect.

11. **B.** Since graded challenge dosing does not modify the immune/nonimmune response to a drug, it is used when the risk of a severe reaction to a drug is low upon reexposure. A is incorrect as a graded challenge is slower than desensitization. C is incorrect as a graded challenge should not be used in patients with a history of a severe drug allergy. D is incorrect as drugs other than the offending allergenic drug may be used.

12. **A.** Patients may still be susceptible to unique side-chain mediated reactions.

13. **B.** The adult dose is 0.3 to 0.5 mg. Typically, the dose is 0.01 mg/kg up to 0.3 mg for children and 0.5 mg for adults.

14. **C.** Type III reactions may be IgG- or IgM-mediated and are characterized by antigen-antibody complexes.

15. **B.** Allergens bind to IgE on basophils in type I reactions. A is incorrect as T cells are involved in Type IV reactions. C is incorrect as cytokines may be released following T cell activation in Type IV reactions. Eosinophils are seen in response to Type IVa reactions making D incorrect.