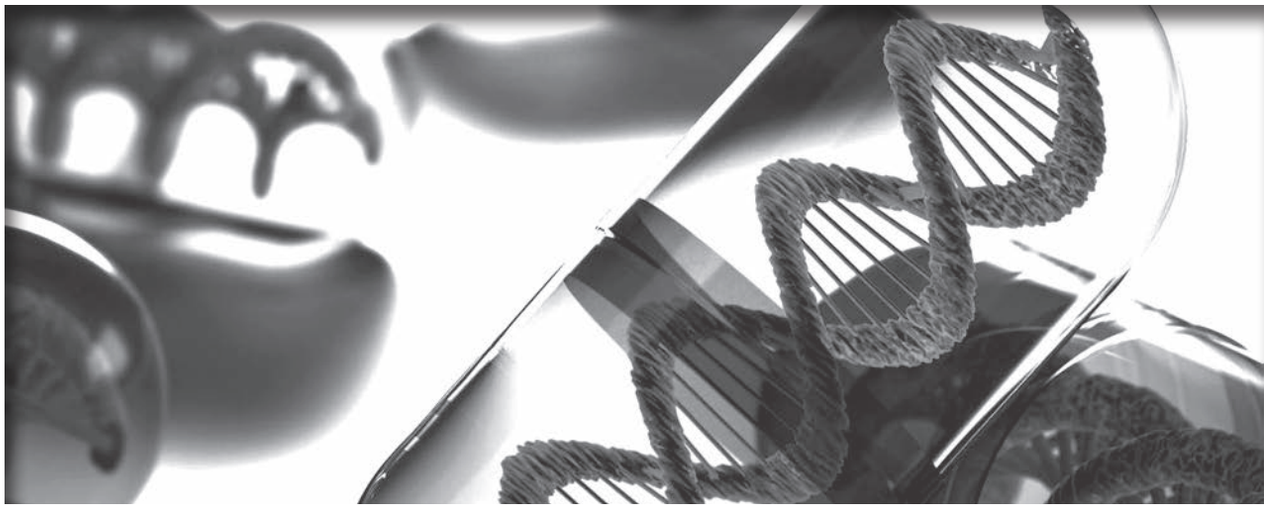

CHAPTER 6

Drug Allergy and Cutaneous Diseases

Lynne M. Sylvia

The terms *drug allergy* and *drug hypersensitivity* are often used synonymously to describe adverse drug reactions mediated by the immune system. According to the International Consensus (ICON) on Drug Allergy, these terms should not be used interchangeably.[1] Drug allergy refers to reactions for which a definite immune mechanism has been proven.[1] The parent drug or its reactive metabolite serves as an antigen, which is subsequently recognized and processed by the immune system, culminating in the production of drug-specific antibodies or sensitized T lymphocytes. The antigen–antibody reaction can target a variety of cells and body tissues, leading to organ-specific or more generalized systemic adverse events. The expert panel on drug allergy recommends that the term *drug hypersensitivity reaction* be used for adverse events that clinically resemble allergy but may or may not be mediated by an immune response.[1] Drug hypersensitivity reactions (DHRs) are more heterogeneous in clinical presentation and underlying mechanism. The implicated drug often has the ability via its chemistry or pharmacology to directly stimulate the release or activation of inflammatory mediators from mast cells, basophils, or other body tissues, causing a reaction that is clinically indistinguishable from drug allergy. The term *drug pseudoallergy*, to describe allergic-like reactions, is no longer recommended. A comparison of the features of drug allergy and DHRs is provided in **Table 6-1**.

Cutaneous eruptions, the most common manifestation of drug-induced disease, can result from both immune- and nonimmune-mediated mechanisms (e.g., pharmacologic effects, idiosyncratic). Therefore, drug-induced skin eruptions and systemic skin diseases are discussed in a separate section of this chapter. Allergic-mediated urticaria, angioedema, and the immune complex diseases associated with dermatologic manifestations (serum sickness-like syndrome, vasculitis) will be discussed in the following section.

DRUG ALLERGY AND DHRs

CAUSATIVE AGENTS

A list of the drugs most frequently implicated in drug allergy is provided in **Table 6-2**.[2,4-139] If a particular drug of concern is not included in this table, it should not be assumed that the drug is

Table 6-1 Differentiating Features of Allergy Versus Drug Hypersensitivity Reactions[1-3]

Characteristic	Allergy	Drug Hypersensitivity Reactions
Clinical presentation	Highly variable; ranging from a localized erythematous rash to life-threatening reactions including anaphylaxis, Stevens–Johnson syndrome, and toxic epidermal necrolysis	Highly variable; ranging from infusion-related reactions such as skin flushing to severe reactions mimicking anaphylaxis
Sensitization period	Required; usually ranging from 5 to 21 days after drug initiation	Not required; reaction can occur within seconds to minutes after administration of first dose
Antibody involvement	Yes; IgE, IgG, IgM, or sensitized T lymphocytes	Not proven; may or may not be mediated by an immune response
Mechanism	Drug can serve as a complete antigen or hapten (parent drug or metabolite) or may bind to T-cell receptor to stimulate immune response	Based on its chemical or pharmacologic properties, drug stimulates release or activation of inflammatory mediators
Risk factors	Highly variable; dependent on drug or patient (host)	Highly variable; dependent on drug or patient (host)
Pretreatment	Not routinely recommended; yield of antibody produced by any given antigenic drug too unpredictable to fully antagonize via pretreatment	Pretreatment regimens are recommended for some drugs; may be recommended to block effects of drug on effector pathways
Treatment	Dependent on signs and symptoms of reaction; includes antihistamines, epinephrine, and corticosteroids	Dependent on signs and symptoms of reaction; may include dose reduction, alteration in rate of infusion, or treatment with antihistamines, epinephrine, or corticosteroids

IgE = immunoglobulin E, IgG = immunoglobulin G, IgM = immunoglobulin M.

Table 6-2 Agents Implicated in Allergic Drug Reactions

Drug	Incidence	Level of Evidence[a]
ANAPHYLAXIS, URTICARIA, ANGIOEDEMA, AND BRONCHOSPASM		
Amphotericin B[4,5]	NK	C
Aprotinin[6]	NK	C
L-asparaginase[7]	NK	C
Aspartame[8,9]	NK	C
Aspirin[10,11]	NK	C
Atracurium[12-14]	NK	C
Azathioprine[15,16]	NK	C
Basiliximab[17]	NK	C
Carboplatin[18]	NK	C
Carboxymethylcellulose[19]	NK	C
Ceftriaxone[20]	NK	C
Cephalosporins[21,22]	0.001–0.1%	C
Cetirizine[23]	NK	C
Cetuximab[24,25]	NK	C
Chlorhexidine[26,27]	NK	C
Chymopapain[28]	NK	C
Cisplatin[7]	NK	C
Clopidogrel[29,30]	NK	C

Table 6-2 Agents Implicated in Allergic Drug Reactions (continued)

Drug	Incidence	Level of Evidence[a]
Clavulanic acid[31]	NK	C
Deferoxamine[32]	NK	C
Diclofenac[10]	NK	C
Etoposide[7]	NK	C
Excipients[8,9,19,33]	NK	C
Fluoroquinolones[34,35]	NK	C
Gentamicin[36]	NK	C
Ibuprofen[10]	NK	C
Infliximab[37]	NK	C
Insulin[38]	NK	C
Iron (intravenous products)[39-41]	NK	C
Isoniazid[42,43]	NK	C
Ketoprofen[44]	NK	C
Lepirudin[45]	NK	C
Leuprorelin[46]	NK	C
Mefenamic acid[10]	NK	C
Mivacurium[14]	NK	C
Omalizumab[47]	0.2%[a]	C
Oxaliplatin[48,49]	NK	C
Paclitaxel[50]	NK	C
Pantoprazole[51]	NK	C
Penicillins[52,53]	0.01–0.05%	B
Phytonadione[54]	NK	C
Polysorbate 80[33]	NK	C
Povidone–iodine[55,56]	NK	C
Prasugrel[57]	NK	C
Protamine[2]	NK	B
Risperidone[58]	NK	C
Rituximab[37]	NK	C
Rocuronium[59]	NK	C
Sodium benzoate[33,60]	NK	C
Streptokinase[61]	NK	C
Sumatriptan[62]	NK	C
Suxamethonium[63]	NK	C
Teniposide[7]	NK	C
Thiopental[12]	NK	C
Ticagrelor[64]	NK	C
Tobramycin[65]	NK	C
Triamcinolone[66]	NK	C
Vancomycin[67]	NK	C
Zidovudine[68]	NK	C

Table 6-2 Agents Implicated in Allergic Drug Reactions (continued)

Drug	Incidence	Level of Evidence[a]
SERUM SICKNESS-LIKE REACTION		
β-lactam antibiotics[69]	NK	C
Bupropion[69-72]	NK	C
Cefaclor[73-75]	NK	B
Ciprofloxacin[76]	NK	C
Fluoxetine[77]	NK	C
Itraconazole[78]	NK	C
Meropenem[79]	NK	C
Minocycline[80-82]	NK	C
Protamine[2]	NK	C
Rituximab[83]	NK	C
Streptokinase[84,85]	NK	C
Sulfites[9,33]	NK	C
Sulfonamides[69]	NK	C
Vaccines[69]	NK	C
VASCULITIS		
Allopurinol[86-88]	NK	C
β-lactam antibiotics[86-88]	NK	C
Celecoxib[89]	NK	C
Cephalosporins[86-88]	NK	C
Colony-stimulating factors[87]	NK	C
Docetaxel[90]	NK	C
Etanercept[87]	NK	C
Fluticasone[91]	NK	C
Fluoroquinolones[87]	NK	C
Hydralazine[87]	NK	C
Infliximab[92]	NK	C
Interferon α-2b[93]	NK	C
Isotretinoin[87]	NK	C
Leukotriene antagonists[94]	NK	C
Methimazole[87]	NK	C
Methotrexate[87]	NK	C
Minocycline[87]	NK	C
Nonsteroidal anti-inflammatory drugs[87]	NK	C
Penicillamine[87]	NK	C
Phenytoin[87]	NK	C
Propylthiouracil[95,96]	NK	C
Rofecoxib[97]	NK	C
Vancomycin[87,98]	NK	C

Table 6-2 Agents Implicated in Allergic Drug Reactions (continued)

Drug	Incidence	Level of Evidence[a]
HYPERSENSITIVITY SYNDROMES		
Abacavir[99,100]	NK	B
Allopurinol[101-103]	NK	C
Carbamazepine[104,105]	NK	B
Dapsone[106-108]	NK	C
Lamotrigine[109]	NK	C
Minocycline[110]	NK	C
Nevirapine[111]	NK	C
Oxcarbazepine[105]	NK	C
Paclitaxel[7]	NK	C
Phenytoin[105]	NK	C
Phenobarbital[105]	NK	C
Valproic acid[112]	NK	C
ALLERGIC-MEDIATED BLOOD DISORDERS		
Cephalosporins[113-115]	NK	C
Heparin[116]	1–5%	B
Histamine H_2-receptor blockers[117-119]	NK	C
Methimazole[120,121]	NK	B
Methyldopa[114]	NK	C
Penicillins[114,115]	NK	C
Piperacillin[122,123]	NK	B
Procainamide[114]	NK	C
Propylthiouracil[120,121]	NK	B
Quinidine[114,115]	NK	C
Quinine[114,115,124]	NK	C
Trimethoprim–sulfamethoxazole[125]	NK	C
Valproic acid[126]	NK	C
Vancomycin[127,128]	NK	C
OTHER		
Cimetidine[129]	NK	C
Clindamycin[130]	NK	C
Corticosteroids[131,132]	NK	C
Diazepam[133]	NK	C
Hetastarch[134]	NK	C
Insulin[38,135]	NK	C
Lidocaine[136]	NK	C
Progesterone[137]	NK	C
Psyllium[138]	NK	C
Vaccines[139]	NK	C

NK = not known.

[a]Definitions for Levels of Evidence: Level A—evidence from one or more randomized, controlled clinical trials; Level B—evidence from nonrandomized clinical trials, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analyses and/or postmarketing surveillance studies; and Level C—evidence from one or more published case reports or case series.

incapable of eliciting an immune response. Many drugs are not identified as antigenic until well after approval and use in an extended patient population. To determine a drug's potential to serve as an antigen, three drug-related properties should be considered. First, the molecular weight of a drug can influence its antigenicity. Drugs of molecular weight >4,000 Da, such as erythropoietin, insulin, or other polypeptide hormones, are more capable of serving as complete antigens than are low-molecular-weight drugs (<1,000 Da).[140] Biologic agents (e.g., antisera, antithymocyte globulin, intravenous immunoglobulin) also fit into this category of large polypeptides. Second, drugs containing foreign proteins or large polypeptides of nonhuman origin (e.g., streptokinase, beef or pork insulin, chimeric/murine-derived monoclonal antibodies, L-asparaginase) have the ability to serve as complete antigens.[1,140] However, the most common antigenic drugs (e.g., penicillins, sulfonamides) are of low molecular weight (<1,000 Da) and do not contain a foreign protein. These agents possess a third drug-related property related to conferring antigenic potential, which is the ability of the parent drug or its reactive metabolite to bind covalently to a carrier protein in vivo, thereby forming a complete antigen. The term *hapten* is used to describe a drug (or a metabolite) that must bind to a tissue or cell protein to serve as a complete antigen.[1] Identifying a drug's reactive metabolites and the potential of these metabolites to bind to carrier proteins is not readily achieved in premarketing studies; thus, the allergic potential of many low-molecular-weight drugs is not determined until postmarketing.

Drugs that are commonly associated with DHRs are listed in **Table 6-3**.[141-161] A drug's ability to cause a nonimmune DHR can often be assessed by a review of the drug's chemical and/or pharmacologic properties. Classic examples are anaphylactoid reactions to radiocontrast media, opioid-induced urticaria or generalized pruritus, red man syndrome with vancomycin, and nonsteroidal anti-inflammatory drug (NSAID)-induced asthma or angioedema.

When reviewing Tables 6-2 and 6-3, it should be noted that some drugs are listed as causing both allergy and DHRs. For example, vancomycin-induced red man syndrome is thought to be a nonimmune DHR, whereas vancomycin-associated blood dyscrasias and anaphylaxis are attributed to more rare allergic reactions.[67,127,128] Captopril, ciprofloxacin, and protamine have also been reported to cause both true allergy and nonimmune DHRs. Intravenous immunoglobulin G (IVIG) is most commonly associated with infusion-related reactions such as fever and arthralgias. However, IVIG can also cause an IgE-mediated reaction in patients with selective IgA deficiency.[3] In situations in which a drug can cause both types of reactions, it is often difficult to distinguish between allergy and a nonimmune DHR. Most importantly, the signs, symptoms, and severity of the reaction, rather than its mechanism, should drive clinicians' decision-making.

EPIDEMIOLOGY

Collectively, drug allergy, intolerance, and nonimmune DHRs have been estimated to comprise 25% of all adverse drug events.[2] Drug allergy is considered to be relatively rare, representing 6–10% of all adverse drug reactions.[2,162] In 2002, Hunziker et al.[163] provided an analysis of 12,785 adverse drug reactions of probable or definite association occurring in inpatients between 1974 and 1993. Drug allergy and nonimmune DHRs accounted for 13% of the adverse drug reactions. Differentiation between allergy and nonimmune DHRs as the cause of the adverse event could not be achieved because of the lack of valid skin testing or other in vitro testing methods to determine the presence of drug-specific antibodies.[163]

The epidemiology of anaphylaxis, including drug-induced anaphylaxis, has been re-evaluated by a working group composed of experts in allergy and immunology.[164] The expert panel estimated the frequency of anaphylaxis in 2006 to be 50–2,000 episodes per 100,000 persons, or a lifetime prevalence of 0.05–2%.[164] More recent estimates suggest that the prevalence is increasing, particularly in younger age groups and in patients treated with biologic agents. Neugut et al.[165] reported that the most serious cases of drug-induced anaphylaxis have been associated with the use of penicillin and radiocontrast media. Penicillin is recognized as the most common cause of anaphylaxis and is estimated to account for approximately 75% of fatal

Table 6-3 Agents Implicated in Nonimmune Drug Hypersensitivity Reactions

Drug	Incidence	Level of Evidence[a]
Adrenocorticotropic hormone	NK	C
Angiotensin-converting enzyme inhibitors[2,141-142]	0.1–0.2%	B
Angiotensin receptor blockers[143-146]	0.11%	B
Acetylsalicylic acid (aspirin)[10,11]	NK	C
Ciprofloxacin[147-149]	NK	C
Corticosteroids[150]	NK	C
Cremophor (polyethoxyethylated castor oil)-containing products[7,9]	NK	C
Enoxaparin[151]	NK	C
Infliximab[152-153]	NK	C
Levofloxacin[154]	NK	C
Midazolam[155]	NK	C
Muromonab[156]	NK	C
N-acetylcysteine[157]	NK	C
Nonsteroidal anti-inflammatory drugs[2]	NK	C
Ondansetron[158,159]	NK	C
Opioids[2,160]	NK	C
Paclitaxel[7]	NK	C
Polymyxin B	NK	C
Protamine[2]	0.06–10.7%	B
Radiocontrast media[161]	1.7%	B
Rituximab[37]	NK	C
Sacubitril	NK	C
Somatostatin	NK	C
Urokinase	NK	C
Vaccines[139]	NK	C
Vancomycin	NK	C

NK = not known.

[a]Definitions for Levels of Evidence: Level A—evidence from one or more randomized, controlled clinical trials; Level B—evidence from nonrandomized clinical trials, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analyses and/or postmarketing surveillance studies; and Level C—evidence from one or more published case reports or case series.

cases in the United States annually.[2] Nonfatal anaphylaxis attributed to penicillin has been reported in 0.7–10% of the general population, whereas fatal cases occur in 0.002% of the general population.[165] Non-IgE-mediated anaphylaxis (i.e., anaphylactoid reactions) associated with radiocontrast media have occurred in 0.22–1% of patients, particularly in those receiving an agent with high osmolarity.[165]

Angioedema is estimated to occur in 0.1–1.2% of patients treated with angiotensin-converting-enzyme (ACE) inhibitors.[141] However, as many as 25–38% of cases of angioedema presenting to the emergency department (ED) have been attributed to ACE inhibitor therapy.[166,167] In an 8-year retrospective study, 12 of 49 patients (24.5%) presenting to the ED with angioedema reported concomitant therapy with an ACE inhibitor.[166] A second retrospective case-control study revealed an association between ACE inhibitors and angioedema in 15 of 40 patients (38%) presenting to the ED.[167] Compared with a control group of patients without angioedema, patients presenting to the ED with angioedema were 5 times more likely to be taking an ACE inhibitor (OR 5.1, 95% CI 2.03–12.89).[167]

The incidences of allergy and nonimmune DHRs associated with the majority of implicated drugs are unknown. The estimated incidences of allergy and nonimmune DHRs associated with some implicated drugs are presented in Tables 6-2 and 6-3.

MECHANISMS

DRUG ALLERGY

The exact mechanisms by which drugs serve as allergens and elicit immune responses are not well understood. Gaps in our understanding of these mechanisms can be attributed, in part, to the lack of a validated animal model of drug allergy.[168] Another influencing factor is the difficulty in identifying and isolating the antigenic components and metabolites of potential drug allergens. Although much is unknown about the mechanisms by which drugs cause allergy, it is known that a single drug, such as penicillin, can cause a variety of allergic reactions via different mechanisms.[168] At least two theories—the prohapten/hapten concept and the p-i concept—have been described to explain the manner in which drugs stimulate the immune response. Each theory will be discussed separately.

PROHAPTEN/HAPTEN THEORY

In this theory, a number of complex stages appear to be involved in the generation of an immune response to a drug. These stages include the following:

1. Formation of a complete antigen
2. Processing of the complete antigen by antigen-presenting cells
3. Recognition of the antigenic determinant by T lymphocytes
4. Generation of a drug-specific antibody or sensitized T cells
5. Elicitation of a clinical immune response

STAGE 1: FORMATION OF A COMPLETE ANTIGEN

Most drugs that serve as immunogens are low-molecular-weight compounds (<1,000 Da) and are too small to initiate an immune response alone. To be recognized by the immune system, these drugs must bind, usually covalently, to a high-molecular-weight carrier protein, thereby forming a complete antigen. Haptens are drugs that bind to tissue or plasma proteins to form a complete antigen.[1,169] The parent drug rarely has the ability to bind to tissue or cell proteins. For most low-molecular-weight drug immunogens, the hapten is a reactive metabolite of the parent drug, formed via metabolism in the liver, skin keratinocytes, or white blood cells.[168,170] As an example, sulfamethoxazole is well recognized as a highly allergenic compound, but a reactive metabolite, the nitroso-sulfamethoxazole derivative, not the parent compound, serves as the primary hapten.[171] In this regard, the parent drug, sulfamethoxazole, would be considered a prohapten.

STAGE 2: PROCESSING OF THE COMPLETE ANTIGEN BY ANTIGEN-PRESENTING CELLS

Once a hapten–protein conjugate has been formed, it must undergo antigen processing. This crucial stage involves recognition of the complete antigen by antigen-presenting cells (APCs). A number of cells serve as APCs, including macrophages, dendritic cells, cutaneous Langerhans cells, and B lymphocytes.[168-170] With many drug immunogens, the complete antigen is believed to diffuse across the cell membrane of the APC and be internalized into the lysosomes of the APC. Metabolism by proteolytic enzymes in the lysosomes allows for breakdown of the complete antigen to a smaller, hapten–peptide fragment.[172] The last step in this stage of processing is the binding of the hapten–peptide fragment with major histocompatibility complex (MHC) class I or II molecules synthesized by the APC.[1,168,169] Expression of the hapten–MHC complex on the surface of the APC allows recognition by T lymphocytes and further progression of the immune reaction.

STAGE 3: RECOGNITION OF THE ANTIGENIC DETERMINANT BY T LYMPHOCYTES

The manner in which T-helper cells recognize the hapten–MHC complex is not fully understood. It is theorized that three signals must occur for T-helper cells to become activated.[168,170,173,174] The first signal is completed by the interaction of the hapten–MHC complex with an antigen receptor on the surface of

the T-helper cell. The second signal is believed to involve an interaction between specific receptors on the APC and the T-helper cell, resulting in the release of cytokines (cell messengers), such as interleukin (IL)-1 or IL-6. If this second signal does not occur, it is believed that the T-helper cells lose their responsiveness to the antigen, and the immune reaction ceases to progress.[168,174] Thus, some patients may process a drug allergen but the immune reaction may be blunted at this stage or at other stages in the process. The third signal involves activation of the CD4+ T lymphocytes with the release of specific cytokines from these activated T lymphocytes. Depending on the cytokines released, the T lymphocytes differentiate into either T-helper type 1 (Th1) or T-helper type 2 (Th2) cells.[173] Differentiation of the T-helper lymphocyte is an important step in the determination of the type of immune reaction to a specific drug allergen. Genetic factors are believed to influence T-helper-cell phenotyping in addition to influencing the type of cytokines released from activated T-helper cells. Dominance of cytokines IL-4 and IL-13 lead to the production of Th2 cells, whereas secretion of IL-2 and interferon β favors the production of Th1 cells.[175]

STAGE 4: GENERATION OF A DRUG-SPECIFIC ANTIBODY OR SENSITIZED T CELLS

Immune responses to a drug can lead to the generation of an antibody (humoral immune response) or sensitized T cells (cellular or delayed immune response). If a patient's response to an allergen is mediated by Th2 cells, a humoral response occurs with IgE, IgG, or IgM as the responding antibody. Th2 cells have the ability to secrete a number of cytokines, primarily IL-4 and IL-13, which stimulate the production of IgE from plasma cells. Th2 cells also secrete IL-5, which activates eosinophils, and IL-3 and IL-10, which are involved in mast cell differentiation.[174] Patients who have a Th1-dominant response to a drug are more likely to generate a cellular immune response with the production of drug-specific sensitized T lymphocytes.[2] At this stage of the immune process, memory cells (either T or B lymphocytes) are also produced to retain memory for the drug allergen. Memory cells allow for a faster onset of an immune reaction upon re-exposure to the antigen.

STAGE 5: ELICITATION OF A CLINICAL IMMUNE RESPONSE

Completion of stages 1 through 4 may not occur until days 5 to 21 of continued drug therapy. This period of sensitization explains the latency in the clinical presentation of the immune reaction. It is also important to consider that some patients may generate an antibody response to a drug allergen, but the event will not progress to a clinical reaction. For example, approximately 40% of patients treated with penicillin for at least 10 days produce drug-specific IgG without manifesting a hypersensitivity response.[2]

The p-i concept: A nonhapten pathway has also been described to explain drug allergy.[1,169,172] Some low-molecular-weight drugs may cause an immune response by "pharmacologically interacting with immune receptors."[1,172] Known as the p-i concept, these drugs do not require binding to a carrier protein or processing by APCs. This theory suggests that drugs bind directly to T-cell receptors in a reversible manner, similar to a ligand binding to a receptor. It is not known whether the drug first binds to the MHC molecule on the APC to signal T-cell activation or whether it directly binds to the T-cell receptor, stimulating the T-cell response. This concept appears most applicable to the initiation of delayed T-cell mediated-reactions, as opposed to humoral reactions.[1,172]

Mechanism-based classification of drug allergy: Since 1968, the Gell and Coombs[176] classification has been used to differentiate allergic drug reactions based on their mechanism and clinical presentation. Using this classification system, allergic reactions are described as types I through IV. It is important to consider that not all allergic drug reactions can be described using this classification. For example, some drug allergies exhibit features of more than one type (e.g., drug rash with eosinophilia and systemic symptoms [DRESS]). In addition, some allergies are mediated by antibodies not included in the classification (e.g., autoantibodies associated with procainamide-induced syndrome resembling systemic lupus erythematosus). The classification system was developed before our understanding of the varied roles of T cells in the immune response. As such, the original classification system has been

Table 6-4 Gell and Coombs Classification of Allergic Drug Reactions[1,2,176,177]

Classification	Timing	Antibody	Targeted Cells	Clinical Presentation
Type I (immediate)	Minutes to 1 hour; usually occurs after the second exposure to the drug; may be delayed for up to 48 hours after exposure	IgE	Mast cells, basophils	Anaphylaxis, isolated urticaria, angioedema, bronchospasm, abdominal cramping, respiratory arrest, cardiovascular collapse, arrhythmias, eosinophilia
Type II (delayed; cytotoxic)	>72 hours and up to weeks after continued initial exposure	IgG or IgM	Blood cells (red cells, platelets, mature neutrophils)	Cytopenias (hemolytic anemia, thrombocytopenia, some neutropenias) Vasculitides (some)
Type III (delayed; immune complex)	>72 hours and up to weeks after continued initial exposure	IgG or IgM	Skin, joint tissue, kidney, liver	Serum sickness-like illness Vasculitides (some) Glomerulonephritis, interstitial nephritis
Type IV (delayed; T-cell mediated)	Variable; >72 hours	Sensitized T lymphocytes	Skin, liver, kidney, lungs	See subtypes below
Type IVa	1–21 days	Th1 cells, interferon γ, monocytes, eosinophils	Skin	Tuberculin reaction, contact dermatitis
Type IVb	1–6 weeks	Th2 cells, interleukin-4, interleukin-5	Skin	Maculopapular rash with eosinophilia
Type IVc	4–28 days	Cytotoxic T cells, perforin, granzyme B, FasL	Skin	Bullous exanthems (SJS, TEN), fixed drug eruptions
Type IVd	>72 hours	T cells and interleukin-8	Skin	Acute generalized exanthematous pustulosis

IgE = immunoglobulin E, IgG = immunoglobulin G, IgM = immunoglobulin M, SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis, Th = T-helper.

adapted in **Table 6-4** to better represent our current understanding of drug allergy.[1,2,176,177]

It is currently recommended that drug allergies be classified as immediate or nonimmediate based on the onset of the reaction.[1,169] According to the ICON expert panel, immediate reactions are those that culminate in the production of an IgE-mediated response.[1] These reactions typically present as angioedema, bronchospasm, or anaphylaxis and usually occur within 1 hour after first re-exposure to the immunogenic drug. Nonimmediate or delayed drug allergies constitute a broader category of events including maculopapular exanthems, delayed urticaria, immune-mediated blood disorders, and serum sickness reactions. Nonimmediate events are typically mediated by activated T cells and occur at least 1 hour after initial drug exposure and up to weeks or months after initial exposure.[1,169] This classification system, as noted by the expert panel, has limitations because the presence of immune cofactors (e.g., viruses) and the route of drug administration may influence the onset or progression of the immune reaction.[1]

If a patient generates IgE as the responding antibody to a drug allergen, the event is classified as an immediate type I reaction. IgE is commonly referred to as a homocytotropic antibody because of its strong affinity for the Fc receptors on mast cells and basophils.[140] IgE avidly binds to basophils in the blood and mast cells located in the skin and respiratory and gastrointestinal tracts and the connective tissue surrounding the blood vessels.[178] When a patient is re-exposed to the allergenic drug, cross-linking occurs between the hapten–protein complex and IgE bound to the surface of mast cells, basophils, or both. Cross-linking between the drug and two molecules of IgE causes an influx of calcium ions that triggers degranulation of the mast cells and

basophils.[178] The end result is the extracellular release of a number of preformed inflammatory mediators such as histamine, heparin, and proteases. Influx of calcium also activates phospholipase A_2 and stimulates the release of arachidonic acids, which can be bio-transformed into a number of secondary mediators, including leukotrienes, prostaglandins, and platelet-activating factor.[164] The cytokine known as tumor necrosis factor α (TNFα) has also been implicated as a mediator. Collectively, these mediators of anaphylaxis can cause increased vascular permeability, a wheal-and-flare reaction, smooth-muscle contraction resulting in bronchospasm, nausea, vomiting, recruitment of inflammatory cells, activation of vagal pathways, decreased coronary blood flow, and delayed atrioventricular conduction.[179,180]

Nonimmediate type II cytotoxic reactions are usually mediated by IgG or IgM. During these reactions, the drug hapten typically binds to a cell-surface protein in the membrane of a blood cell (e.g., red cell, platelet, neutrophil).[113,114] A complexation reaction between the responding antibody (IgG or IgM) and the drug hapten bound to the surface protein leads to destruction of the affected cells (i.e., hemolysis, thrombocytopenia, neutropenia). Cell-bound antibody can also activate complement, a series of 25 plasma proteins that, when activated, assist in cell lysis.[113,114,175] Activated complement proteins possess a variety of properties, including the ability to degranulate mast cells (C3a, C5a), the ability to form a membrane attack complex (C5a and C9a), and the ability to stimulate opsonization to amplify the immune response.[175]

Nonimmediate type III reactions, commonly referred to as immune complex reactions, are usually mediated by IgG. During these events, the drug hapten typically forms a complete antigen by binding covalently with an amino acid component (such as the lysine or cysteine residues) of a plasma protein. The hapten–protein complex then stimulates the production of IgG. Binding between IgG and the circulating complete antigen results in the formation of immune complexes, which often circulate throughout the bloodstream and activate the complement cascade before depositing on targeted cells or tissues.[178] Complement-mediated migration of phagocytes and the release of pyrogens manifests as a fluid phase or serum sickness-like reaction consisting of fever, malaise, and lymphadenopathy. Activation of complement proteins C3a and C5a can also result in degranulation of mast cells with the release of histamine. Eventually, the immune complex may deposit in a variety of tissues, including the walls of blood vessels, glomerular cells, joint tissue, alveoli, and cells in the skin. After deposition on the targeted tissue, the immune complex, with the assistance of complement, mediates cell destruction.

Nonimmediate type IV reactions are subclassified as types IVa through IVd based on the responding T cell, effector mechanism, and clinical manifestations (Table 6-4). On exposure to the antigen, a specific subtype of T cell (e.g., Th1 cell, Th2 cell, cytotoxic T cell) orchestrates an inflammatory response through secretion of specific cytokines (IL-4, IL-5).[1,181] Type IV reactions involve a wide range of clinical events including contact dermatitis from a topically applied medication to more serious dermatologic events such as pustular and bullous exanthems. A complete review of the mechanisms by which drugs cause type IV reactions has been published.[181]

MECHANISMS OF DRUG HYPERSENSITIVITY REACTIONS

DHRs can also be classified as immediate or nonimmediate based on the timing of the event.[1] Drugs cause nonimmune DHRs by a number of mechanisms, including (1) direct stimulation of mast cells resulting in the release of histamine (e.g., opioids, polymyxin, protamine, diamines such as pentamidine, polyethoxylated castor oil), (2) nonimmunologic activation of the complement cascade (e.g., radiocontrast media, protamine), and (3) alteration of the metabolism or production of inflammatory mediators (e.g., ACE inhibitors, aspirin, and NSAIDs).[1,169] The direct stimulatory effects of drugs on mast cells appear to be dose-related and tend to predominate on mast cells in the skin. Ciprofloxacin, vancomycin, and muscle relaxants such as succinylcholine and opiates (e.g., codeine, morphine) have been shown to elicit urticarial reactions in normal skin at concentrations of ≥100 mcg/mL.[182]

The mechanism by which the ACE inhibitors cause angioedema is not completely understood; however, inhibition of the breakdown of bradykinin and substance P may partially explain this adverse event. ACE, a nonspecific dipeptidase enzyme, not only converts angiotensin I to angiotensin II but is also involved in the inactivation of bradykinin, substance P, and neurokinin A.[141] Elevations in plasma concentrations of bradykinin and substance P can lead to inflammation, increased vascular permeability, and vasodilation. Aspirin-induced asthma, also known as aspirin-exacerbated respiratory disease, is believed to result from an imbalance between the production of prostaglandins and leukotrienes from arachidonic acids.[183] Inhibition of cyclooxygenase-1 (COX-1) leads to decreased production of prostaglandin E_2, a modulating prostaglandin in bronchial tissue, and an increased propensity for arachidonic acids to be synthesized via the lipoxy–genase pathway. Increased production of leukotrienes C4, D4, and E4 is associated with smooth-muscle contraction manifesting as bronchospasm, inflammation, and increased mucus production.[183]

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The signs and symptoms of a number of specific allergic syndromes are provided in **Table 6-5**. The clinical presentation of drug allergy is highly variable and dependent on the responding antibody and the targeted tissues. Allergy may manifest as anaphylaxis; angioedema; urticaria; immune-complex diseases manifesting as a serum sickness-like illness, lupus-like reaction, hypersensitivity vasculitis, or DRESS; and mucocutaneous syndromes such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In addition, allergic drug reactions may be the cause of disorders of the blood, kidney, liver, and pulmonary system. Conditions to consider in the differential diagnoses of these syndromes are listed in **Table 6-6**. The mucocutaneous syndromes and DRESS are discussed in the section Cutaneous Diseases.

Anaphylaxis, the most severe form of an immediate type I reaction, constitutes a medical emergency. The onset of anaphylaxis is usually within minutes to 2 hours after exposure to the causative drug.[184] In rare cases, the onset can be delayed for up to 48 hours after exposure. A consensus panel on allergy has defined anaphylaxis as highly likely when one of the following scenarios is present[184]:

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, decrease in blood pressure, and/or persistent gastrointestinal symptoms)
3. A decrease in blood pressure alone after exposure to a known allergen

An elevated serum tryptase concentration is indicative of the release of stored mediators from mast cells. Concentrations of tryptase, an enzyme that is stored in the secretory granules of the mast cell, become elevated in the serum within 1–2 hours after the onset of anaphylaxis and persist for as long as 6 hours after the event.[164,184] β-tryptase is released only during episodes of mast cell degranulation, whereas concentrations of α-tryptase are elevated in patients with a large mast cell burden (e.g., mastocytosis).[184] Anaphylaxis is most suggestive when the ratio of total (α + β) tryptase to β-tryptase is ≤10.[184] Serum platelet-activating factor may also be a biomarker of anaphylaxis.[185] A late phase of anaphylaxis, characterized by erythema, edema, and excess mucus production with mucus plug formation, occurs 8–12 hours after the initial attack and can last for up to 32 hours.[184] The late-phase reaction is attributed to the effects of leukotrienes, such as leukotriene B4, which stimulate migration of macrophages to the sites of tissue damage.[179,180]

Urticaria with pruritis, a common manifestation of anaphylaxis, can also occur as a sole manifestation of an immediate type I reaction. On subsequent exposure to the causative agent, urticaria may

Table 6-5 Signs and Symptoms Associated with Drug-Induced Allergic Syndromes

Anaphylaxis[2,179,180,184]

- Diffuse urticaria
- Facial flushing
- Angioedema
- Bronchospasm (wheezing, chest tightness, hoarseness)
- Laryngeal edema
- Stridor
- Hypotension
- Cardiac arrhythmias (atrial or ventricular)
- Nausea, vomiting, abdominal cramping, diarrhea
- Lightheadedness, feeling of impending doom
- Eosinophilia
- Elevated tryptase concentrations

Urticaria[285,286]

- Asymmetric, circumscribed erythematous (pink) papular lesions of variable shape ranging from small to geographic in size; lesions have raised borders and areas of central clearing
- Pruritus
- May be associated with angioedema
- May be associated with eosinophilia

Angioedema[184,285,286]

- Asymmetric, nonpitting edema of the face (tongue, lips, eyelids)
- Periorbital edema
- Laryngeal edema
- Tingling of the lips
- Hoarseness, difficulty speaking
- Difficulty swallowing
- Diarrhea, nausea, abdominal pain (if visceral involvement)
- Edema of the extremities, genitalia

Allergic-mediated blood disorders[113,114]

- Hemolytic anemia with positive direct or indirect Coombs test
- Thrombocytopenia, with peripheral count <100,000 mm^3
- Granulocytopenia (agranulocytosis, neutropenia)
- Decreased concentrations of C3, C4
- Evidence of antiplatelet or antineutrophil antibodies

Serum sickness or serum sickness-like reaction[69]

- Fever and malaise
- Skin rash—urticaria, maculopapular rash or mixed presentation of urticarial plaques and maculopapular rash usually starting on the extremities (hands, fingers, toes)
- Arthralgias
- Lymphadenopathy
- Glomerulonephritis
- Elevated erythrocyte sedimentation rate (nonspecific marker)
- Reduced concentrations of C4 and C3; possible elevations in C3a

Vasculitis[86,88,188]

- Skin manifestations—purpura, maculopapular rash, hemorrhagic blisters; skin biopsy revealing leukocytoclastic vasculitis with fibrinoid necrosis and lymphocytic infiltrate
- General—fever, nausea, abdominal pain, polyarthritis, joint swelling
- Kidney—urinalysis revealing proteinuria, granular casts, and red cells; kidney biopsy may reveal deposition of IgG, IgM, or activated complement (C3)
- Pulmonary—hemoptysis, wheezing, pleuritic pain, presence of infiltrate on chest x-ray
- Sore throat, hoarseness
- Synovitis
- Elevated erythrocyte sedimentation rate, presence of antinuclear antibodies or antineutrophilic cytoplasmic autoantibodies

IgG = immunoglobulin G, IgM = immunoglobulin M.

progress to include anaphylaxis. Drug-induced angioedema can also occur as a sole manifestation of allergy, or it can occur with urticaria or as part of an anaphylactic event.[186] Angioedema, also known as giant urticaria or angioneurotic edema, presents as nonpitting edema that extends beyond the epidermis to involve the deep dermis, mucous membranes, and subcutaneous tissues.[186] Angioedema secondary to ACE inhibitors is typically confined to the head and neck, presenting as localized swelling of the face (tongue, lips, and eyelids) with edema of the mucous membranes of the mouth, throat, and nose.[141,142] Rarely, the edematous reaction can extend to the gastrointestinal tract, hands, feet, and genitalia.

The clinical presentation of drug-induced allergic blood disorders is included in Table 6-5. Depending on the causative drug, the patient may present with hemolytic anemia, thrombocytopenia, or granulocytopenia.[113,114] These peripherally mediated blood disorders typically occur within 5–21 days after drug initiation.[113,114] The affected blood cell counts decline rapidly, compared with the

Table 6-6 Conditions to Consider in the Differential Diagnosis of Drug Allergy

Anaphylaxis[179,180,184]

- Asthma
- Carcinoid syndrome
- Cardiogenic shock
- Croup
- Exercise-induced anaphylaxis
- Idiopathic anaphylaxis
- Insect stings or bites
- Latex allergy
- Panic attack
- Septic shock
- Systemic mastocytosis
- Systemic capillary leak syndrome
- Scrombroidosis
- Vasodepressor (vasovagal neurocardiogenic) syncope
- Vocal cord dysfunction syndrome

Angioedema[184,285,286]

- Insect stings or bites
- Food allergy
- Idiopathic or hereditary angioedema
- Hereditary or acquired C1 esterase inhibitor deficiency
- Systemic capillary leak syndrome
- Latex allergy
- Systemic mastocytosis

Urticaria[285,286]

- Cutaneous mastocytosis
- Mastocytosis in association with hematologic disorders (e.g., leukemia)
- Cholinergic urticaria
- Exercise-induced urticaria
- Infection (Epstein–Barr virus; hepatitis A, B, C; gastrointestinal parasites)
- Foods (peanuts, nuts, fish, shellfish, wheat, eggs, milk, soybeans, fruits)
- Food additives (benzoates, sulfites, monosodium glutamate, FD&C [food, drug, and cosmetic] dyes)
- Scrombroidosis
- Occupational exposures (latex, chromates in cement industry, cosmetics, plants)

Serum sickness-like reaction[69]

- Autoimmune disease (rheumatoid arthritis, lupus erythematosus)
- Hepatitis A, B, C
- Hypersensitivity vasculitis
- Infection (aspergillosis, histoplasmosis, coccidioidomycosis, blastomycosis, Epstein–Barr virus, cytomegalovirus)

Hypersensitivity vasculitis[86-88]

- Infection (bacterial endocarditis, hepatitis B or C, occult abscess)
- Rheumatic diseases
- Malignancy (lymphoma, Hodgkin disease, metastatic carcinoma, multiple myeloma)
- Autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, Wegener granulomatosis)

Hypersensitivity syndrome[188]

- Cutaneous lymphoma

relatively slow decline in the counts observed with bone-marrow-mediated blood disorders. In some patients, drug-specific antibodies (IgM or IgG) and reduced serum concentrations of C3 and C4 can be observed.[113,114]

The immune-complex diseases consist of a group of conditions including serum sickness-like disease (SSLD), hypersensitivity vasculitis, and lupus-like reaction. SSLD is a mild and transient form of the serum sickness that originally occurred with the administration of horse serum in the form of diphtheria antitoxin. The predominant feature of an SSLD is a cutaneous eruption that manifests within 5–21 days after drug initiation.[187] Approximately 90% of patients have either an urticarial reaction due to complement-mediated activation of the mast cells (one third of patients) or a maculopapular rash on the abdomen and extremities with possible extension to the palms and soles (two thirds of patients).[69,187,188] The rash is usually preceded by a prodromal phase consisting of fever and malaise, arthralgias, and lymphadenopathy. In rare instances, the reaction can extend to involve the kidney (i.e., glomerulonephritis). SSLD has been reported in association with a number of drugs, including β-lactam antibiotics, bupropion, cefaclor, ciprofloxacin, minocycline, and sulfonamides.[69-76,80-82] Drug-induced SSLD is often described as a mild condition that is self-limiting after discontinuation of the causative agent. However, in some cases, it progresses to a more serious vasculitis. Any evidence of mucous membrane involvement (i.e., mucocutaneous lesions of the mouth, genitalia, nares) may suggest the development of a more progressive condition, such as SJS.

Drug-induced vasculitides are associated with acute inflammatory and necrotic lesions of the arteries, arterioles, venules, and capillaries. Consistent with other immune-complex diseases, an initial prodromal period is noted within 1–3 weeks after drug initiation and usually consists of fever, arthralgias, and sore throat.[86,188] Cutaneous vasculitis, described as either a purpuric or maculopapular rash of the lower extremities, is the most common presenting manifestation.[87] The purpuric lesions can progress to necrotic ulcerations, and the vasculitic process can extend to include the kidneys, lungs, nasal mucosa, and ears. A number of drugs, such as propylthiouracil, hydralazine, minocycline, phenytoin, and allopurinol, can induce vasculitis through the production of antineutrophil cytoplasmic autoantibodies.[86] Other terms used to describe this condition include leukocytoclastic vasculitis, polyarteritis nodosa, and Churg–Strauss syndrome.

RISK FACTORS

The rarity of drug allergy suggests a reliance on contributory or predisposing factors. Risk factors for drug allergies have been categorized as either drug-related or patient (host)-related. Many extensive reviews have been published describing predisposing factors for both the induction of an immune response to a drug and the elicitation of an allergic drug reaction.[1,182,189,190] However, debate continues as to the influence of these factors on the risk of reactivity. Most risk factors have been identified through small-scale studies and indirect clinical observations. In addition, the majority of the risk assessments have been determined from the study of penicillin. At present, it is not known whether risk factors associated with the penicillins can be extrapolated with confidence to other antigenic drugs. Proposed risk factors for drug allergy are listed in **Table 6-7**. In addition, risk factors associated with specific drugs (e.g., the penicillins, sulfonamides, radiocontrast media) are identified.

The three most commonly described drug-related risk factors for an allergic reaction are increased molecular size (molecular weight ≥4,000 Da), chemical composition consisting of proteins or polypeptides, and the ability of the drug or its reactive metabolite to bind covalently to a carrier protein.[189] The presence of proteins of nonhuman origin (e.g., chimeric monoclonal antibodies containing murine-based components, pork insulin,

Table 6-7 Risk Factors for Allergic and Nonimmune Drug Hypersensitivity Reactions

Allergic reactions

Drug-related factors[182,189,190]

- Chemical properties (molecular weight, polypeptide composition, foreign protein)
- Dose and duration of therapy
- Frequency of treatment courses

Coexisting conditions

- Active infection with Epstein–Barr virus (aminopenicillins)[201]
- Active infection with human immunodeficiency virus (sulfonamides, dapsone, penicillins, ciprofloxacin, phenytoin)[203]
- Cystic fibrosis (β-lactams)[206-208]
- HHV-6 (DRESS)[204,205]

Genetic factors

- HLA B*5701 (abacavir)[193]
- HLA-B*5801 (allopurinol)[335]
- HLA-B*1502 (carbamazepine, phenytoin, fosphenytoin)[355,356]
- HLA-*DRA* (amoxicillin, penicillins)[196]
- CYP2C9*3 (phenytoin)[358]
- HLA-B*13:01 (dapsone)[108]

Patient history

- History of a previous reaction to the specific agent

Pre-existing IgE antibodies against galactose-α-1,3-galactose[24,25]

- Cetuximab

Nonimmune drug hypersensitivity reactions

Drug-related factors[2,3]

- Dose (vancomycin, opiates)
- Infusion rate (vancomycin, paclitaxel)

Patient factors[2,3]

- Female sex (radiocontrast media)[210]
- Atopy (radiocontrast media, aspirin)[211,216]
- Asthma (radiocontrast media, aspirin)[10,11,215]
- Race (angiotensin-converting enzyme inhibitors)[213,214]

Concomitant drug therapy

- β-blockers (radiocontrast media)[21,212]

DRESS = drug rash with eosinophilia and systemic symptoms, HHV-6 = human herpesvirus 6, HLA = human leukocytic antigen.

streptokinase) or the inclusion of antigenic excipients (e.g., FD&C dyes, peanut oil, soybean emulsion, sulfites) also increase the risk of drug reactivity. Other proposed drug-related factors include route of drug administration, dose, and frequency of administration. Sensitization to a drug can occur via any route of administration, and allergic reactions have been reported in association with all routes.[140,182] However, once a patient has been sensitized to a drug, subsequent administration of that drug by the parenteral route has been associated with increased severity of an allergic drug reaction.[190] This observation is largely explained by the higher rate of drug delivery with the parenteral route versus other routes of administration, particularly the oral route.[189] Allergic reactions can occur with any dose of a drug, but sensitization is more likely to be achieved with continuous drug dosing rather than single-dose therapy.[182] Rarely, an allergic reaction may be dose-dependent, as with penicillin-associated hemolytic anemia, which is observed only with continuous intravenous dosing of ≥20 million units daily. More commonly, once a patient has been sensitized to a drug, the severity of the reaction is usually proportional to the dose administered. The frequency of exposure to a given allergic compound has consistently been shown to increase the risk of an immune response, particularly involving IgE. Humoral drug sensitivity is finite, and there is a large degree of interpatient variation in the duration of sensitivity. As such, the shorter the interval between treatment regimens with a sensitizing drug, the more likely the patient will have retained sensitivity and be able to mount an allergic reaction.[2,140,182,189]

Proposed patient-specific risk factors include age, sex, genetic predisposition, and concomitant conditions. Allergic reactions to some drugs have been reported more commonly among patients in specific age groups; however, age has not been consistently identified as a risk factor.[3,191] For example, anaphylaxis associated with penicillin has been reported more commonly in patients between the ages of 20 and 49 years than in children.[192] This finding relates less to the specific age of the patient than to the number of potential exposures to the specific allergenic drug. Within the age of 20–49 years, a greater likelihood exists that a patient has been previously exposed and possibly sensitized to a penicillin, thereby increasing the risk of reactivity on subsequent exposure. Allergic drug reactions do occur in children, particularly in those who receive frequent courses of antibiotics for chronic otitis media, chronic bouts of bronchitis, or infections associated with cystic fibrosis. Therefore, the frequency and number of exposures, rather than age, are more likely to increase risk. For unknown reasons, drug allergy occurs more frequently in female than male patients. Bigby et al.[191] reported a 35% higher incidence of drug-induced allergic cutaneous reactions in women than in men.

Genetic factors may influence a patient's risk of drug allergy. In order for T-helper cells to recognize a drug as an antigen, the drug immunogen must be copresented with MHC class molecules.[169,170,173] In this regard, patients with certain MHC characteristics (or human leukocyte antigens [HLA]) may be at higher risk of reacting to a given antigenic compound as compared with patients without the specific MHC molecules. For example, in patients infected with human immunodeficiency virus (HIV), susceptibility to abacavir-induced hypersensitivity has been found to be associated with the of HLA-B*5701, HLA DR7, and HLA-DQ3.[193,194] HLA-DR4 was present in 19 of 26 patients (73%) with hydralazine-associated lupus-like syndrome, as compared with 4 of 16 hydralazine-treated patients without lupus (25%).[195] Most recently, a single nucleotide polymorphism of HLA-DRA, a MHC Class II gene, was found to be a predictor of skin-test positivity to amoxicillin and other penicillins, but not cephalosporins.[196] A number of HLA alleles have been found to be associated with allergic-mediated severe cutaneous drug reactions (see section Cutaneous Diseases).

In addition to encoding for histocompatibility phenotypes, genetic factors can influence the metabolic deactivation of drugs via phase 1 or phase 2 metabolism. For example, severe reactions to sulfamethoxazole have been noted in patients with hereditary deficiency in *N*-acetyltransferase (slow acetylators).[197] Rieder et al.[198] reported that 19 of 21 patients (90%) with sulfonamide hypersensitivity were slow acetylators, as compared with a 55% frequency of slow acetylators in a race-matched

control group (p <0.008). It has also been suggested that patients with a hereditary deficiency in epoxide hydrolase are at higher risk of anticonvulsant hypersensitivity syndrome because of a lesser ability to detoxify the arene oxide metabolite of the aromatic anticonvulsants.[199,200] In addition to encoding for drug metabolic activity, genes also encode for the type of T-cell receptor and costimulatory molecules/cytokines involved in the signaling of allergic reactions.

Although often implicated as a predisposing factor, atopy has not been found to increase the risk of drug allergy.[184,190] Patients who are atopic have high IgE responsiveness to environmental allergens, manifesting as allergic rhinitis, allergic asthma, and atopic dermatitis. Originally, it was theorized that the high IgE responsiveness reported in atopic patients could increase the risk of IgE sensitization to drugs. Studies have shown that a history of atopy does not influence the likelihood of a patient being sensitized to a drug. However, if an atopic patient becomes sensitized to a drug, evidence suggests that the reaction will be more severe than that observed in nonatopic patients.[2,189]

Concomitant viral infections may also predispose a patient to an allergic drug reaction. Pullen et al.[201] reported ampicillin-associated morbilliform rash in 18 of 19 patients (95%) with acute Epstein–Barr virus (EBV) infection. In comparison, a morbilliform skin rash develops in approximately 5% to 10% of the general population exposed to an aminopenicillin (e.g., ampicillin, amoxicillin).[202] Patients infected with other viral pathogens, such as human herpesvirus 6 (HHV-6) and HIV, have also exhibited an increased risk of drug allergy. In HIV-infected patients, 29–65% of those treated with sulfamethoxazole exhibited an allergic or allergic-like reaction, and the risk of reactivity to a number of other drugs (e.g., ciprofloxacin, dapsone, foscarnet, penicillins, phenytoin, rifampin) has also been shown to be increased.[203] HHV-6 has been linked to an increased risk of DRESS.[204,205] The mechanism by which viral infections increase the risk of drug reactivity is not completely understood. Proposed mechanisms include virally mediated alterations in drug metabolism, upregulation of MHC class II molecules on APCs, and increased release of cytokines such as interferon β, which amplify the immune response.[168,173,174]

Cystic fibrosis is a risk factor for allergic reactions to β-lactam antibiotics. At least 20% of patients with cystic fibrosis have an allergic reaction during an antibiotic treatment course, and the risk increases with the number of treatment courses.[206] The most commonly reported allergenic β-lactam antibiotic in these patients was piperacillin in a 1994 study[207]; however, increased rates of reactivity have also been demonstrated with other antipseudomonal penicillins and cephalosporins.[208,209] Evidence suggests that these reactions are not typically mediated by the β-lactam ring, but are more likely to be reactions to the side chains of the agents.[206]

Risk factors for nonimmune DHRs are highly dependent on the specific causative drug. For example, the risk of an anaphylactoid reaction associated with a radiocontrast agent is higher in women, patients with atopy or asthma, and patients receiving nonselective or selective β-adrenergic blocker therapy.[210-212] Risk factors for ACE inhibitor-induced angioedema include black race, a history of idiopathic angioedema secondary to a deficiency in complement-1-esterase inhibitor, and receiving longer-acting agents (i.e., enalapril, lisinopril).[141,213,214] Aspirin intolerance manifesting as aspirin-induced asthma is more commonly observed in patients with history of asthma with or without allergic rhinitis or nasal polys.[10,11,215] Aspirin- or NSAID-induced exacerbations of urticaria or angioedema are more common in atopic patients with history of idiopathic urticaria or angioedema.[216]

The most reliable risk factor for hypersensitivity and most nonimmune DHRs is history of a prior reaction to the drug. For example, patients with a history of an anaphylactoid reaction to a radiocontrast agent have a 16–44% risk of having a reaction on re-exposure particularly to a high-osmolarity agent.[217] For the penicillins, a reliable skin testing method with a high negative predictive value has allowed for more accurate determinations of the risk of reactivity on re-exposure. In a patient with a positive history of an IgE-mediated reaction to a penicillin, a positive skin-prick test revealed a 50–70%

risk of an IgE-mediated reaction on re-exposure.[2,218] In contrast, a negative skin test indicates only a 2–3% risk of an IgE-mediated reaction on re-exposure.[218] Unfortunately, reliable skin-test reagents for other highly allergenic drugs have not been produced, thereby limiting the ability to accurately assess the risk of reactivity to other allergenic drugs.

MORBIDITY AND MORTALITY

In 2002, a task force assembled by the Immunotoxicology Technical Committee, part of the nonprofit Health and Environmental Sciences Institute, provided an estimate of the impact of drug-induced allergic reactions on the healthcare system.[219] On the basis of the assumption that 6–10% of adverse drug reactions are immune-mediated, it was estimated that 137,000–230,000 hospital admissions in 1998 in the United States were attributed to drug-induced allergic reactions. Using cost estimates determined in 1997 for the treatment of adverse drug reactions in hospitalized patients, the task force estimated that the annual cost of hospital-based management of drug allergy is $275 million to $600 million.[219] It was further hypothesized that the total annual cost for management of both inpatient- and outpatient-related drug allergic reactions could approach $1 billion.

PREVENTION

ALLERGIC REACTIONS

Drug-induced allergic reactions have consistently been considered as unpredictable in nature and largely unpreventable. However, continuing advances in pharmacogenomics research may alter the level of preventability of these events. Prospective screening for the presence of the HLA-B*5701 allele has been shown to lower the risk of hypersensitivity to abacavir.[193] In a double-blind, controlled study, 1,956 HIV-infected patients were randomly assigned to undergo either prospective screening for HLA-B*5701 prior to the initiation of abacavir or a standard-of-care approach to abacavir therapy.[193] Prospective screening for HLA-B*5701 with subsequent avoidance of abacavir in identified carriers prevented the occurrence of immunologically confirmed hypersensitivity reactions. Screening was associated with a negative predictive value of 100% and a positive predictive value of 47.9% in this primarily white population.[193] The investigators calculated that only 14 patients would have to be screened to prevent one case of abacavir hypersensitivity. Screening for the HLA-B*5701 allele is currently available. Screening for other HLA alleles is also available for patients considered as high risk for serious cutaneous adverse reactions to allopurinol, carbamazepine, phenytoin, and fosphenytoin (see section Cutaneous Reactions).

Once a patient has had an allergic reaction to a drug, a number of measures can be taken to prevent a subsequent reaction. The most important preventive measure is patient education. In particular, patients should be educated regarding avoidance of the causative drug and any cross-reactive drugs in the future. If a potentially immunogenic medication is deemed necessary, the use of graded challenge and induction of drug tolerance (i.e., desensitization) can often be used to prevent reactions on drug re-exposure.[220,221] A graded challenge procedure, or test dosing, involves the cautious administration of a drug when the risk of a reaction is considered to be low. Graded challenge does not alter the immune or nonimmune response to the drug.[221] Instead, it is used when the risk of an immediate reaction to a drug or related drug on re-exposure is deemed low, no alternative agent is equally effective, and a reliable skin testing method is not available. Classic examples include the slow introduction of furosemide in a patient with history of sulfonamide allergy or the slow introduction of a third-generation cephalosporin in a patient who previously developed a reaction to a first-generation cephalosporin. The starting dose is typically 1/10th–1/100th of the final treatment dose, and doses are increased in two- to fivefold increments every 30 or 60 minutes until the full therapeutic dose is attained.[221,222]

In contrast, temporary induction of drug tolerance, also known as desensitization, is used to modify a patient's response to a drug. Such procedures are intended to alter the immune response and render mast cells less responsive to degranulation.

Table 6-8 Skin Testing for IgE Responsiveness to β-Lactam Antibiotics

Step 1. Epicutaneous (scratch, prick) test with benzylpenicilloyl–polylysine (Pre-Pen) and the minor determinants. Make a nonbleeding scratch of the skin with a lancet. Administer the dose of the reagents (below):

- Pre-Pen, full-strength dilution; 1 drop
- Penicillin G, 10,000 units/mL; 1 drop

Step 2. Evaluate the scratch sites within 10–15 minutes. A positive test result is the presence of itching or an erythematous or wheal reaction at either site of the scratch tests. If the reaction is positive, do not proceed with further testing.

Step 3. If the scratch test is negative, proceed with intradermal testing.

- Pre-Pen, full strength; 0.02 mL intradermally
- Penicillin G, 10,000 units/mL; 0.02 mL intradermally
- Administer a positive control (histamine) and a negative control (saline)

Step 4. Evaluate the sites of intradermal injections within 15–20 minutes. A positive reaction is the presence of itching, erythema or wheal >4 mm, or a wheal reaction >50% the size of the original size of the bleb from the injection of either Pre-Pen or the minor determinants (penicillin G). Assess the site of histamine and saline control. If the histamine control site is not positive, consider interference by antihistaminergic agents.

The term *desensitization* should be used when the underlying mechanism of the drug intolerance is believed to be IgE-mediated (e.g., anaphylaxis due to penicillin).[220] The incremental dosing used in a desensitization protocol allows for downregulation of the immune response and temporary administration of the inciting agent. Reactions most amenable to desensitization are IgE-mediated involving the skin (e.g., angioedema, urticaria), upper and lower respiratory tract (e.g., dyspnea and wheezing), and cardiovascular (e.g., hypotension). Neither graded challenge nor desensitization should be used in patients with history of severe non-IgE-mediated drug allergies manifesting as DRESS, SJS, TEN, exfoliative dermatitis, hemolytic anemia, or hepatitis.

Guidelines for the avoidance of allergic reactions to common drug allergens are provided below.

β-LACTAM ANTIBIOTICS

Whenever possible, a non-β-lactam antibiotic should be used in patients with a history of penicillin allergy. If a β-lactam antibiotic is therapeutically necessary (i.e., treatment of syphilis in a pregnant woman, patient with cystic fibrosis and pneumonia) in a patient with history of IgE-mediated allergy, epicutaneous (prick, scratch) skin testing is the preferred technique for assessing the likelihood of a reaction on re-exposure. The skin-testing procedure is described in **Table 6-8**. Penicillin is rapidly hydrolyzed to a number of reactive metabolites or antigenic determinants. Ninety-five percent of the penicillin molecules that covalently bind to proteins are in the form of benzyl penicilloyl, commonly regarded as the major determinant of penicillin. The parent drug and reactive metabolites found in lesser quantities, such as penilloate and penicilloate, are referred to as minor determinants. Both the major and minor determinants can elicit an IgE-mediated response; thus, both are recommended for use when skin testing for IgE responsiveness. Penicilloyl polylysine (PPL), the major determinant bound to protein, is commercially available as Pre-Pen. The minor determinants are not commercially available in the United States; however, kits containing both the major and minor determinants are available in Europe (Diater Labs, Madrid Spain).[223] In the United States, a dilute concentration of penicillin G (10,000 units/mL) is recommended with PPL for skin testing.[224] Studies have shown a similar reaction rate to oral penicillin in patients with skin-test negativity to PPL plus penicillin G versus those with skin-test negativity to the full set of major and minor determinants.[224,225] When used together for skin testing (i.e., PPL and diluted penicillin G), 97% of patients with a negative skin test have subsequently tolerated a penicillin.[226] Patients with a positive skin test to either determinant and a positive allergy history have a 50–70% risk of reacting with an IgE-mediated response to penicillin on re-exposure.[226] This risk of β-lactam mediated reactivity can also be applied to semisynthetic penicillins and, with lesser certainty, to

cephalosporins and carbapenems.[227,228] Little to no risk of a cross-reaction exists between penicillin and aztreonam, a monobactam.[229] A negative penicillin skin test indicates that the risk of an immediate type I reaction to penicillin or another β-lactam is extremely low. These patients are candidates for treatment with full therapeutic doses of a penicillin or a related β-lactam. Of note, skin testing with PPL and the minor determinant(s) does not identify patients who are at risk for unique side-chain mediated reactions to β-lactams (e.g., third-generation cephalosporins, piperacillin).

It is important to keep in mind that skin testing only indicates the potential for an IgE-mediated reaction to penicillin. Skin testing does not quantify the risk of having an IgG-, an IgM- or a cell-mediated reaction. Patients with a history of SJS, exfoliative dermatitis, or TEN associated with a penicillin should not undergo skin testing.

In addition to β-lactam-mediated allergic reactions, side-chain-specific reactions are increasingly reported with a number of penicillins, particularly the aminopenicillins and piperacillin.[230,231] As such, a patient with an allergy to one of these penicillins may not react to other penicillins. Structural similarities and differences between the penicillins are depicted in **Figure 6-1**. In a patient with history of an urticarial or other IgE-mediated reaction to an aminopenicillin or piperacillin, skin testing with Pre-Pen and the minor determinants is the preferred method to rule out β-lactam-mediated allergy. If the skin test result is negative, the patient may be challenged with a penicillin with a structurally different side chain. Dilute concentrations of amoxicillin and piperacillin have also been used to skin test for side-chain-mediated reactions.[232,233] In addition to causing side-chain-mediated allergic reactions, some penicillins have been associated with the development of nonimmunologically mediated drug eruptions. Maculopapular rash with an aminopenicillin (i.e., amoxicillin, ampicillin) may be an idiosyncratic reaction, particularly in a patient with acute EBV infection.[201,230]

The risk of cross-reactivity between penicillins and cephalosporins is low, particularly between penicillin and the second- and third-generation agents. On the basis of laboratory studies, the risk of cross-reactivity between penicillins and the first-generation cephalosporins is less than 10%, and the risk of a cross-reaction between the penicillins and the third-generation cephalosporins is as low as 1%.[2,52] One meta-analysis included nine studies in which the risk of cephalosporin allergy was compared in penicillin-allergic and nonpenicillin-allergic patients. Compared to nonallergic patients, the risk of cross-reactivity in penicillin-allergic patients was highest in association with the first-generation cephalosporins (OR 4.79, 95% CI 3.71–6.17).[234] The first-generation agents included in the analysis (i.e., cephalothin, cephaloridine, cephalexin) had R1 substitutions similar to that of penicillin. The odds ratios for risk of cross-reactivity to the second- and third-generation cephalosporins were not significant at 1.13 (95% CI 0.61–2.12) and 0.45 (95% CI 0.18–1.13), respectively.[234] The lower risk of cross-reactivity between these agents and penicillin may be attributed to structural differences in the R1 substitution on the β-lactam ring. In patients with a history of maculopapular rash associated with a penicillin, the benefits of using a second- or third-generation cephalosporin may substantially outweigh the potential risk of a cross-reaction. In patients with a history of an IgE-mediated reaction and skin-test positivity to penicillin, first-generation cephalosporins should generally be avoided. If deemed medically necessary, a cephalosporin can be administered via a graded challenge, or attempts can be made to desensitize the patient to the cephalosporin.[22]

CARBAPENEMS

Carbapenems contain a β-lactam ring attached to a modified thiazolidine ring with two side chains. The risk of a cross-reaction between a penicillin and a carbapenem appears to be much lower than originally described. In three retrospective studies of patients with a history of penicillin allergy, the rates of cross-reaction to a carbapenem (e.g., imipenem, meropenem) were 9.2%, 9.5%, and 11%.[235-237] Each study was limited by its retrospective design, heavy reliance on self-reported penicillin allergy histories, and the lack of skin testing to confirm IgE reactivity. In prospective studies, both skin testing and carbapenem challenge dosing were used to assess cross-reactive risk.[238-242] In one of these studies, patients

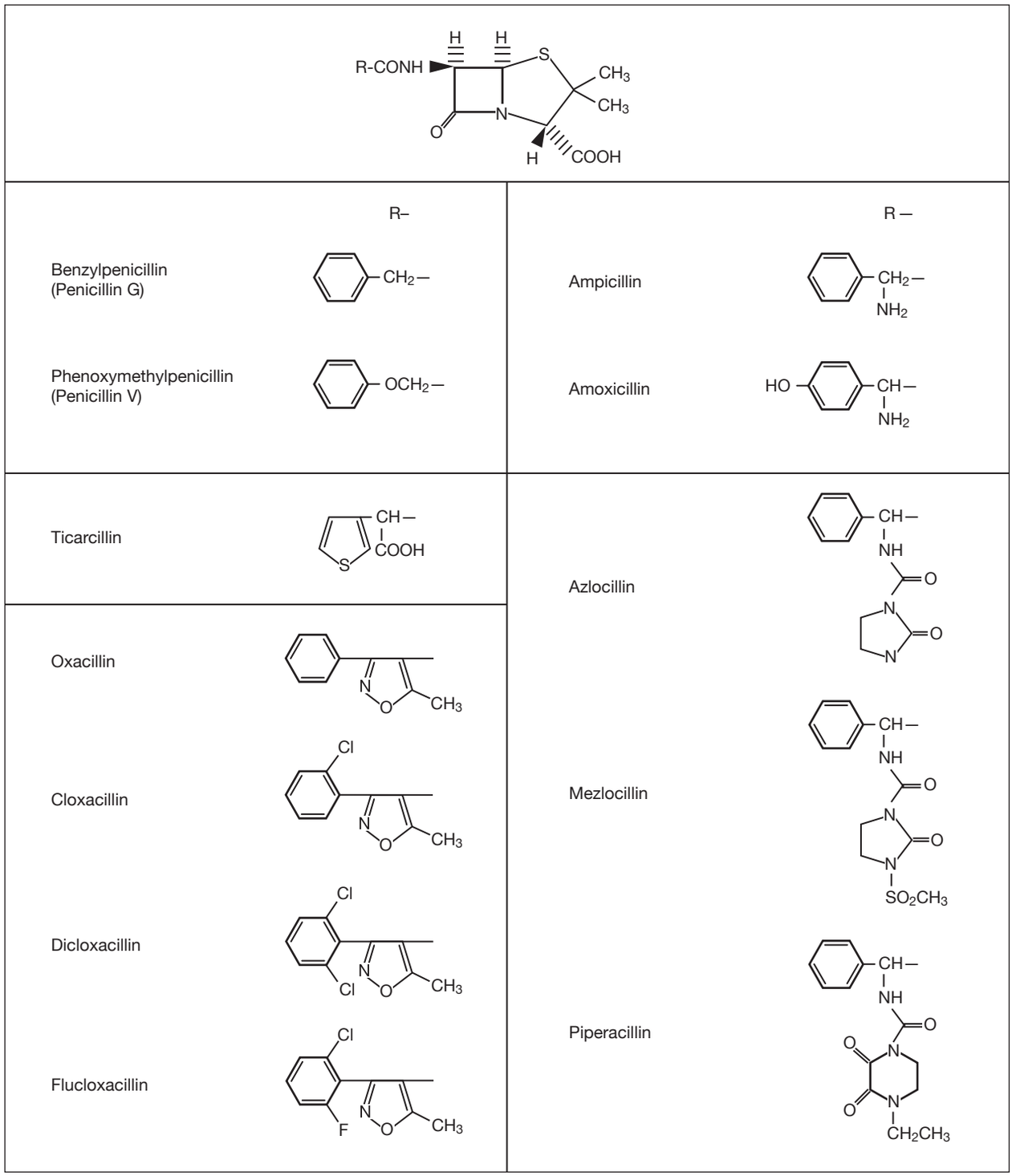

FIGURE 6-1 Similarities and Differences in the Structures of Various Penicillins

Source: Reprinted with permission from Baldo BA. Penicillins and cephalosporins as allergens—structural aspects of recognition and cross-reactions. *Clin Exp Allergy.* 1999; 29:744–9.

with negative results on skin testing for imipenem underwent graded challenge dosing of imipenem to a total dose of 500 mg.[239] None of the 110 patients reacted to imipenem. A low risk of cross-reactivity between meropenem and penicillin was demonstrated in two studies, one involving children ages 3–14 years.[240,241] In both studies, only one patient with skin-test positivity to penicillin had a positive skin test to meropenem. Graded challenge dosing with meropenem was tolerated in 100% of the skin-test-negative patients in both studies.[240,241] Most recently, cross-reactivity between penicillin and ertapenem, meropenem and imipenem was studied in 212 patients with skin-test positivity to a penicillin.[242] None of the 212 patients had skin test positivity to a carbapenem, and 211 successfully completed graded challenge dosing to a full therapeutic dose of each carbapenem.[242] Based on these results, carbapenem use should not be routinely avoided in a patient with history of penicillin allergy. Depending on the allergy history, challenge dosing with the carbapenem may be appropriate. In cases of skin test positivity to penicillin or history of severe penicillin allergy, desensitization may be performed.[243] The risk of cross-reactivity between the carbapenems is also unknown. Imipenem-sensitive patients tolerating meropenem following graded challenge and meropenem desensitization have been reported.[243,244]

CEPHALOSPORINS

A patient with a cephalosporin allergy should be interviewed in depth to obtain information on all antibiotics that have evoked allergic reactions and those that have been administered without adverse incident. Patients with a history of reactivity to one cephalosporin may or may not exhibit reactivity to other cephalosporins or penicillins.[23] Although cephalosporins share the antigenic β-lactam ring of the penicillins, they are more likely to cause allergic reactions mediated by side chains at either the R1 or R2 positions. Structural similarities and differences in the cephalosporins based on R1 and R2 substitutions are depicted in **Figure 6-2**.

In a patient with a history of an urticarial or other IgE-mediated reaction to a cephalosporin, either the antigenic β-lactam ring or an antigenic side chain of the cephalosporin may serve as the antigenic determinant. Skin testing with Pre-Pen and the minor determinant can help to identify the likelihood of a β-lactam allergy. More commonly, allergic reactions to cephalosporins are mediated via the R1 side chain. Examination of the cephalosporin's side chains may aid in the determination of potential cross-reactive agents. For example, cefaclor and cephalexin have identical side chains at the R1 position and cephalothin and cefotaxime have similar side chains at the R2 position.[21] Ceftazidime shares a common side chain with aztreonam.[2,22] Overall, the risk of cross-reactivity between cephalosporin antibiotics is believed to be greater than the risk of cross-reactivity between the cephalosporins and the penicillins.[22] In patients with selective allergy to a cephalosporin, decisions regarding the use of alternative cephalosporins should be based on the severity of the allergic reaction, the availability of equally effective non-β-lactam antibiotics, and the structure-specific feature (i.e., R1 and R2 substitutions) of the cephalosporin.

SULFA DRUGS

In a patient with a documented or reported sulfa allergy, the first step in prevention of a subsequent reaction is accurate and complete history taking. Clarification is needed regarding the specific sulfa drug to which the patient reacted in the past, and whether he or she has taken other sulfa drugs without incident. Sulfa drugs, by definition, possess a sulfamoyl (SO_2NH_2) moiety. Sulfate salts (e.g., morphine sulfate, atropine sulfate), sulfites, and sulfides are not members of the "sulfa" drug class. Sulfa drugs include sulfonamide antibiotics, thiazide diuretics, loop diuretics (e.g., bumetanide, furosemide, torsemide), oral sulfonylurea hypoglycemic agents, carbonic anhydrase inhibitors (e.g., acetazolamide, dorzolamide), celecoxib, metolazone, sumatriptan, and zonisamide.[245] The antiviral agents amprenavir, fosamprenavir, and darunavir are also classified as sulfa drugs. This drug class can be further categorized based on the presence or absence of an aromatic amine group in the N4 position. Sulfonamide antibiotics (e.g., sulfadiazine, sulfamethoxazole, sulfapyridine, amprenavir) have an arylamine at the N4 position, whereas the sulfonamide nonantibiotics (as listed above) do not.[171,245] Presence of

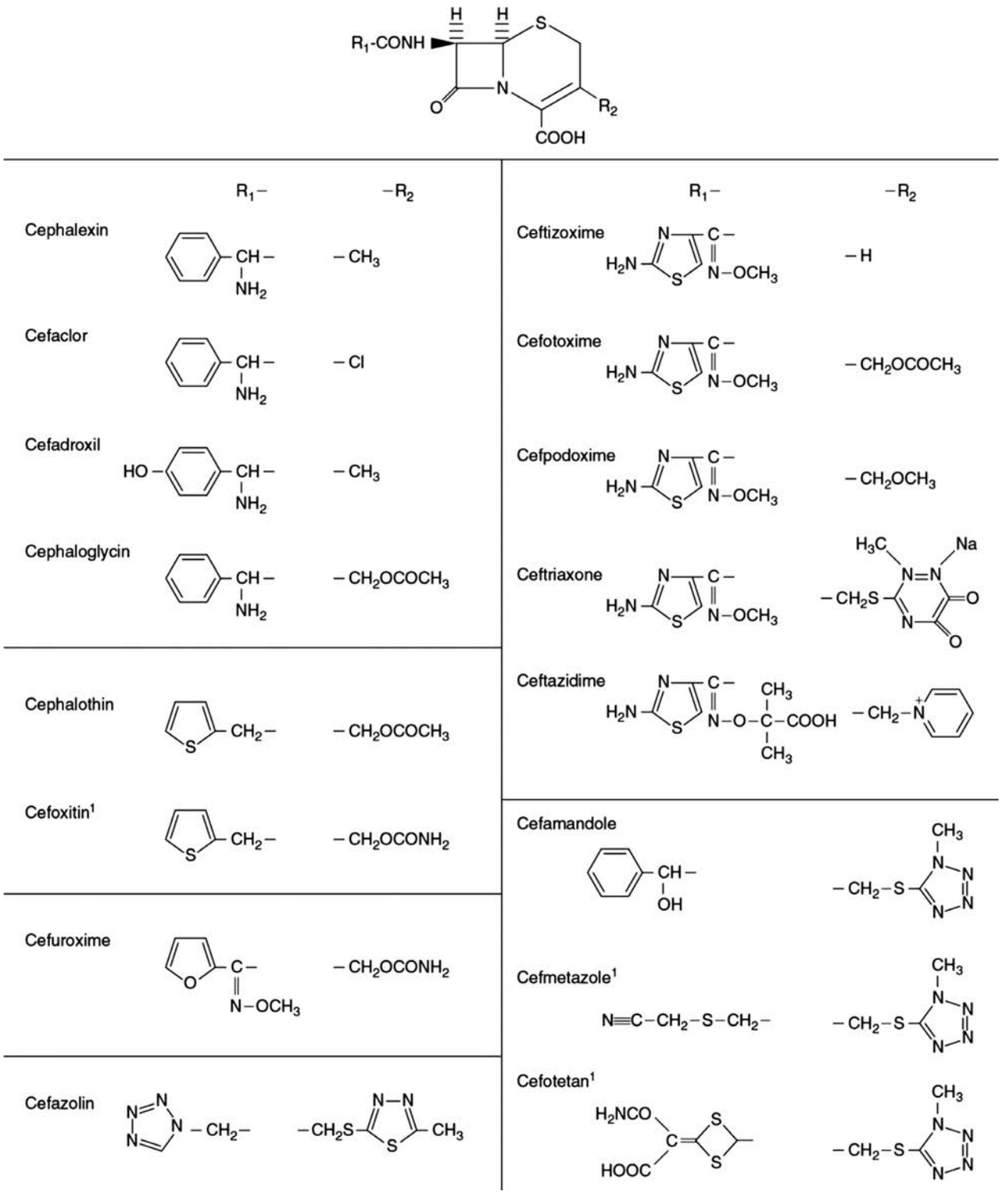

FIGURE 6-2 Similarities and Differences in the Structures of Various Cephalosporins

[1]Cephamycin with an α-methoxy group (-OCH3) at the 7-position.

Source: Reprinted with permission from Baldo BA. Penicillins and cephalosporins as allergens—structural aspects of recognition and cross-reactions. *Clin Exp Allergy.* 1999; 29:744–9.

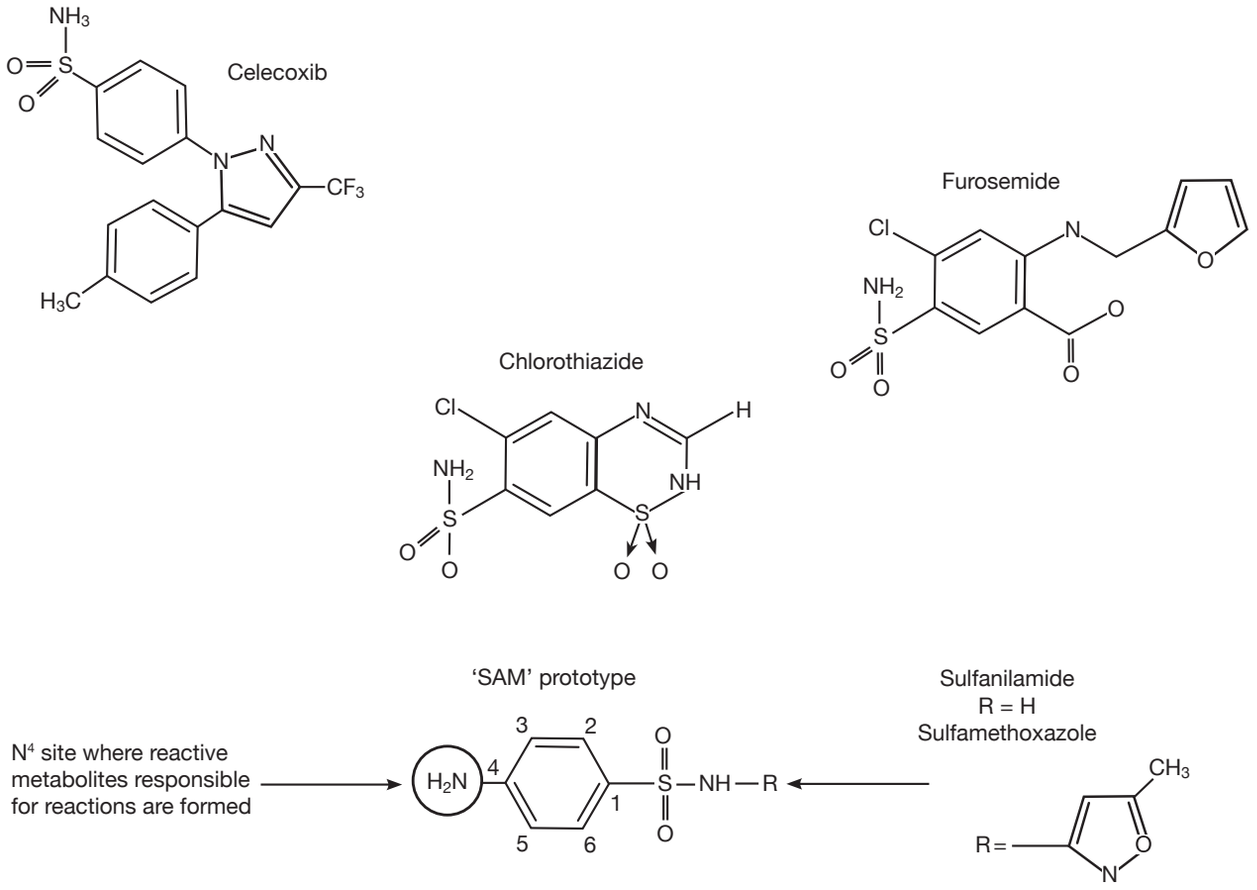

FIGURE 6-3 Structural Differences Between the Sulfonamide Antibiotics and the Nonantibiotic Sulfonamides

Source: Reprinted with permission from Shapiro LE, Knowles SR, Weber E et al. Safety of celecoxib in individuals allergic to sulfonamide: a pilot study. *Drug Saf*. 2003; 26:187-95.

an arylamine at the N4 position may influence the type of reactivity to a sulfa drug and the potential for the sulfa drug to be reactive.[171,246] Compared with nonantibiotic sulfonamides, the sulfonamide antibiotics are associated with a higher frequency of severe allergic reactions such as SJS. Sulfonamide antibiotics also have an N1 substituent consisting of a 5- to 6-member heterocyclic ring containing >1 nitrogen, which has been linked to the development of IgE-mediated reactions.[171,246] Structural differences between the sulfonamide antibiotics and the nonantibiotic sulfonamides are illustrated in **Figure 6-3**.

Although sulfa drugs are well recognized as allergenic, the risk of reactivity to a specific sulfa drug and the risk of cross-reactivity to other sulfa drugs are not completely known. The lack of a commercially available, reliable reagent for skin testing limits the value of such testing for determination of sulfa allergy. Arndt and Jick, as part of the Boston Collaborative Drug Surveillance program, compared the frequency with which different sulfa drugs caused allergic reactions in a cohort of prospectively monitored inpatients.[247] The risk of reactivity to sulfamethoxazole was the highest at 6% (10 of 169), followed by sulfisoxazole (1.7%, or 8 of 462), chlorothiazide (0.28%, or 2 of 707), hydrochlorothiazide (0%, or 0 of 1,263), and tolbutamide (0%, or 0 of 702).[247] On the basis of this study, sulfamethoxazole is frequently cited as the most reactive of the sulfa class. Strom et al.[248] studied the risk of cross-reactivity between a sulfonamide antibiotic (e.g., sulfamethoxazole) and nonantibiotic sulfonamides (e.g., acetazolamide, loop diuretic, sulfonylurea, thiazide) in a retrospective cohort. Study patients received a nonantibiotic sulfonamide at least 60 days

after having experienced an allergic reaction to a sulfonamide antibiotic. The risk of an allergic reaction in these patients within 30 days of receipt of the nonantibiotic sulfonamide was compared with that of a control group of patients without history of sulfa allergy. Of the 969 patients with history of sulfa allergy, 96 (9.9%) had a reaction to the nonantibiotic sulfonamide as compared with 315 (1.6%) of the 19,257 patients without a history of sulfa allergy.[248] Based on the results of this study, the risk of a cross-reaction between the sulfa subclasses is considered low. In fact, patients in this study with a history of sulfonamide antibiotic allergy exhibited a higher risk of subsequent reactivity to a penicillin (14%) than to a nonantibiotic sulfonamide (9.9%). When interpreting the findings of this study, consideration should be given to study design (i.e., retrospective cohort) and the broad definition for drug allergy that included eczematous reactions.

In a patient who is allergic to a specific sulfa drug (e.g., sulfamethoxazole) and requires treatment with another sulfa agent (e.g., a loop diuretic), the severity of the patient's previous allergic reaction is an important factor. Sulfa drugs can cause serious mucocutaneous events such as SJS and TEN, and they can also cause relatively mild maculopapular rash or other isolated skin rash. The severity of the reaction should largely influence the decision as to whether the causative sulfa drug or other sulfa drugs should be administered in the future. Although the structures of the sulfa agents may influence reactivity, cases of suspected cross-reactions between sulfonamide antibiotics and nonantibiotics have been reported.[249,250] If therapy with a sulfa drug is deemed necessary in a patient with history of sulfa allergy, administration of graded challenge doses should be considered. At least two cases have been published describing the successful administration of graded challenge doses of loop diuretics in patients with a history of sulfa allergy.[251,252] Desensitization to hydrochlorothiazide has also been described, starting with 0.025 mg followed by 10-fold incremental dosing every 15 minutes to a final dose of 25 mg.[253]

TETRACYCLINES

The risk of cross-reactivity between the tetracyclines is unknown. Serum sickness-like reactions have been reported in association with tetracycline, doxycycline, and minocycline.[254] Minocycline is considered to be the most antigenic agent in the tetracycline class, based on the number and severity of reported cases (i.e., lupus-like syndrome, serum sickness-like reaction).[82] The antigenicity of minocycline has been attributed to its unique amino acid side chain.[254] Until more is known about the antigenic properties of this drug class, it may be best to avoid the use of all tetracyclines in patients with a history of a severe reaction to any specific tetracycline.

AROMATIC ANTICONVULSANTS

A high degree of cross-reactivity exists between the aromatic anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin).[255] In vitro lymphocyte testing has revealed cross-reactivity between all three of these anticonvulsants in 40 of 50 patients (80%) with anticonvulsant hypersensitivity syndrome (AHS).[199] Thus, patients with AHS associated with one aromatic anticonvulsant should be advised to avoid the others. Moreover, family members of patients with AHS may be at increased risk of this syndrome.[256] In patients in whom AHS develops, underlying seizure disorders can be safely treated with benzodiazepines, gabapentin, or valproic acid. Oxcarbazepine, the 10-keto derivative of carbamazepine, has exhibited both in vitro and in vivo cross-reactivity with carbamazepine. Some patients with carbamazepine-induced AHS have been subsequently treated with oxcarbazepine without incident, while others have had severe cross-reactions.[257,258] Lamotrigine, a structurally dissimilar anticonvulsant, has also been reported to cause an anticonvulsant hypersensitivity syndrome due to an unknown mechanism.[109] For information on prevention of DRESS and SJS due to anticonvulsants, see section Cutaneous Diseases in this chapter.

BIOLOGICS

The increasing overall prevalence of anaphylaxis is attributed, in part, to the increased use of biologics. This drug class consists of monoclonal antibodies, fusion proteins, and recombinant proteins derived from living sources such as yeast, bacteria, animal cells, or mammalian cells.[259] Examples of biologics include recombinant insulin, erythropoietin,

interferon β, human growth hormone, cetuximab, infliximab, omalizumab, adalimumab, ustekinumab, secukinumab, and rituximab. These large proteins can serve as complete antigens. The immunogenicity of these agents is largely related to production methods (e.g., presence of contaminants or stabilizing agents, degree of protein glycosylation, presence of nonhuman protein sequences), and administration (e.g., route of administration, rate of infusion, frequency of use).[259] Some immune reactions to these agents result from the development of neutralizing antibodies that can blunt the biologic agent's ability to exert its intended effect. Neutralizing antibodies occur in up to 60% of patients treated with infliximab, and they have also been shown to develop against natalizumab, interferon β-1b, and interferon β-1a.[259]

Preventive strategies to limit immune-mediated reactions to biologics are highly variable and dependent on the culprit agent. With infliximab, the concomitant administration of prednisone or low-dose methotrexate has been shown to suppress the formation of anti-infliximab neutralizing antibodies.[259,260] Omalizumab, a humanized monoclonal antibody targeted against IgE, is associated with the development of delayed onset anaphylaxis.[261,262] Patients treated with omalizumab are advised to carry an epinephrine auto-injector during and 24 hours after drug administration, and they should be observed for 2 hours after the first three omalizumab injections and for 30 minutes after subsequent injections.[261,262] Cetuximab, a human-murine IgG1 monoclonal antibody, causes anaphylaxis via an oligosaccharide on the Fab portion of the agent's heavy chain.[263] This same oligosaccharide, galactose-α-1,3,-galactose is present in the Lone Star tick and the serum of nonprimate mammals (i.e., certain ingested meats).[25] Up to 20% of cetuximab-treated patients in specific regions of the southern United States developed severe reactions to cetuximab on first exposure, potentially explained by cross-reactions involving pre-existing IgE antibodies against galactose-α-1,3,-galactose.[264] In addition to allergic reactions, biologics may also cause nonimmune DHRs. Depending on the agent, the preventive strategy may include decreasing the rate of drug infusion, pretreatment with antihistamines or corticosteroids, or concomitant administration of corticosteroids. Desensitization protocols have also been described for infliximab, cetuximab, and rituximab.[265,266]

DRUG HYPERSENSITIVITY REACTIONS

Unlike allergic reactions, the administration of pretreatment regimens can prevent many DHRs. Recommended pretreatment regimens for selected agents are provided in **Table 6-9**. In addition, some DHRs are best prevented by avoidance of the causative agent and other pharmacologically similar drugs in the future.

ACE INHIBITORS

Patients with ACE-inhibitor-induced angioedema should be educated to avoid all ACE inhibitors in the future. Re-exposure to the causative agent or to another ACE inhibitor may result in more severe reactions.[267] In addition to women and African Americans, an additional risk factor for ACE-inhibitor-mediated angioedema is concomitant use of the neprilysin inhibitor sacubitril. Inhibition of neprilysin leads to accumulation of bradykinin. To avoid the risk of additive inhibitory effects on bradykinin metabolism, it is recommended that patients undergo a 36-hour washout when switching from ACE inhibitor therapy to combination therapy with sacubitril–valsartan.

Although angiotensin-receptor blockers (ARBs) have no direct effects on the catabolism of bradykinin, angioedema associated with the use of an ARB has been described.[268] In a meta-analysis of 35,000 patients treated with an ARB, the weighted incidence of angioedema was 0.11%.[269] ARBs may cause angioedema by a mechanism independent from that of ACE inhibitors; thus, the term *cross-reactivity* may not directly apply to these events. ARBs are not contraindicated in patients with a history of ACE-inhibitor-induced angioedema, but they should be used with caution after careful weighing of the perceived benefits and risks of therapy. Gavras and Gavras[270] described 10 patients with a history of ACE-inhibitor-induced

Table 6-9 Approaches to Help Prevent Drug Hypersensitivity Reactions

Hypersensitivity reactions (in general)

- With high-risk drugs, monitor for signs and symptoms of allergy during the first 7–30 days of therapy
- Be vigilant in monitoring patients who are frequently exposed to allergenic drugs (e.g., patients with cystic fibrosis, patients with frequent bouts of bronchitis, pneumonia, or otitis media)
- Educate patients about high-risk drugs and the signs of an allergic reaction
- Obtain detailed histories of allergies, with attention to the causative agent(s) and the severity of the reaction(s)
- Educate patients with a documented allergy to avoid the causative drug in the future (depending on the severity of the reaction)
- Educate patients to avoid drugs structurally similar to the causative agent (depending on the severity of the reaction)
- Educate patients to read drug labels, particularly if the patient is reactive to excipients

Immediate reactions to radiocontrast media (high- or low-osmolarity agent)

- Pretreat using prednisone 50 mg orally, administered at 13 hours, 7 hours, and 1 hour before administration of the contrast agent; diphenhydramine 50 mg orally/IV/IM 1 hour before the procedure, and ephedrine 25 mg orally 1 hour before the procedure (avoid ephedrine in patients with unstable angina, hypertension, arrhythmias)[278]
- In an emergency situation, the following pretreatment regimen has been used: hydrocortisone 200 mg IV immediately upon determination of need for the radiocontrast study and every 4 hours until the procedure is completed; diphenhydramine 50 mg IV/IM 1 hour before the procedure[278]

Immediate reaction to paclitaxel

A number of different pretreatment regimens have been used with success:

- Pretreat with dexamethasone 20 mg orally at 12 hours, 6 hours, and 1 hour before paclitaxel infusion; diphenhydramine 50 mg IV 30–60 minutes before the infusion; cimetidine 300 mg IV (or ranitidine 50 mg IV, famotidine 20 mg IV) before the paclitaxel infusion[280]
- Diphenhydramine 50 mg IV, famotidine 20 mg IV and dexamethasone 20 mg IV, each given 30 minutes before the paclitaxel infusion[281]

Vancomycin red man syndrome

- Administer each 1-g vancomycin dose over at least 1 hour; each 1.5-g dose over at least 90 minutes; each 2-g dose over 2 hours
- Pretreat using diphenhydramine 25–50 mg IV, acetaminophen 650 mg orally, hydrocortisone 100 mg IV

IM = intramuscular, IV = intravenous.

angioedema who were subsequently treated with an ARB without incident. In a more comprehensive systematic review of 71 patients with ACE-inhibitor angioedema, the risk of subsequent angioedema associated with an ARB was 9.4% for possible cases and 3.4% for confirmed cases.[146] None of the events was fatal. As a preventive strategy in this setting, consideration should be given to the severity of the event (i.e., diffuse versus localized angioedema) and to prior responsiveness to treatment before switching a patient from therapy with an ACE inhibitor to an ARB.

SALICYLATES

Patients with a history of an allergic or allergic-like reaction to a salicylate present a clinical challenge to the caregiver. Aspirin and NSAIDs can cause both true allergic reactions (e.g., ibuprofen-induced anaphylaxis) and nonimmune DHRs (e.g., exacerbations of asthma, urticaria, angioedema).[271] In this setting, it is crucial to obtain an accurate allergy history. If a patient's history suggests reactivity to a specific NSAID and lack of reactivity to NSAIDs of other chemically dissimilar classes, a true allergic reaction should be suspected.[10] Such patients should be advised to avoid the specific NSAID and any structurally similar agent (e.g., all propionic acid derivatives) because of the risk of cross-reactivity. In patients with asthma who describe an exacerbation after the administration of aspirin or another COX-1 inhibitor, a nonimmune DHR should be suspected.[10] These patients are at risk of severe asthma exacerbations resulting from the pharmacologic effects of aspirin and

other potent COX-1 inhibitors on prostaglandin and leukotriene synthesis.[183] Inhibition of COX-1 results in a shifting in the metabolism of arachidonic acids into leukotrienes that cause bronchoconstriction and increased mucus production. Overexpression of leukotrienes may also explain the development of aspirin-induced angioedema and urticaria. Patients with aspirin- or NSAID-induced asthma, urticaria, or angioedema should be advised to avoid all COX-1 inhibitors.[10,183] Studies of short duration involving small numbers of patients with aspirin-induced asthma have shown that the COX-2 inhibitors celecoxib and rofecoxib do not exacerbate asthma.[272-274] In addition, acetaminophen at single doses <1 g, sodium salicylate, choline salicylamide, and magnesium trisalicylate have not been shown to exacerbate asthma because of their lack of effect on the COX-1 enzyme. In patients with aspirin-induced nonimmune DHRs who require aspirin for prevention of cardiovascular disease, both graded challenge and desensitization is recommended.[275] A two-dose challenge of 40.5 mg (one half of an 81-mg tablet) given 90 minutes apart has shown promising results in patients with a history of isolated dermatologic reactions to aspirin.[275] If no reaction occurs after the second dose, cardioprotective therapy with 81 mg of aspirin may commence. In patients with aspirin-induced asthma, desensitization to aspirin has been achieved.[275] Rapid desensitization protocols for patients with cardiovascular disease requiring aspirin have also been described.[275-277]

RADIOCONTRAST MEDIA

Nonimmune DHRs associated with radiocontrast agents may be prevented by the use of pretreatment regimens, as noted in Table 6-9. In addition, administration of a low-osmolarity agent in conjunction with pretreatment has been shown to reduce the risk of reactivity to approximately 1%.[278] Most recently, there is a trend toward skin testing of patients with prior history of reactivity to a radiocontrast agent. Skin testing with a panel of different agents may aid in the identification of an agent of low reactive risk, thereby reducing the risk of reactivity on subsequent exposure.[279]

MANAGEMENT

Recommended treatment regimens for drug allergy vary based on the signs and symptoms of the reaction and the type of allergic syndrome. Reactions mediated by nonimmune mechanisms are treated in a manner similar to those of true allergic reactions, with the choice of therapy based on the patient's signs and symptoms. **Table 6-10** provides a summary of recommended treatments for a variety of allergic syndromes.

In 2015, the Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Allergy updated the Practice Parameter on the Diagnosis and Management of Anaphylaxis.[184] On the basis of these guidelines, patients with stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmias, shock, or loss of consciousness require immediate treatment. Life-threatening conditions may also develop in patients with nonlife-threatening symptoms on initial presentation (e.g., localized urticaria).[184] Table 6-10 summarizes the Joint Task Force's guidelines for treatment of anaphylaxis. The mainstays of therapy are epinephrine 1 mg/mL dilution administered intramuscularly, oxygen, and aggressive intravenous fluid replacement. In studies of adults and children not experiencing anaphylaxis, epinephrine has been shown to be most efficiently absorbed when administered intramuscularly, rather than subcutaneously.[282] In adults, the preferred intramuscular site of injection is the anterolateral thigh, because of a higher rate of absorption.[283] Consideration should also be given to the addition of a histamine H_1-receptor blocker and histamine H_2-receptor blocker; however, these agents are not rapid-acting and should never be used in place of epinephrine. Patients receiving long-term β-blocker therapy by either oral or topical routes usually require higher doses of epinephrine.[184] In these patients, anaphylaxis is often severe and associated with profound hypotension or bradycardia that are unresponsive to epinephrine. Glucagon may be used in these patients for its inotropic and chronotropic effects that occur independently of α-receptor responsiveness. Corticosteroids have no role in the

Table 6-10 Management of Drug Allergy

Anaphylaxis[179,180,184]

- Discontinue the offending agent
- Establish and maintain airway
- Administer epinephrine 1 mg/mL (adults 0.3–0.5 mg; children 0.01 mg/kg) IM in the lateral aspect of the thigh
- Place patient in a recumbent position
- Oxygen 4–10 L/min through facemask or up to 100% oxygen as needed
- Repeat IM epinephrine every 5–15 minutes for up to 3 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 saline every 20 minutes for 3 doses; in children, 0.15 mg/kg via nebulizer every 20 minutes for 3 doses
- In cases of refractory bronchospasm or hypotension not responding to epinephrine because a β-adrenergic blocker is complicating management, administer glucagon 1–5 mg (20–30 mcg/kg; maximum 1 mg in children) IV over 5 minutes
- Give epinephrine by continuous IV infusion for patients with inadequate response to IM epinephrine and IV saline; add 1 mg (1 mL of 1 mg/mL) of epinephrine to 1,000 mL of 0.9% saline solution; start infusion at 2 mcg/min and increase up to 10 mcg/min based on blood pressure, heart rate, and cardiac function
- Consider intraosseous access if IV access is unsuccessful in either adults or children
- Consider diphenhydramine 25–50 mg IM/slow IV infusion in adults, then 25–50 mg orally every 4–6 hours; 1 mg/kg (up to 50 mg) in children
- Consider ranitidine 50 mg (adults) or 12.5–50 mg (1 mg/kg) in children, diluted in D5W to a volume of 20 mL administered IV over 5 minutes; given every 6–8 hours
- Consider methylprednisolone 1–2 mg/kg/dose up to 125 mg (or equivalent steroid) to reduce the risk of recurring or protracted anaphylaxis; dose can be repeated every 6 hours as required

Angioedema[184,235,286]

- Discontinue the causative agent
- Establish and maintain airway
- Treatment is based on the extent and severity of the clinical presentation; treatment may include the following:
  - Histamine H_1-receptor antagonist (see Urticaria)
  - Epinephrine (see Anaphylaxis)
  - Corticosteroids (see Anaphylaxis)
  - Nebulized (β_2-agonists (see Anaphylaxis)

Urticaria[285,286]

- Discontinue the causative agent
- Administer epinephrine if the diagnosis of anaphylaxis has not been excluded
- First-line therapy (if tolerated): hydroxyzine hydrochloride 25–150 mg daily at bedtime or in divided doses, diphenhydramine 12.5–50 mg per dose every 4 to 6 hours as needed
- Alternative first-line therapy: nonsedating antihistamines such as cetirizine 10–40 mg daily or in divided doses (adults); loratidine 10–40 mg daily in morning; fexofenadine 180 mg daily or 60 mg twice daily
- Second-line therapy: doxepin 25–100 mg/day (adults); 25–50 mg/day initially up to a maximum of 100 mg/day (adolescents); 1–3 mg/kg/day (children)
- Combinations of antihistamines are also recommended
- Short course of oral corticosteroids if symptoms are severe and not resolving with antihistamines

Serum sickness-like disease[69,188]

- Short course of methylprednisolone
- Corticosteroids (1–2 mg/kg prednisone or equivalent) once daily or administered in 2 divided doses for 5 days (if severe systemic event)

Vasculitis[86-88]

- Discontinue the offending agent
- Histamine H_1-receptor antagonist (diphenhydramine or hydroxyzine) for pruritus
- Corticosteroids (1 mg/kg prednisone or equivalent) in divided doses for 7–14 days or bolus IV therapy with 15 mg/kg/day for 3 days followed by 1 mg/kg/day orally

Hypersensitivity syndrome[188]

- Discontinue the offending agent
- Systemic corticosteroids (>0.5 mg/kg/day prednisone or equivalent)

D5W = 5% dextrose in water, IM = intramuscular, IV = intravenous.

acute treatment of anaphylaxis, except for patients with a history of asthma or idiopathic angioedema; however, these drugs are used adjunctively to prevent the late-phase reaction. Patients treated long term with ACE inhibitors may also require aggressive treatment for hypotension associated with anaphylaxis. In these patients, the release of angiotensin II as a normal compensatory mechanism is blunted. Following treatment and resolution of anaphylaxis, the patient should receive education on the self-administration of epinephrine auto-injectors. Patients at high risk for recurrence of anaphylaxis

should be instructed to carry two auto-injectors at all times.[184] Adults should receive the 0.3- or 0.5-mg dose (if available) and children should receive the auto-injector that provides 0.15 mg per dose.[284] The optimal dose for obese patients has not been determined. Concerns in the obese population are optimal weight-based dosing and adequate needle length for intramuscular delivery of epinephrine.[284]

Treatment of immune complex diseases is highly variable and dependent on the patient's presentation. In many cases, discontinuation of therapy with the causative drug is the only treatment required. Supportive therapy may include a mild analgesic/antipyretic, such as acetaminophen, for flu-like symptoms. An oral antihistamine should be considered in patients with pruritus associated with an urticarial, maculopapular, or mixed skin rash. In some patients, a short course of a low-dose oral corticosteroid such as methylprednisolone may be used for treatment of a diffuse erythematous, maculopapular skin rash. High-dose corticosteroids (i.e., prednisone 40–60 mg/day) should be reserved for patients with systemic events involving the kidney or liver, patients with drug hypersensitivity syndromes, or patients with vasculitis.[188] The presence of mucosal involvement (i.e., SJS or TEN) often precludes the use of systemic corticosteroids because of the risk of infectious complications.[188]

INFORMATION FOR PATIENTS

Patients in whom an allergic reaction to a drug develops should be educated as to the name of the specific drug, the terminology used to describe the reaction, and the likelihood of having a similar or more severe reaction upon re-exposure to the drug. If the reaction was severe (e.g., anaphylaxis, SJS), the patient should be advised to wear a medical alert tag or bracelet describing the reaction. In the case of a severe immediate reaction to a drug or chemical, the patient may be prescribed injectable epinephrine in an easily injectable form (e.g., EpiPen or EpiPen Jr.) for use in an emergency situation. Such patients should be advised to have at least two doses of epinephrine in their possession, particularly if they live in a rural area without direct access to emergency care. In addition, these patients must be counseled regarding the appropriate administration technique to ensure rapid absorption (i.e., intramuscularly into the anterolateral thigh).

Patients with a history of allergy to a drug or multiple drugs should be encouraged to ask questions about newly prescribed medications. For example, a patient allergic to a sulfa drug should be advised to question whether any newly prescribed medication is considered a "sulfa medication." Patients with aspirin-induced asthma or reactions to excipients should be encouraged to read the labels of nonprescription medications to identify ingredients of concern. In addition, patients should be educated regarding the avoidance of the causative drug and other cross-reactive drugs in the future.

CUTANEOUS DISEASES

The spectrum of adverse cutaneous reactions ranges from the commonly occurring, often self-limiting erythematous rash to the rare, life-threatening severe cutaneous adverse reactions (SCARs). Approximately 30 different drug-mediated cutaneous reaction patterns have been described.[287] This section will address drug-induced acne, erythematous reactions, fixed drug eruptions, psoriasis, and the SCARs (DRESS, SJS, TEN, warfarin tissue necrosis). The previous section provides discussion of urticaria, angioedema, and skin reactions associated with immune complex diseases. Chapter 8 provides a review of drug-induced photosensitivity.

Standard terms are used to describe the manifestations of skin lesions, including those that are drug-induced. A listing of these terms and their definitions is provided in **Table 6-11**.[287]

CAUSATIVE AGENTS

Identifying the most likely cause of a potential drug-induced cutaneous reaction is complicated by the fact that almost all drugs have been associated with rash as described in the product literature. To streamline the assessment of causality, it is important to consider that antimicrobial agents have been consistently identified as the most frequent

Table 6-11 Glossary of Terms for Skin Lesions[287]

Bullae
- Vesicle filled with serous fluid, >1 cm

Comedone (open)
- Blackhead; dilated hair follicle filled with sebum and bacteria with a blackened mass of skin debris at the surface

Comedone (closed)
- Whitehead; dilated hair follicle filled with sebum and bacteria with an obstructed opening to the skin

Macule
- Circumscribed, nonpalpable, red, flat lesion, <1 cm

Nodule
- Papule that is firm and with depth, 0.5–2 cm

Papule

Solid, palpable, red, elevated lesion, <1 cm

Patch
- Group or cluster of macules

Plaque
- Solid, palpable, elevated solid lesion, 0.5 cm

Pustule
- Vesicle filled with purulent material

Typical target or iris lesion
- Lesion <3 cm in diameter, regular round shape, well-defined border with at least three different zones (two concentric rings around a central area); one ring consists of palpable edema, paler than the central area

Target lesion (flat, atypical)
- Round lesions with only two zones and/or a poorly defined border and nonpalpable, with the exception of a potential central blister

Wheal
- Central blister, irregular, pink in color, superficial area of skin edema

Vesicle
- Circumscribed, elevated lesion filled with serous fluid, 0.5 cm

offenders in cutaneous eruptions, followed in frequency by the NSAIDs.[288,289]

Based largely on reports of single cases, more than 100 drugs have been implicated as causative of SJS or TEN.[288] In a large international case-control study, Roujeau et al.[288] attempted to quantify the association between the use of specific medications and the development of SJS and TEN. Cases (n = 245) were patients admitted to the hospital with a diagnosis of SJS or TEN, and controls (n = 1,147) were patients admitted to the same hospital for an elective procedure or treatment of an acute condition not deemed to be drug related. Of the drugs used for short periods, sulfonamides were the most strongly associated with TEN (crude RR 172, 95% CI 75–396), with trimethoprim–sulfamethoxazole accounting for 69% of these cases.[288] Thiazide diuretics and sulfonylureas were not associated with increased risk. In descending order of frequency, other major drug offenders were chlormezanone (crude RR 62, 95% CI 21–188), cephalosporins (RR 14, 95% CI 3.2–59), quinolones (RR 10, 95% CI 2.6–38), tetracyclines (RR 8.1, 95% CI 1.5–43), and aminopenicillins (RR 6.7, 95% CI 2.5–18).[288] Additionally, acetaminophen was associated with a significant risk (RR 9.3, 95% CI 3.9–22) in all countries other than France. Of the drugs administered for a duration of months to years, carbamazepine, phenobarbital, phenytoin, valproic acid, the oxicam NSAIDs, allopurinol, and corticosteroids were associated with significantly increased risks. The first 2 months of long-term drug administration was identified as the highest-risk period.

In 2007, the results of the Euro-SCAR study offered an update on the risks of SJS/TEN with newly marketed medications.[290] In this international, multicenter case-control study, 379 patients with SCAR and 1,505 controls were enrolled. The results of this study confirmed the high risks previously identified associated with the use of anti-infective sulfonamides, allopurinol, carbamazepine, phenobarbital, phenytoin, and the oxicam NSAIDs.[290] An increased risk of SJS/TEN was also identified with the use of nevirapine (RR >22) and lamotrigine (RR >14), with weaker associations identified with sertraline (RR 11, 95% CI 2.7–46), pantoprazole (RR 18, 95% CI 3.9–85), and tramadol (RR 20, 95% CI 4.4–93).[290] The majority of SCAR cases occurred within 8 weeks of initiation of therapy. Onset of the SCAR within 4–28 days after drug initiation was most suggestive of the drug as the cause.

Medications most commonly associated with the development of skin eruptions are listed in **Table 6-12**.[188,249,250,288,290-334] In addition to

Table 6-12 Agents Implicated in Drug-Induced Cutaneous Diseases

Drug	Incidence	Level of Evidence[a]
ACNE		
Androgenic steroids (methyltestosterone, testosterone, nandrolone)[291]	NK	C
Azathioprine	NK	C
Corticosteroids[292,293]	NK	C
Cyclosporine	NK	C
Danazol	NK	C
EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS[294,295]		
Cetuximab	88–90%	B
Erlotinib	75%	B
Gefitinib	25–33%	B
Panitumumab	70–100%	B
Granulocyte colony-stimulating factor[296]	NK	C
Infliximab[297]	NK	C
Iodides[298]	NK	C
Lamotrigine[299]	NK	C
Lithium[300]	NK	C
Tacrolimus[301]	NK	C
FIXED DRUG ERUPTION		
Acetaminophen[302]	NK	C
Allopurinol[302]	NK	C
Barbiturates[298]	NK	C
Carbamazepine[298]	NK	C
Celecoxib[302]	NK	C
Dipyrone[302]	NK	C
Erythromycin[302]	NK	C
Fluconazole	NK	C
Griseofulvin[302]	NK	C
Ibuprofen[302]	NK	C
Metronidazole[302]	NK	C
Paclitaxel[302]	NK	C
Penicillins[302]	NK	C
Phenophthalein[302]	NK	C
Propofol[303]	NK	C
Pseudoephedrine[302]	NK	C
Quinine[304]	NK	C
Rifampin[302]	NK	C
Sulfamethoxazole[298,302]	NK	C
Tetracyclines[298]	NK	C
Tranexamic acid[305]	NK	C
DRESS		
Allopurinol[188]	NK	C

Table 6-12 Agents Implicated in Drug-Induced Cutaneous Diseases (continued)

Drug	Incidence	Level of Evidence[a]
Azithromycin[306]	NK	C
Captopril[307]	NK	C
Carbamazepine[188]	NK	C
Dapsone[188]	NK	C
Lamotrigine[188]	NK	C
Minocycline[188]	NK	C
NSAIDs[188]	NK	C
Omeprazole[308]	NK	C
Phenytoin[188]	NK	C
Phenobarbital[309]	NK	C
Piperacillin[310]	NK	C
Raltegravir[311]	NK	C
Sulfonamides[188]	NK	B
Teicoplanin[312]	NK	C
Vancomycin[312]	NK	C
PSORIASIS		
ACE inhibitors[313,314]	NK	C
β-blockers[313,314]	NK	B
Chloroquine[313,314]	NK	C
Etanercept[315]	NK	C
Granulocyte colony-stimulating factor	NK	C
Growth hormone[316]	NK	C
Hydroxychloroquine[313,314]	NK	B
Imatinib[313]	NK	C
Infliximab[317]	NK	C
Interferon α and interferon γ[313,314]	NK	C
Lithium[313,314]	NK	B
NSAIDs[313,314]	NK	C
Tetracyclines[313,314]	NK	C
Terbinafine[313,314]	NK	C
Valproate sodium[318]		
STEVENS–JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS[319]		
Acetaminophen[288, 320,321]	NK	B
Allopurinol[322]	NK	B
Aminopenicillins[188]	NK	B
Celecoxib[249]	NK	C
Cephalosporins[188]	NK	B
Ciprofloxacin[290]	NK	C
Fluconazole[323]	NK	C
Hydralazine[324]	NK	C
Imatinib[325]	NK	C
Imidazole antifungal agents[288,290]	NK	B

Table 6-12 Agents Implicated in Drug-Induced Cutaneous Diseases (continued)

Drug	Incidence	Level of Evidence[a]
Lamotrigine[290]	NK	B
Levofloxacin[326,327]	NK	C
Mesalamine[328]	NK	C
Modafinil[329]	NK	C
Moxifloxacin[330]	NK	C
Nevirapine[290,331]	NK	B
Ofloxacin[332]	NK	C
Pantoprazole[290]	NK	B
Phenobarbital[188]	NK	B
Phenytoin[188]	NK	B
Piroxicam[290]	NK	B
Sertraline[290]	NK	B
Tramadol[290]	NK	C
Trimethoprim–sulfamethoxazole[188,288]	NK	B
Valdecoxib[250]	NK	C
Valproic acid[290]	NK	C
Voriconazole[333]	NK	C
SKIN NECROSIS		
Warfarin[188,298,334]	1 in 10,000[b]	B

ACE = angiotensin-converting enzyme, DRESS = drug rash with eosinophilia and systemic symptoms, HHV-6 = human herpesvirus 6, NK = not known, NSAID = nonsteroidal anti-inflammatory drug.

[a]Definitions for Levels of Evidence: Level A—evidence from one or more randomized, controlled clinical trials; Level B—evidence from nonrandomized clinical trials, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analyses and/or postmarketing surveillance studies; and Level C—evidence from one or more published case reports or case series.

[b]Prevalence.

prescription medications, it is important to consider that SCARs have been associated with the use of nonprescription drugs (e.g., acetaminophen, pseudoephedrine) and traditional Chinese herbal medicines.[335]

EPIDEMIOLOGY

Cutaneous and mucocutaneous events are the most commonly reported adverse reactions to medications. Based on the results of the Boston Collaborative Drug Surveillance program conducted in the 1970s and 1980s, it is estimated that a drug-related skin rash develops in 2–3% of all hospitalized patients.[191] In this prospective study of 37,000 hospitalized patients, the majority of the skin reactions were exanthematous (94%), with the remainder urticarial (5%). Approximately 2% of the reactions were fatal.[191] Epidemiologic studies conducted in the 1990s focused on estimating the incidence of SCARs. Compared to exanthematous reactions, SCARs appear to be relatively uncommon. In 1995, Roujeau et al.[188] estimated that serious cutaneous drug events including SJS and TEN occur in 1 of every 1,000 hospitalized patients.

Estimates of the prevalence of drug-induced cutaneous events have been determined from prospective studies of hospitalized patients, outpatients, patients receiving systemic drug therapy, and those exposed to medications via any route of administration.[191,289,336] The estimates have varied based on the type of cutaneous event investigated, the definition used to describe the dermatologic condition, and the population studied. In a 6-month prospective study conducted in 2000–2001, practitioners identified and subsequently a dermatologist assessed all suspected allergic cutaneous reactions that led to hospitalization or occurred during hospitalization.[289] A group of dermatologists and pharmacologists retrospectively evaluated causality. A total of 48 cases

were identified, resulting in an estimated prevalence of 3.6 of 1,000 hospitalized patients.[289] The majority of the allergic reactions were exanthematous (56%), and the prevalence was significantly higher in medical (0.5%) versus surgical patients (0.01%).[289] Thirty-four percent of cases were deemed serious on the basis of leading to hospitalization (18%), increasing the duration of hospital stay (14%), or were life-threatening (2%).[289] Compared to other studies reporting an incidence of cutaneous drug reactions of 2% in hospitalized patients, the lower prevalence determined in this study can be attributed to the restricted focus on allergic-mediated skin reactions and on systemic drug exposures.[289]

TEN is estimated to occur in 0.4–1.3 cases per million person-years, while SJS occurs in 1–6 cases per million person-years.[319] The variability in these estimates of incidence can be attributed to differences in the diagnostic criteria for SJS and TEN. The prevalence or incidence of other cutaneous skin disorders is less well described. The incidence of DRESS is highly variable, occurring in 1 of 1,000 to 1 of 10,000 patients exposed to anticonvulsants and sulfonamides, and the mortality rate has been estimated to be approximately 10%.[337] The wide variability in the reported incidence of DRESS can be attributed to the variable presentation of the condition. Fixed drug eruptions occur more frequently, with reported incidences of 2.5–22%.[302] Tissue necrosis has been reported in 1 of 10,000 patients treated with warfarin and in 0.01–0.12% of patients treated with all oral anticoagulants including the coumarin products.[188,334]

MECHANISMS

Cutaneous reactions to drugs can result from both immune and nonimmune mechanisms (i.e., direct pharmacologic effects, nonimmune DHR, idiosyncrasy). Allergy is the underlying mechanism in 50% of the events, including most cases of urticaria, angioedema, serum sickness-like syndrome with maculopapular rash, fixed drug eruptions, vasculitis, and the SCARs, including DRESS, SJS, and TEN. The skin is a target for immunologically mediated reactions because it possesses APCs such as the cutaneous Langerhans cells. The presence of monooxygenases, cytochromes, and transport-associated proteins in the keratinocytes allow for transformation of low-molecular-weight drug haptens into reactive, immunogenic metabolites.[338]

T cells play a major role in the pathophysiology of drug-related cutaneous reactions. An extensive review of the role of the T lymphocyte in the mediation of a variety of drug-induced eruptions has been provided by Naisbett.[339] Based on immunohistologic studies, allergy-mediated maculopapular rashes have been shown to involve the recruitment of CD4 cells and copresentation of the drug hapten with the MHC class II molecule HLA-DR.[339] Maculopapular rashes are also associated with secretion of high levels of IL-5 and eotaxin, two cytokines involved in the recruitment and differentiation of eosinophils. Bullous reactions are more likely to be associated with the recruitment of CD8+ cells and copresentation of the haptenic drug or reactive metabolite with MHC class I molecules.[339] Cell studies of blister fluid from patients who survived TEN also support a dominant role for T lymphocytes, particularly CD8+ cells, in the pathogenesis of this SCAR. In patients with TEN, activation of cytotoxic T lymphocytes ultimately results in dermal-cell apoptosis, which is believed to be triggered via activation of the perforin–granzyme or the Fas-Fas ligand pathways. Stimulation of these pathways triggers activation of caspases, intracellular proteases that cleave a key protein within the cell, leading to keratinocyte apoptosis. In addition to cytotoxic T lymphocytes, other mediators of TEN include monocytes, macrophages, and TNFα. Overexpression of TNFα, interferon α, IL-2, and IL-5 has been reported in skin lesions of patients with SJS and TEN.[337,340]

Mechanisms by which many drugs cause skin eruptions are not known. Pharmacologic effects may be the underlying mechanism by which most drugs cause acneiform eruptions and provocation of psoriasis. Androgenic drugs (e.g., anabolic steroids, danazol, methyltestosterone) aggravate pre-existing acne or cause acneiform eruptions by activating sebaceous-gland hypertrophy and increasing sebum production. The high incidence of acneiform eruptions associated with the use of epidermal growth factor receptor (EGFR) inhibitors

may also be explained in part by the known pharmacology of these agents. EGFRs are overexpressed in many solid tumors, explaining the effectiveness of EGFR inhibitors in the treatment of refractory colorectal and lung cancers. EGFRs are also expressed in the basal layer of the epidermis and in the hair follicle.[294,295] Although the mechanism by which EGFR inhibitors cause acne-like rashes is not entirely known, the dose-related incidence may be related to inhibition of EGFR signaling on epidermal epithelium leading to impaired cell growth and differentiation.[294] Provocation of psoriasis by nonselective β-blockers such as propranolol may be explained in part by blockade of epidermal β_2-receptors, resulting in a decrease in intraepidermal cyclic adenosine monophosphate and an increase in epidermal-cell turnover.[313] Cyclooxygenase inhibitors such as indomethacin may induce psoriasis by inhibiting prostaglandin synthesis, thereby shunting the metabolism of arachidonic acids to the lipoxygenase pathway. The resultant increase in leukotriene concentrations may contribute to the exacerbation of psoriasis in patients treated with COX inhibitors.[314] Studies support that leukotriene concentrations are 7–11 times higher in psoriatic lesions as compared with normal skin.[313]

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

The discriminating features of specific drug eruptions are provided in **Table 6-13** and the conditions to consider in the differential diagnoses are provided in **Table 6-14**.

The most common type of drug-induced skin eruption is the exanthematous or maculopapular rash, occurring in 1–5% of first-time users of implicated medications.[342] This red, inflamed cutaneous reaction usually appears as a mixture of discrete macules and papules on the trunk or dependent areas of the body (e.g., lower extremities of an ambulating patient, middle to lower back of a bedridden patient). The lesions typically spread outward in a bilateral, symmetrical pattern to involve the neck, upper and lower extremities, and potentially the face.[298,341,342] The rash is often described as "dot-like" in appearance, or measles (morbilliform)-like, and may or may not be associated with fever and pruritis. The discrete lesions typically coalesce over days into patches with large areas of confluence. The rash usually occurs within 4–14 days after the initiation of therapy with the causative drug or within 1–2 days after drug discontinuation.[341] This reaction is usually self-limited, with resolution in 1–2 weeks after drug discontinuation. Upon re-exposure to the drug, the rash may reappear within hours. In rare instances, a maculopapular rash may be the initial sign of a severe cutaneous event such as SJS. Therefore, all patients who initially present with a maculopapular rash should be assessed for hallmark signs of a more severe, progressive reaction. Lesions in the mucous membranes (e.g., conjunctiva, oral cavity, nares, genitalia) are evident in more than 90% of serious cutaneous events, and extension of the rash to the palms and soles often portends a more protracted course.[188,337]

A commonly encountered clinical challenge is differentiation of a maculopapular rash from an urticarial lesion. Unlike maculopapular lesions, urticarial lesions are typically asymmetrical, pink rather than red, and irregular in shape. These superficial wheals, largely confined to the epidermis, are often described as geographic in shape (i.e., similar in shape to the continent of Africa or Asia). Urticarial lesions are highly pruritic, vary in size from 1 mm to several centimeters in diameter, and typically develop on the chest, face, or neck within minutes to 48 hours after drug exposure.[298] Differentiation of a maculopapular rash from urticaria is important, because the latter often indicates IgE-mediated mast cell degranulation. In a patient with drug-related IgE-mediated urticaria, continuation of the causative drug may lead to a more severe reaction, including angioedema or anaphylaxis. Urticaria may also be caused by foods, insect bites/stings, and environmental factors such as sunlight, cold, and heat.[298]

Fixed drug eruptions (FDEs) are the second most commonly occurring drug-related cutaneous reaction, occurring in 0.5–22% of patients exposed to certain medications.[344] FDEs present as solitary lesions or multiple well-demarcated lesions occurring anywhere on the body, but favoring the

Table 6-13 Signs and Symptoms Associated with Drug-Induced Cutaneous Diseases

Acne[298]

- Papules and pustules on face and upper trunk
- Limited number of comedones to no comedones

Erythematous rash[341,342]

- Symmetrical distribution of macules and papules starting on upper trunk or legs
- Rash may progress to entire body including face
- Pruritus (50%)
- Redness without blistering

DRESS[337,343]

- High fever (38–40°C)
- Diffuse, symmetrical maculopapular rash with pruritus (90%)
- Facial and periorbital edema
- Enlarged lymph nodes at ≥2 sites (cervical and inguinal) in >50% cases
- Involvement of at least one internal organ (hepatitis, pneumonitis, pancreatitis)
- Conjunctivitis
- Eosinophilia
- Atypical lymphocytosis

Fixed drug eruption[287,344]

- Initial burning "stinging" sensation or itching of skin
- Round or oval dusky red to violaceous lesions, 1–20 cm in diameter, favoring the face, lips, hands, feet, perineal area, genitalia
- Lesions recur in the same location(s) upon rechallenge
- Blistering of lesions
- Anorexia and malaise (infrequent)
- High fever (infrequent)
- Hyperpigmentation in the area of the lesion following recovery

Psoriasis

- Red or salmon-pink plaques covered by silvery scales symmetrically distributed on elbows, knees, scalp, and lumbosacral region

SJS/TEN[188,319,337]

- Prodrome of nausea, vomiting, sore throat, cough, arthralgias, myalgias for 2–8 days before rash development
- Widespread erythematous, purpuric rash with flat atypical target lesions
- Burning and painful sensation of the skin
- Fever (10–30% of cases of SJS, 100% of cases of TEN)
- Facial edema
- Mucosal lesions of the mouth, lips, nasal cavity, conjunctivae, genitalia (92–100% of cases of SJS; 85–95% of cases of TEN)
- Epidermal detachment (<10% of body surface area with SJS; >30% of body surface area with TEN)
- Positive Nikolsky sign (TEN)
- Neutropenia (30% of cases of SJS and TEN)
- Lymphopenia (90% of cases of TEN)
- Thrombocytopenia (15% of cases of TEN)
- Prerenal azotemia (TEN)
- Elevated aspartate and alanine aminotransferases (50% of cases of SJS and TEN)
- Hypopigmentation or hyperpigmentation (88% of cases of TEN)
- Keratitis and corneal erosions

Warfarin-induced skin necrosis[188,298,334]

- Poorly demarcated, painful red plaques with soft-tissue edema
- Pain
- Petechial hemorrhages that coalesce into large hemorrhagic bullae with areas of gangrenous tissue
- Lesions usually distributed in areas of fatty tissue (buttocks, breasts, hips)

DRESS = drug rash with eosinophilia and systemic symptoms, SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis.

face, lips, hands, feet, and genitalia. The lesions are round or oval in shape and range in size from 1–20 cm in diameter.[287,298] The color of the lesions may vary from dusky red, to blue-gray or violaceous. Patients typically describe a burning sensation or itching, or both, associated with the development of lesions. In some patients, the center of the lesion may become bullous and result in denuding of skin. The diagnostic hallmark of FDE is recurrence of the lesion in the same anatomical location after drug rechallenge.[302] Both topical and oral provocation tests have been performed to confirm the diagnosis. However, oral challenge is more likely to lead to the development of generalized bullous lesions.[302] Following resolution of lesions, the affected tissue may remain hyperpigmented for an extended period. As the name implies, the sole cause of FDE is drugs. Therefore, a complete drug history with attention to prescription, nonprescription, and herbal remedies must be obtained to identify the causative agent.

Table 6-14 Conditions to Consider in the Differential Diagnosis of Drug-Induced Cutaneous Disorders

Erythematous rash[298,342]

- Viral exanthema (Epstein–Barr virus, human herpesvirus 6, parvovirus B19)
- Acute graft-versus-host disease
- Bacterial toxin eruption
- Kawasaki disease
- Still disease

Fixed drug eruption[287,302,344]

- Bullous pemphigoid
- Contact dermatitis
- Herpes (simplex) labialis
- Discoid lupus erythematosus
- Insect bite (if a single lesion)
- Phytophotodermatitis

DRESS[188]

- Cutaneous lymphoma
- Psoriasis (aggravation of)[313,314]
- Alcohol consumption
- Physical trauma
- Psychological stress
- Streptococcal infection
- Viral infection

SJS[188,345]

- Postinfectious erythema multiforme (secondary to herpes simplex or mycoplasma infection)
- Kawasaki disease

TEN[188]

- Exfoliative dermatitis
- Staphylococcal scalded-skin syndrome
- Paraneoplastic pemphigus
- Thermal burns

Warfarin-induced skin necrosis[334]

- Disseminated intravascular coagulation
- Purple toe syndrome
- Pyoderma gangrenosum
- Microembolization
- Leukocytoclastic vasculitis
- Necrotizing fasciitis
- Purpura fulminans
- Venous gangrene
- Heparin-induced thrombocytopenia
- Septicemia

DRESS = drug rash with eosinophilia and systemic symptoms, HHV-6 = human herpesvirus-6, SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis.

Drugs most commonly associated with FDE are listed in Table 6-12.

Acneiform eruptions are an infrequent drug-induced adverse event, accounting for only 1% of all drug-related cutaneous reactions.[298] Unlike acne vulgaris, drug-related acneiform eruptions consist primarily of papules and pustules with limited to no comedones. Similar to those associated with acne vulgaris, these eruptions are typically confined to the face and upper trunk.[298] The classic drug offenders are corticosteroids, adrenocorticotropic hormone, anabolic steroids, combination oral contraceptives, danazol, bromides, iodides, isoniazid, lithium, and azathioprine. Corticosteroids administered orally, parenterally, topically, or by inhalation have been shown to provoke acneiform eruptions or exacerbate underlying conditions of acne.[291,292,293] Steroid-induced acne is common and usually appears within 14 days after initiation of systemic or topical therapy.

An acne-like reaction has also been described in association with the use of the EGFR inhibitors (e.g., cetuximab, panitumumab, erlotinib, gefitinib) used in the treatment of colorectal and non-small-cell lung cancer. The acne-like rash is pruritic, with a predominance of pustules and an absence of open or closed comedones.[294,295] The rash is typically mild to moderate in severity, occurs most frequently on the face and V-shaped areas of the chest, back, or both, and appears within 10–14 days after drug therapy initiation. The severity of the rash has been shown to correlate with both increasing drug dose and the antitumor activity of the agent.[295] Some data support a relationship between the occurrence of rash and the increased likelihood of patient survival.[294] In patients with severe rashes, particularly those involving more than 50% of the body surface area, dose modification or interruption of EGFR inhibitor therapy is recommended.[294,295] The rash is typically reversible following discontinuation of therapy.

Psoriasis is a chronic, immunologically mediated skin disease that is characterized by red or salmon-pink plaques covered by silvery or white scales surrounded by normal skin.[313] The plaques are symmetrically distributed on the elbows, knees, scalp, and lumbosacral region. Several clinical phenotypes of psoriasis exist, including pustular, erythrodermic, and nail psoriasis. However, 90% of cases present as plaque psoriasis (psoriasis vulgaris). This chronic condition involves the activation of T lymphocytes with overexpression of a number of cytokines, including TNFα, interferon α, IL-6, IL-2, and IL-8. Drugs can exacerbate pre-existing lesions (e.g., β-blockers, lithium, synthetic antimalarial drugs), provoke the development of new plaques on the normal skin of patients with psoriasis (e.g., β-blockers, lithium), and cause psoriasis in patients with no history or familial predisposition (e.g., growth hormone).[313-315] Most cases of drug-induced psoriasis are clinically indistinguishable from psoriasis from nondrug-induced causes. In some cases, the offending drug can cause a lichenoid pattern of disease or a transformation to the pustular form of psoriasis.[313] The latency period from initiation of therapy with the offending drug to the exacerbation or appearance of psoriatic lesions varies widely. Mean latency periods of 3 weeks, 6 weeks, and 33 weeks have been described for psoriasis induced by the synthetic antimalarial drugs, ACE inhibitors, and lithium, respectively.[313] β-blockers have been associated with a latency period ranging from days to weeks after initiation of therapy. Drugs used to treat psoriasis, including topically applied agents (e.g., coal tar) and systemically administered agents (e.g., etretinate, etanercept, infliximab), can also aggravate the condition. The TNFα-agents infliximab and etanercept have been reported to aggravate psoriasis in patients undergoing treatment for psoriatic arthritis and have provoked psoriasis in patients treated for Crohn disease, ankylosing spondylitis, rheumatoid arthritis, and ulcerative colitis.[315] In patients treated with infliximab or etanercept, new psoriatic lesions developed as soon as after the second injection.[315]

Serious cutaneous adverse reactions include DRESS, SJS, TEN, and warfarin tissue necrosis. DRESS is a distinct clinical syndrome previously described by the more general term, *drug hypersensitivity syndrome*.[99,102,343] DRESS is characterized by the triad of high fever, rash, and internal organ involvement.[188,343] Compared with immune complex diseases such as SSLD, DRESS is associated with a more delayed onset of symptoms, ranging from 3 to 8 weeks after drug initiation, and a more consistent pattern of internal-organ involvement.[99,343] The initial manifestation of DRESS is diffuse, symmetrical maculopapular eruptions on the upper trunk and face. This rash can extend to include the lower extremities and is typically associated with facial and periorbital edema. The edema may lead to gross distortion of the patient's features. Organs affected by this syndrome include the kidney, liver, pancreas, lungs, and hematologic system. A high degree of interpatient variability exists with regard to the targeted organ and the severity of organ involvement. To better define and classify the syndrome, the RegiSCAR scoring system was developed in 2007.[346] Application of this scoring system in 172 cases of suspected DRESS led to the identification of the following features of a probable or definite case: skin rash, hypereosinophilia, lymphadenopathy, and liver involvement.[346]

Both the anticonvulsant hypersensitivity syndrome and the allopurinol hypersensitivity syndrome are classic examples of DRESS. Anticonvulsant hypersensitivity syndrome, associated with the aromatic anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine), is characterized by the triad of fever (38–40°C), rash (papular, pruritic, often associated with facial or periorbital edema), and lymphadenopathy occurring within 3 months after the initiation of therapy.[255,256] Other diagnostic criteria include hematologic abnormalities (leukocytosis, eosinophilia), myalgias, pharyngitis, and hepatitis or other multisystem involvement (e.g., interstitial nephritis, rhabdomyolysis, pneumonitis).[255,256] Allopurinol hypersensitivity syndrome is associated with a mean (±SD) onset of 47±109 days[102] and also presents with high fever, eosinophilia, and skin rash that may be severe (e.g., SJS or TEN). Kidney failure, hepatomegaly, and abnormalities in liver function tests are also frequently noted. This reaction, attributed to the active metabolite oxypurinol, has

been described as a vasculitic immune complex disease.[101,102]

SJS and TEN are related mucocutaneous disorders that are considered by many as drug-induced variants of erythema multiforme. Like erythema multiforme, both SJS and TEN are associated with the widespread development of multiple types of skin lesions, including macules, blisters, purpuric lesions, and the hallmark target iris lesions. The target lesion is discrete, round, <3 cm in diameter, and identified by its central zone of epidermal necrosis surrounded by two concentric rings of edema and erythema.[345] SJS and TEN are progressive bullous disorders that are considered dermatologic emergencies.[288] Unlike erythema multiforme, which is usually self-limiting and related to recurrent herpes simplex viral infections, both SJS and TEN are usually drug-related and extend from diffuse erythematous reactions to include mucous membrane erosion and epidermal detachment. Drugs are the cause of SJS and TEN in 50% and 80% of cases, respectively.[287,347]

Both SJS and TEN typically occur within the first 4 weeks of drug therapy. Before skin lesions become evident, both SJS and TEN are associated with a prodromal syndrome of nausea, vomiting, sore throat, diarrhea, myalgias, and arthralgias. In patients with TEN, high fevers and a burning sensation of the skin are also frequently reported prior to the eruption of skin lesions. Mucous membrane involvement, typically of the mouth and lips, nasal cavity, and conjunctivae, tends to precede the development of skin lesions by 1–3 days.[287,348] The initial lesions are erythematous and appear on the face and upper trunk, after which they rapidly evolve into blisters and target lesions on the face, trunk, and limbs.[348] Full-thickness epidermal detachment occurs within days after the onset of skin lesions. Rather than considered as two distinctly different syndromes, SJS and TEN are often described as a continuous spectrum of a disease, with TEN as the more severe form.[345] The extent of epidermal detachment has been used to distinguish between SJS and TEN. SJS is described by the presence of mucosal erosions with widespread purpuric macules and epidermal detachment of <10% of body surface area, whereas TEN involves widespread purpuric macules and epidermal detachment of >30% of body surface area.[345,349] The term *SJS-TEN overlap* is used to describe cases in which evidence of epidermal detachment is present on 10% to 30% of the body surface area.[345,349] Although regrowth of the epidermis begins within days after the onset of epidermal loss, TEN is sometimes complicated by the development of acute kidney injury, respiratory failure, neutropenia, electrolyte abnormalities, and sepsis. Long-term sequelae of SJS and TEN may include temporary nail loss, permanent visual impairment, cutaneous scarring, and irregular pigmentation. A severity-of-illness scoring system for TEN, known as SCORTEN (SCORe of toxic epidermal necrolysis), has been described and evaluated as a prognostic indicator.[350] With the use of this system, seven independent risk factors, determined within 24 hours of patient presentation with TEN, are used as patient outcome indicators.[350]

Warfarin-induced skin necrosis (WISN) is a severe cutaneous reaction that typically begins within 10 days after initiation of warfarin therapy, with a peak occurrence between days 3 and 6.[298] WISN initially presents with red, poorly demarcated painful plaques usually in areas of high adipose tissue (e.g., breasts, hips, buttocks). The plaques can progress to hemorrhagic blisters and eventually become necrotic, requiring surgical debridement.[188,298] WISN occurs as a result of an imbalance between the concentrations of the endogenous vitamin K-dependent anticoagulant protein C and the vitamin K-dependent clotting factors.[188,298] The half-life of protein C is much shorter (8 hours) compared with those of clotting factors II, IX, and X (24–48 hours). After warfarin initiation, a rapid decline in the concentration of protein C may lead to a hypercoagulable state, resulting in WISN. This theory is supported by the fact that WISN is more likely to occur in patients who receive excessive initial doses of warfarin and have an underlying protein C deficiency. Patients with a deficiency of protein S, the cofactor for protein C activity, may also be at greater risk of WISN. WISN can be fatal if not treated.

RISK FACTORS

Female sex, concomitant viral infection with HIV or EBV, and the presence of autoimmune disease

have routinely been identified as risk factors for cutaneous drug eruptions.[191,201,203] In a prospective study of 48 patients with allergic-mediated skin reactions, identified risk factors were HIV (19% of patients), connective-tissue disease (10%), and viral or autoimmune hepatitis (12%).[289] In another prospective cohort study of hospitalized patients with adverse cutaneous drug reactions, those with systemic lupus erythematosus had a relative risk of 4.68 (95% CI 1.79–12.18) and patients with acquired immunodeficiency syndrome had a relative risk of 8.68 (95% CI 2.18–33.19).[351] Studies have also been performed to identify predictors of skin rash associated with specific drugs or drug classes. In the antiepileptic drug class, an increased risk of drug rash was identified in women of reproductive age and in those with history of a rash induced by another antiepileptic medication.[352,353] Other risk factors associated with specific drugs, drug eruptions, or both are provided in **Table 6-15**.

The initial dose, rate of dose titration, and concomitant administration of interacting drugs can be risk factors for cutaneous drug eruptions. Both lamotrigine and nevirapine were identified as strongly associated with SJS/TEN in the EuroSCAR study.[290] In addition to female sex, lack of adherence to the 14-day lead-in period of dosing of nevirapine may increase the risk of SCARs.[290] Factors shown to increase the risk of rash with lamotrigine include age <13 years, history of rash caused by another anticonvulsant agent, exceeding the recommended initial dose or recommended rate of dose escalation, and coadministration with valproic acid.[354] In the EuroSCAR study, daily allopurinol doses >200 mg were associated with a higher risk of SJS/TEN (OR 36, 95% CI 17–76) compared with lower daily doses (OR 3.0, 95% CI 1.1–8.4).[290] In other analyses, both kidney disease and the lack of dose adjustment in patients with impaired kidney function have been identified as risk factors for allopurinol-induced DRESS, SJS, or TEN.[92] Excessive starting doses of warfarin, female sex, and obesity have all been identified as risk factors for WISN.[188,298]

Genetic susceptibility has always been suspected as a risk factor for allergic-mediated cutaneous disorders, and evidence has become available to support this hypothesis. The HLA-B*1502 allele has been strongly linked to the risk of SJS/TEN associated with carbamazepine. In a study of Han Chinese patients, all of whom developed SJS/TEN during carbamazepine therapy, had the HLA-B*1502 allele, whereas only 3% of the patients who tolerated

Table 6-15 Risk Factors for Drug-Induced Cutaneous Diseases

Abacavir
- HHV-6[204,205]
- HLA-B*5701[193]

Allopurinol
- Doses >200 mg per day[322]
- Kidney disease[102,103]
- HLA-B*5801[335]

Amoxicillin and ampicillin
- EBV[201]

Aromatic anticonvulsants (carbamazepine, phenobarbital, phenytoin)
- Previous rash in response to an antiepileptic[353]
- Women of reproductive age[352]
- HLA-B*1502 (carbamazepine, phenytoin, fosphenytoin)[355,356]
- HLA-A*3101 (carbamazepine)[357]
- CYP2C9*3 (phenytoin)[358]

Lamotrigine
- Age <13 years[290]
- Exceeding the recommended initial dose[290]
- Coadministration with valproic acid[290]

Nevirapine
- Female sex[290]
- Lack of adherence to recommendation for 14-day lead-in dosing[290]
- HLA-B*3505[359]

Penicillins
- HIV[203]

Sulfonamides
- HIV[203]

Warfarin
- Female sex[334]
- Hereditary protein C or S deficiency[334]
- Large initial doses[334]
- Obesity[334]

EBV = Epstein–Barr virus, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, HHV-6 = human herpesvirus 6.

carbamazepine had the allele.[355] This allele occurs almost exclusively in patients of Asian and South Asian Indian ancestry. In this same patient population, presence of HLA-B*1502 has been shown to increase the risk of SJS and TEN associated with carbamazepine, phenytoin, and fosphenytoin.[356] In European and North Asian populations, HLA-A*3101 has been related to the development of nonblistering reactions such as DRESS induced by carbamazepine.[357] Most recently, a genetic variant in the CYP2C isozyme, CYP2C9*3, was found in association with phenytoin-induced SCARs.[358] Presence of the HLA-B*5701 allele has been shown to increase the risk of abacavir hypersensitivity,[194] and studies in Han Chinese suggest that the HLA-B*5801 allele may be a genetic marker for allopurinol-induced SJS and TEN.[335] Preliminary evidence also suggests a higher frequency of FDEs in association with the HLA-B22 and HLA-C1 antigens.[302]

MORBIDITY AND MORTALITY

Using four national databases, Stern[336] quantified hospitalizations and visits to office-based physicians and hospital clinics for a primary diagnosis of a skin condition. The U.S. Census estimates for 2000 were used to calculate the rates of hospitalization or office visits for a diagnosis of SJS/TEN, drug eruption, drug allergy, and urticaria/angioedema. Overall, 0.06% of hospital admissions were attributed to a skin condition related to drug use.[336] Approximately 5,000 hospitalizations per year resulted from a diagnosis of erythema multiforme, SJS, or TEN, 35% of which were attributed to drug use.[336] The rates of hospitalization for a primary diagnosis of SJS/TEN and drug eruptions were calculated as 16 and 21 admissions per million person-years, respectively. During the 6 years of study (1995–2000), there were 650,000 office visits with a primary diagnosis of erythema multiforme, SJS, or TEN and 1 million visits with a primary diagnosis of drug eruption.[336] Urticaria, angioedema, and anaphylaxis were the most frequent diagnoses associated with outpatient visits, accounting for 3 times as many visits as SJS/TEN, drug rash, and drug allergy combined.[336] When the data were annualized, more than 500,000 office visits per year were attributed to drug eruptions and drug allergies including a dermatologic component.

Although rare in occurrence relative to other dermatologic conditions, SJS and TEN are associated with substantial morbidity, with the potential for lasting disabilities and complications (e.g., corneal ulcers, corneal neovascularization, skin grafts, coagulopathies, hepatitis, glomerulonephritis) in 30–45% of patients.[319] Moreover, estimates of mortality associated with SJS and TEN range from 1% to 5% and 10% to 70%, respectively.[319] In at least one study, the death rate associated with SJS and TEN was found to positively correlate with age and was 10 times higher in patients >65 years of age.[336] In cases of SJS and TEN, the most common causes of death are sepsis, pulmonary embolism, gastrointestinal bleeding, and hypovolemia.

PREVENTION

Advances in genetic testing allow for prospective screening for the HLA-B*1502 and the HLA-B*5701 alleles, biomarkers of an increased risk of severe hypersensitivity reactions to carbamazepine and abacavir, respectively. Screening for the presence of these and other biomarkers may ultimately lead to the prevention of allergy-mediated severe cutaneous reactions. Genetic tests for HLA-B*1502 and HLA-B*5701 are currently available.

Other preventive measures include the avoidance of drugs with a propensity to cause cutaneous diseases in high-risk populations (**Table 6-16**), adherence to recommended dosing guidelines specifically for dosing titration, and avoidance of drug–drug interactions. Patients who have experienced a SCAR associated with a specific drug should be counseled to avoid the use of that drug and any structurally related drug for the rest of their lives. When initiating therapy with a medication known to present a high risk of a severe cutaneous reaction, counseling should be provided regarding the initial warning signs and symptoms (i.e., burning sensation of skin, mucous membrane involvement).

Table 6-16 Approaches to Help Prevent Drug-Induced Cutaneous Diseases

Drug	Condition	Prevention
Abacavir	DRESS	Test for HLA-B*5701[194]
Allopurinol	DRESS/SJS/TEN	Adjust dose in patients with kidney disease[102] Avoid concomitant therapy with thiazide diuretics[103]
Aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital)	SJS, TEN	Avoid use in patients with history of severe rash caused by another aromatic anticonvulsant
Carbamazepine	SJS, TEN	Test for HLA-B*1502[355]
Lamotrigine	SJS/TEN	Adhere to recommended dose and dose-escalation recommendations[354] Avoid concomitant therapy with valproic acid[354]
Nevirapine	SJS/TEN	Adhere to 14-day lead-in dosing recommendation
Warfarin	WISN	Avoid loading or large initial doses In patients with protein C or S deficiency or previous history of WISN, overlap therapy with heparin for at least 5 days and initiate warfarin at low doses[334]

DRESS = drug rash with eosinophilia and systemic symptoms, SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis, WISN = warfarin-induced skin necrosis.

MANAGEMENT

Table 6-17 provides recommended treatment methods for the drug eruptions presented in this section. Of note, maculopapular rashes are generally self-limited and usually do not require treatment. If associated with pruritus, oral antihistamines are advised. Topical corticosteroid creams such as 1% hydrocortisone may be used in patients with nondiffuse limited areas of involvement. In patients with a diffuse maculopapular rash and evidence of systemic symptoms (e.g., arthralgias, muscle pain or weakness), an oral, self-tapering, low-dose steroid regimen (e.g., methylprednisolone) may be appropriate. The recommended treatment of drug-induced urticaria and angioedema is provided in Table 6-10.

Drug-induced psoriasis is usually resistant to treatment and requires discontinuation of the offending agent (e.g., β-blockers, lithium, synthetic antimalarial drug). However, in one case series, 50% of the patients in whom psoriasis associated with either infliximab or etanercept developed were able to continue therapy and their lesions responded favorably to treatment with topical corticosteroids.[315]

Treatment of SJS and TEN is focused on supportive therapy (nutritional support, pain management, fluid replacement) and the prevention of complications such as acute kidney injury and sepsis. Depending on the extent of blistering and epidermal detachment, patients may require treatment in an intensive care or burn unit. Recommended treatment methods for SJS and TEN are provided in Table 6-17. In particular, the topical administration of silver sulfadiazine should be avoided because of the high risk of SJS and TEN associated with sulfonamides and the potential for cross-reactivity with sulfadiazine.[287] The use of systemic corticosteroids remains controversial.[345] To date, there are no large randomized, controlled studies to support the concept that systemic corticosteroids either reduce the time to recovery or prevent the development of complications. In a systematic review, a significant impact on mortality (OR 0.4, 95% CI 0.2–0.9) was demonstrated with corticosteroid use in only 1 of 6 retrospective cohort studies.[361] IVIG has emerged as a potential treatment of SJS and TEN in children and adults.[362-366] IVIG is postulated to inhibit dermal-cell apoptosis triggered via the Fas-Fas ligand pathway.[348] When administered early in the course of the disease, IVIG has shown promising effects on wound healing, progression of disease, and mortality.[362-365] Both low dose (0.2–0.5 g/kg) and high dose (2–3 g/kg) IVIG regimens have been described. Most studies support the use of a

Table 6-17 Management of Drug-Induced Cutaneous Diseases

Disease	Recommended Treatment
Acne[291-298]	May or may not require discontinuation of the offending agent Topical benzoyl peroxide or retinoids
Erythematous reaction[341,342]	Discontinue offending agent Histamine H_1-antagonist (diphenhydramine 25–50 mg orally every 6 hours as needed for itching) Methylprednisolone (6-day self-tapering oral regimen starting with 24 mg on day 1) (if diffuse rash)
FDE[344]	Discontinue offending agent Sunscreen for 6 months to 1 year if areas of hyperpigmentation
DRESS[188,343,360]	Discontinue the offending agent Topical corticosteroids may be of some benefit but most cases are resistant to standard therapies
Psoriasis[270]	Discontinue offending agent Topical corticosteroids may be of some benefit but most cases are resistant to standard therapies
SJS and TEN[188,345,347,349]	IV fluid replacement (saline or lactated Ringer's solution) Nutritional support (enteral or parenteral routes) Pain control (systemic opiate therapy) Eye care—antibiotic eye drops, lubricants Oral hygiene: hydrogen peroxide gargle; anesthetics (viscous lidocaine or benzocaine); antiseptic mouthwash Topical antiseptics (0.5% silver nitrate or 0.05% chlorhexidine) Wound care with biologic dressings (porcine xenografts), synthetic dressings, or silicone dressings Surgical debridement of blisters and necrotic tissue Consider IVIG (1–2 g/kg) or cyclosporine (3–5 mg/kg/day for 7 days)
WISN[188,334]	Discontinue warfarin Vitamin K or fresh-frozen plasma to restore protein C or S Initiate heparin to prevent further thrombosis Protein C concentrate if patient has known protein C deficiency Skin grafting and/or surgical debridement

FDE = fixed drug eruption, DRESS = drug rash with eosinophilia and systemic symptoms, IV = intravenous, IVIG = intravenous immunoglobulin, SJS = Stevens–Johnson syndrome, TEN = toxic epidermal necrolysis, WISN = warfarin-induced skin necrosis.

mean total dose of not less than 2 g/kg.[366] Cyclosporine (3–5 mg/kg/day for 7 days) was shown to offer a greater mortality benefit compared to IVIG (1 g/kg for 3 days) in a single-center retrospective study of 64 patients.[367] Similar to corticosteroids, the optimal doses of IVIG and cyclosporine, times of initiation, and durations of therapy are yet to be determined.

INFORMATION FOR PATIENTS

Patients in whom a drug-induced adverse cutaneous event develops should be educated as to the name of the specific offending drug, the terminology used to describe the rash, and the likelihood of the occurrence of a similar or more severe reaction following re-exposure to the drug. If the reaction was allergic-mediated, the patient should be instructed to question all newly prescribed medications regarding similarity to the offending agent in chemical structure or chemical class. If the cutaneous event was severe, the patient should be advised to wear a medical alert bracelet. Patients with underlying skin conditions such as acne or psoriasis should be instructed to question whether any newly prescribed medication may aggravate the condition.

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