

Drug Hypersensitivity Reactions



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KEYWORDS

- Adverse drug reaction • Drug hypersensitivity reaction • Drug allergy • Drug rash
- Skin testing • Graded challenge • Desensitization

KEY POINTS

- Drug hypersensitivity reactions (DHRs) may be classified based on timing (immediate vs delayed), mechanisms (allergic vs nonallergic), and pattern of clinical manifestations. Classifying DHR based on these characteristics may aid in diagnosis and management.
- Drug allergy management may include selection of alternative, non-cross-reactive agents, drug allergy testing, graded challenge, and/or desensitization.
- Diagnostic tools for DHR are limited. Immediate-type skin testing evaluates only for immediate allergic reactions, not delayed allergic reactions.
- Graded challenge is used when drug allergy suspicion is low. It involves administering several graduated doses and if tolerated, indicates no drug allergy.
- Desensitization is used when suspicion for drug allergy is high. It involves many more steps than graded challenge and induces a temporary state of tolerance that is maintained only so long as the drug is continued.

DEFINITIONS

Adverse drug reactions (ADRs) are defined as any noxious and unintended response to a drug. ADRs may be predictable, based on known pharmacologic properties of a drug, or unpredictable, related to immunologic response or genetic differences in patients.¹ A subset of ADRs is drug hypersensitivity reactions (DHRs), reactions that resemble immunologic reactions (whether or not there is demonstration of immune responses such as drug-specific antibodies or T cells). Drug allergies are DHRs for which an immunologically mediated mechanism is demonstrated.²

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EPIDEMIOLOGY

ADRs are estimated to account for 3% to 6% of all hospital admissions and to occur in 10% to 15% of hospitalized patients.³ DHRs comprise up to 15% of all ADRs.⁴

RISK FACTORS

Important risk factors for DHRs include chemical properties of the drug and host factors. Large molecular weight agents such as proteins and some polysaccharides may be more likely to induce antibody-mediated reactions. Specific structural moieties in smaller molecular weight (≤ 1000 kD) nonprotein agents (eg, antibiotics) and/or their metabolic products may be more likely to covalently react with self-proteins to produce immunogenic hapten-protein conjugates.

Host risk factors for DHRs include female gender, history of drug allergy, recurrent exposure to drugs, concurrent disease state, and genetic factors.³ Patients with cystic fibrosis who require recurrent courses of same or similar antibiotics are more prone to have DHRs, probably reflecting the frequency of drug exposure.⁵ Patients with Epstein-Barr virus (EBV) infections are more prone to developing DHR rashes to aminopenicillin antibiotics.⁶ These rashes are usually nonpruritic and may be due to transient immune-stimulation by EBV.⁷ Patients with a history of nonpruritic, EBV-associated rashes are not at increased risk of life-threatening reactions and most will tolerate future courses of aminopenicillins.^{7,8} Patients with human immunodeficiency virus (HIV) infections are more prone to have reactions to sulfonamides as well as other drugs.⁹

Genetics and Polymorphisms in Drug Metabolism

As examples of genetic risk factors, patients with certain human leukocyte antigen (HLA) alleles have significant increased risk of severe cutaneous drug reactions (SCARs) to certain drugs, for example, HLA B 1502 (carbamazepine) and HLA B 5701 (abacavir).¹⁰ Prospective pharmacogenetic screening for HLA B 5701 and use of alternative agents in patients with HLA-B 5701 has nearly eliminated SCARs to abacavir. Patients who are slow acetylators are twice as likely to have sulfonamide antibiotic DHRs, as they have increased metabolism of sulfonamides through an alternative oxidative pathway that generates production of reactive metabolites that can then elicit an immune response.¹¹

Multiple Drug Hypersensitivity Syndrome

An estimated 1% to 10% of patients have DHRs to multiple chemically unrelated, non-cross-reactive drugs. This should be distinguished from patients who reacts to multiple drugs because of (1) cross-reactivity to drugs due to structural similarities, common metabolic pathways, or pharmacologic mechanisms; (2) flare-up reactions (exacerbation of an existing drug allergy by the early switch of therapy to a novel drug); and (3) multiple drug intolerance syndrome in which there is no confirmation after evaluation and which may be driven by patient anxiety.

CHRONOLOGY, CLINICAL PRESENTATIONS, AND MECHANISMS

Classifying drug reactions based on chronology, patterns of clinical manifestations, and mechanisms may aid in evaluation and management.

Chronology and Clinical Presentations

DHRs may be classified as immediate or delayed, based on the timeline from exposure to onset of clinical reaction. DHRs may also be classified mechanistically as allergic (immunologically mediated by antibody or T-cell mechanisms) or nonallergic (mediated by nonimmunological mechanisms) ([Table 1](#)).

Mechanisms

Immediate reactions

Signs and symptoms from immediate DHRs occur within 1 to 6 hours of drug exposure and may include cutaneous (flushing, pruritus, urticaria, angioedema, laryngeal edema), respiratory (bronchospasm, rhinoconjunctivitis), cardiovascular (hypotension, tachycardia), gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain or cramping), or anaphylaxis.¹² In contrast to anaphylaxis, vasovagal reactions are

Table 1 Immediate and delayed drug hypersensitivity reactions		
Timing	Signs and Symptoms	Mechanisms
Immediate (occurring within 1–6 h from drug administration)	• Urticaria • Angioedema • Rhinitis • Conjunctivitis • Bronchospasm • Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) • Anaphylaxis	Allergic (IgE antibody mediated) Or Nonallergic (examples) • Direct stimulation of mast cell and/or basophils (opiates) • Complement activation • Alterations in metabolic pathways (aspirin and nonsteroidal antiinflammatory drugs through cyclo-oxygenase 1 inhibition)
Delayed (occurring >6 h from drug administration)	Skin ± organ involvement: • Delayed urticaria • Maculopapular eruptions (morbilliform) • Fixed drug eruptions • Vasculitis • SJS/TEN • DiHS/DRESS • AGEP • Symmetric drug-related intertriginous and flexural exanthems Internal organ involvement may include • Hepatitis • Renal failure • Pneumonitis • Anemia • Neutropenia • Thrombocytopenia	<i>Allergic:</i> immunologically mediated by antibodies or T cells ± neutrophils, eosinophils, monocytes

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DiHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Data from Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy* 2014;69(4):420-437.

typically characterized by pallor and bradycardia rather than flushing and tachycardia seen in anaphylaxis.

Signs and symptoms are typically due to massive and sudden release of mediators from mast cells and basophils via immunoglobulin E (IgE) or non-IgE-mediated mechanisms.^{2,13,14} Non-IgE mechanisms may include direct stimulation of mast cell and/or basophils (eg, many reactions from radiocontrast media, vancomycin), complement activation, and cyclooxygenase (COX-1) inhibition.² Phototoxic skin reactions may also occur in an immediate time frame.

Delayed reactions

By definition, delayed-onset DHRs occur 6 or more hours after drug exposure.¹³ However, most delayed-onset reactions occur days to weeks after allergen exposure and can involve multiple organs. Mechanisms include T-cell-mediated reactions or development of toxic metabolites in a genetically predisposed person.

Cutaneous reactions are the most common manifestation of delayed DHRs. Drug eruptions usually occur within 5 to 14 days of drug initiation but may develop within 1 to 2 days in previously sensitized patients. In patients taking antibiotics, drug eruptions may occur up to 2 weeks after treatment has been stopped.¹⁵

Drug-induced exanthems often present with erythematous macules and papules (morbilliform rash) and rarely with pustules or bullae. Rashes are usually pruritic and in a centrifugal pattern, starting with trunk and spreading distally to extremities in a symmetric manner.¹⁶ Systemic manifestations include fever, lymphadenopathy, eosinophilia, and organ dysfunction (primarily liver, bone marrow, and/or kidneys).¹⁷ Photosensitivity rashes may be phototoxic or photoallergic. Phototoxic rashes are more common, may present within minutes to hours of sunlight exposure, and present as an exaggerated sunburn that desquamates within several days. Vesicles and bullae may occur in more severe cases. Mechanistically, drugs absorb ultraviolet light and release excessive energy, causing cell damage. Tetracyclines, especially doxycycline, and nonsteroidal antiinflammatory drugs (NSAIDs) are some of the more common causal drugs. In contrast, photoallergic rashes are T-cell mediated, DHRs against a drug allergen whose antigenicity has been altered by exposure to ultraviolet radiation. Photoallergic reactions typically develop 24 to 48 hours after sunlight exposure, are eczematous, and may occur after days or months of drug exposure. Photoallergic reactions more frequently occur from topically applied agents such as sunscreens or fragrances but may also occur from systemically administered drugs including sulfonamides, quinolones, griseofulvin, ketoprofen, and quinine.¹⁸

SCARs often involve multiple organs. These syndromes include drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DiHS), acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) ([Table 2](#)).

Other organ/organ system manifestations of delayed DHRs include renal (interstitial nephritis, nephrotic syndrome), liver (hepatitis), cardiovascular (myocarditis, vasculitis), pulmonary Löffler syndrome (cough, chest discomfort migratory infiltrates with or without peripheral eosinophilia), and/or hematologic systems (anemia, leukopenia, thrombocytopenia, lymphadenopathy). These manifestations are often times isolated and not associated with skin manifestations. Aseptic meningitis has been reported from NSAIDs, radiocontrast media, intravenous immunoglobulin replacement, and other agents.

Drug fever may occur in isolation or with other allergic manifestations. Drug fever usually occurs 7 to 10 days into a treatment course, with prompt defervescence within 48 hours of discontinuation of the responsible agent.

Table 2
Severe cutaneous adverse reactions

Type	Rash Features	Latent Period	Systemic Features	Laboratory Findings
AGEP	Pustules on erythematous background, flexural accentuation	Usually <3 d	High fever, edema	Neutrophilia, eosinophilia
DRESS/ DiHS	Itchy exanthem or urticarial papules/plaques, erythroderma, nonerosive mucositis, >50% body surface area	2–8 wks ^a	Fever, edema, lymphadenopathy	Eosinophilia, atypical lymphocytes, hepatitis, renal impairment. Skin biopsy: interface dermatitis, apoptotic keratinocytes, scattered eosinophils
SJS/TEN	Painful dusky macular erythema, blisters, Nikolsky sign, erosive mucositis in ≥2 surfaces, palmoplantar tender erythema	4–21 d	Prodrome of flu-like symptoms, high fever, malaise, rarely pneumonitis	Skin biopsy: full-thickness epidermal necrosis
SS and SSLR	Itchy urticarial or seriginous plaques, may start at injection site, predisposition for hands and feet	1–2 wks ^a	High fever, malaise, polyarthralgia or polyarthritis	Neutropenia, mild Eosinophilia, mild Proteinuria, low complement levels in severe cases. Histology nonspecific

Latent period from onset of drug administration.

Abbreviations: AGEP, acute generalized exanthematous pustulosis; d, days; SS, serum sickness; SSLR, serum sickness-like reactions.

^a May be shorter latent period in sensitized patients.

Adapted from Peter JG, Lehloeny R, Diamini S, et al. Severe delayed cutaneous and systemic reactions to drugs: A global perspective on the science and art of current practice. *J Allergy Clin Immunol Pract* 2017;5(3):555; with permission.

Immunologic mechanisms

Most drugs are simple, small molecules (<1000 kD) that, by themselves, are poorly recognized by the immune system. However, drugs may become immunogenic when their native form or reactive metabolites bind to serum or tissue proteins and form hapten-protein carrier conjugates. These conjugates can act as complete antigens that are then recognized by the immune system and stimulate an immune response resulting in a DHR.

In contrast, large, complex drug molecules (eg, proteins) may directly stimulate immune responses through concentration-dependent interactions with immune receptors (eg, pharmacological interaction (p-i) model; see type IV reaction discussed later).

Immunologic reactions may be divided broadly into 4 categories according to the Gell and Coombs classification. Type I, II, and III are antibody mediated, whereas type IV reactions are T-cell mediated.^{2,19} Although the Gell and Coombs framework is useful for recognizing patterns of clinical presentations, DHRs in a patient are sometimes complex and may be caused by combinations of immune responses and multiple effector mechanisms.

Type I reactions have an acute onset and involve drug-specific IgE antibody-mediated activation of mast cells and basophils. On initial exposure, a drug or its hapten-protein conjugate stimulates generation of drug-specific IgE by plasma cells of B-cell lineage, which then bind to high-affinity IgE receptors on the surfaces of mast cells and basophils. This results in a sensitized, asymptomatic state. On reexposure to the drug or one with a structurally similar antigenic region (cross-reacting agent), the drug binds to the IgE molecules, cross-linking them and activating mast cells and basophils. This results in the immediate release of histamine and tryptase as well as the rapid generation of leukotrienes and prostaglandins, resulting in anaphylaxis or any symptoms thereof (see earlier section on Immediate Reactions). Antibiotics are a common cause of type I DHRs.

Type II reactions have delayed onset (usually at least 5–8 days after exposure) and involve IgG or IgM antibody-mediated cell destruction by complement activation or cell clearance by macrophages.²⁰ Although type II reactions often occur after high-dose, prolonged, or frequent exposure to a drug, they may also occur during a treatment course.¹⁹ Clinical sequelae include granulocytopenia, hemolytic anemia, and thrombocytopenia. Common causes include antibiotics, anticonvulsants, sulfonamides, and heparin. In heparin-induced thrombocytopenia, antibodies form against a conjugate of heparin and platelet factor 4 on platelets, triggering platelet destruction.

Type III reactions have delayed onset and result from formation of antibody-drug complexes (IgG > IgM) that are deposited in tissues. These complexes activate complement and other immune cells, causing tissue damage. Signs and symptoms typically occur one or more weeks after drug exposure and may manifest as serum sickness, vasculitis, or drug fever.¹⁹

Serum sickness presents with fever, urticarial or pruritic rash, arthralgia, and/or acute hepatitis glomerulonephritis. Causes may include antitoxins (rabies, botulism, venom) and rituximab. Serum sickness may occur sooner than 1 week in patients with a previous serum sickness reaction.

Antibiotics may also cause serum sickness-like reactions, with amoxicillin being the most common.²¹

Drug-induced antineutrophil cytoplasmic antibodies (ANCA) + vasculitis usually presents with palpable purpura and/or petechiae, fever, arthralgia, and lymphadenopathy. Hydralazine, minocycline, propylthiouracil, and levamisole-adulterated cocaine are the most commonly reported causes.²²

Drug-induced lupus is principally a type III reaction, but lupus from different drugs may vary in both clinical presentation and associated autoantibodies. Hydralazine, procainamide, and minocycline typically cause serositis and less commonly rash. Drug-induced lupus from these agents is more typically associated with antihistone antinuclear antibodies and only rarely anti-double-stranded DNA, except pANCA occurs with minocycline. Drug-induced subacute cutaneous lupus (eg, from hydrochlorothiazide, calcium channel blockers, angiotensin converting enzyme [ACE] inhibitors and statins) is associated with a photosensitive rash as well as SS-A and SS-B antibodies; it is an atypical DHR in that rather than occurring shortly after drug introduction, it can often develop more than 6 months after drug introduction.²³

Type IV reactions have delayed onset and are mediated by activated T cells (4 possible different subtypes) and may involve eosinophils, monocytes, and neutrophils. Type IV reactions typically occur at least 48 to 72 hours and sometimes days to weeks after exposure.¹⁹ Most reactions involving T cells occur in the skin, a large T-cell reservoir.²⁴

Clinical presentation is driven by the T-cell subset activated and may present with severe cutaneous reactions with or without organ involvement or may involve only a

single organ (eg, drug-induced liver injury). Type IV reactions may also be accompanied by fever or present as drug fever only. Drugs or their metabolites may activate T cells (1) when hapten-protein conjugates or drug fragments are presented to T cells by antigen-presenting cells (APCs, eg, dendritic, Langerhans or B cells, or macrophages) or (2) by pharmacologic interaction with immune receptors (the p-i concept) in which drugs in their native state (*not* acting as haptens to form conjugates with proteins) noncovalently bind directly with T-cell receptors on T cells or with HLA molecules on APCs and then activate T cells. Abacavir is an example of a drug that acts through p-i interaction.²⁰ Allergic contact dermatitis and photoallergic reactions also occur through type IV mechanisms.

Nonimmunologic mechanisms

Nonallergic (nonimmunologic) mechanisms include but are not limited to direct stimulation of mast cell and/or basophils, complement activation, and alterations in metabolic pathways.

Drugs may directly (without IgE cross-linking) activate mast cells or basophils. Human G protein-coupled receptor MRGPRX2 has been identified as a mast cell receptor capable of causing histamine release in response to the following drugs/drug classes: quinolones (ciprofloxacin and levofloxacin), neuromuscular blocking agents (rocuronium), icatibant, vancomycin, and opioids.^{13,25,26}

Complement activation and generation of anaphylatoxins C3a and C5a can activate mast cells through complement receptors. This can occur in reactions to Cremophor and oversulfated chondroitin sulfate-contaminated heparin.²⁷

Examples of DHRs that occur because of alterations in metabolic pathways include (1) COX-1 inhibition by NSAIDs, which leads to overproduction of leukotrienes in sensitive individuals resulting in respiratory distress (aspirin-exacerbated respiratory disease [AERD]) and (2) ACE inhibition by ACE-inhibitors, leading to overproduction of bradykinin and other vasomediators.

MANAGEMENT

Acute Management

Acute treatment of DHRs involves immediate discontinuation of suspected drugs and treatment of signs and symptoms.

In anaphylaxis, epinephrine is lifesaving and the only drug proven effective and should be administered immediately. Adjunctive measures include antihistamines and glucocorticoids. Other cardiopulmonary resuscitative measures may also be required.

Itching from isolated, mild maculopapular/morbilliform rashes may respond to antihistamines, although the course of the rash is not altered. Progressive rashes or those associated with fever, nausea, or arthralgia should be treated with systemic steroids. Similarly, those with severe, prolonged drug reactions should be treated with systemic steroids and may require a slow taper over several weeks. DiHS/DRESS may require many months of treatment with systemic steroids.

Diagnostic Evaluations

Diagnosis of drug hypersensitivity requires a thorough history and identification of physical findings and symptoms that are compatible with characteristics and timing of drug-induced reactions. Thus, understanding the chronology, clinical manifestation, and mechanisms mentioned previously is essential. In selected cases, clinical diagnosis could be confirmed with demonstration of an elevated tryptase level obtained shortly after anaphylaxis, identification of IgE (in vitro or immediate-type skin

testing) to a drug suspected to have caused anaphylaxis, or in very limited cases, delayed patch testing (to identify sensitized T cells) to a drug suspected to have caused a delayed reaction. Graded drug challenges can also be considered (see later discussion). Overall, objective testing for the diagnosis of drug allergy is limited (**Box 1**).²⁸

Testing for Tryptase

Serum tryptase levels can aid in diagnosing anaphylaxis when the diagnosis is not clear by history and physical alone. Serum tryptase increases ~30 minutes after onset of anaphylaxis, peaks 1 to 2 hour after onset of reaction, and remains increased for up to 6 to 8 hours.²⁹ Commercial assays measure total tryptase, which is the sum of tryptase continuously secreted at baseline and released during activation of mast cells and basophils.²⁹ Tryptase level greater than 11.4 ng/mL or greater than $\geq 2 + 1.2 \times$ baseline tryptase levels supports anaphylaxis.²⁹ However, a negative tryptase level does not rule out anaphylaxis in part because tryptase is released from different mast cell and basophils subsets, depending on the trigger and severity of the reaction.²⁹

Box 1

General considerations in evaluation of drug hypersensitivity reactions (DHRs)

Identify drugs that have a history of causing problems in the patient.

Determine whether there are cross-reactive agents and avoid them.

If the patient has a late reaction (eg, drug rash), take a careful history of all drugs used in the past month because the possible causative drug may have been discontinued.

Reactions are more likely to result from drugs introduced more recently.

Drugs administered with impunity for prolonged periods (eg, months to years) are rarely responsible for DHRs (notable exceptions are ACE inhibitors and drugs suspected to cause subacute cutaneous lupus erythematosus).

Have a high index of suspicion for drug reactions whenever a patient experiences adverse clinical manifestation.

Be mindful that drug reactions can involve internal organs (eg, nephritis, hepatitis, isolated lymphadenopathy), often in the absence of eosinophilia.

If an immunologic drug reaction is suspected, stop all nonessential drugs and substitute non-cross-reactive drugs (if possible).

Further evaluation may be needed

- When there is a history of prior DHR and the drug is essential (ie, there is no equally effective, structurally unrelated alternative) and the risk/possible benefit ratio for the suspect drug is positive.
- When there is a history of prior severe DHRs for other drugs; the best way to protect the patient is to find the culprit agents.

Further evaluation may not be needed if history does not suggest DHR

- Noncompatible symptomatology
- Noncompatible chronology
- Drug taken since with no reaction
- Same reaction without having taken the drug
- There are alternative diagnoses (eg, herpes virus eruption, chronic urticaria)

Adapted from Dykewicz MS. Drug allergy. In: Slavin R, Reisman R, editors. An Expert Guide to Allergy and Immunology. Philadelphia: American College of Physicians; 1999; p. 155. with permission.

Testing for Allergen-Specific Immunoglobulin E

Diagnosis of an IgE-mediated immediate reaction requires demonstration of allergen-specific IgE (by skin testing or in vitro testing) and clinical reactivity (either by history or supervised challenge). Allergen-specific IgE indicates sensitization, but not all patients with positive skin or in vitro testing will have a clinical reaction on challenge.

Skin and Patch Testing

Immediate-type skin testing (prick-puncture and intradermal) is a bioassay used to detect the presence of allergen-specific IgE on patient's mast cells and is only helpful for identifying risk for immediate reactions. Skin testing for most antibiotics (except penicillin [PCN]) lack negative predictive values. In a patient with history of an immediate drug reaction, a positive test with a nonirritating concentration of the medication suggests the presence of drug-specific IgE. However, a negative test does *not* rule out drug allergy due to the lack of negative predictive value.

Immediate-type skin testing requires knowledgeable personnel to avoid false-negative and false-positives results leading to under- or overdiagnosis of drug allergy, respectively. Skin test reactivity results can be repressed by antihistamines, topical steroids, and omalizumab.

Delayed-type patch testing involves application of drug, mixed into petrolatum or 0.9% saline, to a small area of skin under occlusion for 48 hours and then removed. The application site is then examined at 48 and 96 hours after placement. Conceptually, delayed patch testing might be used to evaluate risk for DHRs (type IV) to drugs. However, it currently has limited established utility for most drug allergens. Standardized and validated test concentrations and vehicles have not been fully studied or are disputed in the literature.

In Vitro Testing

Although a limited number of in vitro tests are available to identify risk for DHRs, most are not adequately standardized and their predictive value is not established. Immunoassays are marketed to assess hypersensitivity to neuromuscular blocking agents (NMBA) and some biological agents.³⁰ An in vitro test offered is the basophil activation test (BAT), which measures histamine release from human peripheral blood incubated with drug allergens. BAT is not standardized and few laboratories perform it.

TREATMENT OPTIONS

Future management of patients with a confirmed allergy to a drug includes administration of a non-cross-reactive alternative agent or desensitization to the culprit drug.

Graded Drug Challenges

Graded challenge testing (drug provocation testing) is used to exclude allergy to a medication in patients with a low probability of having an IgE-mediated drug allergy. Patients are given a test dose at a dose lower than that would cause a serious reaction followed by several escalating doses under continuous observation. Graded challenge does not modify or prevent allergic response to the drug; it is not a desensitization but a method used to confirm or deny drug allergy. Therefore, patients who tolerate a graded challenge are not allergic to the drug at the dose given. Graded challenges should be performed in a setting equipped to recognize and treat reactions. Graded challenge should not be performed in patients with history of SCARs (eg, DRESS/DiHS) to a drug in question because it could be potentially fatal.

Desensitization

Drug desensitization may be considered in patients with confirmed or high probability of an immediate (and in some cases type IV) DHR when the drug is essential.

Desensitization induces a temporary tolerance to allow patients with DHRs to receive an uninterrupted course of medication safely. Drug hypersensitivity returns once the medication is discontinued. Desensitization has been completed successfully for many drugs. However, because of the high risk of adverse reactions, particularly anaphylaxis, desensitization should only be performed by experienced physicians and only when the drug is essential (no alternatives available). Desensitization should never be attempted in patients with history of SCARs (eg, SJS/TEN) because even small doses of the drug may induce irreversible and potentially fatal reactions.

Drug desensitization involves administration of a drug in increasing doses until the therapeutic dose is reached. Temporary tolerance is maintained if the drug is given normally at its usual interval (eg, at least daily). Temporary tolerance is likely lost if 48 hours has elapsed since the last dose and thus, repeat desensitization is required before readministration.³¹

When patients have a history of an immediate reaction thought to be non-IgE mediated (eg, from many chemotherapy agents, most radiocontrast media reactions), pre-medication protocols that include antihistamines and systemic corticosteroids may be useful.

Rare immunologic complications may occur following desensitization in patients who require high dose or extended duration. Complications include serum sickness, hemolytic anemia, nephritis, and thrombocytopenia.³¹

REACTIONS TO SPECIFIC DRUGS

Penicillin and Other Beta-Lactam

IgE-mediated allergic responses are directed toward the drug-protein complex (antigenic determinants) that forms after penicillin (PCN) and/or its metabolites bind to tissue/serum proteins.

The allergic components of PCN are either the beta-lactam core ring structure (common to all PCNs, cephalosporins, and carbapenems) or less commonly, the R-group side chains that distinguish different PCNs from each other.³² PCN cross-reactivity to cephalosporin is primarily due to R1 side chain group.³³ Risk of cross-reactivity to cephalosporin has been estimated to ~2%.³⁴ There is thought to be a lower incidence of immediate-type reactions to third- and fourth-generation cephalosporins than to the first- and second-generation compounds.

Most of the patients with IgE-mediated PCN reactions lose their sensitivity over time. After 5 and 10 years, approximately 50% and 80% of patients lose their sensitivity to PCN.

PCN skin testing is a safe and reliable way to assess for IgE-mediated reactions. Using both major and minor PCN determinants, PCN skin testing has a negative predictive value of 97% to 99%. Following negative skin testing, the absence of an allergy is usually confirmed by graded challenge under 1 to 2 doses to ensure an immediate reaction does not occur. PCN skin testing is contraindicated in patients with history of SCARs. Skin testing is *not* indicated in patients with a family history but no personal history of PCN allergy, because there is no increased risk of reaction.

If PCN testing is positive or cannot be completed in patients with suspected IgE-mediated reaction to PCN, the 2010 Joint Task Force on Practice Parameters for Drug Allergy recommends the following options:

1. Rapid desensitization if PCN is essential (eg, neurosyphilis).⁷
2. Use an alternative, non-beta-lactam drug.⁷ An exception is aztreonam, a monobactam that has no cross-reactivity and can be safely given in PCN-allergic patients.³⁴
3. Give a cephalosporin in graded challenge or via rapid desensitization.⁷
4. Administer a carbapenem via graded challenge.⁷ Cross-reactivity of PCNs with carbapenems is less than 1%.³⁴

In patients with a vague and/or distant history of PCN allergy, a graded challenge to PCN may be performed.⁷ More recent guidelines have proposed that in patients with nonallergic symptoms or family history of PCN allergy, amoxicillin or PCN may be prescribed.³⁴ In patients with pruritis without rash or remote history (>10 years) *without* features of an IgE-mediated reaction to PCN class antibiotics, direct oral challenge to amoxicillin may be performed.³⁴

Nonimmunologic reactions typically present as nonpruritic rash and are frequently seen with ampicillin and amoxicillin in patients with concomitant viral infections, allopurinol use, chronic lymphocytic leukemia, and hyperuricemia. These rashes are not associated with an increased risk of future intolerance to PCN antibiotics.

Cephalosporins

Cross-reactivity among cephalosporins as well as between cephalosporins and PCNs commonly arises from structural similarities in side chain groups (R1 > R2) or, rarely, from sensitization to the core beta-lactam ring present in both PCNs and cephalosporins or to metabolites of this ring. See PCN and other beta-lactams for more information about cross-reactivity.

Skin and in vitro testing for cephalosporin allergy are not validated and are not often used in clinical management. A safe and commonly used approach is selecting an alternative cephalosporin with a different side chain group from the implicated cephalosporin³⁵ (**Table 3**). However, patients with past immediate reactions to ceftazidime should avoid aztreonam because the two share identical side chains and cross-reactivity between the 2 drugs is reported.³⁵ Nonimmunologic disulfiram reaction may occur if cefoperazone is taken after alcohol ingestion.

Sulfonamides

Sulfonamides are divided into 2 distinct groups: antibiotics and nonantibiotics. Hypersensitivity to sulfonamide antibiotics is primarily mediated by immune responses to metabolites of the cyclic arylamine group common to all sulfonamide antibiotics. Notably, nonantibiotic sulfonamides do not contain this arylamine group.³⁶ Sulfonamide antibiotics include sulfamethoxazole, sulfadiazine, sulfadoxine, sulfisoxazole, and sulfapyridine (in sulfasalazine).³⁶

Hypersensitivity reactions to sulfonamide antibiotics occur in ~2% to 4% of healthy patients and up to 50% to 60% of patients with HIV.³⁷ Immediate-type reactions are uncommon, with most hypersensitivity reactions presenting 1 to 2 weeks after start of therapy as a morbilliform rash with fever, with the fever sometimes preceding the rash. This can be accompanied by other organ involvement such as elevated liver enzymes and kidney dysfunction and can progress to SJS. Sulfonamide antimicrobials are highly associated with blistering dermatitis (SJS/TEN). Allergic reactions such as these, with systemic organ involvement such as DRESS and early stages of SJS, should be treated with systemic steroids and may require high doses (1–2 mg/kg q 6–8 hours) with a slow taper over many weeks, although other immunomodulators have been used. The rash may take several days to improve but the fever and malaise usually resolve in 24 to 48 hours. Topical steroids in addition often help speed the recovery

Table 3
Beta-lactam antibiotics with identical R-1 and R-2 side chains

Groups of B-lactam Antibiotics with Identical R-1 Side Chains							
1	2	3	4	5	6	7	8
Amoxicillin	Ampicillin	Cefazolin	Cefoxitin	Cefdaloxime	Cefditoren	Aztreonam	Cefamandole
Cefadroxil	Cefaclor	Ceftazidime	Cephalexin	Cefdinir	Cefepime	Cefiderocol	Cefonicid
Cefatrizine	Cephalexin		Cephalexin	Cefixime	Cefodizime	Ceftazidime	
Cefprozil	Cephalexin		Cephalexin		Cefotaxime		
	Cephalexin				Cefpirome		
	Cephalexin				Cefpodoxime		
	Cephalexin				Ceftriaxone		
	Cephalexin						
Groups of B-lactam Antibiotics with Identical R-2 Side Chains							
1	2	3	4	5	6		
Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten		
Cefadroxil	Cephalexin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime		
Cephalexin	Cephalexin		Cefoperazone				
	Cephalexin		Cefmetazole				
	Cephalexin		Cefpiramide				

Adapted from Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: An updated practice parameter. Ann Allergy Asthma Immunol 2010;105(4):273; with permission.

time of the rash. Tapering is guided by response to therapy and usually can start after 3 to 4 days. Underdosing may result in an incomplete response, and rapid tapering of steroids often results in rebound. Although there has been controversy in the past, most agree that SJS should be treated as such but corticosteroids are not indicated in TEN. In patients with severe cutaneous reactions but no fever or other organ involvement, a short course of systemic steroids (eg, prednisone 1–2 mg/kg/d for 5–7 days) may be beneficial.

Sulfonamide antibiotic allergy is diagnosed clinically based on a detailed history. No testing is available to assist in diagnosis. Patients with history of SCARs or blistering dermatitis should strictly avoid sulfonamides within the same group because reexposure could be fatal.

Cross-reactivity between sulfonamide antibiotics is variable.³⁸ In contrast, there is no convincing evidence of cross-reactivity between the antibiotic sulfonamides (that contain arylamine cyclic structures that generate target antigens through oxidative metabolism) and nonantibiotic sulfonamides (eg, diuretics, which do not contain an arylamine moiety).³⁹ However, sulfasalazine (a nonantimicrobial) should be avoided in patients allergic to sulfonamide antibiotics because sulfasalazine releases sulfapyridine (an antimicrobial) on exposure to gut bacteria.³⁹

Desensitization protocols have been published for trimethoprim-sulfamethoxazole and nonantibiotic sulfonamides including sulfasalazine, tosemeide, and furosemeide.

Vancomycin

The most common vancomycin reaction is Red Man syndrome (RMS), which results from non-IgE-mediated histamine release from mast cells and basophils. This results in flushing, warmth, erythema, pruritus, and urticaria, affecting the face, neck, and torso. RMS usually occurs with rapid parenteral administration (>10 mg/min). Acute management involves stopping the infusion, treatment with H1 blockers (eg, diphenhydramine), and resuming at a slower infusion rate. Tolerance of future readministration is promoted by pretreatment with H1 blockers and a slower infusion rate. Rarely, IgE-mediated anaphylaxis can occur and is usually accompanied by angioedema and respiratory distress. Desensitization can be completed in cases of IgE-mediated anaphylaxis. Other rare severe cutaneous reactions from vancomycin include linear IgA bullous dermatitis, SJS/TEN, and DRESS/DiHS.

Angiotensin-Converting Enzyme Inhibitors

Cough and angioedema from ACE inhibitors are thought to be related to accumulation of bradykinin and other mediators. Cough may occur within hours of the first dose or months after therapy. Cough typically resolves within 1 to 4 weeks after discontinuation of the medication but may linger for up to 3 months. Angiotensin receptor blocker (ARB) agents are generally better tolerated, with a reported rate of cough of 3.3% compared with 9.9% with ACE inhibitors.⁴⁰

ACE inhibitor-induced angioedema occurs in less than 1% of all patients treated, with higher occurrence in women and blacks.⁴¹ More than 50% of episodes occur within the first week but some may occur even years after treatment.⁴² Patients with a history of idiopathic/spontaneous angioedema or hereditary angioedema are at increased risk of developing angioedema from ACE inhibitors,⁴³ and therefore alternative agents (eg, ARBs, generally well tolerated in such patients) should be used, if indicated, in place of ACE inhibitors.

ACE inhibitor-induced angioedema is not associated with urticaria or pruritus and most commonly involves the lips, tongue, face, and upper airway. Angioedema could result in life-threatening airway obstruction and typically presents with throat

hoarseness and inspiratory stridor. Visceral angioedema has been described in case reports and typically presents with diffuse abdominal pain with diarrhea. Acute episodes of ACE inhibitor angioedema will typically resolve over 2 to 5 days even if the ACE inhibitor is not discontinued but may then recur at highly variable intervals.⁴² Alogliptin, an inhibitor of the bradykinin-degrading enzyme DPPIV used in patients with type 2 diabetes, is associated with increased risk of angioedema when taken concomitantly with ACE inhibitors.⁴¹

Management involves discontinuation of ACE inhibitors and if needed, airway support. In a retrospective study, 88% of patients had recurrence of angioedema 1 month after discontinuation of ACE inhibitors.⁴⁴ Intolerance to one ACE inhibitor usually predicts intolerance to the class. In patients unresponsive to usual measures, fresh frozen plasma and purified C1 inhibitor concentrate (if given early) have been beneficial in cases reports.^{42,45} Icatibant has not been effective in trials.⁴⁶

ARBs are generally well tolerated in patients with ACE-inhibitor angioedema. Systematic reviews reported a rate of 3.5% to 10% of recurrent angioedema in patients with a history of ACE-inhibitor angioedema.^{47,48} This rate of recurrence may be contributed by recurrence of ACE-induced inhibitor angioedema.

Aspirin and Other Nonsteroidal Antiinflammatory Drugs

Drug hypersensitivity to NSAIDs may be categorized as pseudoallergic or less commonly, allergic reactions against structural moieties (Table 4). Reactions may manifest as cutaneous (urticaria/angioedema) and/or upper and lower respiratory symptoms (rhinoconjunctivitis, bronchospasm) or anaphylaxis. Skin testing is not helpful and in vitro testing is not available to assess patients with any type of suspected aspirin (acetylsalicylic acid [ASA]) or NSAID hypersensitivity.

Allergic reactions to nonsteroidal antiinflammatory drugs

Allergic NSAID reactions are either IgE (eg, generally anaphylaxis) or T-cell-mediated cutaneous reactions specific to one NSAID or a group of NSAIDs that have similar structural moieties (eg, propionic acid derivatives naproxen and ibuprofen but not ASA)^{49,50} (see Table 4). In contrast to pseudoallergic reactions, patients with anaphylaxis to a particular NSAID structure may be able to tolerate other COX-1 inhibitors that have different chemical structures.

Pseudoallergic reactions to aspirin and nonsteroidal antiinflammatory drugs

Pseudoallergic reactions are thought to be related to drug-induced inhibition of COX-1, which leads to diminished production of prostaglandins (some that have a constitutive inhibitory effect on 5-lipoxygenase that produces proinflammatory leukotrienes). In sensitive individuals, this results in overproduction of leukotrienes. In patients with pseudoallergic reactions, patients may react to ASA or any NSAID that have notable COX-1 inhibition. Patients with pseudoallergic reactions to ASA/NSAIDs generally tolerate drugs that are weak COX-1 inhibitors (eg, salsalate, acetaminophen up to a dose of 1000 mg, or sodium or magnesium salicylate) or COX-2 inhibitors.⁵¹ With exceptions, patient with pseudoallergic reactions tend to segregate into 2 different patient subgroups who have predominantly either respiratory reactions or cutaneous reactions (urticaria and/or angioedema).

Respiratory reactors include those with AERD (formerly termed Samter's Triad), a disorder classically characterized by asthma, chronic rhinosinusitis (CRS) with recurrent nasal polyps, and respiratory reactions induced by ASA and all COX-1 inhibitors. AERD usually presents in early adulthood with a prevalence rate of 7% to

Table 4
Classification of nonsteroidal antiinflammatory drug-induced hypersensitivity reactions

Reaction Timing	Clinical Symptoms	Cross-Reactivity Among COX-1 Inhibitors	Presence of Underlying Disease	Putative Mechanism
AERD				
Acute	Rhinitis, nasal congestion, bronchoconstriction, asthma exacerbation	Cross-reactive	Asthma/rhinosinusitis/nasal polyps	Pseudoallergic COX-1 inhibition
Multiple NSAID-exacerbated urticaria/angioedema in patients with underlying cutaneous disease				
Acute	Urticaria/angioedema	Cross-reactive	Chronic urticaria	Pseudoallergic COX-1 inhibition
Multiple NSAID-induced urticaria/angioedema in otherwise asymptomatic patients				
Acute	Urticaria/angioedema	Cross-reactive	None	Likely pseudoallergic, COX-1 inhibition
Single NSAID-induced anaphylactic reactions				
Acute	Anaphylaxis, urticaria/angioedema	Single-drug-induced, no COX-1-associated cross reactivity. May cross-react with an NSAID in same structural class (eg, propionic acid NSAIDs: ibuprofen and naproxen)	Atopy is common	IgE-mediated (presumed)
Delayed reactions to NSAIDs				
Delayed	Varied: fixed drug eruptions, severe bullous skin reactions, maculopapular drug eruptions	Can be single-drug-induced or cross-reactive	None	Varied: T-cell-mediated, cytotoxic T cells, natural killer cells, other

Abbreviations: AERD, Aspirin Exacerbated Respiratory Disease; NSAID, Non-steroidal Anti-Inflammatory Drug.

Adapted from Laidlaw TM, Cahill KN. Current knowledge and management of hypersensitivity to aspirin and NSAIDs. *J Allergy Clin Immunol Pract* 2017;5(3):539; with permission.

14% in patients with asthma and in 8% to 9% of patients with chronic nasal polyps with CRS.⁵²

ASA desensitization and subsequent daily ASA therapy is an important option for chronic management of AERD, as this may reduce risk for recurrent nasal polyps, improve control of asthma or CRS, and decrease the need for frequent systemic corticosteroids to these symptoms.⁵¹

Cutaneous reactors develop urticaria and/or angioedema to COX-1 inhibitors. Many of these also have chronic spontaneous urticaria. Approximately 20% to 40% of patients with underlying chronic spontaneous urticaria will have worsening of their hives or swelling (angioedema) when they take either ASA or NSAIDs.

Management for pseudoallergic reactions includes avoidance of all significant COX-1 inhibitors, desensitization in selected patients followed by daily ASA/NSAID (to maintain desensitized state), and use of selective COX-2 inhibitors (eg, celecoxib) as needed for pain.⁵¹ Oral challenges to confirm sensitivity may be completed under supervision of an experienced clinician.

ANESTHETIC AGENTS

Local Anesthetics

Most adverse reactions to local anesthetics (LA) are nonallergic. Clinical symptoms are often related to anxiety and pain including psychosomatic responses (hyperventilation and paresthesia), vasovagal symptoms (eg, sweating, nausea, bradycardia, pallor), or to the pharmacologic effects of LA or concomitantly administered epinephrine as a result of overdosing or accidental intravenous administration.⁵³

Allergic reactions to LA are rare and manifest as immediate (eg, urticaria, anaphylaxis) or delayed (eg, allergic contact dermatitis) reaction. IgE-mediated LA was found to be responsible for 0.5% of patients in a retrospective study involving 402 patients.⁵⁴

Evaluation for immediate reactions may involve immediate skin testing and subcutaneous graded challenge, whereas evaluation of delayed reactions (allergic contact dermatitis) involves patch testing.

LA are classified into benzoic acid esters (Group I: eg, benzocaine, procaine) or amides (Group II: eg, lidocaine, bupivacaine, mepivacaine).⁵³ Based on patch testing to assess delayed-type hypersensitivity, Group I LA cross-react with each other, but Group II agents do not cross-react within the group or with Group I agents. For immediate LA reactions, findings regarding cross-reactivity have been conflicting and some investigators feel the best approach is to choose an LA from a different group than that reported to cause a past reaction.⁵³ If the LA that caused the previous reaction is not known and skin testing cannot be completed, lidocaine is preferred due to rare reports of allergic reaction.⁵³ In patients with a delayed reaction, some investigators suggest delayed patch testing to other LA to help identify an agent the patient may tolerate.

Anesthesia-Related Agents

Perioperative anaphylaxis may be caused by antibiotics (PCN, cephalosporin), NMBAs (succinylcholine, alcuronium, pancuronium), induction agents (eg, thiopental), chlorhexidine, sugammadex, opioids, latex, and gelatin (in plasma substitute and sponges).⁵⁵ Anaphylaxis may be immunologically mediated or nonimmunologically mediated (eg, direct mast cell activation by NMBAs, opioids). Although in the United States, there are commercially available *in vitro* studies to assess hypersensitivity for some NMBAs, and skin testing can be performed for many agents, the predictive value of these tests is not validated.

RADIOGRAPHIC CONTRAST MEDIA

Radiocontrast media (RCM) immediate hypersensitivity reactions are believed to be primarily nonimmunologic (eg, direct mast cell activation, complement activation). However, IgE-mediated reactions to RCM may occur, and there is concern that these reactions to RCM are underreported and underrecognized. Skin testing is controversial but a recent panel proposed that skin testing to RCM may identify an alternative RCM agent when a skin test is positive to an RCM agent suspected to have caused a reaction.⁵⁶

A previous reaction to RCM is the strongest indicator of a future reaction to RCM. The risk persists even if a patient has tolerated RCM without a reaction in the interim. Other risk factors include asthma, severe cardiovascular disease, and atopy.⁵⁶

There is a common misconception that RCM reactions are cross-reactions because of shellfish allergy or povidone-iodine dermatitis. Shellfish allergy is due to IgE to shellfish proteins (eg, tropomyosin), which is structurally unrelated to iodine. Patients with shellfish allergy are not at significantly higher risk for RCM reaction and vice versa.⁵⁷ Moreover, patients with contact dermatitis to povidone-iodine do not have increased risk of RCM reactions and vice versa.⁵⁷

For patients with history of RCM reactions, the use of nonionic, low-osmolar contrast with premedications significantly reduces the risk of reaction.⁵⁷ A commonly used pretreatment regimen involves systemic steroids (prednisone, 50 mg, 13 hours, 7 hours, and 1 hour before RCM administration) and H1-antihistamines (diphenhydramine, 50 mg, 1 hour before contrast administration).⁵⁸ In emergent cases, methylprednisolone, 40 mg, intravenously (IV) or hydrocortisone, 200 mg, IV immediately and every 4 hours until contrast given plus diphenhydramine, 50 mg, IV 1 hour before contrast may be helpful.⁵⁸ However, premedication with systemic steroids administered less than 4 hours before RCM exposure may not be reliably effective.⁵⁸

CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agents may cause severe immediate reactions. Although most are nonimmune mediated, most infusion reactions from platinum agents are IgE mediated. Taxane agents may be IgE mediated (to the drug) or non-IgE-mediated (to chemotherapeutic solvents such as Cremophor and Polysorbate).⁵⁹ Skin testing may be useful in identifying sensitivities to platinum drugs and taxanes.

Anaphylactic-type reactions to first or second exposure are not generally IgE mediated. An exception is cetuximab, which may cause anaphylaxis on first initial exposure due to cross-reactivity to the carbohydrate determinant, alpha-gal, which is also present on red mammalian meat. Sensitization to carbohydrate alpha-gal is thought to be primarily due to multiple tick bites.⁶⁰

For immediate DHRs to chemotherapeutic agents, a rapid 12-step desensitization protocol may be completed to induce temporary tolerance in nearly all patients who require chemotherapy. However, non-life-threatening reactions may still occur in ~6% of patients.⁶¹

DISCLOSURE

The authors have nothing to disclose.

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