Drug allergy

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

Key words: *Drug allergy, adverse drug reactions, drug hypersensitivity, graded challenge, desensitization, tolerance, penicillin, cephalosporin, carbapenem, sulfonamide, local anesthetic, radiocontrast media, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drug, biologic modifiers*

Abbreviations used

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

EPIDEMIOLOGY AND CLASSIFICATION OF ADVERSE DRUG REACTIONS

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

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

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

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

CLINICAL MANIFESTATIONS OF IMMUNOLOGICALLY MEDIATED ADRS

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

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TABLE I. Heterogeneity of drug-induced allergic reactions

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

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

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

EVALUATION: HISTORY TAKING

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

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