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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals

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Pharmacy & Therapeutics

Update

Drug Information for Health Care Professionals

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Drug Allergies: Beta Lactams

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Drug allergies are an important consideration in clinical practice, as they are associated with substantial morbidity, mortality, and increased healthcare costs. Adverse drug reactions are the most common iatrogenic illness, with 3 to 6% of all hospital admissions occurring because of an adverse drug reaction, and 6 to 15% of all hospitalized patients experiencing an adverse drug reaction.[1,2]

The classical division of adverse drug reactions classifies reactions into type A and type B (Table 1). Immune-mediated reactions account for 5 to 10% of all drug reactions and constitute true drug hypersensitivity, with IgE mediated drug allergies being included in the type B category. The World Allergy Organization defines a drug allergy as a hypersensitivity reaction for which a definite immunological mechanism, either IgE or T-cell mediated, is demonstrated.[1] Reactions that clinically resemble an allergy but do not have a proven immunological cause should be classified as a non-immune hypersensitivity reaction. Table 1 differentiates between the various types of immunologic reactions.

Certain risk factors have been identified which play an important role in drug hypersensitivity. In order for a medication to be immunogenic (ie, cause an allergic response), it must have a certain molecular weight and structural complexity (eg, large protein), or it must act as a hapten, a molecule that requires binding to a carrier protein to elicit an immune response. While some medications are intrinsically reactive, others can become immunogenic by binding to immune receptors, T cell receptors, and major histocompatibility complex (MHC) peptides.[1,2] Medications administered by the intravenous (IV), intramuscular (IM), or topical routes are more likely to elicit a response than those taken orally. Patient populations at risk for hypersensitivity reactions include females; patients with human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE), cystic fibrosis (CF), or asthma; and those who have experienced previous hypersensitivity reactions to a chemically related medication. Table 2 lists other risk factors for experiencing adverse drug reactions, both immune and non-immune.

Gell and Coombs identified and classified the various types of immune-mediated drug hypersensitivity reactions. Each type varies in its mechanism, immune mediators, clinical presentation, and timing in relation to drug exposure. Table 3 describes each of these reactions and provides examples of particular drug reactions.

Table 1: Immunologic and Nonimmunologic Drug Reactions

Immunologic	Example	Nonimmunologic	Example
Type I reaction *IgE mediated*	Anaphylaxis from beta-lactam antibiotic	**Type A (predictable and dose dependent)**	
Type II reaction *cytotoxic*	Hemolytic anemia from penicillin	Pharmacologic side effect	Dry mouth from antihistamines
Type III reaction *immune complex*	Serum sickness from anti-thymocyte globulin	Secondary pharmacologic side effect	Thrush while taking antibiotics
Type IV reaction *delayed, cell-mediated*	Contact dermatitis from topical antihistamine	Drug toxicity	Hepatotoxicity from methotrexate
Specific T-cell activation	Morbilliform rash from sulfonamides	Drug-drug interactions	Seizure from theophylline while taking erythromycin
Fas/Fas ligand-induced apopotosis	Stevens-Johnson syndrome Toxic epidermal necrolysis	Drug overdose	Seizures from excessive lidocaine
Other	Drug-induced, lupus-like syndrome	**Type B (unpredictable and not dose-dependent)**	
	Anticonvulsant hypersensitivity syndrome	Pseudoallergic	Anaphylactoid reaction after radiocontrast media
		Idiosyncratic	Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy
		Intolerance	Tinnitus after a single dose of aspirin

Anaphylaxis: Anaphylaxis is a severe, life-threatening type I allergic reaction. Approximately 1.2 to 16.8% of the population may experience an anaphylactic reaction (3.3 to 43 million Americans), with around 1500 deaths occurring annually in the United States. Anaphylactic reactions occur when a foreign antigen interacts with IgE receptors on cell surfaces of mast cells and basophils. Receptor binding triggers release of histamines and other bioactive mediators that, in turn, cause smooth muscle spasm, bronchospasm, mucosal edema, and inflammation.

Anaphylactoid reactions are caused by release of the same mast cell and basophil mediators by non-IgE mechanisms. Symptoms of both anaphylaxis and anaphylactoid reactions can range from weakness, dizziness, congestion, and sneezing to upper respiratory tract obstruction, hypotension, vascular collapse, cardiovascular arrhythmias, and/or cardiac arrest.[4] The true incidence and prevalence figures for anaphylaxis are hard to identify as there is no standard diagnostic criteria. Diagnosis can encompass reactions ranging from a systemic allergy to one that is always severe and life-threatening. Patients at highest risk are also hard to identify, as the best predictor for potential anaphylaxis is a patient with a documented history of previous anaphylactic reactions. Antibiotics and radiocontrast media cause the greatest amount of anaphylactic reactions by medications. Table 4 reviews various medications associated with anaphylactic reactions.[4]

Of all classes of medications, antibiotics are the most likely to cause hypersensitivity reactions. Antibiotic allergies are variable in the type and severity of the reaction, organ system affected, and cross-reactivity to other agents. Approximately 2% of reactions to antibiotics are cutaneous, with the most common manifestations being skin eruptions, urticaria, and pruritus. Such reactions most often occur days to weeks after initial exposure;

Table 2. Patient Risk Factors for Adverse Drug Reactions

General drug reactions *(non-immune related)*

- Female gender
- Serious illness
- Renal insufficiency
- Liver disease
- Polypharmacy
- HIV infection
- Herpes infection
- Alcoholism
- Systemic lupus erythematosus

Hypersensitivity drug reactions *(immune related)*

- Female gender
- Adult HIV infection
- Concomitant viral infection
- Previous hypersensitivity to
- chemically-related drug
- Asthma
- Use of beta blockers
- Specific genetic polymorphisms
- Systemic lupus erythematosus

Table 3: Classification of Hypersensitivity Reactions

Gell-Coombs Classification	Time of Onset	Clinical Manifestation	Mechanism	Example
Type I *immediate hypersensitivity*	< 1 hour	Anaphylaxis, urticaria, angioedema, wheezing, laryngeal edema, bronchospasms, hypotension	Antibiotic-specific IgE antibodies binding to mast cells with release of histamine and inflammatory mediators	Penicillin; fatal outcome in 1:50,000 to 1:100,000 treatment courses
Type II *late cytotoxic reactions*	> 72 hours	Immune cytopenia; hemolytic anemia, thrombocytopenia, or neutropenia; vasculitis	Specific IgG or IgM antibodies plus complement directed at drug-hapten coated cells	Anticonvulsants
Type III *immune complex reactions*	> 72 hours (1 to 3 weeks after drug exposure)	Serum sickness, drug fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis	Tissue deposition of IgG and IgM immune complexes with complement activation and inflammation	Diuretics
Type IV *delayed cell-mediated*	> 72 hours	Contact dermatitis, maculopapular drug rash	MHC presentation of drug molecule to T cells with cytokine and inflammatory mediator response	Topical antihistamines

similar reactions may develop much sooner upon secondary exposure to the medication. In contrast, hypersensitivity syndromes and anaphylaxis can occur almost immediately after drug exposure and may result in more significant signs and symptoms such as fever, eosinophilia, bronchoconstriction, and hypotension.

Penicillin allergies: Penicillin is the most common cause of drug-induced anaphylaxis, with an incidence of approximately 0.004% to 0.015% (1:10,000 to 1:5000 courses of therapy). Additionally, penicillin is the most frequently reported drug allergy by patients. While around 10% of patients report a history of penicillin allergy, the true incidence of penicillin allergy in these patients is often less.[6]

Penicillin is the best characterized antibiotic in terms of mechanism of hypersensitivity reactions. Antibodies formed in response to penicillin are directed at the beta-lactam ring. Penicillins bind spontaneously to endogenous and exogenous proteins, forming hapten carriers that become immunogenic and trigger type I hypersensitivity reactions. Penicillin is degraded into products termed major and minor antigenic determinants. The major penicillin determinant, benzylpenicilloyl polylysine, is used for skin-prick testing followed by intracutaneous testing to detect allergen-specific IgE antibodies.[2,5] Approximately 60% of patients with positive skin tests will have an allergic reaction when penicillin is administered.[6,9] Data suggests that in patients with negative skin test results, penicillin administration has a 4% risk of immediate reaction, similar to that of the general population.[5]

For patients who have IgE antibodies to penicillin but must receive therapy for certain conditions (eg, neurosyphilis), desensitization therapy may be considered. These protocols are performed in a hospital setting by giving increasing amounts of drug over a period of hours until a therapeutic dose is reached.[5] A typical starting dose is in micrograms and is

Table 4. Selected Medications Causing Anaphylaxis

Antibiotics	Chemotherapeutic Agents	Miscellaneous
▪ Penicillin and derivatives ▪ Cephalosporins ▪ Tetracycline ▪ Chloramphenicol ▪ Sulfonamides ▪ Ciprofloxacin ▪ Nitrofurantoin ▪ Vancomycin	▪ Asparaginase ▪ Vincristine sulfate ▪ Cyclosporine ▪ Methotrexate ▪ Fluorouracil	▪ Aspirin ▪ Nonsteroidal anti-inflammatory drugs ▪ Allergy extracts ▪ Immune globulin ▪ Insulin Heparin ▪ Vaccines ▪ Dextran ▪ Opiates ▪ Protamine sulfate ▪ Local anesthetics ▪ Glucocorticosteroids

doubled every 15 to 30 minutes; therapeutic doses can be reached in 4 to 5 hours. During this time, the patient should be monitored and given antihistamines and inhaled beta-agonists for urticaria and bronchospasm, respectively.[5] The procedure may resume at the last tolerated dose if mild flushing or urticaria occurs; however, an alternative antibiotic should be selected if the patient experiences a severe reaction such as hypotension or severe bronchospasm.

Cephalosporin allergies: Like other antibiotics, cephalosporins tend to produce allergic reactions manifesting as rashes (1 to3%).[7] Antigenic cross-reactivity between penicillins and cephalosporins may occur in certain patients, as these antibiotics have similar chemical configurations. Varying degrees of cross-reactivity between cephalosporins and penicillins have been reported in the literature, confounded by the lack of a standardized definition of drug allergy and absence of confirmed diagnosis by IgE antibody presence.

The most quoted study comparing cephalosporin cross-reactivity in patients with penicillin allergies examined records of 15,708 patients in clinical trials who received cephalothin, cephaloridine, cephalexin, cefazolin, or cefamandole. Of the patients with a history of allergy to penicillin, 8.1% had an allergic reaction to the cephalosporin, as compared with 1.9% of patients who did not have a history of penicillin allergy.[6] However, many of these first-generation cephalosporins contained trace amounts of penicillin as a result of their manufacturing process. Additionally, many of the patients with self-reported history of penicillin allergy did not have confirmatory skin testing. As patients with penicillin allergies have a 3-fold higher rate of allergic reactions to any drug, even those structurally unrelated, concomitant allergy may not be due to cross-reactivity.[6,9]

While penicillin allergy depends on the beta lactam ring structure, cephalosporin allergies develop more from their side chain molecular structure. The side chains of cephalothin and cephaloridine closely resemble penicillin; the side chains of cefadroxil, cephalexin, cefaclor, cephradine, cefprozil, cefatrizine, and cefadroxil resemble those of ampicillin and amoxicillin.[6,7,9] Administration of these medications have a 0.5% to 6.5% greater likelihood of producing allergic reactions among patients with a history of allergy to penicillin or amoxicillin, respectively.[6] Other cephalosporins are unlikely to produce allergic reactions in patients with a history of reactions to compounds with different molecular structures (Table 5). Cross-reactivity is low between penicillin and second-, third-, and fourth-generation cephalosporins.[9]

Recently, the American Academy of Pediatrics (AAP) published evidence-based guidelines that advocate using certain cephalosporins in patients with penicillin allergies for the treatment of acute bacterial sinusitis and acute otitis media.[6] Reactions that are IgE mediated, manifested as bronchospasm, angioedema, hypotension, urticaria, or a pruritic rash, are likely to become more severe with time. Guidelines recommend in patients with a history of IgE-mediated reactions that alternative therapies should be considered. However, patients who report nonurticarial and non-pruritic rash or any type II, III, or IV reactions may be given cephalosporins with caution.[6]

Carbapenem and monobactam allergies: Carbapenems differ from penicillins in they are unsaturated and contain a carbon atom instead of sulfur.[8] Carbapenem allergy is present in about 11% of penicillin allergic patients and less than 3% of non-allergic patients.[9,12]

One recent review noted an overall frequency of carbapenem hypersensitivity in 9 to11% of penicillin allergic patients based on a retrospective review.[12] The authors noted that carbapenem therapy should be avoided in patients in documented type I hypersensitivity reactions; however, it may be considered for infections with multidrug-resistant organisms in patients with a less clearly defined allergic history. These patients should

Table 5. Chemical Structure of 7-Position (R1) Side Chain Penicillin and Cephalosporins

Similar Structure, Possible Cross-Reactivity Within Group			Dissimilar Structure, Unlikely Cross-Reactivity	
▪ Penicillin G ▪ Cefoxitin ▪ Cephaloridine ▪ Cephalothin	▪ Ampicillin ▪ Amoxicillin ▪ Cefaclor ▪ Cefadroxil ▪ Cefatrizine ▪ Cefprozil ▪ Cephalexin ▪ Cephradine	▪ Cefepime ▪ Cefotaxime ▪ Cefpodoxime Ceftizoxime ▪ Ceftriaxone	▪ Cefamandole ▪ Cefazolin ▪ Cefdinir ▪ Cefixime ▪ Cefonicid ▪ Cefoperazone	▪ Cefotetan ▪ Ceftazidime ▪ Ceftibuten ▪ Cefuroxime ▪ Cephapirin ▪ Moxalactam

be closely monitored for signs and symptoms of drug hypersensitivity and treated with appropriate therapies should a reaction occur.

Aztreonam is a monocyclic beta lactam, also known as a monobactam, with the same side chain as ceftazidime.[8] No specific IgE antibodies have been identified for aztreonam. While cross-reactivity between aztreonam and ceftazidime has been reported, many patients with penicillin allergies have been able to tolerate aztreonam in previous studies.

Conclusion: In summary, adverse events, particularly drug allergies and anaphylaxis, in response to beta lactam antibiotics are common and well documented. Most adverse events from antibiotics manifest as cutaneous reactions, resulting in skin eruption, urticaria, and pruritus. More serious reactions such as anaphylaxis may occur and result in respiratory, cardiovascular, and gastrointestinal symptoms. Penicillin is responsible for approximately 75% of fatal anaphylaxis reactions in the United States, causing approximately 500 to 1000 deaths per year.[4] Structurally related cephalosporins may provoke allergic and even anaphylactic reactions in penicillin allergic patients; however, true risk for cross-reactivity has not been clearly defined. Patients experiencing a non-urticarial rash to penicillins may be cautiously given other beta-lactam antibiotics; however, those patients with documented IgE-mediated allergy or anaphylaxis should receive alternative therapies.

References available upon request.

Glossary of Terms

Anaphylaxis	acute mucocutaneous signs (pruritus, flushing, urticaria, angioedema) coupled with respiratory obstructive symptoms (edema, bronchospasm), cardiovascular symptoms (hypotension), gastrointestinal symptoms (nausea, vomiting, diarrhea); caused by the interaction of a foreign antigen with IgE receptors on basophils and mast cells
Anaphylactoid reaction	symptoms closely resemble an anaphylactic reaction; caused by the release of mast cell and basophil mediators triggered by non-IgE events
Beta lactam	antibiotics in the penicillin, cephalosporin, carbapenem, and monobactam categories; with the exception of the monobactam aztreonam, these drugs all contain a 5-membered ring attached to a beta-lactam ring
Cross-reactivity / cross-sensitivity	after production of IgG and IgM in response to a specific antigen, these antibodies may react to structurally similar antigens; does not include coincidental IgE-mediated drug allergy
Drug allergy	IgE- or T-cell-mediated response to a drug agent in a sensitized patient
Drug hypersensitivity	immune-mediated response to a drug agent in a sensitized patient
(Adverse) Drug reaction	all adverse events related to drug administration, regardless of etiology
Type A reaction	dose-dependent and predictable reaction to a drug; majority of all drug reactions
Type B reaction	not dose-dependent, unpredictable; approximately 5 to 15% of all drug reactions; includes hypersensitivity reactions

Virtual Drug Information Database (VDI)

Search pre-answered questions regarding disease therapy management, compatibility/stability, compounding formulations, drug interactions, or other general drug information questions. The VDI is available at: www.muschealth.com/vdiSearch/Login.aspx? (Use NetID login/ password for access). If you are unable to find the information needed, contact the Drug Information Service for assistance.

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FORMULARY UPDATE FOR JANUARY 2010

In January 2010, the Pharmacy and Therapeutics Committee approved the actions listed below. The formulary effective date was February 17, 2010, unless otherwise noted.

ADDED WITH RESTRICTION:

Prasugrel (Effient™) -

Prasugrel is a new platelet inhibitor which showed greater efficacy than clopidogrel in preventing secondary ischemic events in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI); however, more bleeding events were reported versus clopidogrel. It may have a therapeutic use in patients resistant to clopidogrel; however, it is more expensive. Prasugrel will be restricted to the attendings or fellows on the Cardiology service. A preprinted order form is being created; once the order form/ CPOE form has been finalized, a formulary effective date will be announced.

Tablets: 5 and 10 mg

ADDED:

Hylan G-F 20 (Synvisc One®)

Hylan G-F 20 is a high molecular-weight hyaluronan. It is as efficacious as other hyaluronan products available, including Hyalgan®, the current product on the formulary. Due to decreased number of injections, Synvisc One® may increase patient satisfaction and offer a cost-savings advantage.

Injection: 10-mL syringes (48 mg/6mL of Hylan G-F 20)

CHANGE IN RESTRICTION:

Daptomycin (Cubicin®)

Per the Anti-infective Subcommittee, it was recommended to include **Hematology/Oncology** as an approved service for daptomycin per clinical guidelines utilizing the febrile neutropenia order form.

CHANGE IN AUTOMATIC THERAPEUTIC SUBSTITUTION (ATS) PROTOCOL:

Per the Anti-infective Subcommittee, the hemodialysis dose for doripenem on the ATS protocol was increased to 500 mg q24h, dosed after dialysis on days of dialysis.

UPDATED ATS PROTOCOL:

The ATS protocol for the antihistamine class is being updated to include levocetirizine (Xyzal®).

NOT ADDED:

Norfloxacin (Noroxin®)

Norfloxacin is recommended for the prophylaxis of spontaneous bacterial peritonitis (SBP) in some national guidelines, but current information do not relate efficacy over standard treatments like ciprofloxacin or trimethoprim/sulfamethoxazole. Per the Anti-infective Subcommittee, it was recommended that norfloxacin not be added, since other proven therapies (eg, ciprofloxacin) are already on the formulary.

Dronedarone (Multaq®)

Dronedarone is a noniodinated benzofuran derivative structurally and mechanistically related to amiodarone. Dronedarone may interact with other medications that undergo metabolism via the CYP3A system. Clinical studies have shown increased mortality in patients with Class IV or decompensated Class II or III heart failure, leading to a black-box warning and contraindicated use in this population. Its efficacy compared with other antiarrhythmics, specifically amiodarone, or its current place in therapy is still unknown. The monthly cost of dronedarone is significantly higher than that of its competitor amiodarone. At this time, it was not felt that dronedarone had enough data to warrant addition to the formulary.

LINE EXTENSIONS

- Rotavirus vaccine (Rotarix®) 1-mL injection
- Lidocaine (Xylocaine® MPF) 1% DUOFIT unit
- Selegiline (Eldepryl®) 5-mg capsule
- Efavirenz (Sustiva®) 50-mg capsule
- Betamethasone (Valisone®) cream

DELETIONS

- Chlordiazepoxide (Librium®) 10-mg capsule
- Trimethobenzamide (Tigan®) 300-mg capsule 100-mg/mL injection
- Fluocinolone cream, solution, ointment
- Geri-silk® 2-oz bath oil
- Lanolin (anhydrous) 1-ointment
- Thera-Derm® 8-oz lotion
- Acetic acid/aluminum acetate (Domeboro®) solution
- Selegiline (Eldepryl®) 5-mg tablet
- Efavirenz (Sustiva®) 100-mg capsule
- Betamethasone (Diprolene®) cream

CHARTS, GUIDELINES, AND ORDER FORMS:

The Febrile Neutropenia Guidelines and preprinted order form have been updated to reflect changes to first-line therapies, as well as the inclusion of daptomycin for VRE colonized patients meeting criteria.

The Sepsis preprinted order forms have been updated to include changes/clarification of a documented penicillin allergy, as well as new vancomycin dosing recommendations.

The following policies have been updated and will be posted online:

- C26 - Sample Medication Policy
- C60 - Patient Care Unit Refrigerators,
- C61 - Medication Administration,
- C68 - Standing Orders,
- C78 - Medication Orders
- C82 - Formulary Management
- C159 - Continuous Infusion Policy.