

Evaluation and Management of Pediatric Drug Allergic Reactions

Brett L. Buchmiller, MD, and David A. Khan, MD

Corresponding author

David A. Khan, MD
University of Texas Southwestern Medical Center, 5323 Harry
Hines Boulevard, Dallas, TX 75390-8859, USA.
E-mail: dave.khan@utsouthwestern.edu

Current Allergy and Asthma Reports 2007, 7:402–409
Current Medicine Group LLC ISSN 1529-7322
Copyright © 2007 by Current Medicine Group LLC

Drug allergy is a common reason for consulting an allergist. Determining whether a particular drug is involved can be accomplished with a careful history and physical examination, knowledge of the common and idiosyncratic reactions of the drugs in question, and selective skin testing. If a drug reaction is suspected, alternatives exist to allow continued appropriate treatment. A practical approach to the pediatric patient is outlined along with a general discussion of common drug allergic reactions encountered in clinical practice.

Introduction

Adverse reactions to drugs are a common but significantly underreported cause of morbidity and mortality [1]. Adverse drug reactions are broadly characterized as either *predictable* (type A) or *unpredictable* (type B) reactions. Unpredictable reactions include drug allergy, pseudoallergic reactions, drug intolerance, and idiosyncratic reactions. This review focuses on drug allergy and pseudoallergic reactions that may be seen in the pediatric population.

Drug allergy and *drug hypersensitivity* describe immune-mediated responses to pharmaceutical agents or excipients. Drug allergic reactions require prior sensitization to the drug. The immune response in drug allergy is variable but may involve production of drug-specific antibodies, drug-specific T cells, or a mixed immunologic response.

Pseudoallergic reactions, as the name implies, clinically resemble immunoglobulin (Ig) E-mediated drug allergy. However, in contrast to IgE-mediated reactions, pseudoallergic reactions do not involve drug-specific IgE antibodies; because no sensitization is required, they may occur with the first dose. Pseudoallergic reac-

tions are due to mast cell activation and subsequent mediator release through non-IgE-dependent activation. This is often referred to as *nonspecific mast cell activation*. In children, most pseudoallergic reactions are caused by radiocontrast media, vancomycin, and opiates.

Evaluation of the Patient with Suspected Drug Allergy

Drug allergic reactions can affect most organ systems; however, they commonly involve the skin, which is typically when drug allergy is considered. Once an allergic reaction to a drug is suspected, obtaining an appropriate history is the key tool in assessing whether allergy is likely and which drug is most responsible. It is important to clinically characterize the reaction in order to determine a potential mechanism. For example, an IgE-mediated reaction would be suspected in a child with urticaria after receiving amoxicillin, whereas a morbilliform reaction would lead to concern for concomitant Epstein-Barr virus (EBV) infection. All medications must be identified in the history, as well as the temporal relationship from drug initiation to reaction. A prior exposure to the drug or a cross-reacting agent should also be determined. For infants, this exposure can occur in utero or through breast milk. Finally, knowledge about the propensity for a given drug to cause a specific reaction may be crucial in narrowing the list of potential culprit drugs. A detailed history is often sufficient to make (or disprove) a diagnosis of drug allergy, and is clearly the best tool in evaluating the patient with suspected drug allergy.

Because most drug allergic reactions are noticed through cutaneous manifestations, the ability to recognize the various patterns of cutaneous reactions is important. Although the skin manifestations of drug reactions are myriad, some are more common than others. Distinguishing between urticarial eruptions and other exanthems is important because urticaria suggests an IgE-mediated, pseudoallergic, or serum-sickness reaction. The most common cutaneous manifestation of drug allergy is an exanthem, typically referred to as a *maculopapular eruption*. Exanthems are not associated with IgE-mediated

ated reactions but occasionally may evolve into more serious skin reactions (eg, toxic epidermal necrolysis). Morbilliform reactions may also be seen in drug reactions. However, in the pediatric patient, there is a high incidence of viral-induced morbilliform eruptions. One point of distinction is the presence of lesions on the palms or soles, which is more suggestive of a viral reaction than a drug reaction.

Other cutaneous manifestations include purpura, suggesting a vasculitic process, and target lesions, which suggest erythema multiforme. Target lesions in association with mucosal involvement (ie, conjunctiva, oropharynx, genital) are worrisome for Stevens-Johnson syndrome. Cutaneous drug reactions are beyond the scope of this article, and are extensively reviewed elsewhere [2]. Finally, drug reactions may also manifest with fever, lymphadenopathy, respiratory problems, hepatitis, renal dysfunction, and arthralgias.

Pediatric Mimics of Drug Reactions

Reactions labeled as hypersensitivity to a medication may also be due to death of the organism targeted by the medication and reaction to the released cellular debris [3,4]. Common pediatric exanthems that occur by chance with administration of a medication may be mistaken for a reaction to the medication itself. Six classic exanthems are commonly encountered in pediatric practice: rubeola, rubella, scarlatina, Dukes' disease (rubeola-scarlatina, pseudoscarlatina), erythema infectiosum (fifth disease), and exanthem subitum (roseola infantum).

Specific Drugs

Vancomycin

Red man syndrome, a pseudoallergic reaction, is the most common adverse drug reaction experienced with the administration of vancomycin, a glycopeptide. Red man syndrome generally presents with pruritus, erythema, or flushing of the face with or without upper torso involvement. In addition to erythroderma, patients may develop urticarial lesions. Hypotension, especially as an isolated finding, is rare. Up to 90% of healthy volunteers experienced symptoms with an infusion of 1 g of vancomycin over 60 minutes [5]. Because red man syndrome is a pseudoallergic reaction, it may occur with the first dose administered.

Management includes decreasing the infusion rate and administering antihistamines at least 45 minutes before the infusion [6]. Avoidance of opiates may also be required for tolerance to vancomycin because they can contribute to nonspecific mast cell activation. Although true IgE-mediated anaphylaxis has been reported, it is exceedingly rare. Patients with red man syndrome that does not respond to decreased infusion

rate and antihistamine premedication should be considered for a drug-tolerance induction procedure or desensitization [7,8].

Vancomycin is the most common drug responsible for linear IgA-bullous disease [9]. Other, more severe, drug allergic reactions to vancomycin include Stevens-Johnson syndrome and toxic epidermal necrolysis [10].

Aminoglycosides

Aminoglycosides have a significant amount of inherent, generally dose-related, toxicity. The nephrotoxicity and ototoxicity ascribed to these agents can occur with either topical or parenteral administration. Despite their known detrimental effects, aminoglycosides are commonly used in clinical practice because they are effective in treating gram-negative and enterococcal infections. Hypersensitivity and contact reactions to aminoglycosides are typically minor [11–13]; however, although rare, anaphylactic reactions to tobramycin and streptomycin have been reported. Successful aminoglycoside desensitization has also been reported [12].

β -lactams

The β -lactam antibiotics are responsible for a significant number of adverse, often IgE-mediated, drug reactions. Consequently, much time and research have been devoted to defining the haptens responsible. More is known about the biochemical nature of hypersensitivity reactions to β -lactams than any other drug class. The major determinant, penicilloyl, has been conjugated to poly-d-lysine to create penicilloyl-polylysine (PPL). Historically, this was available as Pre-Pen (Hollister-Stier, Spokane, WA). However, this reagent is no longer available commercially in the United States. The only commercially available minor determinant of penicillin is penicillin G. Skin testing to the combination of PPL and penicillin G has a very good negative predictive value [14]. Although structurally related, cephalosporins appear to generate a wider variety of metabolites than do penicillins. As a result, skin testing may or may not detect the relevant IgE when cephalosporins are involved [15].

Prior to the 1980s, reports suggested a cross-reactivity of more than 10% in patients with a history of penicillin allergy who were administered cephalosporins. This may have been due to the presence of trace amounts of penicillin in these earlier cephalosporin preparations [16]. Currently, the risk is much lower that a patient with a history of penicillin allergy will react to a cephalosporin. This is partially explained because only 10% of patients with a history of penicillin allergy have detectable penicillin-specific IgE on skin testing. Among adults with a history of nonsevere (nonanaphylactic) reactions to penicillin, the frequency of reaction was only 0.17% in a study from our institution [17•]. In fact, the evidence-based guidelines from the American

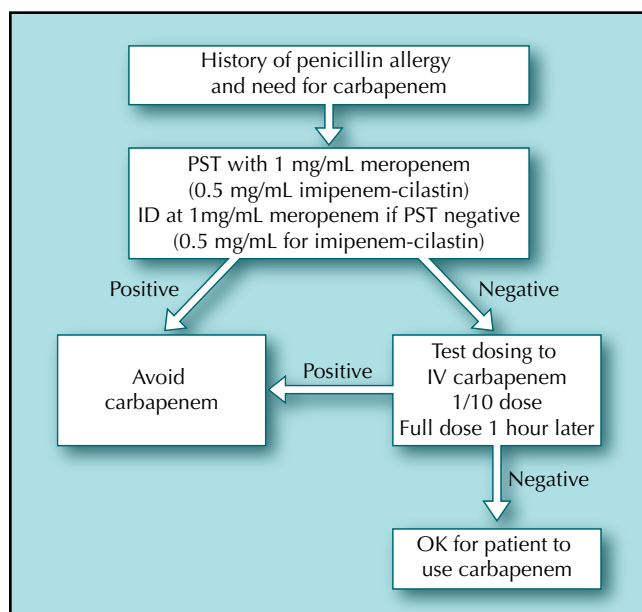


Figure 1. Algorithm for carbapenem use in penicillin-allergic patient. ID—intradermal test; IV—intravenous; PST—percutaneous (prick) skin test.

Academy of Pediatrics endorse using second- and third-generation cephalosporin antibiotics to treat acute bacterial sinusitis and acute otitis media in patients with reported allergies to penicillin [18]. Nonetheless, this approach has its risks, because fatal anaphylaxis has been reported in penicillin-allergic adults receiving cephalosporins [19], although no pediatric cases have been reported to date.

Recent data suggest the value of skin testing for cephalosporins. Studies by Romano et al. [20] reveal that among patients with a history of cephalosporin allergy, at least 70% will have a positive skin test to a concentration of 2 mg/mL. Furthermore, the negative predictive value also appears to be good for cephalosporin skin testing. Romano et al. [21••] studied 128 patients with convincing histories of penicillin allergy confirmed by penicillin skin testing. Of these 128 subjects, 114 had negative skin tests to cephalosporins at 2 mg/mL; 90 underwent challenges to cefuroxime and ceftriaxone, and all were negative. Therefore, particularly in patients with convincing histories for penicillin allergy who require cephalosporins, skin testing to the cephalosporin followed by graded challenge appears to be very useful.

Although monobactams do not cross-react with penicillins, carbapenems have been reported to cross-react (based on skin testing) in about 50% of penicillin-allergic patients [22]. Recently, Romano et al. [23••] and Gueant et al. [24] have shown that this rate of cross-reactivity is indeed markedly lower. In separate studies evaluating patients with penicillin allergy proven by skin testing, these researchers performed skin testing to either imipenem (0.5 mg/mL) or meropenem (1 mg/mL). Only

one of 122 patients reacted to imipenem and one of 104 reacted to meropenem on skin testing. Challenges to carbapenem skin-test-negative patients were tolerated in all subjects. These data suggest that the negative predictive value for carbapenem skin testing is quite good, and that pretreatment skin testing followed by graded challenge is a practical approach in penicillin-allergic patients who need carbapenems (Fig. 1).

Certain β -lactam antibiotics are more likely than others to be responsible for specific types of reactions. Ampicillin and amoxicillin have a higher incidence of nonpruritic macular rash than the other penicillins. This can be enhanced in patients with infectious mononucleosis (up to 90%). Nonpruritic macular rashes occur with other penicillins at a rate of about 2% [25]. Children have been reported to experience serum sickness-like reactions, characterized by arthralgias and rash, when taking cefaclor [26]. This reaction has not been described in adults, and has been suggested to be due to an inherited defect in metabolism. Serum sickness-like reactions have also been reported with loracarbef, which is structurally similar to cefaclor. The cross-reactivity between cefaclor and loracarbef is unknown.

β -lactams have also been reported to cause every other type of reaction in the Gell and Coombs classification. Cephalosporins have been associated with other skin eruptions, drug fever, and a positive Coombs test (clinical hemolysis is unusual). Although rare, drug-induced cytopenias and acute interstitial nephritis (AIN) also have been described.

Patients who have lost their hypersensitivity to penicillin appear to have a low incidence of resensitization upon future oral courses of penicillin [27]. Mendelson et al. [28] performed penicillin challenges on children with a history of a reaction to penicillin or one of its analogs but with negative penicillin skin tests. To evaluate for resensitization, they performed skin tests again 4 or more weeks later, and found that only two of 219 (< 1%) patients had a positive result upon retesting.

Anticonvulsants

The anticonvulsants as a class are responsible for several adverse drug reactions. On a dose-for-dose basis, they are the class most frequently responsible for Stevens-Johnson syndrome and toxic epidermal necrolysis.

Hypersensitivity syndrome was first described in association with phenytoin after it was on the market for 1 year. Later, hypersensitivity syndrome was reported with other aromatic anticonvulsants (eg, phenobarbital and carbamazepine) [29]. Initial research into the cause showed an association with a deficiency in epoxide hydrolase. This enzyme is required to break down arene metabolites produced during hepatic metabolism of aromatic anticonvulsants. The presentation of hypersensitivity syndrome is defined by the triad of fever, dermatologic eruption, and internal organ involvement

(single or multiple), often with lymphadenopathy. Most patients present within 1 to 8 weeks after beginning the offending agent. Hepatic followed by renal involvement is typical; however, other organ systems may also be involved. The degree of internal organ involvement does not correlate with the severity of cutaneous symptoms. Hepatic involvement can progress to fulminant hepatic necrosis. The overall mortality is 10%.

Many other drugs have now been associated with this syndrome. As a result, *anticonvulsant hypersensitivity syndrome* has been renamed *drug reaction with eosinophilia and systemic symptoms* (DRESS). The newer name is preferred, because the term “hypersensitivity” is nonspecific. The three most common precipitants are phenytoin, carbamazepine, and trimethoprim-sulfamethoxazole, but DRESS has also been described with dapsone, minocycline, lamotrigine, allopurinol, non-steroidal anti-inflammatory drugs, captopril, nevirapine, and others. Although the exact mechanism for DRESS is unknown, infection with or reactivation of human herpesvirus (HHV)-6 has been implicated [30].

Treatment involves removing the offending agent; corticosteroids often are administered. Unlike Stevens-Johnson syndrome or toxic epidermal necrolysis, mucosal involvement almost never occurs with DRESS. Unlike serum sickness-like reactions, there is usually no arthralgia. Compared to almost all other drug reactions, DRESS is atypical because symptoms and organ involvement can continue to progress after the offending agent has been discontinued. Furthermore, symptoms may persist for many months after drug discontinuation. Relapses have occurred after tapering of corticosteroids. Data are limited on using intravenous immunoglobulin and other immunomodulatory agents in resistant cases [31].

Chemotherapeutic agents

Chemotherapeutic agents target rapidly dividing cells. Because of this indiscriminate toxicity, organs with high metabolic rates—gastrointestinal mucosa, hair, nails, and skin—tend to be affected. Excellent reviews are available on the cutaneous manifestations of chemotherapeutic agents [32].

Hypersensitivity reactions are well known to occur with the taxanes and the platinum salt-based agents, often requiring their withdrawal. Reactions to taxanes are often anaphylactoid, usually occur with the first dose, and are unlikely to be IgE-mediated. Skin testing is typically negative and pretreatment with antihistamines and corticosteroids reduces these reactions. In contrast, platinum compounds (eg, cisplatin) may cause hypersensitivity reactions after several courses, suggesting an immunologic mechanism [33]. Intracutaneous skin testing using 0.02 mL of undiluted carboplatin has shown excellent negative predictive value [34]. If desensitization is required, rapid protocols exist that have been success-

ful with several chemotherapeutic agents [7], including those used in children [35].

Imatinib mesylate is a tyrosine kinase inhibitor with low molecular weight. Unlike nearly all other chemotherapeutic agents, imatinib has a specific target and does not affect all tissues with a high metabolic rate. The fusion protein Bcr-abl is the intended target, with additional activity seen with c-kit (stem cell factor receptor) and platelet-derived growth factor receptor (PDGF-R). Imatinib is associated with a high incidence of exanthems and hypersensitivity symptoms that appear to be dose-related. Successful desensitization protocols exist [36].

Biologic agents

Biologic agents have revolutionized the treatment of many disorders. Their novel activity as direct modulators of the immune system coupled with their biologic origins present new opportunities for treating disease and for developing adverse effects. Unlike typical pharmacologic agents that require the formation of haptens, biologics are generally high-molecular-weight, protein-based molecules. They must be administered parenterally to maintain their efficacy and prevent digestion in the gastrointestinal tract. Because they are proteins, they are subject to the same mechanisms of degradation, processing, and immunosurveillance as any other foreign protein. The high incidence of serum sickness after repeat injections of antisera from horses suggests their strong immunogenic potential. Many of these pitfalls have been reduced by “humanizing” the relevant proteins to the extent possible.

A classification system has been proposed to categorize adverse reactions to biologic agents; this system shares mechanistic qualities with the classification already mentioned for common pharmaceuticals [37]. The proposed system would use the Greek alphabet to distinguish that biologic agents are involved. Type α reactions represent adverse reactions due to excess, possibly dose-related, but known and predictable effects, and are analogous to type A reactions with other drugs. Examples would be cytokine-release syndrome seen with interleukin (IL)-2 and rituximab, which may present with fever, nausea, bronchospasm, exanthems, elevated liver function tests, and elevated uric acid levels. This is unique to biologic agents because the compound itself may have no intrinsic effect. Acting on a receptor or preventing the activation of a receptor may have severe systemic results.

Type β reactions represent idiosyncratic reactions analogous to type B reactions with other drugs; however, they become more problematic with biologic agents. Whereas hapten formation and IgE-mediated responses are unusual and unpredictable with low-molecular-weight agents, biologic agents are proteins and present good targets for immune responses. Hypersensitivity

resulting from IgE (immediate) or IgG (delayed) would be classified as a type β reaction.

Steps have been taken to minimize type β reactions. Initial monoclonal antibodies were of murine origin, which presented a foreign protein to the host, often eliciting a strong immune response. Newer agents have been produced by fusing murine variable regions with human Fc or Fab portions, resulting in "humanized" antibody. Other agents are produced entirely from human genes, but harvested from bacteria. These agents still present possible immune targets because differences exist in glycosylation. In general, the potential for a direct immune response against these agents decreases with increasing humanization.

Cytokines (ie, IL-2) are humanized, but may have differing glycosylation. They can be administered with polyethylene glycol to reduce their degradation.

Antibodies can be produced through a variety of means resulting in xenogeneic (ie, from mice), chimeric (ie, fusion products), or humanized products. Chimeric products are designated by the ending "-ximab," whereas names of humanized agents end in "-zumab." Fully human products end in "-mumab." Names of fusion proteins contain the suffix "-cept" [37].

Type γ reactions involve imbalances of the immune system caused by the biologic agent. These reactions would include the induction of autoimmunity, immunodeficiency, or imbalance syndromes. Examples exist with the tumor necrosis factor (TNF)- α blocking agents. All TNF- α blocking agents have demonstrated an increase in reactivation of *Mycobacterium tuberculosis*. Unlike typical reactivation, it tends to be miliary. The incidence of such reactivation has been reduced by appropriately screening patients before initiating treatment.

When hypersensitivity reactions to biologics occur, the reaction is drug-specific, based on the specific epitope recognized by the immune system. If hypersensitivity develops to a TNF- α blocking agent, another agent in this class can be substituted without risk [38]. Desensitization has been attempted successfully for type I hypersensitivity reactions to monoclonal antibodies, especially in those with demonstrated skin reactivity to nonirritating doses of the biologic in question [7]. Immune reactions due to the effects of TNF- α blockade (not hypersensitivity) would not be expected to change by changing the agent [39].

Drug Skin Testing

For low-molecular-weight drugs, skin testing has demonstrated validity in the diagnosis of IgE-mediated reactions only when using penicillin reagents. At the present time, penicilloyl-polylysine, the major determinant of penicillin, is not commercially available. As discussed previously, skin tests with cephalosporins

and carbapenems appear to have good negative predictive value based on reports from a single center. Nonetheless, confirmatory graded challenge should still be performed. Although valid diagnostic tests are lacking for non- β -lactam antimicrobials, testing with nonirritating concentrations may provide useful information. The nonirritating concentrations of 15 commonly used antibiotics have been published elsewhere [40]. If the nonirritating skin test is positive, it is likely that drug-specific IgE antibodies are present. Therefore, the patient should receive an alternative non-cross-reacting antibiotic or undergo rapid desensitization. In contrast, a negative skin test does not denote that drug-specific IgE antibodies are absent, because it is possible that a drug metabolite not present in the test reagent may be the relevant allergen. In such a case, a graded challenge or desensitization may still be required to safely administer the drug. As mentioned previously, skin testing has recently been shown to be useful in assessing allergy to platinum salt-based chemotherapeutic agents [41••].

Graded Challenges

A graded challenge (eg, test dose) is a procedure to determine if a drug may be administered safely to an individual with a potential drug allergy. Graded challenges should be performed in patients who, based on a detailed evaluation, are deemed unlikely to be allergic. If skin testing has been done, the results should be negative. Graded challenges should not be performed in patients with a history of a severe cutaneous drug eruption (eg, Stevens-Johnson syndrome).

Drug challenge protocols vary. One reasonable approach is to give an initial challenge of 1/100th of the treatment dose (1/1000 if the previous reaction was severe), and then proceed to the treatment dose after an appropriate observation period, based on the drug and route of administration [42]. It is important to recognize that drug challenges do not modify the immune response.

Drug Desensitization

If the history and physical examination are consistent with an IgE-mediated process, and there is a clear need for the drug that cannot be met by substituting another drug class, drug desensitization may be performed. Desensitization procedures modify the immune response to make the patient temporarily tolerant of the drug. Criteria to consider for drug desensitization include 1) IgE-mediated reactions; 2) immediate positive reaction upon skin test of drug; 3) no alternate medication available; and 4) risk of fatal allergic reaction less than risk of fatal outcome if medication is not used. Although typically well tolerated, desensitization is not without risk, and

Table 1. Schedule for oral penicillin desensitization: administer penicillin V elixir orally every 15 minutes

Dose	Penicillin V, units/mL	Dose volume, mL	Dose, units	Cumulative dose	Record vitals/reaction
1	1000*	0.1	100	100	
2	1000	0.2	200	300	
3	1000	0.4	400	700	
4	1000 [†]	0.8	800	1500	
5	1000	1.6	1600	3100	
6	1000	3.2	3200	6300	
7	1000	6.4	6400	12,700	
8	10000 [‡]	1.2	12,000	24,700	
9	10,000	2.4	24,000	48,700	
10	10,000	4.8	48,000	96,700	
11	80,000 [§]	1.0	80,000	176,000	
12	80,000	2.0	160,000	336,700	
13	80,000	4.0	320,000	656,700	
14	80,000	8.0	640,000	1,296,700	

Total time: 3 hours, 45 minutes; total dose: 1.3 million units; total volume: 36.1 mL.
 *One (1)—1-cc syringe filled with 1000 units/mL penicillin V elixir
[†]Two (2)—10-cc syringe filled with 1000 units/mL penicillin V elixir
[‡]One (1)—10-cc syringe filled with 10,000 units/mL penicillin V elixir
[§]One (1)—20-cc syringe filled with 80,000 units/mL penicillin V elixir
 Use penicillin V elixir 250 mg/mL = 80,000 units/mL (1 mg = 1600 units).
 To make 10,000 units/mL penicillin V solution: add 2 mL of 80,000 units/mL to 14 mL of normal saline.
 To make 1000 units/mL penicillin V solution: add 2 mL of 10,000 units/mL to 18 mL of normal saline.

reactions vary depending on the drug. A clear indication for the drug should be documented in the chart and informed patient consent obtained. Consultation with the appropriate specialist should also be obtained to validate the need for the drug.

Protocols have been published for several drugs. In general, drug desensitization begins with 1/10,000th of the final dose; doses are doubled every 15 to 20 minutes until a therapeutic dosage has been achieved. A protocol used at our institution for penicillin V is outlined in Table 1. We prefer desensitization via the oral route, when possible, based on enhanced safety; however, no comparative studies have been performed to prove this. A recent study demonstrates that desensitization can be performed in a standardized manner for many drugs with positive outcomes [43••].

The term *drug desensitization* is usually reserved for drug reactions thought to be IgE-mediated, but it has also been used to describe procedures for non-IgE-mediated reactions, including reactions to aspirin, sulfonamides, and allopurinol. All these procedures are used to induce drug tolerance, but vary considerably in methodology. The timing and starting doses vary widely based on the medication and type of reaction. For example, a commonly cited

protocol for desensitization to allopurinol requires 28 days [44]. Protocols also exist for clopidogrel [45] and imatinib [36], among others. For the reasons mentioned earlier, the literature should be consulted before performing desensitization to less common drugs.

Conclusions

Drug allergy is a common reason for consultation with an allergist. A careful history is the best diagnostic aid in determining whether the reaction in question is truly due to a drug, or is some other idiosyncratic reaction. Knowledge of the known dose-related and common reactions associated with the drug or drugs in question can also be invaluable. Skin testing is generally of limited value but may be helpful in select circumstances.

Many courses of action exist, depending on the drugs suspected to be involved in the patient's symptoms: changing to an alternative treatment; supporting the patient through the symptoms and continuing treatment; performing a graded challenge; and desensitizing the patient if a protocol exists. Using these tools, most patients can receive appropriate pharmacologic medical care for their condition.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Hazell L, Shakir SA: Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006, 29:385–396.
 2. McKenna JK, Leiferman KM: Dermatologic drug reactions. *Immunol Allergy Clin North Am* 2004, 24:399–423, vi.
 3. Gelfand JA, Elin RJ, Berry FW Jr, Frank MM: Endotoxemia associated with the Jarisch-Herxheimer reaction. *N Engl J Med* 1976, 295:211–213.
 4. Pound MW, May DB: Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. *J Clin Pharm Ther* 2005, 30:291–295.
 5. Polk RE, Healy DP, Schwartz LB, et al.: Vancomycin and the red-man syndrome: pharmacodynamics of histamine release. *J Infect Dis* 1988, 157:502–507.
 6. Wallace MR, Mascola JR, Oldfield EC 3rd: Red man syndrome: incidence, etiology, and prophylaxis. *J Infect Dis* 1991, 164:1180–1185.
 7. Castells M: Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol* 2006, 6:271–277.
 8. Wazny LD, Daghigh B: Desensitization protocols for vancomycin hypersensitivity. *Ann Pharmacother* 2001, 35:1458–1464.
 9. Wakelin SH, Allen J, Zhou S, Wojnarowska F: Drug-induced linear IgA disease with antibodies to collagen VII. *Br J Dermatol* 1998, 138:310–314.
 10. Vidal C, Gonzalez Quintela A, Fuente R: Toxic epidermal necrolysis due to vancomycin. *Ann Allergy* 1992, 68:345–347.
 11. Yung MW, Rajendra T: Delayed hypersensitivity reaction to topical aminoglycosides in patients undergoing middle ear surgery. *Clin Otolaryngol Allied Sci* 2002, 27:365–368.
 12. Schretlen-Doherty JS, Troutman WG: Tobramycin-induced hypersensitivity reaction. *Ann Pharmacother* 1995, 29:704–706.
 13. Morris SD, Rycroft RJ, White IR, et al.: Comparative frequency of patch test reactions to topical antibiotics. *Br J Dermatol* 2002, 146:1047–1051.
 14. Green GR, Rosenblum AH, Sweet LC: Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. A cooperative prospective study of the penicillin study group of the American Academy of Allergy. *J Allergy Clin Immunol* 1977, 60:339–345.
 15. Madaan A, Li JT: Cephalosporin allergy. *Immunol Allergy Clin North Am* 2004, 24:463–476, vi–vii.
 16. Kelkar PS, Li JT: Cephalosporin allergy. *N Engl J Med* 2001, 345:804–809.
 17. Daulat S, Solensky R, Earl HS, et al.: Safety of cephalosporin administration to patients with histories of penicillin allergy. *J Allergy Clin Immunol* 2004, 113:1220–1222.
- Patients with histories of nonsevere reactions to penicillin appear to tolerate cephalosporins.
18. American Academy of Pediatrics, Subcommittee on Management of Sinusitis and Committee on Quality Improvement: Clinical practice guideline: management of sinusitis. *Pediatrics* 2001, 108:798–808.
 19. Pumphrey RS, Davis S: Under-reporting of antibiotic anaphylaxis may put patients at risk. *Lancet* 1999, 353:1157–1158.
 20. Romano A, Gueant-Rodriguez RM, Viola M, et al.: Diagnosing immediate reactions to cephalosporins. *Clin Exp Allergy* 2005, 35:1234–1242.
 21. Romano A, Gueant-Rodriguez RM, Viola M, et al.: Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004, 141:16–22.
- Discusses strategy for cephalosporin skin testing to assess safety of administering cephalosporins in patients with penicillin allergy.
22. Saxon A, Adelman DC, Patel A, et al.: Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988, 82:213–217.
 23. Romano A, Viola M, Gueant-Rodriguez RM, et al.: Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Ann Intern Med* 2007, 146:266–269.
- Discusses low frequency of positive skin tests after meropenem in penicillin-allergic patients and tolerability of meropenem challenge if skin test is negative.
24. Gueant JL, Gueant-Rodriguez RM, Viola M, et al.: IgE-mediated hypersensitivity to cephalosporins. *Curr Pharm Des* 2006, 12:3335–3345.
 25. Ditto AM: Drug allergy. In: *Patterson's Allergic Diseases*, edn 6. Edited by Grammer LC, Greenberger PA. Philadelphia: Lippincott Williams & Wilkins; 2002:295–385.
 26. Murray DL, Singer DA, Singer AB, Veldman JP: Cefaclor—a cluster of adverse reactions. *N Engl J Med* 1980, 303:1003.
 27. Solensky R, Earl HS, Gruchalla RS: Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med* 2002, 162:822–826.
 28. Mendelson LM, Ressler C, Rosen JP, Selcow JE: Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol* 1984, 73:76–81.
 29. Wolf R, Orion E, Marcos B, Matz H: Life-threatening acute adverse cutaneous drug reactions. *Clin Dermatol* 2005, 23:171–181.
 30. Descamps V, Valance A, Edlinger C, et al.: Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001, 137:301–304.
 31. Fields KS, Petersen MJ, Chiao E, Tristani-Firouzi P: Case reports: treatment of nevirapine-associated dress syndrome with intravenous immune globulin (IVIG). *J Drugs Dermatol* 2005, 4:510–513.
 32. Payne AS, James WD, Weiss RB: Dermatologic toxicity of chemotherapeutic agents. *Semin Oncol* 2006, 33:86–97.
 33. Quock J, Dea G, Tanaka M, et al.: Premedication strategy for weekly paclitaxel. *Cancer Invest* 2002, 20:666–672.
 34. Markman M, Zanotti K, Peterson G, et al.: Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003, 21:4611–4614.
 35. Morgan M, Bowers DC, Gruchalla RS, Khan DA: Safety and efficacy of repeated monthly carboplatin desensitization. *J Allergy Clin Immunol* 2004, 114:974–975.
 36. Park MA, Volcheck GW, Guarderas JC: Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc* 2004, 25:345–347.
 37. Pichler WJ: Adverse side-effects to biological agents. *Allergy* 2006, 61:912–920.
 38. van Vollenhoven RF: Switching between biological agents. *Clin Exp Rheumatol* 2004, 22:S115–121.
 39. Lee SJ, Kavanaugh A: Adverse reactions to biologic agents: focus on autoimmune disease therapies. *J Allergy Clin Immunol* 2005, 116:900–905.
 40. Empedrad R, Darter AL, Earl HS, Gruchalla RS: Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol* 2003, 112:629–630.

- 41.●● Leguy-Seguin V, Jolimoy G, Coudert B, et al.: **Diagnostic and predictive value of skin testing in platinum salt hypersensitivity.** *J Allergy Clin Immunol* 2007, **119**:726–730.

Diagnostic value of skin testing for alternative platinum salt chemotherapeutic agents rather than desensitizing all patients requiring continued treatment.

42. Shepherd G: **Allergy to B-lactam antibiotics.** *Immunol Allergy Clin North Am* 1991, **11**:611.

- 43.●● Castells M: **Desensitization for drug allergy.** *Curr Opin Allergy Clin Immunol* 2006, **6**:476–481.

Standardized protocol for intravenous desensitization to variety of common agents.

44. Fam AG, Dunne SM, Iazzetta J, Paton TW: **Efficacy and safety of desensitization to allopurinol following cutaneous reactions.** *Arthritis Rheum* 2001, **44**:231–238.

45. Lee-Wong M, Gadhvi D, Resnick D: **Clopidogrel desensitization.** *Ann Allergy Asthma Immunol* 2006, **96**:756–757.