

Overview of Penicillin Allergy

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Abstract Allergy to penicillin is the most commonly reported antibiotic allergy. However, most patients who report a positive history of a prior reaction to penicillin are not found to be allergic to penicillin upon skin testing. Often, this history is vague or based on a parent's recollection of an event that occurred in the distant past. Avoidance of penicillin based on self-reported allergic history alone often leads to the use of an alternate antibiotic with greater cost or side effect profile. Patients with a negative skin test to both major and minor determinants may generally be given penicillin, with a statistical risk of developing an allergic reaction similar to that observed in the general population. A more cautious approach in these cases where the degree of suspicion is low, an allergic etiology is unproven, or there is a negative skin test, is to do a graded challenge. If the skin test is positive, an alternate antibiotic should be used. If, however, an alternate antibiotic is not available, then desensitization may be performed, but there are limitations to desensitization as well, and tolerance is not permanent. Avoidance of cephalosporins may be recommended in cases of penicillin allergy, but newer generation cephalosporins have demonstrated less cross-reactivity to penicillin than earlier generation ones. Desensitization protocols for cephalosporins are

available but not standardized. The mechanisms of antibiotic sensitization are not clearly understood.

Keywords Penicillin · Drug allergy · Cephalosporin · Anaphylaxis · Stevens–Johnson syndrome · Amoxicillin allergy

Introduction

The penicillin class of drugs includes beta-lactam antibiotics of varying cost and coverage spectrum. Penicillins are the drug of choice for upper and lower respiratory infections (*Streptococcus pyogenes*), meningococcal disease (*Neisseria meningitidis*), syphilis (*Treponema pallidum*), and anaerobic infections. Adverse reactions to penicillin have been reported ever since it was introduced approximately 70 years ago [1]. Only a small percentage of those patients who report an adverse reaction to penicillin actually have a true immune-mediated allergic reaction. Because it is difficult to distinguish patients who are at risk for anaphylaxis from those patients who can tolerate penicillin safely simply by history alone, treatment options may be unnecessarily limited if further evaluation by objective testing is not carried out. The proper identification, evaluation, and management of patients with a reported history of penicillin is an essential component of patient care [2].

Classification, Chemical Structure, Properties, and Mechanism of Action of Beta-Lactam Antibiotics

The beta-lactam antibiotics include penicillins, aminopenicillins, cephalosporins, cephamycins, carbapenems, mono-

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bactams, and beta-lactamase inhibitors. The different classes of beta-lactam antibiotics are illustrated in Fig. 1. All of these compounds share the characteristic beta-lactam ring—a cyclic amide with a heteroatomic ring structure consisting of three carbon atoms and one nitrogen atom. The building block of penicillin is penicillanic acid. An antibiotic is classified as a “penicillin” if the beta-lactam ring is fused to a 5-member thiazolidine ring, or *penam*; and classified as a cephalosporin if fused to a 6-member dihydrothiazine ring, or *cephem* (Fig. 2). Penems such as imipenem and meropenem have a beta-lactam ring structure with a double bond in the attached 5-member ring. Penicillins have only one side chain (6-position) while cephalosporins have two side chains (3- and 7-position). The monobactam group is unique in that the beta-lactam ring is isolated and not fused to another ring. This group has several members, tigemonam, nocardiacin A, tabtoxin, and aztreonam. Only aztreonam is commercially available. Monobactams have activity only against gram-negative bacteria. Table 1 shows medications of the various subgroups of beta-lactam antibiotics.

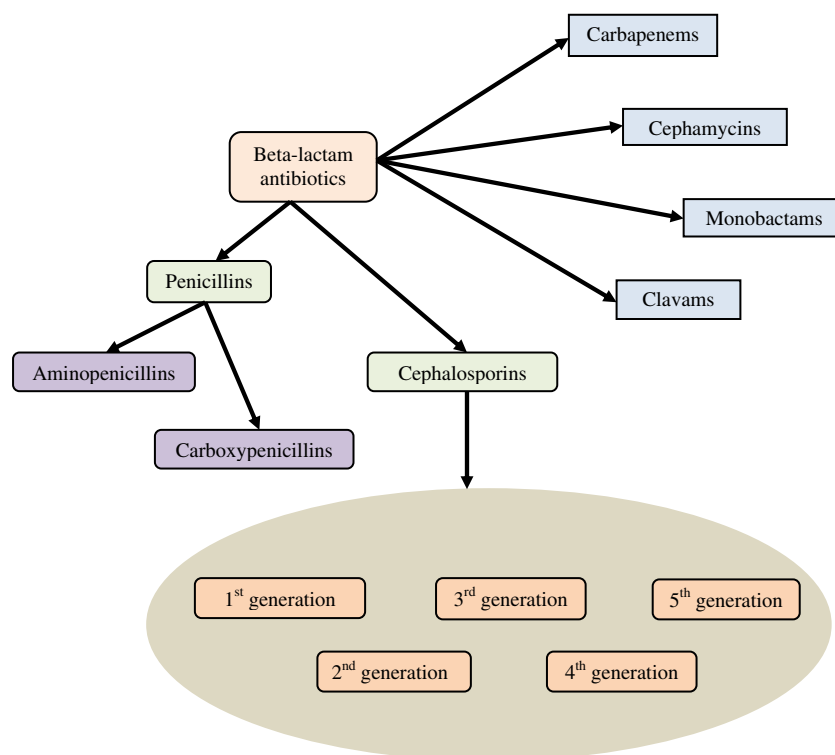
The metabolic parameters and activity of individual antibiotics within a specific class are dependent on the side chain. Substitution at the 6-position side chain of penicillin results in antibiotics with increased potency such as amoxicillin and ampicillin. These belong to the group of antibiotics named aminopenicillins and are still some of the most popular antibiotic used to treat common childhood

infections such as otitis media, pharyngitis, and acute sinusitis. For cephalosporins, substitutions at the 3-position affects pharmacokinetics, whereas substitutions at the 7-position alter the antimicrobial activity of the drug [3].

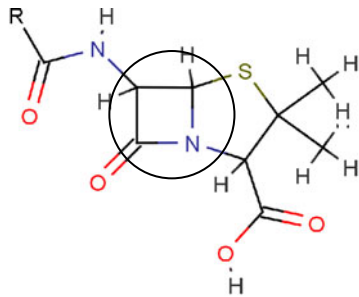
Beta-lactam antibiotics are bactericidal by virtue of their ability to bind to the enzyme DD-transpeptidase which links the peptidoglycan molecules in bacteria cell walls. This binding leads to disruption of cell wall architecture, which results in cytolysis due to the osmotic pressure gradient. In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the bacteria's existing peptidoglycan. Penicillin also binds to penicillin binding protein (PBP) which is located beneath the bacterial cell wall and at the cell surface membrane. The carboxypeptidation reactions of cell wall assembly are catalyzed by PBPs. The type, number, and concentration of PBPs vary amongst different bacteria. By binding PBPs, penicillin may inhibit bacterial cell division, induce a change in morphology, or induce cell death. The activity of the antibiotic against the bacterium is partially determined by the relative affinity of the antibiotic to the PBP [4].

Bacteria become resistant against beta-lactam antibiotics by expressing beta-lactamase which hydrolyzes the beta-lactam ring rendering it inactive. Gram-positive bacteria secrete beta-lactamase just outside the bacterial cell wall and gram-negative bacteria secrete beta-lactamase into the

Fig. 1 Classification of beta-lactam antibiotics



A. Penicillin nucleus – the beta-lactam ring, consisting of three carbons and a nitrogen is circled



B. Cephalosporin nucleus – note the two side chains, R1 and R2

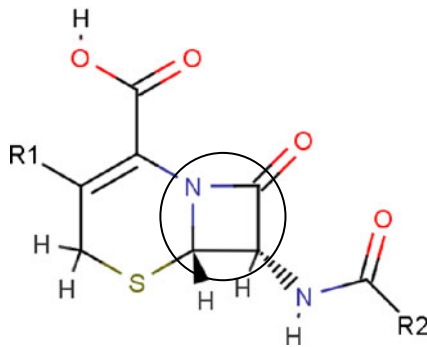


Fig. 2 Chemical structures of penicillin and cephalosporins

periplasmic space. Adding a beta-lactamase inhibitor such as clavulanic acid, sulbactam, or tazobactam will overcome beta-lactamase producing organisms. Clavulanic acid has the characteristic beta-lactam ring but lacks significant intrinsic antimicrobial activity; its mechanism of action is to act as a competitive inhibitor of beta-lactamases. Sulbactam irreversibly binds to beta-lactamase and thereby prevents it from interfering with the function of the antibiotic.

A second mechanism through which bacteria become resistant is by producing alterations in PBPs, leading to decreased binding activity of the antibiotic to the modified PBPs and a subsequent decrease in antimicrobial activity. Methicillin-resistant *Staphylococcus aureus* is an example of resistance due to alterations in PBPs. Bacteria may also develop penicillin resistance by preventing beta-lactam antibiotics from accessing and traversing pore channels and reaching PBPs in the cell membrane of gram-negative bacteria. *Pseudomonas aeruginosa* is an example of a bacterium which uses genetic code mutations of porin proteins to alter these channels and thereby prevent beta-lactam antibiotics from penetrating the cell wall [4].

Adverse Effects of Penicillin

Penicillin is metabolized into benzyl penicilloyl (95%) which is considered the major determinant. Other by-

Table 1 Penicillin and related antibiotics

	Penicillins	Aminopenicillins	Monobactams	Carbapenems	Clavam	Cephalosporins	Cephameycins
Classification	Penem	Penem		Carbapenem	Penem	Cephame	O-methylated cepham nucleus
Core structure	6-aminopenicillanic acid	6-aminopenicillanic acid	Beta-lactam ring unfused to thiazole ring	Carbon	Oxygen	7-aminocephalosporanic acid (7-ACA)	7-ACA
Position 1	Sulfur						
Side chains	R1	R1	R1	Imipenem	Clavulanic acid	R1 and R2	
Examples	Penicillin G Penicillin V Benzathine penicillin Procaine penicillin	Ampicillin Amoxicillin	Aztreonam Tigemonam Tabtoxin Nocardicin	Meropenem Ertapenem Doripenem Panipenem Biapenem Razupenem		See Table 3	Cefoxitin Cefmetazole Cefotetan Flomoxef

products of penicillin metabolism include penilloate, penicilloate, and benzyl-*n*-propylamine which are the minor determinants. The major determinants are formed when the beta-lactam ring is opened, and the minor determinants are formed by drug degradation in the gastrointestinal tract. Both major and minor determinants play an important role in allergic reactions to penicillin [5].

Adverse reactions to any beta-lactam antibiotic may occur in up to 10% of patients. Common adverse reactions include diarrhea, hypersensitivity, rash, urticaria, and superinfection such as candidiasis. Inflammation and pain at the injection site are also common for parenterally administered penicillins. Less common adverse reactions include fever, vomiting, erythema, dermatitis, angioedema, and seizures. Anaphylaxis can occur in approximately 0.01–0.04% of patients [6, 7].

Only a fraction of reported adverse reactions to penicillin is allergic or immune-mediated IgE reactions. The Gell–Coombs classification system is used to classify the predominant immunologic mechanisms. Table 2 provides a summary of these reactions and also presents an overview of which diagnostic tests are beneficial. Penicillin can lead to any of the four types of adverse immune reactions. Type I reactions are IgE-mediated immediate hypersensitivity reactions. After initial sensitization, the offending drug binds to IgE which in turn induces release of histamine and other inflammatory mediators from mast cells and basophils. Such reactions may lead to urticaria, pruritus, angioedema, bronchospasm, and anaphylaxis. Typically Type I hypersensitivity reactions occur

within 1 h of drug exposure, though less frequently they can occur later in the course of penicillin therapy. Patients with increased levels of specific IgE for a particular antibiotic are at higher risk for developing drug-related anaphylaxis.

Type II immune reactions are antibody-dependent cytotoxicity reactions and are mediated by IgG and IgM. In the case of penicillin, the IgG and IgM may be directed against a haptenized protein. Effects typically occur around 72 h after drug exposure. The binding of antibody to renal interstitial cells or red blood cells results in activation of the complement system leading to hemolytic anemia, thrombocytopenia, cytopenia, proteinuria, and/or hematuria.

Delayed immune complex reactions are Type III and are also mediated by IgG and IgM. Circulating immune complexes induce complement fixation and are deposited in blood vessels of kidneys, joints, or skin. The resulting fever, vasculitis, serum sickness, interstitial nephritis, arthralgia, lymphadenopathy, splenomegaly, and/or erythema multiforme can manifest 10–21 days after exposure to the offending agent [8].

Type IV reactions are cell-mediated reactions which are caused by the induction of T cells interacting with an antigen once sensitization has occurred. Proinflammatory cytokines lead to tissue inflammation and clinical manifestations can include morbilliform eruptions or contact dermatitis. It has been suggested that the pathophysiology of Stevens–Johnson syndrome or toxic epidermal necrolysis (TEN) while unknown, may involve components of a Type IV hypersensitivity reaction. Type 4 reactions typically occur after 48 h or longer after exposure [8].

Table 2 Immunopathologic penicillin reactions

Gell–Coombs classification	Mechanism	Time of onset	Examples of adverse penicillin reactions	Which test can be performed		
				skin testing	drug challenge	patch test
I	IgE mediated	minutes to hours	anaphylaxis, urticaria, angioedema, pruritus, hypotension, respiratory distress/bronchospasm	yes	yes ^a	no
II	Complement dependent, IgG/IgM	>72 h	hemolytic anemia, thrombocytopenia, cytopenia, proteinuria, hematuria	no	no	no
III	Immune complex mediated, IgG/IgM	10–21 days	fever, serum sickness, vasculitis, erythema multiforme, interstitial nephritis, lymphadenopathy, splenomegaly, arthralgias	no	no	no
IV	Delayed/cellular hypersensitivity	2–4 (or more) days	Morbilliform eruptions, Stevens–Johnson syndrome, no Toxic Epidermal Necrolysis, contact dermatitis Fixed drug eruption.	no	yes ^b	yes ^c

^a Caution with history of anaphylaxis; use lower starting dose with slower rate of increase

^b Only indicated for morbilliform eruptions; contraindicated in Stevens–Johnson, TEN

^c Patch test or drug challenge can be performed in fixed drug eruption [12]

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens–Johnson syndrome and toxic epidermal necrolysis are both forms of a disease affecting skin and mucous membranes in which cell death causes detachment of the dermis from the epidermis. The term TEN is used in cases where greater than 30% of the skin surface is involved. The etiology of these disorders is unknown, but medication use, including penicillins, and viral infections constitute the two most common associations. It is debatable whether or not erythema multiforme is a less severe form of these disorders, which themselves are dermatologic emergencies that carry a high morbidity and mortality. Because of the severity of these disorders and the potential for long-term morbidity, testing or challenge to penicillin is not indicated if there is a reasonable suspicion that penicillin is the etiology of Stevens–Johnson syndrome (SJS) or TEN. Rather, avoidance of all penicillins is advised in these cases.

Allergy to Clavulanic Acid

The antibiotic amoxicillin coupled with clavulanic acid is widely used to treat more severe respiratory and skin infections that may be resistant to amoxicillin alone. The clavulanic acid, which originates from *Streptomyces clavuligerus*, functions as a suicide inhibitor by binding to a serine residue on the active site of the beta-lactamase. The change in structure in clavulanic acid leads to subsequent binding of the now more reactive clavulanic acid to another amino acid in the active site which results in inactivation of beta-lactamase, and abrogation of the resistance of the bacteria to the accompanying beta-lactam antibiotic.

Occasionally, patients present with a history of an adverse reaction to amoxicillin–clavulanic acid. In most cases, these patients are considered to be penicillin allergy and are advised as such, the occurrence being documented in their record as “penicillin” allergic. While clavulanic acid has historically been shown to have low immunogenicity [9], allergic reactions have been reported. A case report in 2002 describes a case of a 1 1/2-year-old female cystic fibrosis patient given amoxicillin and clavulanic acid to treat pneumonia [10]. Several days later, she developed a rash which resolved after discontinuation of the antibiotic. She subsequently tolerated amoxicillin alone, but upon re-introduction to the combination, she developed urticarial wheals. She had a positive intradermal test to potassium clavulanate. Since this patient had an underlying disorder which may require the use of multiple antibiotics, it is important to define accurately the true allergy, in this case, most likely clavulanic acid.

A study of 307 patients with a history of allergic reaction after administration of amoxicillin–clavulanic acid between

2006 and 2008 suggests that up to 30% of individuals allergic to amoxicillin–clavulanic acid may indeed be selectively allergic to the clavulanic acid component [11].

Mechanism of Action of Penicillin Allergy

With the exception of the newer biologics, most drugs are small molecules which by themselves are incapable of producing an immunogenic response. Haptenization with a carrier protein is necessary to confer immunogenicity. Current formulations of penicillin no longer contain bacterial protein contaminants. The carrier proteins for penicillin are therefore mostly endogenous proteins that have not been identified. The epitopes for penicillin allergy have been identified to include the R side chain, the thiazolidine ring and the part of the molecule at the binding site between the carbonyl group of the antibiotic and the amino group of the carrier protein. Immediate reactions to penicillin are mediated by presentation of the entire penicillin-carrier protein complex by antigen presenting cells to T cells, leading to the generation of a Th2 response, and the production of penicillin specific IgE. Subsequent release of inflammatory mediators and further recruitment of inflammatory cells leads to the generation of the typical symptoms of a Type I hypersensitivity reaction. Non-Type I-mediated allergic reactions to penicillin occur through different mechanisms.

Residents in the fixed drug eruption lesions are intra-epidermal CD8+ T cells that have a major contributory role in the initiation of destructive immune responses while protecting the epidermis from repeated infections. This phenotype of T cells resembles that of effector-memory T cells and they express TCR $\alpha\beta$, CD3, CD8, CD45RA, and CD11 β but not CD27 and CD56. [12]

The pathogenesis of SJS or TEN is unknown. Granulysin, a cytolytic protein released by cytotoxic T cells and natural killer cells, has been implicated as a mediator of cytotoxicity [13]. However, the regulation of granulysin expression in these cell lines is unknown. Other theories have suggested a role of apoptosis of keratinocytes, and mediators of apoptosis such as tumor necrosis factor alpha, granzyme B, and perforin have been detected in high levels in blister fluid from the lesions of SJS and TEN patients [14]. Soluble fas ligand levels were also detected in five of seven patients with drug reactions that went on to become SJS [15].

Clinical Assessment and Testing for Penicillin Allergy

History and Physical

Taking a thorough medical history is critical in the evaluation of penicillin allergy and in distinguishing allergic reactions

from other causes [16, 17]. Information that may be helpful in establishing a cause and effect relationship between exposure and illness include the time course, character and severity of recent and previous reactions, the route of administration of the drug, concomitant medications given at or around the time of the reaction and response to any treatment given. Other helpful information might include a history of reactions to other beta-lactam antibiotics, as well as any previous testing that may have been done.

A review of previous documentation of the reaction is sometimes helpful, and yet sometimes adds to the confusion surrounding the event. If the description of the reaction in the past medical record is sketchy, incomplete, or inaccurate, or if the medical record reflects an incorrect interpretation of the event, this can lead to situations in which testing to elucidate an IgE mediated reaction is restricted or limited. For example, if a diagnosis of erythema multiforme is found documented in the chart, then future skin testing or at least challenge may be impossible to do because of the perceived risk, correct or incorrect, of precipitating Stevens–Johnson syndrome.

The symptoms and signs of a Type 1 hypersensitivity reaction are generally well characterized and include urticaria, angioedema, gastrointestinal symptoms, respiratory symptoms such as cough and wheezing, and in severe cases, hypotension or anaphylaxis. But the clinical presentation of a drug reaction is typically much more variable, and penicillin “allergy” has been known to present atypically with morbilliform rashes, fevers, arthralgias or arthritis, mouth ulcers, and other less well-described symptoms. These may be an indication that the reaction is not IgE mediated. For example, the lesions of fixed drug eruptions secondary to penicillin are pruritic, well circumscribed, erythematous macules that evolve into edematous plaques. These lesions usually appear within 8 h of drug exposure and typically occur at the same sites with each administration of the offending agent.

In other cases, history alone is notoriously scant or inaccurate and can frequently produce “red herrings,” leading to incorrect diagnosis and inaccurate labeling of patients. It has been observed that less than 20% of patients with a reported drug reaction is actually allergic. Avoiding penicillin based on self-reported allergic reaction frequently leads to the use of an alternate antibiotic, which may be detrimental to the health of the patient, increase antibiotic resistance in the community, and lead to higher health care costs.

Risk Factors for Penicillin Allergy

Of the many variables in presentation of penicillin allergy, several factors have been found to increase the risk of a true allergy. The most interesting of these is the age of the

patient, with patients between the ages of 20 and 49 being more likely to have a true IgE-mediated allergy. It is not clear whether this is a fictitious observation or if this reflects a true increase in incidence during this age range. The route of administration is also important. Topical penicillin applied to the skin has been shown to lead to significant sensitization. Parenteral administration is a more favorable route for sensitization than oral exposure, and in patients who are already sensitized, parenteral administration can result in more severe reactions. There is also some evidence that certain genetic markers may be related to a higher risk of sensitization. A study of 248 patients with penicillin allergy (immediate reactions or urticaria) and 101 healthy Chinese subjects demonstrated an increased frequency of the HLA-DR9, HLA-DR17, and HLA-DR4 allele, and a decreased frequency of the HLA-DR14.1 allele in patients who were penicillin allergic. Recently, two polymorphisms, at position 607A/C and position 137G/C of the promoter gene for IL-18, were demonstrated to have an association with individuals who have penicillin allergy. A history of atopy may also be associated with an increased risk of penicillin allergy [18]. The potential risk factors for penicillin allergy are summarized in Table 3.

Skin Testing—In Vivo Testing

Skin testing is highly accurate for the identification of penicillin allergy [17]. Skin prick testing is optimally performed using the penicillin major determinant benzylpenicilloyl (BPO) conjugated to poly-L-lysine to form benzylpenicilloyl polylysine (Pre-pen), as well as a mixture of minor determinants (MDM) that usually includes a 10^{-2} M mixture of benzyl penicilloate, benzyl penilloate, and benzyl-*n*-propylamine. MDM is not commercially available, though some pharmacies or laboratories may be able to synthesize these for skin testing purposes. Penicillin G is a natural (or native) penicillin and a source of minor determinants after degradation. It is itself often a component of the minor determinant mixture (MDM) or is diluted to 10,000 U per millimeter and used alone as a testing reagent in lieu of MDM. The nomenclature of the various moieties and the different skin testing materials for penicillin allergy is sometimes very confusing, and availability of these compounds has changed over the years as

Table 3 Risk factors for penicillin allergy

Age of the patient
History of sensitivity to other drugs
Frequencavy of administration of penicillin antibiotics
Route of administration (intravenous vs oral)
Atopy

well. A glossary of penicillin-related terminology is given in Table 4. Testing only with major determinant will miss approximately 10% of penicillin allergic patients; similarly testing only with minor determinants will miss approximately 30–60% of patients [2]. Skin test positivity to minor determinants is usually predictive of severe reactions such as anaphylaxis; whereas positive skin tests to major determinants may be predictive of either anaphylaxis and/or urticaria. If skin prick testing is negative at 15 min, then intradermal testing should be performed. A positive test is indicated by a 3-mm increase in the wheal diameter as compared with the negative control. When both skin tests to the major and minor determinants are administered, the negative predictive value for successful patient tolerance to penicillin is 99%. In this case, penicillin can be administered to the patient and the incidence of a serious reaction is not any more than that of a reaction in the general population, which is <4% [19]. Approximately 60% of patients with a positive skin test will have an allergic reaction after taking penicillin. Patients who are allergic to semisynthetic penicillins may have negative skin tests to major and minor determinants of penicillin, but may react to a side chain or a unique metabolite. Side chain specific allergy can be detected by skin testing to amoxicillin [20].

Graded Drug Challenge (Test Dosing)

If the intradermal test results are ambiguous or if the patient has a history of a morbilliform or fixed drug eruption, then a graded drug challenge can be performed to exclude penicillin allergy. A graded drug challenge involves administration of three to six doses of the offending agent in gradually increasing doses until the therapeutic dose is achieved. This method can be utilized in patients in whom there is a low index of suspicion for penicillin allergy. The

preferred route of administration for a graded challenge is oral since the risk of a severe reaction is less than that for parenteral administration [21, 22]. The risk–benefit ratio for an individual patient needs to be considered before proceeding with such testing. Factors to consider include the severity and type of prior reactions and the possibility of anaphylaxis. A graded drug challenge is contraindicated in patients with prior history of non-IgE-mediated life-threatening reactions such as Stevens–Johnson syndrome, drug-induced hemolytic anemia, or immune complex reaction. For patients in whom a true penicillin allergy is suspected and there is no alternative antibiotic, it is more appropriate to perform drug desensitization (see below). Another difference between a graded challenge and desensitization is that immunological changes in the host are not expected to occur with a graded challenge. An example of a graded drug challenge is shown in Table 5.

In Vitro Testing

Several methods have been described for in vitro testing for drug allergies. All of these methods lead to the detection of drug-specific IgE in serum. The familiar acronym radioallergen sorbent test (RAST) developed in 1974 is actually only one of many methods utilizing the same principles. Subsequent ELISAs have been developed including the Immunocap system by Pharmacia, and all such immunoassays all analyze for the presence of antigen-specific IgE. The advantage of these methods compared with skin testing and graded drug challenge test is the absence of risk to the patient. However, these tests are usually more expensive and less sensitive than in vivo testing. The sensitivity of these methods ranges from 40% to 74% with a specificity of 85–100% [23]. A study of the Pharmacia CAP System RAST FEIA for amoxicilloyl (AMOX) and BPO in patients

Table 4 Nomenclature of penicillin moieties and glossary

Penicillin G (Benzylpenicillin)—“G” means “gold standard.” This is generally given parenterally because the oral form is susceptible to degradation in the acidic environment of the stomach. In the absence of PPL, Penicillin G was often used for skin testing, is the sole source of minor determinants, and is often a component of MDM itself.
Penicillin V (phenoxymethylpenicillin)—an orally active form of penicillin which is less active than Penicillin G.
Penicillanic acid—a building block of penicillin, which has no inherent antibacterial activity
Benzylpenicilloyl (BPO)—the major determinant of penicillin metabolism
Pre-pen (Benzylpenicilloyl polylysine)—was not available for several years and was re-introduced in 2009 for testing for penicillin allergy. Used in the assessment of allergy to penicillin. The negative predictive value of a negative skin test with pre-pen for an immediate allergy reaction is greater than 95%. The negative predictive value of a negative skin test with pre-pen (major determinant) and penicillin G (a source of minor determinants) is greater than 97%.
Penicilloate—a minor determinant of penicillin G metabolism.
Penilloate—a minor determinant of penicillin G metabolism.
PPL (benzylpenicilloyl polylysine)—Pre-pen
MDM—Minor determinant mixture, not commercially available but generated in independent laboratories for investigational purposes, usually consisting of penicilloate, penilloate and benzyl- <i>n</i> -propylamine and/or penicillin G.

Table 5 An example of a graded drug challenge for penicillin

1. Preparation
 - a. Obtain history to verify patient is suitable candidate for graded drug challenge
 - b. Patient should be off antihistamines for 5–7 days
 - c. Informed consent should be administered to patient
 - d. Resuscitative equipment must be available
 - e. Take vital signs
 - f. Prepare dilutions of Pre-pen and Penicillin G
 - g. Prepare oral amoxicillin concentrations of 1, 10, and 100 mg/ml
2. Skin prick testing
 - a. Administer saline negative control, histamine positive control and skin test to Pre-pen and Penicillin G (if MDM can be prepared, then MDM can be administered instead of Penicillin G)
 - b. Wait 15 min and measure reaction. If negative proceed to step 3.
3. Intradermal testing^a
 - a. Administer saline negative control and 1:10,000 dilution of Pre-pen and Penicillin G
 - b. After 15 min, measure reactions, if negative, proceed to 1:1,000 dilution of Pre-pen and Penicillin G
 - c. After 15 min, measure reactions, if negative, proceed to 1:100 dilution of Pre-pen and Penicillin G
 - d. After 15 min, measure reactions, if negative, proceed to 1:10 dilution of Pre-pen and Penicillin G
 - e. After 15 min, measure reactions, if negative, proceed to full strength Pre-pen and Penicillin G
4. Graded challenge
 - a. If skin testing is negative, administer 1 ml of a 1-mg/ml dose of Amoxicillin orally
 - b. Observe for 15 min; if no reaction occurs, administer 1 ml of a 10-mg/ml dose of Amoxicillin orally (Cumulative dose 11 mg)
 - c. Observe for 15 min; if no reaction occurs, administer 1 ml of a 100-mg/ml dose of Amoxicillin orally (Cumulative dose 111 mg)
 - d. Observe for 15 min; if no reaction occurs, administer 4 ml of a 100-mg/ml dose of Amoxicillin orally (Cumulative dose 511 mg)
5. If no reaction occurs at any of the above steps, the patient has passed the graded challenge and the patient is able to tolerate Amoxicillin

In a graded challenge, no change in the immune system is expected. Therefore, there is no need for persistent administration of penicillin. Patient should be observed at home following challenge for any late phase reaction and this should be reported to physician immediately

Adapted from protocols developed at the Division of Allergy, Asthma and Immunology of Thomas Jefferson University

^a Alternatively, one intradermal test with the concentrate of Pre-pen and Penicillin G can be done

with allergy to penicillin demonstrated a low sensitivity (32% BPO, 43% AMOX, and 50% for both BPO and AMOX in patients who were skin test or history proven positive), but a very high specificity in patients who had non-immediate reactions or who tolerated penicillin by history (96–98%) [24].

Flow Cytometry

Although flow cytometry remains investigational in the field of drug allergy, it is increasingly being studied. One cell type that has been used in the evaluation of allergies is the basophil. The basophil is a histamine releasing leukocyte that is activated by cross-linking of the high-affinity IgE receptor (FcεRI) upon interaction with a relevant allergen. Other mechanisms of basophil cross-linking can also lead to activation of the basophil, and basophil activation can also occur in the absence of FcεRI cross-linking. Another activation specific cell surface marker is CD203c. Assessments of drug-induced basophil activation by measurement of CD63 and CD203c have been investigated in the diagnosis of hypersensitivity reactions to penicillin. This is called the basophil activation test or BAT. The sensitivity of this test is only approximately 50% with a specificity of approxi-

mately 93% [25], but this is comparable or perhaps even slightly better than skin testing or immunoCAP.

Lymphocyte transformation tests (LTTs) are a type of lymphocyte activation test that measures the in vitro proliferation of T cells in response to a specific antigen. These tests do not have a clear role in the diagnosis of immediate type IgE-mediated allergy to penicillin, but may be useful in evaluating the extent of involvement of T cells in type IV delayed type hypersensitivity reactions, as well as fixed drug reactions, maculopapular reactions, and urticaria. Lymphocyte activation tests have been studied only in a small number of drugs, including beta-lactam antibiotics and anti-epileptics. In the past, these tests were done by culturing lymphocytes in the presence of a mitogen, but more recently, flow cytometry has been developed to perform LTTs as well.

The evaluation of intracellular cytokines by flow cytometry to demonstrate a role of Th2 cytokines in cases of drug allergy has been shown to improve sensitivity when used in conjunction with ELISA [26]. Along with measurement of transcription factors and the previously mentioned lymphocyte activation tests [27], these techniques may prove useful in the study of mechanisms and patho-

physiology, but have so far not been available or useful in the diagnosis of penicillin allergy in the clinical setting.

Management of Penicillin Allergy

The management of true penicillin allergy involves prevention by avoidance of the antibiotic, and treatment in the case of accidental exposure. Determining if the allergic reaction is mediated by IgE is a critical step in the decision-making process for managing penicillin allergy. An algorithmic approach to managing penicillin allergy is presented in Fig. 3.

Penicillin Desensitization

The decision to perform drug desensitization over a graded drug challenge depends on the history of the reaction, the degree of suspicion that true penicillin allergy exists, and the

objective of the procedure. A graded drug challenge is generally performed when the degree of suspicion that a true penicillin allergy exists is low, either because of an unconvincing history or because a long time had elapsed between the reported event and the time of evaluation. The purpose of a graded drug challenge is to satisfy the patient and physician that there is no penicillin allergy. A desensitization procedure is performed in the case of a true, documented drug allergy, and the purpose is to induce tolerance in these patients. Penicillin desensitization should only be done in cases where there is a high certainty that the reaction is IgE mediated and when there is no reliable alternative non-cross-reacting antibiotic (as in the case of neurosyphilis). Another difference between a graded drug challenge and desensitization is that there is no modulation of the immune system in the former, while in the latter, desensitization results in the development of tolerance. The differences between a graded drug challenge and desensitization are illustrated in Table 6.

Fig. 3 Algorithm for the management of penicillin allergy

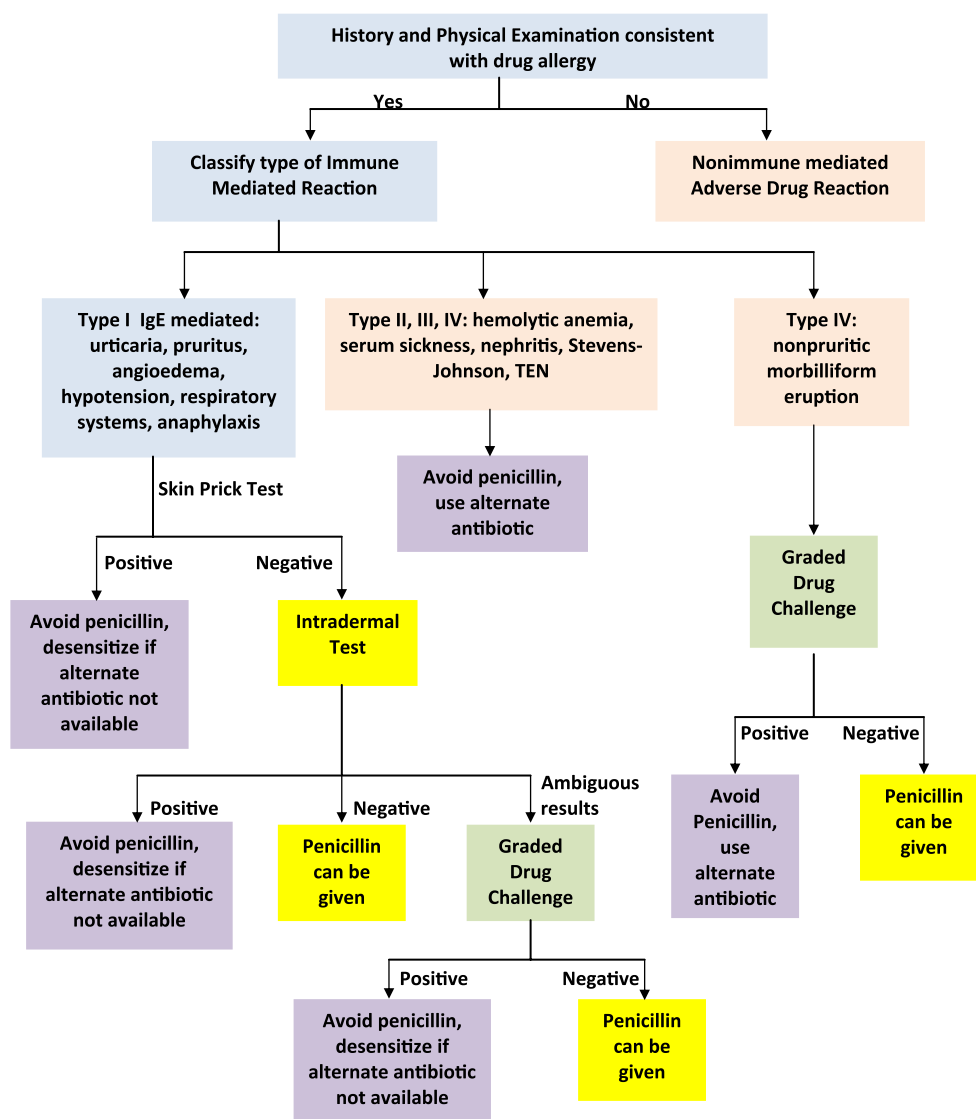


Table 6 Differences between a graded drug challenge and a desensitization

	Graded drug challenge	Desensitization
IgE-mediated allergy	Unlikely	Proven
History of potential candidates	Vague, often occurring in childhood with no objective documentation	Clear IgE-mediated allergic event, including hives, angioedema, anaphylaxis
Reasons to perform	To disprove hypersensitivity	No other antibiotic alternatives
Goal	To confirm ability to receive penicillin	To generate temporary tolerance
Contraindications ^a	Concurrent illness, suspect true IgE allergy	Uncontrolled asthma, concurrent illness, hemodynamic instability, contraindicated drugs e.g. beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, history of anaphylaxis
Absolute contraindications	Non-IgE-mediated immune related event (e.g., SJS, TEN, DIHS, DRESS, DIL)	Non-IgE-mediated immunologic event (e.g., SJS, TEN, DIHS, DRESS, DIL)
Risk of allergic reaction	Low	Variable
Starting dose	1:100 of therapeutic dose	1:1,000,000 or 1:100,000 of therapeutic dose
Steps to complete test	3–5	10–20
Interval between steps	20–30 min	15–20 min
Time taken to complete test	1–3 h	2–6 h
Location	Clinic or inpatient	Inpatient, Emergency Department or Intensive care unit
IV Access	Usually not necessary	Usually indicated
Emergency equipment	Available	Available
Effect on immune system	None	Generation of tolerant state
Mechanism	Not applicable	Unknown, but may involve mast cell and basophil sensitivity and involvement of regulatory factors and cells
Disposition	Able to treat patient	Continue administration of penicillin during treatment phase
Sustainability	Yes, once allergy has been disproven, drug can be given in future	Desensitization is usually temporary, for some drugs, e.g. penicillin or aspirin, ongoing administration may be needed to maintain tolerance

SJS Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis, *DIHS* drug-induced hypersensitivity syndromes, *DRESS* drug reaction with eosinophilia and systemic symptoms, *DIL* drug-induced lupus erythematosus

^a These are relative contraindications; in all cases, the risk–benefit ratio of various treatment options should be evaluated

Penicillin desensitization carries a risk of anaphylaxis and death. After obtaining informed consent, desensitization should only be performed in a closely monitored setting by a physician experienced in the recognition and treatment of anaphylaxis. Before initiating desensitization, it is important to document the absolute need for penicillin and the lack of an acceptable alternative. Epinephrine, antihistamine, normal saline, and oxygen should be made readily available. If the patient is taking a beta blocker, it should be discontinued since it can complicate the treatment of anaphylaxis. The oral route for desensitization is preferred since it carries a lower risk of anaphylaxis as compared to the intravenous route. The typical starting dose is in micrograms and the dose is doubled every 15–30 min until a full therapeutic dose is reached. Both oral and intravenous desensitization protocols have been established and are readily available in the literature [5]. A sample protocol is illustrated in Table 7.

The patient should be monitored closely throughout the procedure. Antihistamines may be administered for urticarial reactions and inhaled beta agonist may be needed for

bronchospasm. If mild reaction occurs (flushing, urticaria), the procedure can be stepped back to the last tolerated dose. If a severe reaction occurs (hypotension, severe bronchospasm), the procedure should be aborted. Long-term desensitization may be maintained with chronic twice daily dosing of penicillin. If the maintenance dose is discontinued and if penicillin is required again, desensitization would need to be repeated. For non-IgE-mediated reactions, good treatment options do not exist and it is best to avoid the antibiotic altogether.

The mechanism of action of penicillin desensitization is not known. Woo et al. studied four possible mechanisms for oral desensitization, including hapten inhibition, IgE consumption, mediator depletion, and mast cell desensitization [28]. Using a murine model of IgE-dependent Pen V anaphylaxis that is 100% fatal in C57BL/6 mice, they observed that during oral desensitization, mediator depletion did not occur, and Pen V-serum IgE levels did not change during oral desensitization. Moreover, the authors argued that if hapten inhibition were the mechanism by which oral desensitization occurred, then

Table 7 An oral desensitization protocol for amoxicillin

	Dose no.	Amount (mg)	Concentration (mg/ml)	Volume (ml)	Cumulative dose (mg)
	1	0.001	0.01	0.1	0.001
	2	0.01	0.01	1	0.011
	3	0.02	0.01	2	0.031
	4	0.04	0.1	0.4	0.071
	5	0.08	0.1	0.8	0.151
	6	0.15	0.1	1.5	0.301
	7	0.3	1	0.3	0.601
	8	0.6	1	0.6	1.201
	9	1.3	1	1.3	2.501
Oral doses are administered every 15 min if no reaction occurs. Resuscitation equipment must be on hand at all times. Appropriate personnel should be available at all times Adapted from protocols developed at the Division of Allergy, Asthma and Immunology of Thomas Jefferson University	10	2.5	10	0.25	5.001
	11	5	10	0.5	10.001
	12	10	10	1	20.001
	13	20	10	2	40.001
	14	40	100	0.4	80.001
	15	80	100	0.8	160.001
	16	150	100	1.5	310.001
	17	250	100	2.5	560.001

administration of large amounts of free antibiotic together with the challenge agent Pen V-BSA should lead to a markedly diminished anaphylactic reaction. This was not observed. The authors then tested the hypothesis that antigen-specific mast cell desensitization occurred during desensitization by measuring the effect of oral desensitization of penicillin V on challenge with Pen V-BSA. They found an attenuation of the increase in plasma levels of histamine and platelet-activating factor, which are markers of mast cell degranulation. An assay for active cutaneous anaphylaxis also demonstrated a diminished response after oral desensitization with Pen V. The effect was temporary, with sensitization reoccurring after 60 min, consistent with the pattern seen with desensitization in humans. How mast cells become desensitized is not clear, and other cells and regulatory compounds may be involved in the mechanism of penicillin desensitization that was not evaluated in this study. Some that have been implicated in other studies include basophils [29], the signaling molecules syk [29] and lyn [30], and signal transducer and transcription activator STAT6 [31].

Cross-Reactivity of Other Medications with Penicillin

Like penicillin, cephalosporin is derived from a fungus, in this case *Cephalosporium acremonium*. Originally isolated in 1948 in Sardinia, it was discovered that products from cultures of *C. acremonium* had activity against *Salmonella typhi*. The building block of cephalosporin antibiotics is the cephalosporin nucleus, 7-aminocephalosporanic acid, which is derived from cephalosporin C. Modification of

the side chains is necessary to induce antibiotic activity. Cephalothin was the first medication of this class and was developed in 1964 by Eli Lilly and Company. As cephalosporins are being synthesized, new generations of medications have emerged, reflecting new advances in the development and characteristics of the drugs. These are shown in Table 8.

A recent report indicates that penicillin allergy may be present in up to 25% of patients with cephalosporin allergy. Romano studied 98 patients who had severe allergic reactions to cephalosporin and found that 25 had positive serum specific IgE to penicillin or a positive penicillin skin test [32]. It was found that significant cross-reactivity was predictable by the presence of a common side chain between the cephalosporin and the penicillin. The limitations of the study in the determination of penicillin allergy that were raised included the size of the reaction used to define positivity and the issue of the clinical relevance of penicillin sensitization, as this was not evaluated [33].

Early reports suggested that there was up to a 10% cross-sensitivity between penicillin and the penicillin derivatives cephalosporins and carbapenems, due to the sharing of the beta-lactam ring [34]. However, recent studies have shown a diminishing risk for cross-allergy between penicillins and 3rd generation or later cephalosporins. The primary factor determining immunological cross-reactivity is now believed to be the similarity of the R1 side chain of first generation cephalosporins to the R side chain of penicillins, rather than the beta-lactam structure that they share [35] (see Fig. 1).

Can penicillin allergy patients be given cephalosporin? As mentioned, it does appear that third generation cephalosporins

Table 8 Generations of cephalosporins

Generation Characteristic	First generation Mostly g+ coverage, ineffective against methicillin-resistant <i>Staphylococcus aureus</i>	Second generation Better g- coverage Less g+ coverage	Third generation Broad spectrum	Fourth generation Zwitterions	Fifth generation
Examples	Cephalexin Cefazolin Cefadroxil Cefalotin Cefradine Cefapirin Cefatrizine Cefaloglycin Cefacetrile Cefaloridine	Cefaclor Cefoxitin ^b Cefuroxime Cefonicid Cefotetan Cefuzonam Cefuprozil Cefbuperazone ^b Cefminox ^b Loracarbef ^a Cefmetazole ^b	Ceftriaxone Cefotaxime Ceftizoxime Cefixime Cefdinir Cefpodoxime Cefperazone Ceftazidime Ceftibuten Cefovecin Cefcapene Cefditoren Cefodizime Ceftiofur Ceftiolene Cefteram Cefetamet Cefdaloxime Latamoxef ^c	Cefepime Cefclidine Cefpirome Cefquinome Cefoselis Cefluprenam Flomoxef ^c	Ceftaroline Ceftobiprole

^a A carbacepham^b A cephamycin^c A oxacephem**Table 9** An example of a desensitization protocol for ceftriaxone

	Dose no	Amount	Concentration (mg/ml)	Volume (ml)	Cumulative dose
	1	20 µg	0.01	2	20 µg
	2	40 µg	0.01	4	60 µg
	3	80 µg	0.01	8	140 µg
	4	160 µg	0.1	1.6	300 µg
	5	320 µg	0.1	3.2	620 µg
	6	640 µg	0.1	6.4	1,260 µg
	7	1,250 µg	1	1.25	2,510 µg
	8	2,500 µg	1	2.5	5,010 µg (5 mg)
	9	5,000 µg (5 mg)	1	5	10 mg
IV desensitization protocol is performed in the intensive care unit. Doses are administered 15 min apart if no reaction occurs. Resuscitation equipment on hand at all times	10	10 mg	10	1	20 mg
	11	20 mg	10	2	40 mg
	12	40 mg	10	4	80 mg
	13	80 mg	10	8	160 mg
	14	150 mg	100	1.5	310 mg
Adapted from protocols developed at the Division of Allergy, Asthma and Immunology of Thomas Jefferson University	15	300 mg	100	3	610 mg
	16	600 mg	100	6	1,210 mg
	17	600 mg	100	6	1,810 mg

demonstrate significantly a lower incidence of cross-reactivity than the earlier drugs. Since only about 2–4% of patients with a history of penicillin allergy test positive to penicillin, the likelihood of cephalosporin allergy in a patient with only a history of penicillin allergy is very small. Adding a negative skin test makes that probability even smaller. In a penicillin allergic patient, there are four possible management options for the administration of cephalosporins. The first is to just go ahead and to administer cephalosporin without any testing, given the fact that the incidence of cross-reactivity is low. In most cases, this would not lead to a serious adverse reaction, but the chance for one is always present. The second course of action would be to skin test to penicillin, and if negative, to go ahead and administer a cephalosporin. This is probably the most widely accepted management strategy as it brings the likelihood of a cephalosporin reaction down to an extremely low level. The third way to manage this patient is by skin testing to the cephalosporin and to follow this with a graded challenge. If the skin test is negative and the patient passes his challenge, then the cephalosporin can be administered safely. Finally, an option is to avoid all cephalosporins altogether, regardless of penicillin skin testing results. This is the safest when it comes to addressing a cephalosporin allergy, but the caveat to this approach is that many times this will lead to use of an antibiotic with an inferior safety profile to the original cephalosporin. It is also important to note that not all cephalosporins are equal, and depending on the similarities of the side chain, cross-reactivity may or may not be present within certain members of this group of medications. [36]

Testing and Desensitization to Non-Penicillin Antibiotics

Desensitization protocols for cephalosporins have been developed and are available in the literature. Desensitization to cephalosporins should be done with non-irritating concentrations of the drug. Non-irritating concentrations for cephalosporins and other antibiotics are available elsewhere, as are a number of desensitization protocols [37]. An example of a desensitization regimen for cephalosporins is shown in Table 9, however, the mechanism of desensitization to cephalosporins is unknown, and there are no standardized protocols available for these procedures.

Conclusion

Management of patients with a history of adverse drug reaction to penicillin is often complicated by unreliable history and multiple drug hypersensitivities. A detailed history and proper documentation of the specific adverse reaction may assist in determining future management. Most patients who present with a history of a prior reaction to penicillin are

not found to be allergic to penicillin upon skin testing. If the skin test is negative to both major and minor determinants, penicillin may be administered and the risk of developing an allergic reaction is not higher than that of the general population. If the skin test is positive, penicillin should be avoided and an alternate antibiotic should be used. If, however, an alternate antibiotic is not acceptable, then desensitization may be performed. Tolerance resulting from a drug desensitization is usually temporary, and repeat use of the drug necessitates repeated desensitization. The mechanism for penicillin desensitization is unclear. Desensitization should only be done for IgE-mediated Type I hypersensitivity reactions. Stevens–Johnson syndrome and toxic epidermal necrolysis are absolute contraindications to desensitization to penicillin. Other reactions to penicillin may include fixed drug eruptions, immune complex disorders, and contact allergy.

Cross-reacting antibiotics include the cephalosporins and carbapenems. Monobactams do not cross react with penicillin. The reported incidence of cross-reactivity between cephalosporins and penicillin has been variable, and newer cephalosporins tend not to be as cross-reactive. Reports of allergy to clavulanic acid have been reported. Skin testing to cephalosporins should be done with non-irritating concentrations of the drug. Desensitization protocols for cephalosporins are available in the literature, but none are standardized.

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