

Antibiotic Selection in the Penicillin-Allergic Patient

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Many individuals with an infectious disease have a history of penicillin allergy. When a patient says that he or she is allergic to penicillin, the physician should clarify the nature of the penicillin allergy. Many patients do not, in fact, have a true penicillin allergy but rather an adverse effect to the medication, such as gastrointestinal intolerance, which is not related to drug allergy. The spectrum of penicillin allergy ranges from drug fever to anaphylactic reactions. After the nature of the penicillin allergy is determined, the clinician then selects an antimicrobial appropriate for the infectious disease being treated, while taking into account the patient's allergy history. In clinical practice, it is rarely if ever necessary to do skin testing for a penicillin allergy. Because so many antibiotics have no cross-allergenicity to penicillin, clinicians can almost always select an appropriate and safe antimicrobial for the penicillin-allergic patient. Skin testing for penicillin allergy and desensitization are rarely necessary in the hospital or outpatient setting [1–6].

Multiple drug hypersensitivity reactions are stereotyped in nature. In penicillin-allergic patients who develop a maculopapular rash to penicillins, the penicillin allergy has the same clinical manifestation on rechallenge. Re-exposure to penicillin will not result in a rash, hives, or anaphylaxis. This principle is important in selecting antimicrobial therapy in the penicillin-allergic patient. Clinicians can take comfort in being able to predict the type of penicillin reaction if a patient, upon re-exposure to the drug, has a hypersensitivity reaction. Physicians unaware of this fact usually are concerned that patients with a rash may develop hives or anaphylaxis. This is not the case. Hypersensitivity drug reactions are stereotyped and there is no progression of severity with repeated exposure. If the nature of the

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penicillin allergy is known, the nature of potential subsequent exposures can be accurately predicted [3,7–10].

Determining the nature of the penicillin allergy

Many patients report a history in childhood to penicillin allergy in a way that is difficult to interpret. Others report that relatives have a penicillin allergy and therefore they think that they may be allergic to penicillin as well. In both of these situations, the probability of penicillin allergy is low and certainly is not anaphylactoid in nature. In clinical practice, the three main categories of clinical expression of penicillin allergy are drug fever, drug rash, and anaphylactic reactions [1,3,5,6,8–10].

Drug fever

Drug fever refers to hypersensitivity reaction to any medication, including antimicrobials, which is manifested clinically only by an increase in temperature. Many nonantibiotic drugs are more common causes of allergic reactions than most antibiotics, some antibiotics cause drug fevers. Drug fevers due to other medications or antibiotics are manifested clinically by increases in temperature from 100°F to over 106°F. Most drug fevers occur in the 102°F–104°F range. A clinical clue to the presence of drug fever is the “relatively good” appearance of the patient. That is, the patient does not appear to be toxemic from a bacterial infection. Drug fevers are regularly accompanied by a pulse–temperature deficit (ie, relative bradycardia). Physiologically, there is an increase in 10 beats per minute in the heart rate for every degree of temperature elevation above 98°F. This physiological relationship is an appropriate pulse–temperature response. For example, for a patient with 103°F fever, an appropriate pulse response would be a pulse of about 120 beats per minute. Alternatively, a patient with a 103°F temperature and a pulse rate of 88 beats per minute, has a pulse–temperature deficit and relative bradycardia. Relative bradycardia is an important clue to the presence of drug fever in a patient with an otherwise unexplained obscure fever. Relative bradycardia cannot be used as a diagnostic clue to the presence of drug fever if the patient is receiving β -blockers, verapamil, or diltiazem. These drugs in febrile patients do not allow an appropriate increase in pulse, and these patients have a blunted pulse response to fever. In trying to determine if relative bradycardia is present, patients on these medications, those with pacemaker-induced rhythms, and those with certain conduction abnormalities, such as Lev’s disease and Lenegre’s disease, should be excluded from consideration. In these patients, drug fever has to be diagnosed using other means [10,11].

Drug fever is a diagnosis of exclusion. It assumes that blood cultures, excluding skin contaminants obtained during venipuncture, are sterile. Patients may be ill with drug fevers, but look “inappropriately well” in terms

of infection for the degree of fever. Laboratory tests also provide clues to the possibility of a drug fever. The presence of eosinophils in the peripheral smear in a patient with otherwise unexplained fever, should suggest the possibility of a drug hypersensitivity reaction. When the patient has eosinophilia, the relationship to the fever is likely to be realized. Unfortunately, eosinophils in the peripheral smear are more common than frank eosinophilia in patients with drug fever. Another difficulty in identifying eosinophils is that they are not routinely reported in complete blood cell counts (CBCs) obtained by automated cell counters in the laboratory. Automated CBCs are relatively insensitive to eosinophils and atypical lymphocytes. If the clinician suspects drug fever, then a manual CBC should be ordered. A manual CBC identifies low numbers of eosinophils in the peripheral smear that would be missed in an automated differential white blood cell count (WBC). Atypical lymphocytes, even if present in low numbers (ie, without atypical lymphocytosis) are also clues to a drug hypersensitivity reaction in a patient with an otherwise unexplained fever. Physicians often associate atypical lymphocytes with viral infections. Indeed, most, but not all, viral infections contain atypical lymphocytes, which are also present in certain parasitic disorders, and importantly, in drug fevers. With drug fever, the number of atypical lymphocytes present in the peripheral smear is low, as in the case of eosinophils, and uncommonly reaches levels out of the normal range that would be reported. As with the eosinophils, atypical lymphocytes are best detected by manually performed WBC differential counts, which should be specifically requested when drug fever is a potential diagnosis [10–12].

Drug fevers often cause an increase in the WBC count with or without a left shift, which can mimic an infectious process. Less commonly, drug hypersensitivity reactions may also result in mild leukopenia or thrombocytopenia. Drug-induced leukopenia and thrombocytopenia are readily reversible when the drug causing a hypersensitivity reaction is discontinued. Other indirect tests indicating potential drug fever are an early and mild increase in the serum transaminases. Elevations of the aspartate aminotransferase are most common. Less common are mild elevations of the alanine aminotransferase. Serum transaminase elevations occur early and may reach levels of up to twice normal. The erythrocyte sedimentation rate (ESR) is also elevated in drug hypersensitivity reactions with fever. Few patients with drug fever have all of the laboratory abnormalities mentioned, but all patients have sufficient clues in the proper clinical setting to suggest the possibility of drug fever [10–12].

Maculopapular drug rashes

Drug rashes are drug hypersensitivity reactions manifested with cutaneous manifestations. Unless otherwise stated, drug rash implies a maculopapular eruption, not hives. Drug rashes are usually distributed about the body and are not localized. That is, they are not limited to the anterior trunk or

the extremities, for example. Drug rashes may also involve the palms and soles, particularly if part of a total body maculopapular eruption. Early in the drug eruption process, maculopapular rashes are usually not pruritic but may become pruritic over time. Rarely are drug rashes pustular or vesiculopustular. Drug rashes may or may not be accompanied by fever. The diagnosis of drug rash is straightforward, unlike that of drug fever, because of the obvious presence of a rash. The most common diagnostic error made with drug fevers is to ascribe a localized rash, almost always representing contact dermatitis, as an allergic drug rash. Therefore, to be diagnosed with drug rash, a patient must be on a sensitizing medication and have a generalized maculopapular rash or an otherwise unexplained pruritic maculopapular rash [13–16].

Hives are cutaneous manifestations of a hypersensitivity reaction. Hives are discrete raised lesions, in contrast to the generalized exanthem of a maculopapular rash. As with other hypersensitivity drug reactions, patients with a history of hives to a given agent will, when re-exposed, again manifest a hypersensitivity reaction with hives. Hives are more serious manifestations of a hypersensitivity reaction than a maculopapular rash.

Anaphylactic reactions

The most severe clinical manifestations of a drug hypersensitivity reaction are anaphylactic reactions. Anaphylaxis may be clinically manifested by laryngospasm, bronchospasm, or hypotension, and shock. Anaphylactic reactions are life threatening and occur immediately after drug exposure. Patients with drug-induced hives usually do not have any of the laboratory abnormalities associated with drug fever or maculopapular drug eruptions [3,17–18].

Penicillin cross-reactivity with β -lactams

Penicillins as a group consist of penicillin G as well as extended spectrum penicillins, which are the antipseudomonal penicillins (carbenicillin, ticarcillin, mezlocillin, azlocillin, and piperacillin) and the antistaphylococcal penicillins (dicloxacillin, oxacillin, and nafcillin). Penicillin derivatives also include ampicillin and ampicillin derivatives (amoxicillin and bacampicillin). In the general category of penicillins are also β -lactamase-inhibitor combinations, which include a penicillin derivative. Among these combinations are ampicillin-sulbactam and piperacillin-tazobactam. β -lactamase inhibitors are hypoallergenic and if a drug hypersensitivity reaction occurs with β -lactam- β -lactamase-inhibitor combinations, the offending agent is always the β -lactam component. β -lactam antibiotics are structurally similar to the penicillins. For this reason, the cross-allergenicity rate between penicillins and β -lactams are 3% to 5%. Thus, earlier studies indicated much higher cross-reactivity rates between penicillins and β -lactams, such

as cephalosporins. But the cross-reactions were not on the basis of cross-allergenicity but rather were reflective of individuals with multiple drug allergies [8–10,19–23].

Monobactams and carbapenems resemble β -lactam antibiotics but, from an allergy perspective, are unrelated. The only carbapenem with minimal potential for cross-reactivity with penicillins or β -lactams is imipenem [24,25]. Unlike other carbapenems, imipenem is combined with cilastatin and it probably is the cilastatin rather than the imipenem that is responsible for the rare cases of cross-reactivity between imipenem and β -lactams. There is no data suggesting cross-reactivity between meropenem and β -lactams, although ertapenem has been used for a shorter duration than the other carbapenems. To date, there are no reports of cross-allergenicity between β -lactams and ertapenem either. The only monobactam available for clinical use is aztreonam. As with carbapenems, there is no cross-allergenicity between monobactams and β -lactams [10,26,27].

Clinical approach to the penicillin-allergic patient

Penicillin allergy with drug fever or rash

For patients with penicillin allergy manifested by a drug fever or a maculopapular rash, the cross-reactivity with β -lactams is 3% to 5%, which is so low that β -lactams may be safely given in penicillin-allergic patients with either a drug fever or a maculopapular rash. β -lactams should not be given to patients with a history of penicillin allergy manifested by hives or anaphylaxis [10,18,28–30].

Penicillin allergy with hives or anaphylaxis

Antibiotics that have no cross-reactivity with penicillins or β -lactams should be used to treat infections in penicillin-allergic patients with serious systemic manifestations of drug allergenicity. Antibiotics that have no cross-allergenicity to either penicillin or β -lactams include aminoglycosides, tetracyclines, macrolides, clindamycin, chloramphenicol, metronidazole, vancomycin, quinupristin–dalfopristin, linezolid, daptomycin, tigecycline, quinolones, nitrofurantoin, monobactams, and carbapenems (eg, meropenem and ertapenem) (Table 1). Antibiotic selection depends on the severity of infection, route of administration, and a spectrum appropriate for the presumed pathogen, which is determined by the site of infection. In a group of patients with penicillin allergy, meropenem was given as appropriate therapy for the infection in those with a stated but unknown history of penicillin allergy and those with known anaphylactic reactions to penicillins or β -lactams. No patient receiving meropenem for 1 to 4 weeks had any allergic reaction. Significantly, no cross-allergenicity occurred in the penicillin anaphylactic group when treated with meropenem [31].

Table 1
Antibiotic alternatives in penicillin-allergic patients

Type of penicillin allergy	Alternative non-β-lactam antibiotics
Anaphylactic reaction or hives (hives, laryngospasm, bronchospasm, hypotension, shock)	Aminoglycosides (IV) Clindamycin (IV, PO) Macrolides (PO) Linezolid (IV, PO) TMP-SMX (IV, PO) Vancomycin (IV) Quinupristin-dalfopristin (IV) Colistin (IV) Polymyxin B (IV) Quinolones (IV, PO) Chloramphenicol (IV) Minocycline (IV, PO) Doxycycline (IV, PO) Aztreonam (IV) Meropenem (IV) Ertapenem (IV) Tigecycline (IV) Daptomycin (IV)
Drug fever (fever without rash) or drug rash (maculopapular rash, generalized)	β-Lactam antibiotic therapy or any of the non-β-lactam antibiotics listed

Abbreviations: IV, intravenous; PO, oral; TMP-SMX, trimethoprim-sulfamethoxazole.

Summary

Because of the numerous oral and parenteral antibiotics now available, clinicians can almost always find a suitable antibiotic that does not cross-react with penicillins or penicillin derivatives. Skin testing for penicillin allergy is rarely necessary because of the many therapeutic alternatives available [10,31]. In the rare instance of the need for penicillin desensitization, such as in the case of a pregnant patient with neurosyphilis and an anaphylactic reaction to penicillin, such desensitization should be done by an allergist or immunologist [32–34]. After 30 years of infectious disease practice, the author has never found it necessary to desensitize a patient because of a lack of an alternative medication for the clinical situation [10,31]. Most patients who give a history of penicillin allergy do not in fact have an allergy to penicillin, and skin testing is not always predictive of penicillin allergy [5,6,34]. To determine the nature of the penicillin allergy, if indeed it is present, the clinician must inquire for details regarding the nature of the penicillin allergy. This determination is important because patients with penicillin allergies manifested by drug fever or rash may safely be given β-lactam antibiotics, such as cephalosporins. In the worst-case scenario, if there is a reaction in 3% to 5% of patients that exhibit true cross-allergenicity to

penicillin, then the patient will experience the same reaction (eg, drug fever or rash) that was experienced previously. Both drug fevers and drug rashes are recognizable clinical entities and readily reversible upon early discontinuation of the antibiotic. For patients with hives or an anaphylactic reaction to penicillin, then neither penicillins nor β -lactams should be used. An antibiotic with no cross-allergenicity with penicillins or β -lactams should be selected. That is, aminoglycosides, tetracyclines, fluoroquinolones, vancomycin, tigecycline, linezolid, daptomycin, and carbapenems, particularly meropenem, may be given safely in penicillin allergies, including anaphylactic reactions, with virtually no potential for an allergic reaction [10,27,31].

Clinicians should be familiar with which antibiotics are safe to use for different types of penicillin-allergic reactions. Clinically, it is convenient to divide patients with penicillin reactions into three categories: those with unknown or possible reactions to penicillin, those with a drug fever or rash, and those with hives or anaphylactic reactions. β -lactam antibiotics may be used safely for patients with drug fever or rash. Penicillins or β -lactams should not be used for patients with hives or anaphylactic reactions. For such patients, clinicians should employ antimicrobial therapy with an antibiotic that does not cross-react with penicillins or β -lactams.

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