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Penicillin Allergy Is Not Necessarily Forever

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Audio (20:21) Penicillin Allergy—It's Less Common Than You Think

Penicillin allergy is often diagnosed early in life, and the history of penicillin allergy persists in a patient's medical record for many years without verification. Some physicians' consideration of a patient having penicillin allergy is based on patient experience that may have occurred early in childhood. This results in the use of alternate antibiotics that are less effective, more toxic and expensive, and that have inappropriately broader coverage than penicillin.[1] Accumulating evidence suggests that excessive use of unnecessarily broad-spectrum antibiotics increases the risk of antibiotic resistance, including *Clostridium difficile* infection.[2] The inability to use an antistaphylococcal penicillin (eg, nafcillin) for patients with methicillin-susceptible *Staphylococcus aureus* sepsis or other serious infections for which penicillins are the first-line therapy (eg, ampicillin for *Enterococcus faecalis* or benzathine penicillin for syphilis) places patients at risk of treatment failure, resistance generation, and increased mortality.

Most patients who have a history of penicillin allergy are not really allergic to penicillin. Approximately 10% of all patients in the United States carry a label of penicillin allergy,[2] yet less than 10% of those with penicillin allergy histories who are tested in specialized allergy clinics are found to be at risk for acute allergy to penicillins.[3] True pencillin allergy is somewhat rare since only 1% of the general population is actually allergic to penicillin. False attribution of penicillin allergy might occur because viral rashes in children may be mistaken for penicillin allergy when these children are unnecessarily given antibiotics for a viral syndrome. Patients may have had a documented acute penicillin reaction caused by allergic (IgE) antibodies, but those antibodies decline and can disappear with time, resulting in most patients becoming skin-test negative after a decade. Individuals who have lost skin

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test reactivity to penicillins are at negligible risk of becoming resensitized when exposed to penicillin or other β-lactam antibiotics in the future.[4] Most allergy and immunology specialists can provide skin testing and challenge procedures for individuals with a history of penicillin allergy.

Penicillin desensitization, which involves administration of increasing incremental doses of penicillin performed under close clinical monitoring, can delay initiation of appropriate therapy and should be used discriminately in high-risk patients with recent histories of immediate reactions to penicillin or patients who test positive to a penicillin skin test. Desensitization often takes place in a high-acuity setting, requires specialty pharmacy services, must be repeated every time a patient needs the allergic drug in question, and ultimately does not establish if a patient is truly allergic to penicillin. Since more than 90% of those who undergo penicillin skin testing and oral challenge can tolerate penicillin, ideally penicillin desensitization should be reserved for those who are penicillin skin-test positive or have a history suggestive of IgE-mediated penicillin allergy and an urgent need for treatment that precludes prior testing.[1]

When penicillin-allergic patients were challenged with cephalosporins, less than 5% demonstrated cross-reactivity.[8] For third- and later-generation cephalosporins, penicillin-cephalosporin cross-reactivity was less than 2%.[5] The shared R1 group of β-lactam antibiotics, in particular for aminopenicillins (amoxicillin, ampicillin) and aminocephalosporins (cephalexin, cefaclor, cefadroxil, ceprozil), was shown in pharmacoepidemiology studies to be important for cross-reactivity. Newer protocols recommend avoiding retreatment with another β-lactam with the same R1 side chain as the original penicillin to which the patient was allergic.[5] However, this practice does not eliminate the possibility of cephalosporin cross-reactivity. Skin testing and provocational dosing with candidate cephalosporins may still be warranted. The carbapenem and monobactam β-lactam antibiotics only occasionally have cross-reactivity, precluding the need for allergy evaluations in most cases.[6] In view of these very low rates of cross-reactivity, even patients with true IgE-mediated penicillin allergy may receive a β-lactam antibiotic,[6] appropriate for the infection being treated, rather than use alternative restricted antibiotics (eg, cefazolin for invasive methicillin-susceptible *S aureus* infections or cefepime for febrile neutropenia) that are associated with inappropriate prescribing and antimicrobial resistance through low or incremental observed challenge of the alternative β-lactam.[7]

IgE-dependent acute allergic reactions, including anaphylaxis, are the principal hypersensitivity reactions precluding readministration of β-lactam antibiotics to patients who have had prior allergic reactions. Late-onset T-cell–mediated delayed mild to moderate exanthems occur in 2% to 12% of β-lactam antibiotic courses.[8] These reactions can usually be treated symptomatically and resolve without sequelae. In most cases, a history of this type of uncomplicated rash should not be a contraindication to using β-lactam antibiotics again, especially if it is another member of the β-lactam family.

Delayed-reading skin tests, multiple oral-dose challenge, or both can predict rash recurrence when readministering these antibiotics, but this approach has not been widely adopted in the United States. The specific β-lactam cross-reactivity patterns for severe and life-threatening

delayed adverse drug reactions (ADRs), such as drug rash with fever, severe rash with mucosal involvement to suggest the possibility of Stevens-Johnson syndrome/toxic epidermal necrolysis, or organ involvement (eg, hepatitis, nephritis) are not well understood. When these reactions have occurred, readministration of β-lactam antibiotics is not advisable. Many severe T-cell–mediated ADRs occur by noncovalent and dose-dependent interactions with known HLA risk alleles. This has facilitated pretreatment screening strategies in some instances such as HLA-B*57:01 for abacavir hypersensitivity.[9]

For penicillins, HLA markers have been defined for flucloxacillin- (HLA-B*57:01) and amoxicillin-clavulanate (HLA-DRB1*15:01)–associated hepatitis. However, the low positive predictive value (<1%) of the respective HLA risk alleles for these diseases results in a high number needed to test to prevent 1 case (>10000), making HLA screening impractical.

Incorporation of standardized procedures for accurate classification and reconciliation of the correct penicillin allergy phenotype into the electronic health record (EHR) is important to ensure that the highest-quality information about drug allergies is documented. Accuracy can be optimized by prospective documentation of an ADR at the time of the reaction. If this information is included in the EHR, it can, in theory, be communicated across different EHR platforms to various community pharmacies and to treating clinicians. Accurate allergic reaction information in the EHR could suggest that a drug may not have to be avoided in the future or, in contrast, could help ensure the drug is not administered to patients at risk for a serious ADR such as Stevens-Johnson syndrome/toxic epidermal necrolysis.

An accurate medical history combined with validated penicillin skin test results and oral challenge of penicillin can identify patients who can safely receive penicillin and other β-lactams antibiotics. A clearly documented nonallergic antibiotic ADR history (nausea, vomiting, diarrhea) should be removed from the allergy record and patients counseled regarding the true nature of their ADR. Many patients are not aware of the details of their original remote reaction to penicillin. Because of the long time that usually has elapsed, these patients have a low risk for an allergic reaction to penicillin. A study of patients with a remote or uncertain history of penicillin allergy have shown that they have positive penicillin skin testing rates (1.7%) similar to patients without a history of pencillin allergy (1.7%).[3] Ideally all patients who are being denied β-lactam antibiotics because of their prior history of penicillin allergy should be referred for testing. Although penicillin skin testing combined with oral challenge is safe and effectively removes risk of an immediate reaction to penicillin from the vast majority of patients, this may be difficult to implement because of the absence of readily available specialty testing services.[10] The use of antibiotics for low acuity community-acquired and viral infections should be discouraged. High-risk patients and those with underlying comorbidities that put them at risk for more frequent antibiotic use should be prioritized for penicillin allergy testing by a specialty service.[10]

The large numbers of patients reporting a penicillin allergy history make it important to incorporate penicillin allergy management into antimicrobial stewardship programs. Clinicians often have patients with a remote, persistent history of penicillin allergy that has never been verified but influences antibiotic selection. In hospital settings, penicillin allergy

history is associated with greater risk for prolonged length of stay, readmissions, and acquisition of multidrug-resistant organisms.[2]

In January 2017, the Joint Commission in the United States mandated that all hospitals have an antibiotic stewardship program aimed at reducing the emergence of antimicrobial resistance. The Infectious Diseases Society of America antimicrobial stewardship program guideline states that penicillin allergy assessment and testing could aid the use of appropriate first-line antibiotic therapy. Inpatient and outpatient penicillin testing programs are now being implemented to improve antibiotic prescribing and antibiotic appropriateness. Systematic reconciliation of the ADR history with penicillin allergy testing tools provides a further mechanism to advance antibiotic appropriateness. In addition, effectiveness measures need to be in place to ensure that revised penicillin allergy information is maintained across all aspects of the EHR and pharmacy record.[1]

Careful assessment of a patient's history of antibiotic allergy, combined with testing strategies, will result in very few of the estimated 25 million to 30 million US residents labeled as allergic to penicillin to not receive penicillins or other β-lactam antibiotics when those drugs are indicated.

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