Evaluation and Management of Penicillin Allergy

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) discuss key aspects of the clinical history when evaluating penicillin allergy; (2) describe testing for penicillin allergy; and (3) discuss management options for penicillin allergy on the basis of allergy testing results.

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Abstract

Penicillin allergy is the most commonly reported drug allergy in the United States. Although penicillin allergy is widely reported, 80% to 90% of individuals with self-reported penicillin allergy are actually able to tolerate penicillins after undergoing evaluation for penicillin allergy. Because most patients with self-reported penicillin allergy will have subsequent negative allergy testing results and tolerate penicillins, they may be unnecessarily exposed to broader-spectrum antibiotics. Use of such antibiotics leads to increased risks of developing antibiotic-resistant microorganisms and incur higher health care utilization costs. In this article, we provide an overview of penicillin allergy and its clinical manifestations as well as an approach for the evaluation and management of penicillin allergy.

 ■ Mayo Clin Proc. 2018;93(1):101-107

Penicillin allergy is the most commonly reported drug allergy in the United States.[1] Clinical decisions regarding its evaluation and management markedly affect both individual patient care and public health. The prevalence of self-reported penicillin allergy is approximately 8% of the general population and nearly 10% of hospitalized patients.[1,2] Remarkably, although penicillin allergy is commonly reported, several studies found that 80% to 90% of individuals with self-reported penicillin allergy are actually able to tolerate penicillins after undergoing evaluation for penicillin allergy. Thus, most patients who report penicillin allergy are unnecessarily avoiding penicillin class antibiotics because either their penicillin allergy waned over time or previous reactions should not have been attributed to penicillin.[3]

Penicillins represent the most commonly prescribed antibiotic class in the United States and worldwide.[4,5] Although the prompt use of antibiotics to treat infections has proven to reduce morbidity and mortality, decisions regarding antibiotic selection must be made judiciously. Currently, most health care providers avoid prescribing penicillin or related β-lactam antibiotics in patients with self-reported penicillin allergies. However, using alternative antibiotics without further evaluation of self-reported penicillin allergy has considerable ramifications, especially for costs and antibiotic resistance.

Antibiotic costs are 63% to 158% higher for those with reported penicillin allergy than for those not allergic to penicillin. Moreover, patients labeled as penicillin allergic have significantly longer hospitalizations with associated increased costs.[6-9] In one specific health care system, evaluation of penicillin allergy with testing and consultation resulted in savings exceeding $2 million over a 3.6-year time period.[10]

Not only does self-reported penicillin allergy lead to significantly increased costs, but it may also contribute to the threat of drug-resistant microorganisms. Commonly used alternatives to penicillin, such as vancomycin, clindamycin, and fluoroquinolones, are clearly associated with the development of resistant organisms such as vancomycin-resistant *Enterococcus* and increased rates of *Clostridium difficile*. The Center for Disease Control and Prevention[11] recently estimated that more than 2 million people have infections with antibiotic-resistant microorganisms each year, resulting in 23,000 deaths annually.

Because most patients with self-reported penicillin allergy will have subsequent negative allergy testing results and tolerate penicillins, they may be unnecessarily exposed to broader-spectrum antibiotics. Use of such antibiotics leads to increased risks of developing antibiotic-resistant microorganisms and incur higher health care utilization costs. Therefore, penicillin allergy evaluation and management should be a key component of antibiotic stewardship and can significantly improve health care quality and value for individual patients and health care systems as well as the public at large.

CLASSIFICATIONS AND CLINICAL MANIFESTATIONS OF PENICILLIN ALLERGY

Adverse drug reactions are defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at standard doses used in humans for prophylaxis, diagnosis, or treatment.[12] Drug allergies encompass adverse reactions that have an immunological pathogenesis and are typically dose independent and unpredictable. Immune mechanisms in drug allergic reactions involve antibodies and/or activated T lymphocytes directed against the specific drugs or their metabolites. Drugs are capable of inducing all the pathophysiological mechanisms as described by the traditional Gell and Coombs classification system of hypersensitivity, but the most common reactions are IgE and T-cell mediated.[13]

Clinically, penicillin and other drug allergic reactions may be classified as immediate or nonimmediate/delayed depending on the onset of signs and symptoms during treatment. Immediate drug allergic reactions are typically IgE mediated and occur within minutes to hours after the last drug administration. Symptoms of immediate reactions include urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, or anaphylaxis and anaphylactic shock. In contrast, nonimmediate/delayed-onset drug allergic reactions usually occur days to weeks after drug administration and are associated with a T-cell—dependent immune mechanism. Most delayed-onset reactions are uncomplicated cutaneous manifestations such as maculopapular exanthemas and delayed urticaria. However, delayed-onset reactions also include severe reactions that may be life-threatening, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms syndrome.[13]

APPLICABILITY OF CLINICAL HISTORY WHEN EVALUATING PENICILLIN ALLERGY

A comprehensive history is an essential element of penicillin allergy evaluation (Table). The clinical history provides information that can influence decisions such as choice of diagnostic testing, recommendations after allergy testing is completed, and safety regarding reintroduction of penicillin or similar-type antibiotics. Specific questions that are particularly important include the following[14]:

Mayo Clin Proc. ■ January 2018;93(1):101-107 ■ https://doi.org/10.1016/j.mayocp.2017.09.020
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TABLE. Essential Clinical History Questions for Penicillin Allergy

• What were the signs, symptoms, and timing of the adverse drug reaction?
• Were other medications used concurrently at the time of the adverse drug reaction?
• Had the same or a similar medication been used before the reported adverse drug reaction?
• Has the same or a similar medication been used since the previous adverse drug reaction?
• Why was penicillin or a related antibiotic prescribed?
• Have symptoms similar to the adverse drug reaction occurred in the absence of medication therapy?
• Has the medical record been reviewed for documentation of penicillin allergy and antibiotic use?

- *What were the signs and symptoms of the adverse drug reaction and when did they occur?* Signs and symptoms consistent with IgE-mediated reactions may corroborate that an allergic reaction had occurred. Symptoms that are more likely non-IgE mediated, such as dyspepsia, diarrhea, or headache, may raise the question whether a previous reaction should have been attributed to penicillin allergy. Penicillin allergy tends to wane over time, so individuals experiencing reactions years ago may have a greater likelihood of being nonallergic.
- *What was the time course of the adverse drug reaction?* Symptoms occurring either during or immediately after a treatment course would be consistent with an IgE-mediated allergic reaction. Delayed-onset reactions occurring well after a treatment course is completed would be expected to have negative penicillin allergy skin testing results.
- *Were other medications used concurrently at the time of the adverse drug reaction?* Although penicillin and other antibiotics are frequent causes of drug reactions, other medications such as nonsteroidal anti-inflammatory drugs or opiates may cause similar symptoms.
- *Had the same or a similar medication been used before the reported adverse drug reaction?* Classically, IgE-mediated drug allergic reactions require previous exposures during which allergic sensitization occurs. After this period of sensitization, reexposure to the drug may elicit an allergic reaction.
- *Has the same or a similar medication been used since the previous adverse drug reaction?* If individuals have tolerated the reintroduction of penicillin or a related antibiotic, their allergy may have waned over time. Repeated reactions to the same or similar medications suggest ongoing allergy.
- *Why was penicillin or a related antibiotic prescribed?* Signs and symptoms that were attributed to an adverse drug reaction may have been due to the underlying condition being treated. For example, streptococcal pharyngitis may cause a rash unto itself, no matter that penicillin was used as therapy.
- *Have symptoms similar to the adverse drug reaction occurred in the absence of medication therapy?* In some instances, chronic idiopathic urticaria may mimic aspects of drug allergic reactions.
- *Has the medical record been reviewed for documentation of penicillin allergy and antibiotic use?* Individuals may not recall specific details of their previous reactions or whether penicillin was actually the antibiotic used with previous reactions. They may also not realize that penicillin or a related antibiotic has been used since their initial reaction.

Although obtaining a thorough clinical history clearly aids decisions regarding options for diagnostic testing, the reaction history alone cannot accurately diagnose or exclude penicillin allergy. A large review found that about one-third of individuals with positive penicillin allergy skin testing results had vague histories such as nonpruritic maculopapular rashes, isolated gastrointestinal symptoms, or simply unknown details of the previous reaction.[15] For patients with histories consistent with IgE-mediated—type symptoms, subsequent negative evaluation results may be due to multiple reasons including the following: (1) specific IgE antibodies to penicillin may wane over time; (2) penicillin was misidentified as the antibiotic used during the previous reaction; (3) previous symptoms were caused by an underlying illness rather than penicillin; or (4) previous reactions were the result of interactions between an underlying infection and the antibiotic.[3] Thus, individuals with either consistent or vague histories concerning penicillin allergy should be considered for penicillin skin testing before the use of penicillins.

PENICILLIN ALLERGY TESTING

Penicillin is chemically inert in its natural state and spontaneously converts to form reactive

intermediates under physiological conditions. These reactive intermediates may then bind to tissue and serum proteins, forming complexes capable of eliciting an immune response. Approximately 95% of penicillin binds in the penicilloyl form, which is known as the *major antigenic determinant*. The remaining penicillin either remains in the native state or degrades to form other derivatives referred to as *minor antigenic determinants*, of which penicilloate and penilloate figure prominently in inducing allergic reactions.[3]

Penicillin skin testing includes prick and intradermal skin testing with both the major and minor determinants of penicillin. The major determinant used for penicillin skin testing is penicilloyl-polylysine. The minor determinants of penicillin that have been used for testing include benzylpenicillin (penicillin G) and minor determinant mixtures including benzylpenicilloate, benzylpenilloate, or benzylpenicilloyl-*n*-propylamine.[16]

Penicillin skin testing should be performed only by personnel skilled and experienced in the administration and interpretation of such testing. A positive control using histamine and a negative control consisting of saline should be placed during testing. Skin prick testing is performed first, and if the results are negative, it is followed by intradermal testing. A wheal 3 mm or greater than that of the negative control for either prick or intradermal testing constitutes a positive skin testing response.[3] Penicillin skin testing is considered safe, with serious reactions because of testing being extremely rare. When undergoing stepwise skin prick and intradermal testing by appropriate personnel using proper technique, the incidence of systemic reactions to penicillin testing is considered to be less than 1%.[3,16]

When both major and minor determinants are used for penicillin allergy testing, the negative predictive value for serious immediate-type reactions is 97% to 99%.[17-19] A precise positive predictive value is unknown because penicillin is typically avoided with positive testing results owing to the possible risks of an adverse reaction to penicillin. Based on limited penicillin challenges in individuals with positive skin testing results, the positive predictive value ranges from 50% to 67%.[17,20]

Another approach involves skin testing with only the major determinant and penicillin G followed by oral challenge to amoxicillin in those with negative skin testing results. With this methodology, individuals with negative skin testing results had an oral challenge reaction rate of 1%. These reactions typically involved urticaria only, although epinephrine was required to treat the reaction in rare instances.[21] Recent studies have explored the utility and safety of direct oral challenges in low-risk individuals, with a limited role of penicillin skin testing. These studies suggest a possible role for direct oral challenges without preceding penicillin skin testing in certain patient populations.[22-24] However, each of these studies were single-center experiences with limited numbers of patients, and thus these practices are not yet considered standard of care.

In vitro testing for the detection of specific IgE antibodies to penicilloyl-polylysine, penicillin G, penicillin V, amoxicillin, and ampicillin is commercially available. However, such testing is not considered an adequate alternative to allergy skin testing because of their unknown predictive value. The sensitivity of in vitro testing has been reported as low as 45% as compared with that of skin testing. Although a positive in vitro specific IgE to penicillin testing result in the appropriate clinical context suggests the presence of an IgE-mediated penicillin allergy, a negative in vitro testing result does not exclude penicillin allergy. Thus, penicillin skin testing is the most reliable method for the evaluation of penicillin allergy.[3]

MANAGEMENT OF PENICILLIN ALLERGY

For patients with a history of an adverse reaction to penicillin that is consistent with an IgE-mediated allergic reaction, penicillin testing with major and minor determinants is recommended. The results of penicillin skin testing are only predictive of IgE-mediated reactions to penicillin. Penicillin testing offers no predictive value for non—IgE-mediated events such as serum sickness, interstitial nephritis, or thrombocytopenia or for more severe non—IgE-mediated reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms. A history of severe non—IgE-mediated reactions related to penicillin use requires strict avoidance of penicillins.[3,16,25]

Mayo Clin Proc. ■ January 2018;93(1):101-107 ■ https://doi.org/10.1016/j.mayocp.2017.09.020
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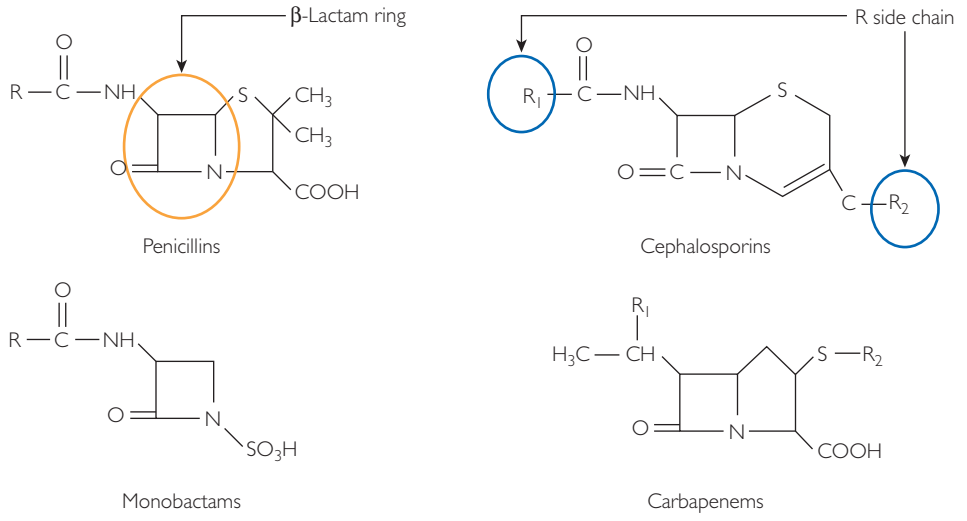

FIGURE. Chemical structures of penicillins and other β-lactam antibiotics.

When the penicillin skin testing result is negative, a patient has a low risk of having an immediate-type allergic reaction to penicillin. The negative predictive value of penicillin skin testing for serious immediate-type reactions is 97% to 99%, which is essentially the baseline 1% to 3% risk of penicillin allergy in individuals with no history of allergic reaction to penicillin.[17-19] If a penicillin skin testing result is positive, then an alternative antibiotic is recommended or a penicillin desensitization procedure may be considered.[3,16]

Drug desensitization, appropriately described as temporary induction of drug tolerance, refers to a procedure by which a patient's response to a drug is modified, thereby allowing the drug to be used safely on a temporary basis. This procedure is not without risks and is indicated only when alternative medications cannot be used. In penicillin induction of drug tolerance, the initial dose of administered penicillin is typically 1/10,000 of the full therapeutic dose. Subsequently, increasing doses of penicillin are given at 15- to 30-minute intervals, with the full therapeutic dose achieved within 4 to 12 hours. Approximately one-third of patients undergoing penicillin induction of drug tolerance experience allergic reactions. Induction of drug tolerance procedures should be performed only by experienced personnel in an appropriate setting with continuous patient monitoring and the ability to readily treat any reactions, including anaphylaxis, that may occur. In addition, when induction of drug tolerance procedure is completed, the achieved drug tolerance state is temporary and is maintained only as long as the specific medication is continuously used.[3]

CROSS-REACTIVITY ISSUES WITH PENICILLIN ALLERGY (CEPHALOSPORINS, CARBAPENEMS, MONOBACTAMS)

Structurally, penicillins and cephalosporins have a 4-member β-lactam ring and may have similar R side chains. Metabolic derivatives of these structural similarities may account for allergic cross-reactivity between penicillins and cephalosporins. Structurally, monobactams and carbapenems also have a β-lactam ring that could potentially cause cross-reactivity issues in those with penicillin allergy (Figure).[26,27]

Compared with penicillins, cephalosporins have an approximately 10-fold lower overall reaction rate. Studies involving patients with a history of penicillin allergy and positive penicillin skin testing results who subsequently received cephalosporins find an overall reaction rate of 2%. Although a 2% reaction rate may be considered infrequent, anaphylactic reactions—some fatal—have occurred with cephalosporin administration in patients with penicillin allergy.[3] Consequently, penicillin allergy testing

should be considered in patients reporting penicillin allergy before the administration of cephalosporins, as most patients with negative penicillin testing results may receive all β-lactams safely. Alternatively, in the absence of a severe or recent penicillin allergy reaction, cephalosporins may be given directly with a reaction rate of approximately 1% within 24 hours. However, this alternative management strategy is controversial because the reactions that do occur may be anaphylactic in nature. Patients with positive penicillin testing results who require cephalosporins may undergo a graded challenge or induction of drug tolerance procedure.[3,25]

When considering carbapenems, both prospective and retrospective studies have found low cross-reactivity rates between carbapenems and penicillins, likely less than 1%.[3,27] Current practice guidelines recommend that patients with negative penicillin skin testing results may safely receive carbapenems. Patients with positive penicillin skin testing results or patients with a history of penicillin allergy who do not undergo penicillin skin testing should receive carbapenems via a graded challenge procedure.[3]

Similar to carbapenems, allergic reactions to the monobactam aztreonam are uncommon because aztreonam appears less immunogenic than both penicillins and cephalosporins. Previous testing and challenge studies have reported no cross-reactivity between either penicillins or cephalosporins and aztreonam with the exception of ceftazidime, which shares an identical R side chain with aztreonam.[3,28] Thus, patients with either penicillin or cephalosporin allergy may safely receive aztreonam, except those allergic to ceftazidime.[3]

CONCLUSION

Penicillin allergy is widely reported in the general population, thereby significantly affecting health care decisions and potentially increasing morbidity and financial burden. A comprehensive history is essential for penicillin allergy evaluation, but alone it cannot predict positive penicillin allergy skin testing results. Individuals with a history of penicillin allergy and negative penicillin testing results with both major and minor determinants have a low risk of IgE-mediated, immediate-type reactions to penicillin or cephalosporins. When penicillin skin testing results are positive, an alternative antibiotic is recommended or a penicillin desensitization procedure may be considered.

Potential Competing Interests: The authors report no competing interests.

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