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Evaluation and Management of Penicillin Allergy
A Review

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IMPORTANCE β-Lactam antibiotics are among the safest and most effective antibiotics. Many patients report allergies to these drugs that limit their use, resulting in the use of broad-spectrum antibiotics that increase the risk for antimicrobial resistance and adverse events.

OBSERVATIONS Approximately 10% of the US population has reported allergies to the β-lactam agent penicillin, with higher rates reported by older and hospitalized patients. Although many patients report that they are allergic to penicillin, clinically significant IgE-mediated or T lymphocyte–mediated penicillin hypersensitivity is uncommon (<5%). Currently, the rate of IgE-mediated penicillin allergies is decreasing, potentially due to a decreased use of parenteral penicillins, and because severe anaphylactic reactions to oral amoxicillin are rare. IgE-mediated penicillin allergy wanes over time, with 80% of patients becoming tolerant after a decade. Cross-reactivity between penicillin and cephalosporin drugs occurs in about 2% of cases, less than the 8% reported previously. Some patients have a medical history that suggests they are at a low risk for developing an allergic reaction to penicillin. Low-risk histories include patients having isolated nonallergic symptoms, such as gastrointestinal symptoms, or patients solely with a family history of a penicillin allergy, symptoms of pruritus without rash, or remote (>10 years) unknown reactions without features suggestive of an IgE-mediated reaction. A moderate-risk history includes urticaria or other pruritic rashes and reactions with features of IgE-mediated reactions. A high-risk history includes patients who have had anaphylaxis, positive penicillin skin testing, recurrent penicillin reactions, or hypersensitivities to multiple β-lactam antibiotics. The goals of antimicrobial stewardship are undermined when reported allergy to penicillin leads to the use of broad-spectrum antibiotics that increase the risk for antimicrobial resistance, including increased risk of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Broad-spectrum antimicrobial agents also increase the risk of developing *Clostridium difficile* (also known as *Clostridioides difficile*) infection. Direct amoxicillin challenge is appropriate for patients with low-risk allergy histories. Moderate-risk patients can be evaluated with penicillin skin testing, which carries a negative predictive value that exceeds 95% and approaches 100% when combined with amoxicillin challenge. Clinicians performing penicillin allergy evaluation need to identify what methods are supported by their available resources.

CONCLUSIONS AND RELEVANCE Many patients report they are allergic to penicillin but few have clinically significant reactions. Evaluation of penicillin allergy before deciding not to use penicillin or other β-lactam antibiotics is an important tool for antimicrobial stewardship.

Author Audio Interview

JAMA Patient Page page 216

Video and Supplemental content

CME Quiz at jamanetwork.com/learning

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Antibiotics are among the most commonly prescribed medications across health care settings.[1] A substantial portion of antibiotic use is inappropriate, which contributes to antimicrobial resistance and a variety of adverse outcomes, including *Clostridium difficile* infection (also known as *Clostridioides difficile*).[1-4] Expert bodies, including the World Health Organization, the Centers for Disease Control and Prevention (CDC), the President's Council of Advisors on Science and Technology, and the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria, have all recommended implementation of policies and practices to reduce inappropriate antibiotic use and have underscored the importance of such efforts for public health and patient safety. Antibiotic selection is often guided by a patient's allergy history, with an allergy to penicillin commonly reported. About 32 million people in the United States have a documented penicillin allergy.[5-7] Yet, true IgE-mediated allergies that cause anaphylaxis are uncommon. More than 95% of patients labeled as having a penicillin allergy ultimately are able to tolerate this class of drugs.[8] Most patients labeled with penicillin allergy do not undergo any evaluation to determine the accuracy or persistence of the allergy.[9,10] This review summarizes the epidemiology of, clinical consequences of, and methods for evaluating penicillin allergy and provides toolkits to facilitate these evaluations.

Methods

The American Academy of Allergy, Asthma, and Immunology (AAAAI), the Infectious Diseases Society of America (IDSA), and the Society for Healthcare Epidemiology of America (SHEA) boards appointed at least 1 society representative to form a writing group. Review of the literature included a PubMed search of English-language articles published between January 1, 2005, and September 30, 2018, using the following search terms: penicillin, β-lactam, antibiotic, hypersensitivity, adverse reaction, allergy, skin test, test dose, stewardship, clinical outcome, quality improvement, delabeling, antibiotic utilization, hospitalization, inpatient, pharmacist, surgery, emergency, oncology, nursing, and rehabilitation. Relevant AAAAI, IDSA, and SHEA guidelines and articles referenced therein were reviewed. Additional articles recommended by professional society committee and board members supplemented the literature review.

The manuscript, supplement, and toolkits underwent review by all 3 society boards. During the review process, additional committees provided input, including the AAAAI Practice and Policy Division, the IDSA Antimicrobial Resistance Committee, the SHEA Guidelines Committee, and the SHEA Antimicrobial Stewardship Committee. The final revised manuscript was approved and endorsed by the boards of all 3 societies.

Penicillin Allergy Epidemiology

Penicillin is commonly associated with hypersensitivity reactions,[5,6] most likely related to their frequent use and infection-related drug interactions, such as a patient developing a maculopapular rash from an Epstein-Barr virus infection but also given an aminopenicillin.[11] About 0.5% to 2.0% of penicillin administrations result in a reaction that could be consistent with a hypersensitivity reaction, most often a rash, but that could also be nonallergic.[12,13] Currently, the rate of IgE-mediated penicillin allergies is decreasing, potentially due to the decrease in use of parenteral penicillins.[14] Among 100 million people exposed to oral amoxicillin between 1972 and 2007 in the United Kingdom, only 1 death after anaphylaxis in association with oral amoxicillin was identified.[15]

Most reports of penicillin allergy describe an unknown or cutaneous reaction. Many patients with a reported penicillin allergy do not have any reaction characteristics documented in the electronic health record (EHR).[16] "Unknown" is a frequently documented type of reaction in EHRs in cases of allergy to penicillin (26%) with other commonly documented reactions including rash (38%), hives (18%), angioedema (9%), gastrointestinal upset (6%), anaphylaxis (5%), and itching (5%).[17] Patients presenting for penicillin allergy evaluation have similar reported reactions, with hives and rash being the most common.[18,19]

For patients whose allergy history excludes blistering rash, hemolytic anemia, nephritis, hepatitis, fever, and joint pain suggestive of organ involvement or severe cutaneous adverse reactions (SCAR) in response to penicillin, an allergy evaluation of some form is indicated. More than 95% of patients who do not have a history of serious penicillin allergy reactions are penicillin tolerant because[8] (1) the most commonly reported penicillin hypersensitivity reaction is a delayed benign rash, likely a type IV hypersensitivity reaction (eTable S1 in Supplement 1) and these reactions may or may not recur when patients are reexposed to penicillin; (2) IgE-mediated penicillin allergy wanes over time, with 80% of patients becoming tolerant after a decade[7]; and (3) many patients were never allergic, but may have had an intolerance or another cause for the symptoms they thought represented a penicillin reaction, such as a concomitant viral infection.[11,20]

Clinical Consequences

The consequences of being labeled as having a penicillin allergy include the use of alternative antibiotics that cause more treatment failures and adverse effects than β-lactams and contribute to antimicrobial resistance development.

Treatment Choice

β-Lactam agents, specifically penicillins and cephalosporins, are the treatment of choice against many pathogens that cause common diseases (**Table 1**). Often, a label of penicillin allergy alters treatment decisions resulting in suboptimal treatment. Examples of these alterations include the use of vancomycin to treat patients with methicillin-susceptible *Staphylococcus aureus* bacteremia[10] and avoidance of cephalosporins in the management of gram-negative bacteremia.[21,22] Nafcillin and cefazolin are more effective than vancomycin in treating patients with methicillin-susceptible *S aureus* infections.[23] Among *S aureus* strains that are sensitive to methicillin, up to 25% are also sensitive to penicillin. Using penicillin in cases of penicillin-susceptible *S aureus* infections may result in improved patient outcomes; however, in these cases, clinicians should consider requesting β-lactamase testing to detect penicillinase production.[24-27] Benzathine penicillin is the treatment of choice for patients with syphilis and ceftriaxone is the treatment of choice for patients with gonorrhea.[28]

Table 1. Pathogens and Common Syndromes for Which β-Lactams Are Considered the Treatment of Choice

Organism	Examples
Group A *Streptococcus*	Pharyngitis, skin and soft tissue infections (cellulitis, erysipelas, pyoderma), necrotizing fasciitis, myositis, acute rheumatic fever, acute glomerulonephritis, pneumonia, postpartum endometritis, toxic shock syndrome, bacteremia
Group B *Streptococcus*	Meningitis, puerperal sepsis
Viridans group streptococci and *Streptococcus gallolyticus* (bovis)	Endocarditis
Listeria monocytogenes	Meningitis
Actinomyces spp	Cervicofacial, pelvic, and respiratory infections
Cutibacterium acnes (formerly *Propionobacterium acnes*)	Bone and joint and central nervous system shunt infections
Staphylococcus aureus	Skin and soft tissue, bone and joint, and respiratory tract infections[a]
Pasteurella multocida	Skin and soft tissue infections, bacteremia, and respiratory tract infections
Neisseria gonorrhoeae	Urethritis, epididymitis, pharyngitis, conjunctivitis, cervicitis, proctitis, disseminated disease (septic arthritis, endocarditis)
Neisseria meningitidis	Meningitis
Treponema pallidum (syphilis)	Primary syphilis (chancre), secondary syphilis (rash, condylomata lata), tertiary syphilis (aortitis), meningitis

[a] Nafcillin and cefazolin are first-line treatment options for methicillin-susceptible *Staphylococcus aureus*. Penicillin is the first-line treatment option for penicillin-susceptible *Staphylococcus aureus*.

Antimicrobial Prophylaxis

Antimicrobial prophylaxis includes dental prophylaxis to prevent infective endocarditis in select high-risk patients.[29,30] Administration of perioperative antibiotics reduces the risk of surgical site infections (SSIs).[31,32] Amoxicillin is the recommended prophylactic agent for dental procedures in high-risk patients, and cefazolin is the recommended prophylactic agent for many surgical procedures. Non–β-lactam perioperative prophylaxis has been associated with increased risk of SSIs.[17,33,34]

Other Adverse Consequences of Antimicrobial Choice

Patients who are allergic to penicillin may be given broad-spectrum antimicrobial agents[35] that increase the risk of developing *C difficile* infection, methicillin-resistant *S aureus* (MRSA), and vancomycin-resistant enterococcus (VRE).[9,36] Replacement of broad-spectrum antibiotics with narrower-spectrum agents by performing a penicillin allergy evaluation and removing the penicillin allergy label should reduce antimicrobial resistance, although this reduction has not yet been demonstrated in clinical studies. Nevertheless, the CDC has identified evaluation of penicillin allergy history as an important tool to improve the quality of antibiotic prescribing.[37]

Penicillin allergies are associated with increased health care costs.[38] Evaluation of a penicillin allergy resulting in removing the penicillin allergy label may facilitate the use of less expensive medications, which would reduce pharmacy costs.[39-41] Although the cost of penicillin allergy evaluation is modest,[42] to date, the cost-effectiveness of penicillin allergy evaluation across patient populations has not been assessed.

Being labeled as having a penicillin allergy results in more adverse events and drug reactions[43,44] because penicillin alternatives, such as vancomycin, clindamycin, and fluoroquinolones, and other non–β-lactams alone or in combination, are used to achieve the desired spectrum of activity (**Table 2**). Vancomycin can cause nephrotoxicity and hematologic effects.[45] "Red man syndrome" is an IgE-independent reaction to vancomycin that results from direct mast cell activation. Other vancomycin reactions include morbilliform eruptions and drug rash eosinophilia and systemic symptoms (DRESS) syndrome.[46] Clindamycin and fluoroquinolones are commonly associated with *C difficile* infection.[47]

Methods for Clinical Evaluation of Reported Penicillin Allergy

Overview

Performing a comprehensive history is essential for proper evaluation of a patient with a reported penicillin allergy. The elements of this history and their interpretation, as well as the procedures to objectively assess the presence of a penicillin allergy, are shown in the toolkits in Supplement 2. In some settings, specialists (eg, allergists) are readily available to perform penicillin allergy evaluations and assist in developing protocols, pathways, and referral streams to maximize the safety and efficiency of these evaluations, especially for patients at higher risk of reaction.[35,48-50] The majority of patients with reported penicillin allergies, however, are likely to be evaluated by nonspecialists because of the high prevalence of reported penicillin allergies in the United States. There are not enough specialists to evaluate every patient with a suspected penicillin allergy, and there is evidence supporting implementation of penicillin allergy evaluations by emergency clinicians,[51] internists,[52] intensivists,[53] pharmacists,[48,54] and infectious diseases specialists,[55] as well as part of antibiotic stewardship programs.[49] In the United States, the evaluation of a penicillin allergy is reimbursed by accounting for clinician time (evaluation and management codes) and testing procedures (Current Procedural Terminology allergy testing codes CPT95018 for drug skin testing and CPT95076 for the first 2 hours of the oral drug challenge).[42,56]

Allergy History

Obtaining a precise allergy history can improve management of infectious diseases. A decision model to project clinical outcomes for patients with methicillin-susceptible *S aureus* bacteremia and reported penicillin allergy found that risk stratification based on allergy history resulted in fewer treatment failures and deaths compared with prescribing an alternative antibiotic.[44] Another study reported that including more allergy details in the EHR of patients with penicillin allergy resulted in more patients being given a β-lactam antibiotic.[16] There are no validated allergy history questionnaires or uniformly accepted risk levels to date. Allergy history tools should incorporate the time course of the reaction as well as the reaction phenotype. Toolkit A in Supplement 2 is a sample allergy history tool.

Hypersensitivity reactions to drugs are often grouped into the Gell and Coombs classification of hypersensitivity reaction types (eTable Supplement 1).[57] Although there are many types of rashes that result from infectious, environmental, and/or autoimmune triggers, familiarity with the following 3 general categories of rashes in drug allergy practice is useful for nonspecialists[35]: IgE-mediated

cutaneous reactions (eg, urticaria), benign T-lymphocyte–mediated cutaneous reactions, and SCAR (**Figure 1**).

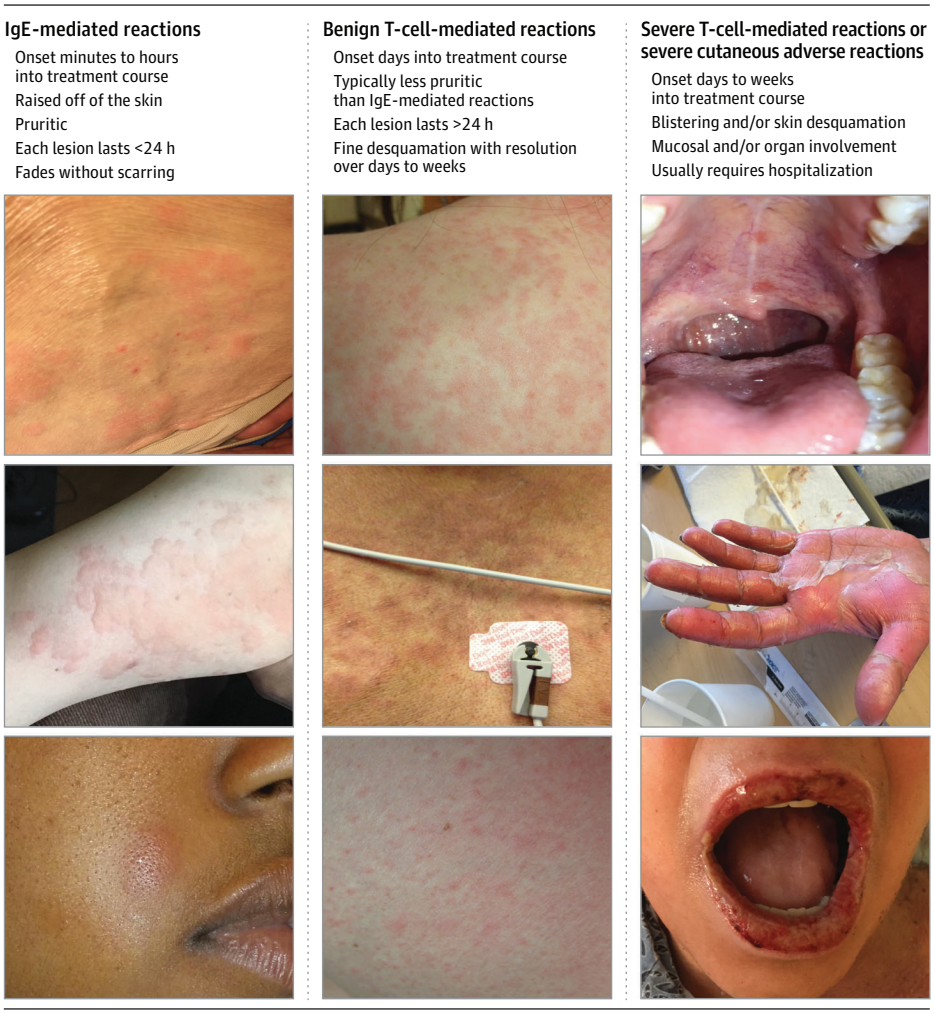
After the allergy history is determined to be inconsistent with SCAR, hemolytic anemia, an organ-specific reaction (eg, acute interstitial nephritis), drug fever, or serum sickness, patients can be stratified into low, moderate, and high risk using the allergy history (**Table 3**). Risk stratification enables previous observational studies to be applied more broadly to different patient populations and clinician groups. Based on a patient's allergy history, clinicians can decide if penicillin skin testing or drug challenges are appropriate. Although many remote and minor rashes may be considered low risk, it is often challenging to distinguish urticaria from a benign rash. Thus, considering all patients with nonsevere cutaneous eruptions as moderate-risk may be appropriate. Moreover, even in the context of a low-risk allergy history, patients with unstable or compromised hemodynamic or respiratory status and pregnant patients should be considered as having at least a moderate-risk history because of host factors that may result in poor outcomes.

Patients with a history of drug allergies are at a higher risk for reactions than patients without them.[58] The baseline risk for any reaction to β-lactam antibiotics is approximately 2.0%.[13] Patients with a history of penicillin allergy may react to a placebo during

Table 2. Commonly Used β-Lactam Agents and Alternatives

Drug Class	Common US Examples
β-Lactam	
Penicillins	Penicillin, amoxicillin ± clavulanic acid, ampicillin ± sulbactam, dicloxacillin, nafcillin, oxacillin, piperacillin/tazobactam
Cephalosporins	Cefazolin, cephalexin, cefoxitin, ceftriaxone, ceftazidime, cefpodoxime, cefepime, ceftaroline
Carbapenems	Ertapenem, imipenem, meropenem
Monobactam	Aztreonam
Non–β-lactam alternatives	
Fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin
Macrolides	Azithromycin, clarithromycin, erythromycin
Tetracyclines	Tetracycline, doxycycline, minocycline
Aminoglycosides	Gentamicin, tobramycin, amikacin
Sulfonamides	Trimethoprim-sulfamethoxazole
Glycopeptides	Vancomycin
Lipopeptides	Daptomycin
Oxazolidinones	Linezolid
Lincosamides	Clindamycin
Nitroimidazole	Metronidazole

Figure 1. Symptoms Distinguishing Groups of Cutaneous Drug Reactions



IgE-mediated reactions, benign T-lymphocyte-mediated reactions, and severe T-lymphocyte–mediated or severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms. Although benign T-cell–mediated eruptions are low-risk for rechallenge, it is often difficult to distinguish these from IgE-mediated reactions, and, therefore, considering all nonsevere cutaneous eruptions moderate risk is recommended.

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

[a] No penicillin allergy testing should be performed on patients with possible penicillin-associated severe cutaneous adverse reaction, hemolytic anemia, organ-specific reaction, drug fever, or serum sickness. Patients with unstable or compromised hemodynamic or respiratory status and pregnant patients should never be considered low risk.

[b] IgE features classically include cutaneous symptoms, such as itching, flushing, urticaria, and angioedema, but also involve respiratory system (rhinitis, wheezing, shortness of breath, bronchospasm), cardiovascular system (arrhythmia, syncope, chest tightness), and gastrointestinal system (abdominal pain, nausea, vomiting, diarrhea) symptoms.

[c] The most severe IgE-mediated reaction is anaphylaxis (eFigure 1 in Supplement 1). Allergy/immunology consultation is advised.

[d] Considering patient comfort level with trying penicillin again and whether resources exist for observation.

[e] If skin testing is not possible, a graded amoxicillin challenge can be considered for medium-risk histories. A graded challenge often requires administration of a one-tenth to one-fourth full dose of the desired drug and a 30- to 60-minute period of monitoring followed by administration of a full dose of the desired drug and a final 30- to 60-minute period of monitoring (Toolkit C in Supplement 2).

Figure 2. Penicillin Allergy Evaluations: Methods, Resources, and Locations

drug challenges; a nocebo effect has been documented in up to 10% of drug-challenged patients.[59] Individuals with underlying chronic urticaria do not have an increased risk for immunologically mediated penicillin hypersensitivity.[60]

Low-Risk History: Prescribe Amoxicillin or Perform a Direct Amoxicillin Challenge

Low-risk penicillin allergy histories include patients who have had isolated nonallergic symptoms (eg, gastrointestinal symptoms) or patients solely with a family history of a penicillin allergy, pruritus without rash, or remote (>10 years) unknown reactions without features suggestive of an IgE-mediated reaction. Most patients that have a documented penicillin allergy have low-risk histories.[61,62] For patients with nonallergic symptoms or a family history, amoxicillin can be prescribed, though patient preference may dictate whether a direct oral amoxicillin challenge is performed under medical observation first. For patients with other low-risk histories, such as pruritus without rash or remote (>10 years) unknown reactions without features suggestive of an IgE-mediated reaction, a direct oral amoxicillin challenge under medical observation should be performed (Toolkit B in Supplement 2).

When performing any allergy procedures in the health care setting, obtaining informed consent and ensuring appropriate monitoring and access to medications to manage symptoms of an allergic reaction are strongly recommended (**Figure 2**). The toolkits in Supplement 2 and the accompanying video provide information on how to perform these tests.

Allergists have used drug challenges to exclude the presence of IgE-mediated allergies for decades,[63,64] especially after negative skin testing results. For a penicillin allergy, administration of 250 mg of amoxicillin with 1 hour of observation demonstrates penicillin tolerance,[65] although some allergists prefer using 500 mg of amoxicillin, consistent with typical adult dosing.[48] A graded drug challenge, administration of a full drug dose divided into 2 or 3 separate administrations with concomitant medical observation, may also be used for patients who have low- or moderate-risk histories (Toolkit C in Supplement 2). Demonstration of amoxicillin tolerance enables future use of all penicillin antibiotics, including aminopenicillins. Penicillin is generally not recommended for demonstrating penicillin tolerance because selective allergy to ampicillin and amoxicillin (ie, aminopenicillins) has been described, although largely in European populations.[66] For patients with a history of only penicillin allergy, after amoxicillin challenge is tolerated without an adverse reaction, all β-lactams can be administered as indicated.

In a study of direct drug challenges performed by allergists in ambulatory clinics, only 1.5% of 402 healthy young military recruits with reported penicillin allergy proved to have true penicillin allergy.[67] In another study of 155 outpatients with reported penicillin allergy, only 2.6% were allergic to penicillin.[59] Among over 800 general pediatric patients with varied penicillin allergy histories, 94% tolerated their drug challenge.[18] Similarly, drug challenges have been performed on hospitalized patients by nonallergist clinicians, including internists (trainees and staff), nurse practitioners, and physician assistants, with results demonstrating improved antibiotic choices and first-line therapy for select infections.[10,35,50]

Moderate-Risk History: Skin Test and Amoxicillin Challenge

Moderate-risk histories include patients who have had urticaria or other pruritic rashes or reactions with features of IgE-mediated reactions (eg, swelling), but not anaphylactic reactions. Unless the history for penicillin allergy is low risk, all unstable patients, patients receiving supplemental oxygen or patients with compromised cardiac function, and pregnant patients should be considered high-risk.

Penicillin skin testing results in improved antibiotic choice for patients in outpatient, inpatient, perioperative, and obstetric settings.[68-71] Registered nurses, advanced practice practitioners, and physicians from any discipline who have been adequately trained can perform penicillin skin testing.[55] In some states, pharmacists are permitted under state laws and regulations to perform penicillin skin testing.[54] Clinicians performing penicillin skin testing should have training to ensure proficiency. Allergists are a good resource to assist with this training. Clinicians who perform penicillin skin testing should periodically undergo skin testing proficiency evaluation to ensure they safely perform this procedure. The testing is performed using a step-wise skin-based evaluation, and results can be read 15 minutes after reagents are scratched into the skin or placed intradermally (eFigure 2 in Supplement 1). Patients with a positive skin test result are allergic to penicillin and should not be challenged. Negative penicillin skin testing results carry a predictive value that exceeds 95%,[72] and that approaches 100%[12] when combined with oral amoxicillin challenge. Details regarding skin testing procedures and interpretation are provided in eFigure 2 in Supplement 1 and Toolkit D in Supplement 2).

High-Risk History: Referral to Allergy/Immunology Specialist or Desensitization

Patients with a history of high-risk reactions, including anaphylaxis (eFigure 1 in Supplement 1), positive penicillin skin testing results, recurrent penicillin reactions, and hypersensitivities to multiple β-lactam antibiotics, should be evaluated by specialists. If penicillin is required immediately for optimal patient care, a desensitization procedure may be pursued.

Desensitization is indicated for patients who likely have an allergy, such as patients with recent, severe, and/or life-threatening immediate hypersensitivity reactions to the medication that they require.[73] Desensitization is also indicated for patients who are unable to undergo penicillin skin testing to determine if they are truly allergic and for patients with hemodynamic or respiratory compromise, unstable angina, or other clinical conditions in which anaphylaxis would be harmful. Desensitization may also be used when penicillin skin testing is uninterpretable (eg, histamine-positive control is nonreactive; eFigure 2 in Supplement 1). Desensitization is reserved for scenarios in which penicillin or a penicillin-related drug is superior to alternative antibiotics. Antibiotic desensitizations are frequently performed in hospitalized patients, often in the intensive care unit, because 1:1 nursing support is typically required. Desensitization procedures have a risk of complications and, like all medical procedures, physicians overseeing these procedures must be adequately trained and credentialed and patient informed consent should be obtained.

Other β-Lactams and Cross-reactivity

Cephalosporin allergies are an increasing problem in the United States; about 2% of patients have a reported cephalosporin allergy, and cephalosporins are emerging as a common cause of anaphylaxis, especially in the perioperative setting.[5] Allergies to carbapenem and monobactam are uncommon.[5]

Cross-reactivity between penicillin and cephalosporin occur in about 2% of cases, less than the 8% reported previously.[74] However, in the subset of patients with history of anaphylaxis after penicillin, almost 40% have demonstrated cross-reactivity with a cephalosporin, although this is almost exclusively with the aminocephalosporins that have shared chemical side chains or R_1 groups (eTable 2 in Supplement 1).[75] Cefazolin, notably, has a unique side chain and very low cross-reactivity with penicillin.[74] Cross-reactivity between penicillins and carbapenems is less than 1%, and there is no cross-reactivity between penicillins and monobactams.[12]

Algorithms exist to help prescribe β-lactam agents to patients with a reported penicillin allergy.[35,50,76] However, evaluating the penicillin allergy directly, using amoxicillin challenge with or without penicillin skin testing, is the simplest approach. If there is no evidence of penicillin allergy, the possibility of cross-reactivity is rendered irrelevant.

Implementation Across the Care Continuum, and Special Populations

In addition to evaluation at the time that the patient needs the antibiotic, penicillin allergy evaluation should be initiated during routine care delivery to guide future antibiotic use and prevent the need for emergent drug testing and desensitization if a patient develops a serious illness. Penicillin allergy evaluation can be safely performed before the need for antibiotic use in infants, children, pregnant women, older adults, hospitalized patients, and patients in the intensive care unit. Programs to evaluate penicillin allergies depend on services available and the type of facility in which care is delivered (Figure 2).

Ambulatory Care

Over 260 million courses of antibiotics are prescribed annually in ambulatory settings.[77] Antibiotics are prescribed during 10% of all ambulatory visits; broad-spectrum antibiotics account for 61% of these prescriptions.[78] Dentists prescribe 25 million courses of antibiotics annually.[29] Ambulatory antibiotic stewardship includes both reduc-

ing unnecessary antibiotic use and improving antibiotic choice. Ambulatory environments are ideal for penicillin allergy evaluation, because patients are well enough to tolerate testing and, for many visits, there is no urgent need for antibiotic therapy.

Although specialists evaluate patients with reported penicillin allergy in ambulatory settings, nonspecialty ambulatory practices are encouraged to establish the infrastructure to perform low-risk amoxicillin challenges and to consider implementing penicillin skin testing. With access to testing materials, standard antianaphylaxis medications, and trained personnel for testing and monitoring, penicillin allergy evaluations can be accomplished in all ambulatory practices.

Hospitalized Patients

Antibiotics are prescribed to more than half of patients admitted to acute care hospitals.[79] Penicillin skin testing programs implemented in general medical and intensive care unit settings have identified benefits, such allowing narrower-spectrum antibiotics to be chosen.[52,53] Although some programs have been managed by nonallergy specialists,[49,52,55] specialists have often assisted in the design or implementation of the programs.[48,50] Inpatient areas are staffed by the necessary personnel and have materials required for penicillin skin testing. Studies have identified barriers to inpatient penicillin skin testing, including short length of stays and inadequate time to perform penicillin skin testing in light of the many other tests performed in an inpatient setting.[69] When penicillin skin testing is not feasible, a graded challenge can be implemented for patients with moderate-risk histories after consideration of potential for benefit vs potential for harm (Toolkit C in Supplement 2).[35,50,69] Hospitalized patients with infections may benefit from challenge to specific β-lactam drugs if it is likely to cure the infection (eg, cefazolin in patients with methicillin-susceptible *S aureus* bacteremia). This short-term solution should be followed by penicillin allergy evaluation to potentially remove the penicillin allergy label if the patient can tolerate that assessment.

Periprocedure

Evaluation of β-lactam allergy histories before elective surgical procedures can support decision making for the best choice of antibiotic prophylaxis. In general, cefazolin, or an equivalent cephalosporin, is the most common first-line recommended antibiotic.[32] Patients who report being allergic to penicillin most often receive cefazolin alternatives, such as clindamycin or vancomycin. These alternatives are considered less effective antibiotics for managing prophylaxis and are associated with an increased risk of SSIs[17] and, possibly, *C difficile* infection.[80] In addition, given the logistical challenges of completing vancomycin infusion (1 to 2 hours depending on the dose) within the recommended time frame (1 to 2 hours prior to incision), insufficient antibiotic may be present in the tissues at the critical time of skin incision.[17] Preoperative penicillin allergy evaluation has been successful for general,[70] cardiac,[81] and orthopedic surgical procedures.[82] A study showed that 300 patients with low- and moderate-risk penicillin allergy histories received cephalosporins (largely cefazolin) and there was only 1 possible reaction.[83]

Pediatric Patients

Common childhood infections, such as otitis media and pharyngitis, are often managed with penicillins. Higher rates of adverse events with no apparent benefit have been observed when broader-spectrum antibiotics are used to manage these infections.[84] Compared with adults, when children are evaluated for penicillin allergy, less time has elapsed since the reported reaction. Despite this, rashes in children are more likely a result of an infection-related exanthem or a drug-infection interaction than from an immunologic response to the antibiotic. In 2 studies, 94% to 100% of infants and children evaluated with direct amoxicillin challenge were found to be penicillin-tolerant, suggesting that a recent reaction should not preclude a penicillin allergy evaluation in children.[18,62]

Pregnant Patients

Antibiotics are among the most commonly prescribed medications during pregnancy.[85] Amoxicillin and cephalexin are first-line therapies for management of asymptomatic bacteriuria and susceptible urinary tract infections in pregnancy.[86] Penicillin in combination with aminoglycoside drugs are commonly used to treat patients with chorioamnionitis.[87] Syphilis in pregnancy is managed with penicillin.[88] Being labeled with a penicillin allergy during pregnancy is associated with substantial morbidity, including increased risk of cesarean delivery, postcesarean wound complications, and longer length of hospital stay.[89,90] Although penicillin skin testing is safe, it is infrequently performed during pregnancy[71]; however, third trimester referral to specialists for expectant mothers with planned cesarean delivery, group B *Streptococcus* colonization, and other indications are currently performed at some US institutions.[71]

Long-term Care

Fifty percent to 80% of older adults in long-term care facilities (LTCFs) receive at least 1 course of antibiotics each year, with up to half of the antibiotic courses being inappropriately prescribed.[91] The prevalence of reported penicillin allergy increases with age, and older adults are more likely to suffer the adverse effects associated with use of alternative antibiotics.[92] In addition to increased risk of *C difficile* infection, fluoroquinolones, a frequently employed alternative antibiotic class, have significant drug-drug interactions with medications commonly prescribed to older adults (eg, warfarin).[93] Recent efforts from the Centers for Medicare & Medicaid Services focus on strategies to reduce inappropriate antibiotic prescribing in LTCFs. Using the same methods employed in other settings, penicillin allergy evaluation could have a significant benefit for older adults in LTCFs.

Oncology

Patients with cancer are commonly prescribed antibiotics for both prophylaxis and treatment and have a higher prevalence than the general population of reported antibiotic allergy.[94] For example, β-lactam antibiotics are important for management of common infectious syndromes, such as fever and neutropenia.[95] Patients with cancer are at a high risk for developing resistant organisms and complications, such as *C difficile* infection.[96,97] Thus, efforts to evaluate reported penicillin allergy in patients with cancer may improve treatment decisions and potentially affect outcomes, such as hospital length of stay.[94] Interventions for clinical evaluation implemented in either outpatient or patient settings, ideally before the initiation of chemotherapy or bone marrow transplant, may improve outcomes. Patients receiving immunosuppressant agents

Figure 3. Management of Drug Challenge Reactions

Response to challenge	Actions	Results
Subjective symptoms Pruritus without rash Scratchy throat, tongue, or palate Vague gastrointestinal symptoms (eg, nausea)	Obtain vital signs Perform physical exam looking for objective signs to support a minor cutaneous or systemic reaction Increase observation time by 30 min to observe for objective signs of reaction	**If no objective signs of reaction, symptoms unlikely an allergic reaction** If objective signs of reaction, consider following the "Minor cutaneous reaction" or "Possible systemic (anaphylactic) reaction" pathways below Consider specialty evaluation
Minor cutaneous reaction Flushing Rash Urticaria	Obtain vital signs Ask patient about symptoms, including skin symptoms and other organ systems that are involved in systemic (anaphylactic) reactions Perform physical exam looking for rash type and extent, as well as any other signs suggestive of a systemic (anaphylactic) reaction Treat with antihistamine[b] Nonsedating: cetirizine or fexofenadine Sedating: dephenhydramine Epinephrine for diffuse urticaria[b] Increase observation period by 30 min to observe for signs of systemic reaction or symptom resolution	**Patient labeled as penicillin-allergic** Consider specialty evaluation
Possible systemic (anaphylactic) reaction **Typically involves ≥2 organ systems** Cutaneous: pruritus, flushing, rash, urticaria, or swelling Respiratory: nasal congestion, runny nose, cough, shortness of breath, chest tightness, wheezing Cardiovascular: faintness, tachycardia, tunnel vision, chest pain, hypotension, sense of impending doom, loss of consciousness Gastrointestinal: nausea, vomiting, cramping, diarrhea **Hypotension alone in the setting of a known allergen exposure is also considered anaphylaxis**	Assess airway, breathing, circulation Obtain vital signs[a] Place patient in supine position and elevate legs If automated external defibrillator is available, retrieve and bring to bedside Administer intramuscular epinephrine[b] mid-upper outer thigh; repeat every 5-15 min as needed Call 911 Administer oxygen and intravenous fluids, if available Administer adjunctive treatments such as antihistamine, steroids, and bronchodilators[b]	**Patient labeled as penicillin-allergic** Consider specialty evaluation

[a] Vital signs should be checked every 15 minutes, but patients do not typically require continuous pulse oximetry or cardiac monitoring.
[b] Medication and dosages are provided in Toolkit E.

This algorithm provides the suggested management for reactions precipitated by drug challenges in ambulatory settings. The most common reactions will be subjective symptoms and minor cutaneous reactions. Rarely, reactions that are anaphylactic may be encountered. Anaphylaxis requires timely treatment with epinephrine. Antihistamines and corticosteroids may be used for symptom control and corticosteroids may be used to inhibit a biphasic anaphylactic reactions, but these are adjunctive treatments only. Anaphylaxis guidance for emergency and acute care settings exists.[100]

can be skin tested, although they may have increased likelihood of a nonreactive histamine.

Sexually Transmitted Infection Clinics

β-Lactam antibiotics are first-line treatment for patients with syphilis and gonorrhea, with no equivalently efficacious alternative antibiotics for patients with severe penicillin allergy.[28] Approximately 15% of patients evaluated in a sexually transmitted infection (STI) clinic reported a penicillin allergy.[98] Treatment of STIs in patients with a penicillin allergy is particularly challenging because many STI clinics may not have the resources to offer skin testing; however, direct challenges should be considered. Guidelines recommend initiation of STI treatment at the clinic visit with direct observation of the patient by the clinic staff to minimize the risk for curative therapy not being administered.[28,99]

Management of Drug Challenge Reactions

Most reactions that occur as a result of testing are either subjective symptoms or minor cutaneous reactions, such as pruritus or a rash. Subjective symptom management includes increased observation (**Figure 3**). Cutaneous reactions are typically treated with increased observation and antihistamines, preferably a nonsedating antihistamine (eg, cetirizine, fexofenadine) rather than a sedating antihistamine (eg, diphenhydramine). Epinephrine may also be used for more diffuse urticaria. Rarely (<1 in 500), patients may develop anaphylaxis, a systemic reaction. Anaphylaxis often includes a cutaneous sign or symptom (eg, pruritus, urticaria, flushing) as well as other organ system involvement (eFigure 1 in Supplement 1). For example, respiratory system involvement may be manifested as wheezing, dyspnea, or coughing. Gastrointestinal system involvement may be manifested as abdominal pain, diarrhea, or vomiting. Timely recognition and management of anaphylaxis, including the administration of intramuscular epinephrine, can be lifesaving, and a delay of administration of epinephrine can be fatal. An anaphylaxis and adjunctive treatment kit is useful for all settings to allow for immediate treatment of allergic reactions (Toolkit E in Supplement 2).

After Negative Penicillin Allergy Evaluations

If an amoxicillin challenge is tolerated (with or without penicillin skin testing), the medical record notation that a patient is allergic to penicillin should be deleted. Patients should be educated so that they understand that they do not have an allergy to penicillin and they should be reassured that repeated courses of penicillin, including intravenous penicillin, can be given without an increased

risk of hypersensitivity reaction.[101,102] Some institutions have used wallet cards or apps to allow patients to maintain their active allergies.[103] Active allergy lists should be communicated to all care providers and pharmacies. Amoxicillin challenges virtually exclude IgE-mediated allergies, but patients may experience other, benign skin rashes at an incidence similar to the general population.[104] To completely exclude benign delayed rashes, a longer course of antibiotics is required, but this is not recommended because it exposes patients to unnecessary antibiotics.[104]

EHRs can accommodate a large amount of information in the allergy module, including the allergen (drug), reaction, reaction type (eg, intolerance, allergy), date noted, and comments. However, allergy documentation is often vague, with up to 80% of allergies lacking descriptions of the reactions.[16] Many entries may be inaccurate; in 1 study, only one-third of entries were confirmed by patients.[105] While nonclinicians may enter patient-reported allergies, clinicians should assess whether the entry has clinical utility and, if so, enter additional reaction details.

After allergy evaluations, proper updating regarding allergy information should be performed. EHR allergy modules often include historical allergies that have been added, modified, or deleted over time. When penicillin is tolerated in a patient with a history of penicillin allergy, the active penicillin allergy should be deleted from the EHR. When it is not appropriate to remove or delete the allergy, qualifying comments should be added in to provide detail. For example, "penicillin skin test positive" or "tolerates cephalexin" can inform future care. If the allergy is not removed from the record after a negative penicillin skin testing result, or is erroneously re-entered at a later date, the benefits of the clinical evaluation will not be achieved. Unfortunately, failure to modify the allergy history listing may occur in more than 1 in 5 tested patients.[68,106]

Evaluation of penicillin allergy has substantial benefits for patients by allowing improved antimicrobial choice for treatment and prophylaxis. As a component of antimicrobial stewardship efforts, evaluation of penicillin allergy leads to more appropriate antibiotic administration and may reduce antimicrobial resistance and cases of *C difficile* infection. Testing for penicillin allergy is recommended by the CDC and multiple professional societies.[37,107-109]

Antibiotic challenge procedures are gaining acceptance, but many clinicians do not know how to perform these procedures. Beyond infrastructure and resources, the major barrier to evaluation of penicillin allergy is clinician knowledge and comfort.[110] Specialists cannot address this problem alone, but should be engaged directly or through collaborations with clinicians across the care continuum to address this problem. Practical educational materials and testing procedures are provided with this review to facilitate implementation of penicillin allergy assessment.

Conclusions

Many patients report they are allergic to penicillin, but few have clinically significant reactions. Evaluation of penicillin allergy before deciding not to use penicillin or other β-lactam antibiotics is an important tool for antimicrobial stewardship.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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