Penicillin and Beta-Lactam Hypersensitivity

Daniel Har, MD[a,1], Roland Solensky, MD[b,c,*]

KEYWORDS

• Penicillin • Beta-lactam • Allergy • Hypersensitivity

KEY POINTS

- More than 90% of individuals with history of penicillin allergy tolerate penicillins, and skin testing is the optimal method for evaluation.
- "Penicillin allergy" is associated with antimicrobial resistance, prolonged hospitalizations, readmissions, and increased costs.
- There is minimal allergic cross-reactivity between penicillins and cephalosporins, except selective allergy to aminopenicillin R-group side chains, which greatly increase the risk of reactions to cephalosporins with identical R1 group side chains.
- There is minimal allergic cross-reactivity between penicillins and carbapenems.
- Allergy to cephalosporins is usually side-chain specific and may warrant graded challenge with cephalosporins containing dissimilar R1 or R2 group side chains.

PENICILLIN ALLERGY

Background

Drug allergy is defined as an unpredictable reaction, or type B reaction, which is mediated by immune mechanisms.[1] Penicillin allergy is the most commonly reported medication allergy.[2] Immunoglobulin (Ig)E-mediated (or type I) reactions are one type of drug allergy, and they are the focus of this review. For further information on delayed reactions, please refer Caitlin M.G. McNulty and Miguel A. Park's article, "Delayed Cutaneous Hypersensitivity Reactions to Antibiotics, Management with Desensitization," in this issue. IgE-related reactions are typically immediate, with symptoms occurring within minutes to 6 hours of last administered dose, although onset is classically within

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[a] Division of Allergy and Immunology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA; [b] Division of Allergy and Immunology, The Corvallis Clinic, 3680 NW Samaritan Dr, Corvallis, OR 97330, USA; [c] Oregon State University/Oregon Health & Science University College of Pharmacy, 1601 SW Jefferson Way, Corvallis, OR 97331, USA
[1] Present address: 1955 Market Center Boulevard, Apartment 2201, Dallas, TX 75207.
* Corresponding author. 3680 Northwest Samaritan Drive, Corvallis, OR.
E-mail address: roland.solensky@corvallisclinic.com

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1 hour. IgE-related symptoms may include pruritus, flushing, urticaria, angioedema, bronchospasm, laryngeal edema, nausea, emesis, and hypotension.

Epidemiology

Penicillin allergy is self-reported by approximately 10% of patients.[3] However, following thorough evaluation, 90% or more of individuals with a history of penicillin allergy tolerate penicillins.[4–7] As a result, a history of penicillin allergy is unreliable in predicting reactions with subsequent administration of the medication. There are various reasons for this incongruity. Often, reaction histories are poorly characterized and very remote. Symptoms may simply have been a consequence of an underlying illness, such as a viral infection, or from an interaction between a penicillin antibiotic and an infectious agent. A well-characterized example of the latter is when actively infected patients with Epstein-Barr virus are treated with ampicillin and develop a morbilliform rash.[8] Another important contributor to the discrepancy is loss of penicillin sensitivity over time. Approximately 50% of penicillin-allergic patients lose their sensitivity over 5 years, and approximately 80% over 10 years.[9,10]

Based on the rate of positive penicillin skin tests, the prevalence of immediate reactions to penicillin antibiotics is decreasing over the past 2 decades.[11,12] Penicillin-induced anaphylaxis is relatively rare, with several studies suggesting a rate of approximately 0.01% to 0.04% of treated patients.[13,14] In the United States, it has been estimated that 500 to 1000 deaths per year are secondary to penicillin-induced anaphylaxis.[15]

Detriment of "Penicillin Allergy" Label

Physicians frequently choose alternative antibiotics for those labeled with "penicillin allergy."[16–22] Unfortunately, this is associated with increased antimicrobial resistance, increased *Clostridium difficile* infections, prolonged length of hospital stays, increased intensive care admissions, increased hospital readmissions, and increased mortality.[19,23–26] Beyond compromising one's health, there are significantly higher costs associated with the "penicillin allergy" label.[18–21,27] Recently, King and colleagues[27] calculated that an average of $297 per patient would be saved if patients switched from a non–beta-lactam antibiotic to a beta-lactam antibiotic. Macy and Contreras[19] reported "penicillin-allergic" patients stayed an extra 0.59 days longer than control patients, resulting in an estimated $64.6 million cost. Cost-analysis studies thus far focus on one patient encounter, but extrapolating these data to the lifetime of a patient with potential future intensive care admissions, hospital readmissions, and expensive second-line antibiotic prescriptions could result in an overwhelming financial burden for patients.

Immunochemistry

Penicillin, like most drugs, is generally too small to be immunogenic; therefore, the immune response is directed against complexes of penicillin degradation products covalently bound to self-proteins.[28–30] The allergic components of penicillin are derived from either the beta-lactam core ring structure or from a specific side chain R group (**Fig. 1**). The core beta-lactam ring structure is shared among all penicillin antibiotics, whereas the R-group side chains differentiate penicillin antibiotics from each other.

After penicillin administration, the beta-lactam ring opens spontaneously to form several breakdown products. The most prevalent of these is penicilloyl polylysine, or major allergenic determinant, which comprises 95% of the breakdown products.

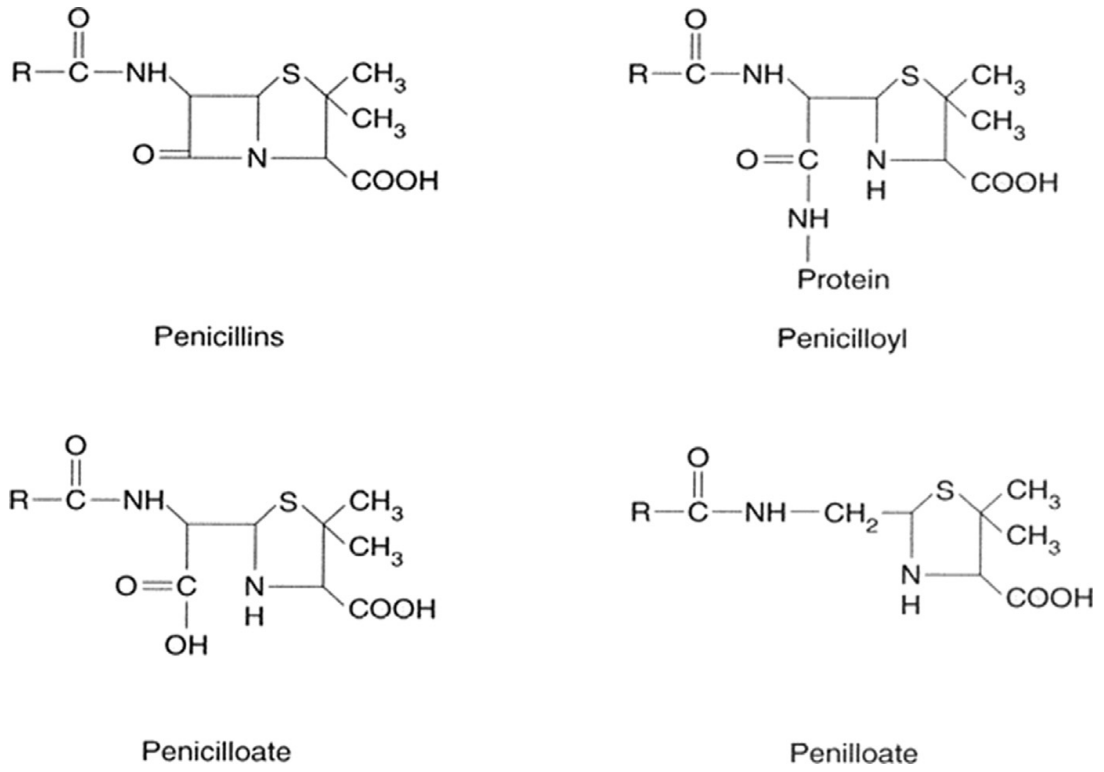

Fig. 1. Structures of penicillin breakdown products. The 4-membered square-shaped ring is the beta-lactam ring, which opens up to form covalent bonds with self-proteins. The "R" represents the side chains which differentiate various penicillins. (*From* Solensky R. Drug hypersensitivity. Med Clin N Am 2006;90(1):238; with permission.)

Of the remaining minor allergenic determinants, penicilloate and penilloate are the most important. Some patients do not react to the core ring, but instead to the R-group side chain. For example, an individual may tolerate penicillin, but develop an allergic response to amoxicillin or ampicillin (eg, the aminopenicillins).[31–33] The prevalence of aminopenicillin-specific allergy is much lower in the United States (fewer than 5% of skin test–positive patients), compared with Southern Europe (25%–50% of skin test–positive patients).[34–37] Additionally, some patients react only to clavulanic acid, and not to other penicillin determinants. In other words, they tolerate amoxicillin but react to amoxicillin-clavulanate. The frequency of clavulanate-selective allergy is unclear due to limited data (all from Southern Europe).[38,39]

Penicillin Skin Test Reagents

Penicillin skin test reagents are based on the immunogenicity and include major and minor determinants. Penicilloyl polylysine (PPL) is the synthetically made major determinant, whereas penilloate, penicilloate, penicillin G, amoxicillin and ampicillin are grouped as minor determinants (**Table 1**). Sometimes the minor determinants are combined into a "minor determinant mixture" (MDM), and this consists of either penilloate and penicilloate, or penilloate, penicilloate, and penicillin G. PPL has been commercially available in the United States as Pre-Pen, but minor determinants have never been approved by the Food and Drug Administration. Some laboratories synthesize penicilloate and penilloate, whereas diluted penicillin G and ampicillin are used off-label for skin testing.

Table 1
Penicillin skin test reagents

Reagent	Concentration Used for Skin Testing
Penicilloyl-polylysine (Pre-Pen)	6×10^{-5} M
Penicillin G	10,000 units/mL
Penicilloate	0.01 M
Penilloate	0.01 M
Ampicillin/amoxicillin	3–25 mg/mL

Skin Testing Predictive Value

PPL is necessary for skin testing, as up to 84% of penicillin skin test–positive patients are positive to PPL, and up to 75% react to PPL only.[5,34,40–43] The positive predictive value (PPV) of PPL is unclear, given obvious patient safety and ethical concerns with challenging skin test–positive patients. However, limited retrospective data demonstrate that the PPV of penicillin skin testing is approximately 50% (with a range of 33%–100%).[32,40,42,44] The negative predictive value (NPV) of PPL ranges from 84% (in European studies) to 99%, with the theory that the variability is due to a higher prevalence of selectively allergic amoxicillin/ampicillin patients in Europe.[5,6,34,42,45–47]

With respect to minor determinants, approximately 10% of penicillin skin test–positive patients are positive to only penicilloate and/or penilloate.[11,34,35,48,49] Similar to PPL, there is a scarcity of literature regarding the PPV of penicilloate and/or penilloate.[29,50,51] As it is rare to skin test without PPL, the overall NPV of PPL and MDM (with all 3 reagents) is greater than 95%, which parallels that of PPL and penicillin G.[5,40,42,46,52–54] However, there is controversy regarding the accuracy of these NPVs, as selection bias and lack of standardized challenges may have effected results.[40,46,55] Regardless, many experts still favor penicilloate and penilloate as relevant skin testing reagents, and the Academy of Allergy, Asthma and Immunology supports the expedited approval by the Food and Drug Administration of a penicillin skin test kit that includes PPL, penicillin G, penilloate, penicilloate, and amoxicillin (Pre-Pen Plus).[56]

In Vitro Testing

In vitro tests using enzyme-linked immunosorbent assays to PPL, penicillin G, penicillin V, amoxicillin, and ampicillin are commercially available but are of limited value. Sensitivity of in vitro IgE antibodies is as low as 45% and studies with positive in vitro tests report a high number of false-positive results.[57,58] The basophil activation test, which uses flow cytometry, is another in vitro test that has been shown to be inferior to skin testing.[59,60]

Clinical Management

Role of history taking

As discussed earlier, most patients who claim they are allergic to penicillin can tolerate penicillin. Nevertheless, taking a detailed history is still critical for evaluation and management. Discounting reactions because they are vague may miss some truly allergic patients, because one-third of penicillin skin test–positive individuals have a vague reaction history.[61] When taking a history, the following questions are important to help guide management:

Are the symptoms consistent with a possible IgE-related mechanism? Did symptoms consist of pruritus, flushing, urticaria, angioedema, bronchospasm, laryngeal edema,

nausea, emesis, or hypotension? If the answer is yes, the patient is a candidate for evaluation with an allergist for penicillin skin testing. The timing of the reaction (ie, soon after the last dose) is also suggestive of an IgE-mediated mechanism, but is often difficult to determine.

Are the symptoms consistent with a severe non–IgE-mediated mechanism? It is important to determine if the historical reaction had features of possible severe cutaneous adverse drug reaction, because strict avoidance of the culprit drug is required, and there is no role for skin testing or desensitization. These reactions include acute generalized exanthematous pustulosis, serum sickness–like reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms. Similarly, avoidance is the only option for other severe non–IgE-mediated reactions, such as immune cytopenias, drug fever, interstitial nephritis, and fixed drug eruption.

Is the reaction history unclear or not compatible with a possible allergy? Many times, patients are unable to provide useful details regarding their previous penicillin reactions, or, if they have experienced reactions due to more than 1 antibiotic, they may be unsure which antibiotic caused which type of reaction. Typically, in these cases, it is reasonable to pursue skin testing and challenge. If the reaction is incompatible with an allergy, such as isolated gastrointestinal symptoms or headache, then skin testing is not necessary and the patient may receive treatment with penicillins again.

When to evaluate

Penicillin allergy is ideally evaluated when the patient is well and not in need of antibiotic treatment. Because of the detrimental consequences resulting from a mislabeled penicillin allergy, all patients with a history of possible IgE-mediated penicillin allergy should be candidates for skin testing. Skin testing as a routine screen in the absence of clinical history is not recommended. Recent literature has shown via fine mapping genome-wise association studies and targeted genotyping that variants in HLA-DRA, HLA-DRB5, and interleukin-4 may be potential genetic predictors of penicillin allergy.[62,63] Regardless, patients who have never taken penicillin before but have a family history of penicillin allergy do not need evaluation and can safely take penicillins. Recently, the American Academy of Allergy Asthma & Immunology and others have urged more widespread use of drug allergy testing.[64,65]

Skin Testing

Penicillin skin testing is the most optimal method to evaluate for IgE-mediated penicillin allergy. When skin testing is executed properly, it is very safe; it has been studied in young children, pregnant women, emergency department patients, preoperative patients, and hospitalized critically ill patients. However, there is a rare risk of systemic reactions.[66,67] Therefore, skin testing should be performed only by trained personnel and in an environment capable of treating potential anaphylaxis.

Regarding the procedure itself, the first portion involves applying the skin test reagents along with positive (histamine) and negative (saline) controls via the prick technique. Measurements should be taken 15 minutes after placement. If the skin prick results are negative, intradermal testing should be performed with the same reagents and controls. Measurements should likewise be obtained 15 minutes after intradermal placement. If intradermal results are negative, the “penicillin allergy” label should be removed and patients should be educated about their tolerance to penicillins.

Challenge

In general, drug challenges should be performed when there is a low likelihood of a drug allergy, as the purpose is to confirm that a patient is not allergic and can tolerate the drug. Despite having a very high NPV, a survey by Warrington and colleagues[68] revealed that 52% of patients with negative penicillin skin tests still prefer to avoid penicillin, with some patients reporting that their family physicians thought it was safer to use an alternative antibiotic. For this reason, to unequivocally exclude the diagnosis of penicillin allergy, it has become standard of care to routinely perform a challenge immediately after a negative skin test.[7,53,69] Typically, the challenge is either a single dose or a 2-step graded challenge (one-tenth of full dose, followed 30–60 minutes later by the full dose). Amoxicillin is the preferable penicillin, because it has both the immunologically significant core beta-lactam ring and the potentially immunologically significant R-group side chain. If patients report reactions to amoxicillin-clavulanate, they should be challenged with that antibiotic, rather than amoxicillin.

Given the very low rate of positive penicillin skin tests, another recently studied approach is direct amoxicillin challenge without prior skin testing. Mill and colleagues[70] demonstrated that in 818 children with histories of cutaneous reactions to amoxicillin, a graded amoxicillin challenge was tolerated in 94%, with the remaining developing mild hives or a maculopapular rash. Of note, none of their patients had a history of anaphylaxis and most patients reported reactions during their first course of amoxicillin. Pending further research, this approach should be considered only in children with history of mild cutaneous reactions. Patients who fail challenges should either continue avoiding penicillin antibiotics or, if necessary, undergo desensitization.

Desensitization

Desensitization should be reserved for either those who have positive skin test results or are strongly suspected to have an IgE-mediated penicillin allergy, and for whom there are no alternative antibiotics available. Details will be further addressed in Sevim Bavbek and Min Jung Lee's article, "Subcutaneous Injectable Drugs Hypersensitivity and Desensitization: Insulin and Monoclonal Antibodies," in this issue.

Benefit of evaluation

There are significant benefits to an allergist's evaluation of penicillin allergy, namely the ability to remove a patient's "penicillin allergy" label. Most research up to this point has been pilot projects in hospital settings, where it is easier to track outcomes (such as transition to beta-lactam antibiotics and cost).[69,71–77] The most extensive penicillin skin-testing program is at the Mayo Clinic (Rochester, MN), where preoperative patients with a history of penicillin allergy routinely undergo penicillin skin testing. Because approximately 95% of the patients are skin test–negative, it allows surgeons to choose first-generation cephalosporins rather than vancomycin. In an effort to remove the "penicillin allergy" label on a more wide-scale level, some researchers have used clinical pharmacists along with allergists, both in inpatient and outpatient settings.[69,75] Despite recommendations to expand utilization of penicillin skin testing,[64,65] it is clear that there is a need for increased education.[78]

Remarkably, up to 49% of patients who are penicillin skin test–negative and 82% of those tolerant to penicillins may continue to be labeled as "penicillin-allergic."[78] Others are relabeled as allergic after having the label removed, with significant risk factors, including age older than 65 years ($P = .011$), acutely altered mentation ($P < .0001$), and dementia ($P < .0001$).[76] Interventions, such as detailed follow-up letters to primary care physicians succinctly listing antibiotic allergies, have decreased those not following recommendations from 26% to 15%.[79]

Resensitization

Resensitization is the redevelopment of penicillin allergy after initial resolution. Numerous studies have demonstrated that the rate of resensitization following treatment with oral penicillins is comparable to the rate of sensitization.[6,80,81] Therefore, the article by Solensky and colleagues,[82] Drug Allergy: An Updated Practice Parameter, does not recommend routine repeat penicillin skin testing in patients with a history of penicillin allergy who have tolerated 1 course or more of oral penicillins. Data on resensitization following parental penicillin are more limited; therefore, repeat penicillin skin testing may be considered in patients with a history of penicillin allergy who have tolerated parental penicillins.[82]

ALLERGIC CROSS-REACTIVITY BETWEEN PENICILLINS AND OTHER BETA-LACTAM ANTIBIOTICS

Penicillin/Cephalosporins

Penicillins and cephalosporins share a common beta-lactam ring and hence the potential for allergic cross-reactivity (**Fig. 2**). Additionally, some penicillins and cephalosporins share identical R-group side chains, and these are another source of potential allergic cross-reactivity (**Table 2**). There are 3 potential methods to evaluate cross-reactivity: (1) in vitro analysis, such as specific IgG, IgM, and IgE antibodies directed against penicillins and cephalosporins, (2) penicillin and cephalosporin skin testing,

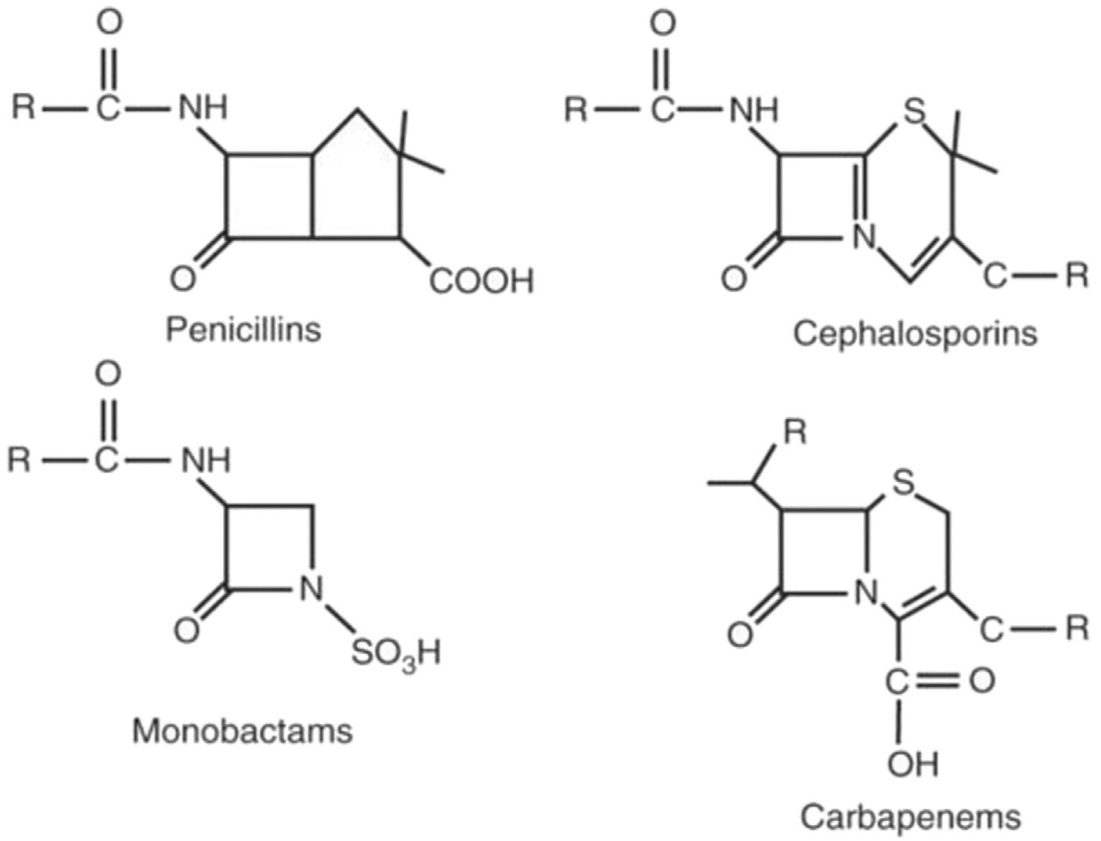

Fig. 2. Structures of beta-lactam antibiotics, which share a common beta-lactam ring (the 4-membered square-shaped ring). The "R" represents side chains; cephalosporins and carbapenems have 2, whereas monobactams have 1. (*From* Solensky R. Drug hypersensitivity. Med Clin N Am 2006;90(1):242; with permission.)

Table 2
Aminopenicillins and cephalosporins with identical R/R1 group side chains

Amoxicillin	Ampicillin
Cefadroxil	Cefaclor
Cefprozil	Cephalexin
Cefatrizine	Cephradine
	Cephaloglycin
	Loracarbef (a carbacephem)

and (3) cephalosporin challenges in patients with history of penicillin allergy (either with or without prior penicillin skin testing). Early studies using IgG and IgM antibodies and skin testing showed as much as 50% cross-reactivity between penicillin and first-generation cephalosporins,[83,84] but clinically, it became evident that cross-reactivity was much lower.

Several studies have evaluated patients with a history of penicillin allergy treated with cephalosporins (without preceding penicillin skin testing). As shown in **Table 3**, in the 1970s there appeared to be a fourfold to eightfold increased risk of cephalosporin reactions in patients with a history of penicillin allergy, compared with those without such a history.[85,86] However, very little detail was presented on the types of cephalosporin reactions observed. Also, before 1980, cephalosporins were contaminated with penicillin, meaning that exceptionally penicillin-allergic patients may have reacted to the penicillin within the cephalosporins rather than to the cephalosporin. Another limitation is that 90% or more of the subjects were probably not allergic to penicillins at time of cephalosporin treatment. Because these studies were retrospective in "real-world" settings, there was likely a selection bias in deciding which patients received cephalosporins versus other classes of antibiotics, meaning patients with more severe or recent penicillin reactions may have been less likely to be treated with cephalosporins. For example, in Daulat and colleagues,[87] inpatient pharmacists regularly denied cephalosporin prescription due to the severity of patients' penicillin allergy history (such as anaphylaxis). Furthermore, cephalosporin challenges were not blinded or placebo-controlled. Additionally, there was no attempt to include active controls, such as patients with a history of allergy to non–beta-lactam antibiotic treated with cephalosporins, or reaction rate of patients with history of penicillin allergy to non–beta-lactams. This is important because it is known that patients with a history of allergy to drugs are more likely to react to structurally unrelated drugs,[88,89] referred to as "multiple drug allergy syndrome."

Studies in which patients with a history of penicillin allergy were proven to be penicillin skin test–positive before cephalosporin challenge are most informative. Overall, as shown in **Table 4**, only approximately 3% of penicillin skin test–positive patients reacted to cephalosporins. Some investigators performed cephalosporin skin testing (using nonirritating concentrations) before challenging with cephalosporins, and that approach decreased the reaction rate to 0%. Some of the limitations discussed previously still apply, such as contamination of cephalosporins with penicillin (before 1980), lack of blinding, lack of inclusion of placebo or other controls, and "multiple drug allergy syndrome."

Patients who are selectively allergic to aminopenicillins (tolerant of penicillin VK) appear to have a higher risk of reacting to cephalosporins with identical R1 group side chains, but this conclusion is based on limited data.[90–92] Audicana and colleagues[90] challenged 10 patients selectively allergic to ampicillin with cephalexin (which has an identical R1 group side chain) and 1 (10%) reacted. Similarly, Sastre

Table 3
Cephalosporin challenges in patients with history of penicillin allergy (without prior penicillin skin testing)

	Cephalosporin Reaction Rate			
Study	**History of Penicillin Allergy**	**No History of Penicillin Allergy**	**Cephalosporins Administered**	**Type of Reaction**
Dash,[85] 1975	25/324 (7.7%)	140/17,216 (0.8%)	Cephalexin and cephaloridine	No details
Petz,[86] 1978	57/701 (8.1%)	285/15,007 (1.9%)	Cephalexin, cephaloridine, cephalothin, cefazolin,	No details
Goodman et al,[112] 2001	1/300 (0.3%)	1/2431 (0.04%)	Cefazolin (all but 1 patient)	Reaction questionable
Daulat et al,[87] 2004	1/606 (0.17%)	15/22,664 (0.07%)	1st generation (42%) 2nd generation (21%) 3rd generation (37%)	Eczema (cefazolin)
Fonacier et al,[113] 2006	7/83 (8.4%)	Not applicable	1st generation (59%) 2nd generation (8.4%) 3rd generation (25%) 4th generation (7%)	Reactions convincing: cephalexin-1, cefaclor-2, cefuroxime-2, cefixime-1, ceftriaxone-1
MacPherson et al,[114] 2006	0/84	Not applicable	Cefazolin, cefotetan, ceftriaxone	
Crotty et al,[115] 2015	7/186 (3.8%)	Not applicable	Cephalexin, cefoxitin, ceftriaxone, cefepime	6/7 cefepime; 3/7 immediate
Beltran et al,[116] 2015	1/153 (0.7%)	Not applicable	Cefazolin (84%) cefoxitin (17%)	Urticaria (cefazolin)

Table 4
Cephalosporin challenges in patients with history of penicillin allergy and positive penicillin skin testing

Study	No. of Patients	No. of Reactions (%)	Cephalosporin Skin Testing	Reaction(s) to
Girard,[117] 1968	23	2 (8.7)	No	Cephaloridine
Assem and Vickers,[84] 1974	3	3 (100)	No	Cephaloridine
Warrington et al,[118] 1978	3	0	Yes	
Solley et al,[32] 1982	27	0	No	
Saxon et al,[119] 1987	62	1 (1.6)	No	Not noted
Blanca et al,[120] 1989	16	2 (12.5)	No	Cefamandole
Shepherd and Burton,[121] 1993	9	0	No	
Audicana et al,[90] 1994	12		Yes	
Pichichero and Pichichero,[122] 1998	39	2 (5.1)	No	Cefaclor (other cephalosporin not indicated)
Novalbos et al,[123] 2001	23	0	Yes	
Macy and Burchette,[48] 2002	42	1 (2.4)	No	Cefixime
Romano et al,[124] 2004	75	0	Yes	
Greenberger and Klemens,[125] 2005	6	0	No	
Park et al,[3] 2010	85	2 (2.4)	No	Cefazolin and cephalexin
Ahmed et al,[126] 2012	21	0	No	
TOTAL	446	13 (2.9)		

and colleagues[92] and Miranda and colleagues[91] collectively challenged 37 patients selectively allergic to amoxicillin with cefadroxil and 10 (27%) reacted.

Based a comprehensive review of the published literature and consensus opinion, The American Academy of Allergy, Asthma and Immunology Cephalosporin Administration to Patients with a History of Penicillin Allergy Workgroup Report made the following recommendations.[93] The use of penicillin skin testing was encouraged, because by virtue of ruling out penicillin allergy in the vast majority of patients, it greatly simplifies the approach to treatment of cephalosporins. Namely, penicillin skin test–negative patients may receive any beta-lactams safely without increased risk of allergic reactions. If penicillin skin testing is positive, then cephalosporins should be given via graded challenge or desensitization, but given that the risk of reaction is only approximately 3%, graded challenge is preferred. If penicillin skin testing is unavailable and patients with history of "severe" penicillin allergy are excluded, then cephalosporins may be given via full dose or graded challenge, depending on the reaction history, stability of the patient, and route of administration. There is no uniform definition for what constitutes a "severe" penicillin allergy, but exclusion of these patients was a common theme in **Table 3** studies, and hence the basis for the Workgroup Report recommendation. For patients believed to be selectively allergic to aminopenicillins, cephalosporins with identical R1 group side chains should be avoided (cefadroxil, cefprozil, and cefatrizine for amoxicillin; cephalexin, cefaclor, cephradine, and cephaloglycin for ampicillin). However, these patients may receive other cephalosporins via full dose or graded challenge, as outlined previously. Last, cephalosporin

skin test may be considered to further reduce the risk of reaction, but this is not standardized and only possible with intravenous (IV) cephalosporins, not oral ones. The article by Solensky and colleagues,[82] Drug Allergy: An Updated Practice Parameter, made similar recommendations regarding cephalosporin administration to patients with a history of penicillin allergy.

A novel approach to decrease overuse of broad-spectrum antibiotics in hospitalized patients with a history of penicillin allergy, targeting nonallergist inpatient providers, has been implemented in several hospitals in Boston.[94,95] After educational intervention, a drug allergy history–based clinical guideline was developed specifically for use by general inpatient providers. Depending on type of penicillin reaction history, the treatment algorithm allowed cephalosporin treatment either via graded challenge or full dose. This novel strategy does not require specialty consultation services or training to perform penicillin skin testing. Studies of this approach have shown that it results in increased use of beta-lactams instead of broad-spectrum antibiotics such as vancomycin and quinolones.[94,95]

Penicillins/Carbapenems

The data on allergic cross-reactivity between penicillins and carbapenems mirrors the discussion on penicillin/cephalosporin cross-reactivity. **Table 5** summarizes published studies in which patients with a history of penicillin allergy were challenged with carbapenems (without preceding penicillin skin testing), and they showed an increased rate of reactions. The studies are subject to several confounding factors including lack of confirmation of penicillin allergy, lack of placebo and other controls, probable selection bias in avoiding carbapenems in patients with more severe or recent penicillin allergy histories, and "multiple drug allergy syndrome." Studies in which patients were proven to be penicillin-allergic before being challenged with carbapenems are superior in design. **Table 6** summarizes studies in which penicillin skin test–positive patients were challenged with carbapenems, and remarkably the reaction rate was 0%. Moreover, all the patients underwent carbapenem skin testing, but only 1% were positive (and therefore were not challenged with carbapenems). The PPV of carbapenem skin testing is uncertain, meaning that at least 99% of penicillin-allergic patients tolerate carbapenems. Solensky and colleagues[82] recommend that penicillin skin test–positive patients and patients with a history of penicillin allergy who do not undergo skin testing receive carbapenems via graded challenge.

Penicillins/Monobactams

Aztreonam is the only monobactam and the only beta-lactam antibiotic that contains a monocyclic ring structure, in contrast to the bicyclic core of other beta-lactams.

Table 5
Carbapenem in patients with history of penicillin allergy (without prior penicillin skin testing)

	Carbapenem Reaction Rate		
Study	**History of Penicillin Allergy**	**No History of Penicillin Allergy**	***P***
McConnell SA,[127] 2000	4/63 (6.3%)	N/A	N/A
Prescott et al,[128] 2004	11/100 (11%)	3/111 (2.7%)	.024
Sodhi et al,[129] 2004	15/163 (9.2%)	4/103 (0.04%)	.164
Cunha et al,[130] 2008	0/110	N/A	N/A
Crotty et al,[115] 2015	3/56 (5%)	N/A	N/A

Abbreviation: N/A, not indicated.

Table 6
Carbapenem challenges in patients with history of penicillin allergy and positive penicillin skin testing

Study	No. of Patients	No. of Reactions (%)	Carbapenem Given	Comments
Romano et al,[131] 2006	110	0	Imipenem	1 patient imipenem skin test–positive
Romano et al,[132] 2007	103	0	Meropenem	1 patient meropenem skin test–positive
Atanaskovic et al,[133] 2008	107	0	Meropenem	1 patient meropenem skin test–positive
Atanaskovic et al,[134] 2009	123	0	Imipenem	1 patient imipenem skin test–positive
Gaeta et al,[135] 2015	211	0	Imipenem Meropenem Ertapenem	No patients carbapenem skin test–positive Patients challenged with all 3 carbapenems
TOTAL	654	0		

All patients also underwent skin testing with carbapenems and only those who were skin test–negative were challenged.

In vitro studies demonstrated virtually no immunologic cross-reactivity between penicillins and aztreonam.[96–99] Likewise, skin testing and challenge studies revealed no evidence of allergic cross-reactivity between penicillins and aztreonam, including no positive aztreonam challenges in penicillin skin test–positive patients.[96,98,100,101] Therefore, patients with history of penicillin allergy may receive aztreonam in usual fashion, without special precautions. The only beta-lactam that shows cross-reactivity with aztreonam is ceftazidime, and these 2 antibiotics share an identical R-group side chain.

ALLERGY TO CEPHALOSPORINS

Allergic reactions to cephalosporins are not as common as those to penicillins. The incidence of beta-lactam–related cutaneous reactions (mostly maculopapular eruptions and urticaria) in a large inpatient prospective trial was 5.1% of exposed patients (amoxicillin), 4.5% (ampicillin), 1.6% (penicillin G), and 1.5% (cephalosporins).[102,103] It is not known how many were due to drug-specific IgE antibodies. Limited data suggest that the incidence of anaphylaxis due to cephalosporins is approximately 1 order of magnitude lower than penicillins.[104]

The lack of standardized validated skin testing makes evaluation of possible cephalosporin-induced IgE-mediated allergy more difficult than penicillin allergy. Skin testing (prick/puncture followed by intradermal, analogous to penicillin skin testing) with nonirritating concentrations of native cephalosporins can be of some value, but its predictive value is unknown. A positive skin test using a nonirritating concentration is suggestive of IgE-mediated allergy, but a negative result does not necessarily rule out sensitivity. Also, intradermal skin testing is usually limited to IV cephalosporins, not with cephalosporins available only in oral forms. Several studies have investigated nonirritating skin test concentrations of cephalosporins in healthy nonallergic control subjects. Empedrad and colleagues[105] found cefuroxime, cefotaxime, ceftriaxone, and ceftazidime to be nonirritating at 10 mg/mL, whereas cefazolin

was nonirritating at 33 mg/mL. Similarly, Testi and colleagues[106] reported the same 5 cephalosporins to be nonirritating at 20 mg/mL, whereas cefepime was irritating at 20 mg/mL. Romano and colleagues[107] showed cephalexin, cefaclor, cefadroxil, cefazolin, and ceftibuten to be nonirritating at 20 mg/mL, whereas other cephalosporins (cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, cefepime, cefoperazone, cefodizime) were nonirritating at 2 mg/mL.

When evaluating allergies to cephalosporins, a common dilemma is whether patients who have reacted to one cephalosporin are able to tolerate other cephalosporins. The immune response in IgE-mediated allergy to cephalosporins is likely directed mostly at the R1 or R2 group side chains, implying that patients allergic to some cephalosporins can tolerate cephalosporins with dissimilar side chains. However, the evidence for this is limited to largely single-patient case reports and small case series,[108–111] and one recently published larger case series.[107] In the largest case series, Romano and colleagues[107] studied 102 patients with recent convincing immediate-type allergic reactions to cephalosporins. A total of 83% of the patients reported anaphylaxis (including hypotension in two-thirds and loss of consciousness in three-eighths) and 9% urticaria. All the patients underwent skin testing with at least 11 different cephalosporins (including the culprit cephalosporins), and based on the skin test responses, were categorized into 4 groups. Group A comprised 73 patients and included patients who had historical reactions to and were skin test–positive to ceftriaxone or other cephalosporins with identical/similar R1 group side chains (cefotaxime, cefuroxime, cefepime, ceftazidime, and cefodizime). Thirteen patients in group B reported historical reactions and were skin test–positive to so called amino-cephalosporins (cephalosporins that contain R1 group side chains identical to amoxicillin or ampicillin: cephalexin, cefaclor, and cefadroxil). Group C contained 7 patients and the following cephalosporins with similar R1 group side chains: cefazolin, cefamandole, cefoperazone, and ceftibutin. Group D (9 patients) showed skin test positivity to cephalosporins from more than 1 group, which suggests the immune response was directed at cross-reacting core determinants, rather than side chains. Graded challenges were performed with selected (not all) cephalosporins to which skin tests were negative, and none of the patients reacted. Notably, patients were not challenged with cephalosporins with similar R-group side chains as the culprit cephalosporin, even if skin testing to those cephalosporins was negative. To summarize, approximately 90% of patients were found to have IgE-mediated allergies to cephalosporins directed at R-group side chains, whereas 10% showed positivity to various cephalosporins with dissimilar side chains.

Based on the available evidence, the approach to patients with history of cephalosporin reactions that could be IgE-mediated, and who require treatment with other cephalosporins, is 2-step to 3-step graded challenge with a cephalosporin with dissimilar side chains. If possible, a negative skin test using a nonirritating concentration of the cephalosporin to be administered may provide additional evidence of lack of allergy. A positive skin test should be assumed to indicate IgE-mediated allergy and the patient should avoid that cephalosporin (and similar ones), or receive it via rapid desensitization if there are no alternate treatment options.

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