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REVIEW



# Self-reported beta-lactam intolerance: not a class effect, dangerous to patients, and rarely allergy

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## ABSTRACT

**Introduction:** About 8% of the United States population carries an unconfirmed penicillin ‘allergy’ in their medical record. Many physicians needlessly avoid other beta-lactam use in individuals with unconfirmed penicillin allergies. There is a significantly increased risk of developing serious antibiotic-resistant infections, and increased morbidity and mortality in those who report penicillin allergy.

**Areas covered:** Within this study, we reviewed the relevant literature on self-reported beta-lactam allergy. We discuss how the myth of serious allergy to penicillin developed and then discuss in detail clinically significant immunologically mediated hypersensitivity reactions. Following this discussion, we delineate the risks of not using a beta-lactam when it is the drug of choice and then discuss the epidemiology of beta-lactam-associated anaphylaxis, serious cutaneous adverse reactions, and serious systemic immunologically mediated reactions. Following these topics, we further discuss the consensus current best practices to de-label patients with reported penicillin allergy.

**Expert opinion:** An unconfirmed allergy to penicillin offers considerable harm to patients. Many patients have low-risk allergy symptoms to penicillin who could likely tolerate the medication without having an allergic reaction. The current best practices to de-label reported penicillin allergy is the utilization of a single dose oral challenge, with 1 h of observation, in low-risk patients.

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## KEYWORDS

Adverse drug reaction;  
cephalosporin; drug allergy;  
oral challenge; penicillin

## 1. Introduction

The goal of antibiotic stewardship is giving the safest, most effective, antibiotic for the shortest duration necessary [1]. For many common bacterial infections, this is less than 1 week of a narrow-spectrum oral penicillin. For decades beta-lactams, penicillins, and more recently cephalosporins, carbapenems, and monobactams, have been the most widely used, and unfortunately often over-used, antibiotic class [2]. Penicillin is the most commonly reported drug family allergy [3]. There is a certain predictable rate of adverse reactions that will occur after all antibiotic exposures [4]. Some of these will result in a self-reported ‘allergy’. Currently, in the United States, about 8% of the population carries an unconfirmed penicillin ‘allergy’ in their medical record [3]. Many physicians still needlessly avoid other beta-lactam use in individuals with unconfirmed penicillin allergies [5]. The understanding of the risks associated with unconfirmed beta-lactam allergies, and optimal methods to confirm or de-label individuals with penicillin allergies, has advanced significantly over the past 20 years [6]. There reference standard to confirm or refute a current clinically significant immunologically mediated hypersensitivity is a challenge with a therapeutic dose [7]. Only a small fraction of these reported adverse reactions are reproducible with re-exposure [6]. Currently, the greatest risk to the most patients with a penicillin ‘allergy’ is continued avoidance of penicillins, or other beta-

lactams, when they are clinically indicated [8–13]. There is a significantly increased risk of developing serious antibiotic-resistant infections, including *Clostridioides difficile* (C. Diff), methicillin-sensitive *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), along with an increase in morbidity and mortality in those who report penicillin allergy in both hospitalized and outpatient population-based cohorts [14,15].

### 1.1. How we got here

Penicillin became available for widespread use in the mid-1940s; however, early preparations were impure, which likely contributed to enhanced immunogenicity [16]. A recollection of the first use of penicillin in a civilian in the United States described the use of an orange-brown fluid that was filtered through asbestos prior to intravenous administration [16]. By 1946, urticarial rashes after exposure to penicillin were reported to occur at a rate of 0.5–5.7%, along with multiple cases of serum sickness-like reactions [17]. In 1956, the two most feared parenteral penicillin-associated adverse drug reactions were severe delayed-onset serum sickness and fatal anaphylaxis, with an estimated annual incidence of 100 cases occurring in the United States in 1952 [18]. This high level of fatal anaphylaxis resulted in virtually all individuals with any rash after any penicillin use in the 1950s to be told never to be exposed to any penicillin again because they

**Article highlights**

- About 8% of the United States population carries an unconfirmed penicillin 'allergy' in their medical record.
- Many physicians needlessly avoid other beta-lactam use in individuals with unconfirmed penicillin allergies.
- There is a significantly increased risk of developing serious antibiotic-resistant infections, along with an increase in morbidity and mortality in those who report penicillin allergy.
- Less than 5% of the individuals with an unconfirmed penicillin allergy will have clinically significant acute or delayed onset hypersensitivity confirmed after appropriate testing.
- Low-risk patients can safely undergo a direct oral amoxicillin challenge to confirm current tolerance.
- Higher-risk patients warrant Allergy or other specialist consultation able to perform penicillin skin testing prior to an oral amoxicillin challenge to confirm current tolerance.

could 'die.' This fear has influenced future generations of physicians and is still present to some degree today, even though the current risk of anaphylaxis is orders of magnitude lower [6].

The last-published consensus recommendations on the evaluation of penicillin allergy are out of date [19]. There is an extensive European literature, mainly produced by centers of excellence that have concentrated on the evaluation of anaphylaxis and other serious reactions, that recommend very complex algorithms for penicillin allergy evaluations, that would lead to numerous false-positive determinations, if applied to average-risk individuals [20]. There are newly published consensus recommendations, endorsed by the American Academy of Allergy Asthma and Immunology (AAAAI), the Infectious Diseases Society of America (IDSA), and the Society for Healthcare Epidemiology or America (SHEA), on the evaluation of penicillin allergy that have advanced the field significantly, specifically with respect to the use of direct oral challenges to confirm tolerance in low-risk individuals [21].

Beta-lactams are good immunogens in humans. They have strong antigenic properties, which are affected by preparation and route administration. Penicillins are unstable in aqueous solutions and when given by slow infusion induce higher rates of anti-penicillin specific IgG and T cells than bolus, oral, or IM administration [22,23]. Lower rates of parenteral penicillin administration in primary care over the past several decades have probably also contributed to lower rates of immunologic sensitization. Topical exposures to penicillin, that can accidentally occur in health-care workers administering aqueous preparations, can result in high rates of IgE-mediated sensitization [24].

There has been a lingering concern of possible cross-reactivity between penicillins and cephalosporins that significantly affect the care that patients receive [5]. Original reports of cross-reactivity between penicillins and cephalosporins were not based on credible clinical data [25]. Penicillins may have physically contaminated cephalosporins, which could have contributed to falsely high cross-reactivity estimates [25]. More recent reports about cross-reactivity, relying exclusively on skin testing or immunochemistry, without confirmation by challenge, also contribute to this unwarranted fear of clinically significant cross-reactivity [26,27].

## 2. Clinically significant immunologically mediated hypersensitivity

The epidemiology of penicillin 'allergy' reports in the medical record is well understood at present. Females have a higher prevalence of penicillin allergy than males and also have higher incidence rates of new 'allergy' reported after each penicillin exposure [3,4]. Older individuals are more likely to be labeled as penicillin 'allergic' than younger individuals. Surveys of hospital populations show a higher prevalence of penicillin 'allergy' compared to outpatient cohorts [3,13]. Penicillin 'allergy' prevalence is higher in countries with greater rates of penicillin use and overuse. There is a higher incidence of penicillin 'allergy' reported after each exposure to penicillin in individuals with any other drug 'allergy' reported [3].

### 2.1. Definitions

Words matter. What something is called influences how people think about it. When allergies to beta-lactams are reported within the medical record, many providers fear the possibility of an anaphylactic reaction or a serious cutaneous adverse reaction (SCAR) occurring with any subsequent administration of that, or any other, beta-lactam. The word 'allergy' should not be used to describe most cases of suspected or reported penicillin, or any other beta-lactam, intolerance [28]. Unconfirmed or incompletely characterized adverse reactions should be labeled by default as adverse and not allergic in the electronic health record (EHR). Hypersensitivity is the term that should be reserved to describe immunologically mediated adverse drug reactions. Allergy is a very specific subgroup of hypersensitivity, mediated through mast cell activation, typically via antigen-specific IgE bound to the mast cells. It is possible to desensitize individuals with true allergy and safely give them the needed penicillin or other beta-lactams [6]. Tolerance implies the individual did not have a problem with the last exposure.

Immunologically mediated hypersensitivity can be caused by antigen-specific IgE activating mast cells, antigen-specific IgG, T cell-mediated reactions and complement activating mast cells, or direct mast cell activation [29,30]. The key feature of immediate-onset hypersensitivity, true allergy, is typical symptom onset <1 h, but by international definition, up to 6 h after the first exposure during the last therapeutic course and the ability to desensitize [29]. Allergy can be mediated through antigen-specific IgE activating mast cells, antigen-specific IgG and complement activating mast cells, or direct mast cell activation [29]. Other clinical patterns of immediate reactions usually occur in the form of isolated urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea), or anaphylaxis with or without cardiovascular collapse (anaphylactic shock) [30]. Individuals with a penicillin allergy, who have a life-threatening infection that can be best treated with penicillin, can be desensitized by giving doubling doses of the needed drug every 15 to 30 min, starting at about 1/5000<sup>th</sup> to 1/10,000<sup>th</sup> of the desired final therapeutic dose. It is then critical to continue constant exposure. If more than five half-lives expire prior to re-exposure, then desensitization needs to be repeated to avoid anaphylaxis [29].

The key feature of delayed-onset hypersensitivity, T-cell-mediated reactions, is maculopapular rashes onset >24 h, but by international definition down to 6 h, after the first dose of the last therapeutic course [29]. Bircher and coworkers have noted that delayed, or T cell-mediated reactions have a typical time course of beginning at 2 days, but may start as early as 8 to 12 h [30]. The time to onset is often longer, 4 to 24 days, for SCARs and other serious systemic immunologically mediated reactions (SSIMRs) such as severe hepatitis, nephritis, immune-mediated cytopenias, and serum sickness. Because these reactions are mediated by antigen-specific T-cells, it is not possible to desensitize [20]. Rechallenges can be considered in the setting of suspected benign delayed-onset hypersensitivity to confirm current tolerance. A single therapeutic dose challenge with 5 days of observation is adequate to safely rule out a clinically significant T-cell-mediated hypersensitivity [29]. Minor-delayed onset rashes can often be treated through if the risk of the underlying infection outweighs the risk of the rash [20].

If there is fear of a full dose challenge, one can give 1/10<sup>th</sup> of the dose followed by a full dose, if desired, for 'graded' challenges to confirm tolerance [29]. The use of two steps has not been shown to increase safety but may increase the number of patients and physicians willing to proceed with a challenge, particularly in settings where challenges are not routinely done.

When the clinical presentation of the suspected penicillin-associated adverse reaction is headache, nausea, vomiting, yeast infection, delayed onset hives, other benign rashes, other benign reactions or associations, fear because of family history, other benign reasons, or unknown, the mechanism is likely to be from an underlying viral or bacterial infection, a pharmacologic effect, or other non-immunologically mediated side-effect [6]. These account for 93% to 96% of the 'allergy' reports in the EHR. When the presentation is a delayed onset rash, if it is immunologically mediated, it is likely to be T-cell mediated and this can occur 3–5% of the time. Acute onset IgE-mediated hives only occur about 1–2% of the time, and anaphylaxis accounts for less than 1 in 1000 of these acute IgE-mediated reactions but can be life-threatening. Delayed onset T-cell-mediated SCARs or SSIMRs are even rarer, occurring less than 1/10,000<sup>th</sup> as often as benign T-cell-mediated rashes. In a recent review, we noted that in 3299 low-risk individuals, children, and adults, with an unconfirmed penicillin allergy given a direct oral amoxicillin challenge to confirm current tolerance there were only 42 (1.3%) [95% CI 0.9% to 1.7%] who were acutely positive and an additional 130 (3.9%) [95% CI 3.3% to 4.7%] who had delayed-onset hypersensitivity [6,31–36].

### 3. The risks of not using a beta-lactam when it is the drug of choice

Many previous studies have confirmed that avoidance of cephalosporins in patients with penicillin allergy results in negative outcomes, which include an increased risk of adverse events, suboptimal treatment of infections, and treatment failures [8–13].

Elliot and coworkers reported a retrospective, nested, case-control trial in children comparing monotherapy with a beta-lactam, clindamycin, or co-trimoxazole for the treatment of community-acquired non-cultured skin and soft-tissue infections in an MRSA endemic region [37]. They found that clindamycin

monotherapy conferred no benefit compared to beta-lactam monotherapy and that co-trimoxazole was associated with an increased risk of treatment failure.

Blumenthal and coworkers found that patients with a reported, but unconfirmed, penicillin allergy had a 50% increased odds of surgical site infection (SSI) directly attributable to the receipt of second-line perioperative antibiotics [11].

Murphy and coworkers also found an increased risk for SSI in patients who received clindamycin as perioperative prophylaxis during head and neck surgical procedures [12].

Blumenthal and coworkers also found that patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia, for which first-line therapy is a beta-lactam, were often given vancomycin instead, which resulted in the fewer patients achieving MSSA cure, the higher rates of recurrence, and a greater frequency of adverse drug reactions [9].

Not using a beta-lactam, when it is the preferred agent leads, to increased risks of infection to patients, but there is also significant burdens to hospital systems as well. MacFadden and coworkers evaluated the impact of reported beta-lactam allergy at three academic hospitals [8]. This study found that when patients reported beta-lactam allergy, and it was the preferred treatment agent, 35% of those patients did not receive that therapy. This occurred even if the reported allergy was non-severe. After adjustment for confounders, they found that those who did not receive preferred beta-lactam therapy, due to reported allergy, were at greater risk of adverse events compared with those without reported allergy. Adverse events were defined as readmission for the same infection, acute kidney injury, C diff infection, or drug-related adverse reactions requiring discontinuation.

We have recently reported that testing for penicillin allergy results in fewer hospital days and significant cost savings [38]. Kaiser Permanente Southern California removed the warning in their electronic medical record system not to use cephalosporin in individuals with penicillin allergy in December 2018.

There is a very small increased risk of having a new cephalosporin 'allergy' reported in the presence of an unconfirmed penicillin 'allergy'; however, in patients with a confirmed penicillin allergy there may be a 10–33% increased risk for cephalosporin skin test positivity with the same side chain [38,39]. Oral challenge data confirming that this represents clinically significant hypersensitivity are lacking. True IgE mediated cross-reactivity between cephalosporins (which have an R and R<sub>1</sub> side chain) and penicillins (R<sub>1</sub> side chain only) is hypothesized to occur due to the presence of a shared R<sub>1</sub> side chain [40]. However, additional testing to document acute tolerance to a cephalosporin in the setting of a penicillin allergy, before therapeutic use of the cephalosporin, is not clinically useful and it does not improve overall patient safety or clinical outcomes [5]. Avoiding the use of cephalosporins in penicillin-allergic patients will likely result in the greater use of less effective non-beta-lactam antibiotics [5].

### 4. Epidemiology of beta-lactam-associated anaphylaxis, SCARs, and SSIMRs

Beta-lactam-associated anaphylaxis is much rarer than commonly feared. In un-audited reviews of EHR reports, many times when anaphylaxis is coded contemporaneously with

a beta-lactam exposure it was erroneously coded or related to some other issue not acutely associated with the beta-lactam administration. Historical reports of penicillin and cephalosporin-associated anaphylaxis are typically of very poor quality [19]. We know that the risk of causing death with an oral amoxicillin exposure is extremely low, as there was only one fatality noted after oral amoxicillin and a total of 7 deaths associated with parenteral or unknown routes of amoxicillin exposure in over 100,000,000 amoxicillin courses given in Great Britain over a 35-year period [41].

We recently audited 2,115,406 individuals exposed to 4,558,196 courses of oral penicillins and 192,925 individuals exposed to 285,894 courses of parenteral penicillins over an 8-year period, between 1 January 2009 and 31 December 2017 [42]. We identified 22 cases (1 in 207,191 (0.00048%)) of confirmed anaphylaxis associated with oral penicillin exposures and 3 cases (1 in 95,298 (0.00105%)) of confirmed anaphylaxis associated with a parenteral penicillin exposure.

We previously audited 622,456 individuals exposed to 901,908 courses of oral cephalosporins and 326,867 members exposed to 487,630 courses of parenteral cephalosporins over a 3-year period, from 1 January 2010, through 31 December 2012, and that during this time confirmed cephalosporin-associated anaphylaxis occurred after only 5 oral exposures and 8 parenteral exposures [42].

With regard to anaphylaxis progressing to death, an additional review completed by Jerschow, found that over a 12-year period there were 2,458 cases of death due to anaphylaxis and beta-lactams were only attributed to 68 (0.02%) of those deaths [41]. It is also important to note that anaphylaxis varies in incidence and cause between countries [43].

Beta-lactam-associated SCARs or SSIMRs are even rarer than anaphylaxis. There is no accurate population-based incidence data for penicillin or cephalosporin-associated SSIMRs. In the same cohorts audited for penicillin and cephalosporin-associated anaphylaxis commented on above, we identified only 2 cases of penicillin-associated SCARs with 4,844,090 exposures and 3 total cases of cephalosporin-associated SCARs with 1,389,538 exposures. All cephalosporin-associated SCARs were also associated with the use of another antibiotic at the same time as the cephalosporin [38,42].

#### 4.1. The key elements of a beta-lactam-associated adverse reaction history

The key questions that need to be answered when determining the appropriate management, direct oral challenge, skin test prior to oral challenge, or continued avoidance are outlined in Table 1. [6,29]

### 5. Current best practices to de-label penicillin allergy

Direct oral amoxicillin challenge can be performed in any patients with a history of the following symptoms, associated with penicillin, occurring more than 12 months ago: any benign rash, GI symptoms, headaches, other benign somatic symptoms, or unknown history [6]. Consider penicillin skin testing first with penicilloyl-polylysine (PrePen®) if the index reaction to

penicillin occurred within the past 12 months, the patient has any history of shortness of breath or anaphylaxis associated with penicillin, or the patient or the physician is afraid of a direct oral challenge. Proceed to the confirmatory amoxicillin challenge only if skin test negative [6].

Do not perform any penicillin allergy testing if there is a history of penicillin-associated SCAR or SSIMR, including any blistering rash involving  $\geq 10\%$  of the body surface area with skin loss, hemolytic anemia, nephritis, or hepatitis [6]. Penicillin allergy testing is not useful in evaluating isolated cephalosporin-, carbapenem-, or monobactam-associated reactions [44]. Reconfirming acute penicillin tolerance is not necessary if a penicillin class antibiotic has been used and tolerated since the index reaction.

We currently recommend that a direct oral amoxicillin challenge with 60 min of observation post-challenge in patients with low-risk histories to confirm acute tolerance and 5 days of observation to confirm the lack of a clinically significant delayed-onset T-cell-mediated hypersensitivity. An objective reaction, acutely hives or anaphylaxis and chronically an observable rash, is necessary to be considered positive. Subjective reactions such as itching without rashes, headaches, or anxiety are considered negative challenges, and these patients are recommended to use penicillin in the future. Patients are also informed that there is about a 3% chance of having some sort of reaction with each and every future penicillin usage [38]. We only penicillin skin test first if there is a higher-risk history or fear of direct oral challenge. We have tested 1205 individuals in San Diego using this protocol in the past 2 years, and the outcome data are presented in Table 2.

The optimal time to refer someone for skin testing, prior to an oral challenge, is at least 6 weeks after resolution of the acute reaction. This ensures that if there was an episode of acute post-infection urticaria, it would have adequate time to resolve and not result in dermatographism precluding accurate skin testing or a false-positive oral challenge. Additional reasons to consider referring for skin testing are if the patient is unwilling to do a challenge without skin testing first, or if the treating physician feels uncomfortable with providing their patient a direct oral challenge [12].

The major determinant, penicilloyl-poly-lysine (Pre-Pen®) accounts for the majority of positive penicillin skin test results. Puncture testing followed by intradermal testing is recommended. It is critical to use at least 5 mm of wheal, with flare greater than wheal, as the criteria for a positive penicillin puncture or intradermal test result [45]. Minor determinants are not needed at this time [6]. Penicillin skin testing, particularly when using non-standardized minor determinates, has many false-positive results [46]. An oral amoxicillin 250 mg challenge, with 1 h of observation, is given to all skin test negative individuals to confirm current tolerance. This dose can be adjusted down for children under age 5, where 125 mg is typically used. Subjective acute oral challenge reactions are about 3 times as common as objective challenge reactions. Delayed challenge reactions are typically benign and occur 2 to 5 days after the oral challenge. Longer challenges, over multiple days, may result in more benign challenge reactions, without any increase in overall safety.



**Table 1.** Elements of a beta-lactam intolerance history.

Elements	Comments
Antibiotic*	The specific beta-lactam implicated needs to be listed Do not list 'Cephalosporins' as only the specific cephalosporin implicated needs to be avoided.
Date of index exposure	The longer the time since the index reaction, the lower the probability there is any clinically significant anti-beta-lactam IgE present.
Route of exposure	Oral Parenteral
Time to symptom onset after 1 <sup>st</sup> dose of last course*	Clinically-significant IgE-mediated allergy typically presents within the first hour after oral exposure and always within 30 minutes of a parenteral exposure. Maculopapular T-cell mediated reactions benign cutaneous typically occur 2 to 5 days after the first dose of the last course.
Time to symptom resolution	SCARs and SSIRMs may have delayed onset up to 4 weeks after exposure. Individual hives, by definition, only last hours in a single site. Individual site affected by T-cell mediated rashes may be evident for days to weeks. SCARs take weeks to resolve and SJS must affect at least 10% of the body surface area and TEN at least 30% of the body surface area, by definition.
Symptoms*	Benign rash Hives Shortness of breath Anaphylaxis GI upset Headache Serious cutaneous adverse reaction (SCAR) Serious systemic immunologically-mediated reaction (SSIMR) including hepatitis, nephritis, immune cytopenias, and serum sickness reactions Other benign symptoms
Treatment given	Unknown None- just stopped the drug Antihistamine Epinephrine Systemic or topical steroids

\* essential elements

**Table 2.** Penicillin allergy testing outcomes at Kaiser Permanente San Diego (1 January 2017 to 31 December 2018).

- 1205 children and adults
  - 399 (33.1%) had penicillin skin testing first
    - 6 (1.5%) skin test positive
    - 7 (1.8%) acute oral challenge positive after negative skin testing\*
    - 1 (0.3%) delayed oral challenge positive †
    - 16 (4.0%) subjective oral challenge reactions
  - 806 (66.1%) had direct oral amoxicillin 250 mg challenge
    - 2 (0.2%) acute oral challenge positive\*
    - 9 (1.1%) delayed oral challenge positive †
    - 23 (2.9%) subjective oral challenge reactions
  - Overall 25 (2.1%) positive
    - 15 (1.2%) acutely positive (IgE-mediated)
    - 10 (0.8%) delayed-onset positive (T-cell-mediated)
    - 39 (3.2%) subjective oral challenge reactions

\* (p = 0.0072)

† (p = 0.1799)

Acute subjective reactions were more common than acute objective reactions (p = 0.0008).

None of the acute reactions was serious, and all were managed with oral antihistamines or intramuscular adrenaline. None of the delayed reactions was serious. All subjective reactions were considered negative results, and the patients were recommended to use penicillins in the future if clinically indicated. This cohort has been previously reported in part [6].

## 6. Where we need to be

There are about 26 million Americans who need to be evaluated for their unconfirmed penicillin 'allergies' and about another 4.2 million who carry an unconfirmed cephalosporin 'allergy' [21]. Only about 1.3 million currently need to continue to avoid penicillins. Every physician needs to get an accurate drug intolerance history before avoiding a beta-lactam when it is the drug of choice. When possible based on a careful and complete history, patients with an unconfirmed penicillin 'allergy' should be challenged with a single oral amoxicillin

250 dose to confirm current tolerance. Continue to expect adverse reactions with all antibiotic use, even after negative challenges [37,47]. Use the right antibiotic, for the shortest effective period of time, every time.

## 7. Conclusions

Penicillin is still the most commonly reported drug allergy. There is likely no clinically significant immunologically mediated cross-reactivity between unconfirmed penicillin allergy and other beta-lactams. Unconfirmed penicillin 'allergy' leads to substantial harm to patients, increased adverse reactions to second-line agents, increased hospitalization, and increased morbidity from Cdiff, VRE, and MRSA. Beta-lactam-associated anaphylaxis and SCARs are much rarer than commonly feared. A structured history of the penicillin-associated reaction will place patients into low-risk, higher-risk, and absolutely contraindicated groups. Low-risk patients can safely undergo a direct oral amoxicillin challenge to confirm current tolerance [48]. Higher-risk patients warrant Allergy or other specialist consultation able to perform penicillin skin testing prior to an oral amoxicillin challenge to confirm current tolerance. Patients with a confirmed beta-lactam allergy, who need that specific beta-lactam for a life-threatening infection, can safely undergo desensitization. Only patients with SCARs or SSIMRs need continued avoidance.

## 8. Expert opinion

The understanding of the risks associated with unconfirmed beta-lactam allergies, and optimal methods to confirm or de-label individuals with penicillin allergies, has advanced significantly over the past 20 years. Patients with reported beta-lactam allergy have been found to have increased adverse events that

include treatment failures, development of antibiotic-associated illnesses, and increased mortality. Additionally, the presence of this reported allergy has a significant economic impact on both patients and health-care systems. Therefore, addressing unconfirmed beta-lactam allergy on a large scale would lead to a dramatic reduction in the morbidity and mortality associated with unconfirmed beta-lactam allergy and would also lead to a significant reduction in healthcare-associated costs. Approximately 26 million Americans need to be evaluated for an unconfirmed penicillin 'allergy', and an additional 4.2 million carry the diagnosis of an unconfirmed cephalosporin 'allergy'. The sheer volume of patients with reported beta-lactam allergy is overwhelming and the practice of solely relying on specialized allergy clinics is limiting the ability to address the issue. Currently, a knowledge gap on how to conduct these de-labeling practices exists for providers outside of the field of allergy and immunology. However, recent studies have outlined a standardized approach of completing single step oral penicillin challenges in patients with low-risk allergy symptoms that can de-label unconfirmed allergy. The dissemination of this information through scientific publications, academic conferences, and media coverage is the key to changing clinical practice and addressing reported beta-lactam allergy on a large scale. However, this only addresses the issue from a provider perspective.

It is well known that patients often identify with their labeling of allergy to beta-lactams and that there is an inherent fear of being re-exposed to the medication. Patients often fear that re-exposure will lead to a serious allergic reaction or death, when the vast majority are not actually allergic and could tolerate the medication without any significant adverse or allergic reaction. Qualitative studies that examine patient perceptions of their beta-lactam allergy, along with barriers to de-label them from their perspective would be informative. In order to have a sustainable impact on reported beta-lactam allergy, novel approaches to disseminate information to patients will also need to be developed. Potential options could include: patient educational pamphlets/tutorials, organized media campaigns to disseminate study findings, and enhanced focus on provider/patient interactions regarding unconfirmed allergy.

In patients with unconfirmed low-risk beta-lactam allergy, the future of study lies in the transition from 'research' on the subject into the adoption of standardized procedures that may be considered 'quality improvement'. This can be done through the adoption of standard procedures for allergy de-labeling that are outlined in a vast amount of recent studies, and European position paper. It is easily foreseeable to see an end-point in which the majority of patients who report allergy can be easily de-labeled which would dramatically decrease the millions of patients who report allergy. Once low-risk patients are addressed in this fashion, patients with high-risk allergy symptoms can be more easily focused on, and the development of novel techniques to address their reported allergy can become a primary focus.

Why it is important and how to effectively delabel individuals with unconfirmed penicillin allergy is now well established. It is less clear on how to proceed with unconfirmed non-penicillin beta-lactam allergies. There are limited data on rechallenges with cephalosporins, carbapenems, or monobactams. Because of the

lack of clinically significant immunologically mediated cross-reactivity between individual cephalosporins, carbapenems, and monobactams, each of these non-penicillin beta-lactams becomes an individual case. Given the relative rarity of specific non-penicillin beta-lactam allergy, it is difficult to get large numbers of cases at a single institution. There are limited data on the clinical outcome associated with just avoiding the specific non-penicillin beta-lactam when it is the drug of choice. Without this data, it will be difficult to determine a risk/benefit ratio for testing or rechallenges. Many non-penicillin beta-lactams are only available in parenteral formulations, and the risk of anaphylaxis with parenteral rechallenge is typically higher than for oral rechallenges. This remains an area in need of active research.

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## Reviewer disclosures

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