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Is a Reported Penicillin Allergy Sufficient Grounds to Forgo the Multidimensional Antimicrobial Benefits of β-Lactam Antibiotics?

George Sakoulas,[1,2] Matthew Geriak,[1] and Victor Nizet[2,3]

[1]Sharp Memorial Hospital, San Diego, and [2]School of Medicine and [3]Skaggs School of Pharmacy, University of California, San Diego, La Jolla

The majority of patients with reported penicillin allergy are not allergic when tested or challenged. Penicillin allergy testing has been shown to significantly reduce annual healthcare expenditures. Data have emerged showing β-lactams have multidimensional antibacterial effects in vivo, far beyond what is appreciated in standard bacteriological susceptibility testing media. These include enhancing bacterial killing by the innate immune system. Supporting the clinical relevance of these secondary underappreciated effects are recent clinical and pharmacoeconomic analyses that show worse outcomes in patients with reported penicillin allergies who receive non-β-lactam antibiotics when compared to their non-penicillin-allergic counterparts. This is particularly relevant in the treatment of *Staphylococcus aureus* bacteremia. This article reviews the tremendous advantages offered by β-lactam therapy and makes a strong case that the debunking of false penicillin allergies through a detailed allergy history and penicillin allergy testing should be a vital component of antimicrobial stewardship practices.

Keywords. penicillin allergy; clinical outcomes; innate immunity; β-lactams; allergy testing.

In the history of medicine, antibiotics are the class of medications with the greatest impact on human health, reflected in a 2-decade increase in life expectancy in developed countries since the dawn of the antibiotic era in the 1940s. Antibiotics control common infectious diseases such as pneumonia, urinary tract infections, and skin infections through microbial killing, and support the success of many modern clinical therapeutic modalities such as cancer chemotherapy, surgery, and transplantation where infectious risk is increased [1].

The β-lactam class of antibiotics has its origin in Sir Alexander Fleming's serendipitous observation of the antibacterial properties of the *Penicillium* mold and the subsequent discovery of penicillin [1]. Approaching the 90th anniversary of this historic event in September 2018, our understanding of the therapeutic properties of β-lactam drugs beyond their direct activities in bacteriological media is still unfolding. The goals of this commentary are 2-fold. We will first review how β-lactam drugs possess numerous adjunctive pleural pharmacodynamics activities, not exhibited by other antimicrobial classes, that modulate bacterial interaction with, and susceptibility to, the innate immune system—all in a manner that benefits patients. Second, we will explore the negative consequences of withholding β-lactam antibiotics in favor of other drug classes in patients with purported (but unproven) penicillin allergies, and how penicillin allergy testing can prove to be a very cost-effective element of a successful antimicrobial stewardship initiative.

THE NATURE OF PENICILLIN "ALLERGIES"

A sensitivity to penicillin is the most common "allergy" noted among patients in the United States, self-reported by 10% of adult patients, thus accounting for approximately 25 million people [2, 3]. However, as many as 98% of these patients are deemed nonallergic by subsequent penicillin allergy testing, and tolerate future β-lactams with only a slightly greater risk than average individuals [4–6]. Allergies to penicillin may have become part of the medical record because the reaction recalled by the patient was due to another medication, the reaction was nonimmunologic (eg, gastrointestinal upset, nausea, diarrhea), or the patient was simply told of a reaction by their family decades earlier, without any recollection of details. Likewise, one cannot discount the possibility of a rash produced by an intercurrent (usually viral) infection or, as exemplified by the diffuse rash experienced by some patients receiving amoxicillin during acute mononucleosis, a transient immunologic reaction rather than a true allergy [7]. Whatever their story, the vast majority of patients with such purported allergies in their medical records are destined to receive alternative classes of antibiotics, with some direct and indirect adverse consequences to treatment and outcomes, which we review below.

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Correspondence: G. Sakoulas, Division of Host-Microbe Systems and Therapeutics, UC San Diego School of Medicine, Biomedical Research Facility II, Rm 4114, 9500 Gilman Drive, Mail Code 0760, La Jolla, CA 92093-0760 (gsakoulas@ucsd.edu).

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ADVERSE OUTCOMES IN PATIENTS ALLERGIC TO PENICILLIN

In a matched retrospective cohort study, Macy and Contreras [8] found several adverse consequences among patients with reported penicillin allergy matched to similar patients without reported allergies. The "penicillin-allergic" patients experienced significantly longer hospital stays, a 23% increase in *Clostridium difficile* infection, 14% more methicillin-resistant *Staphylococcus aureus* (MRSA) infections, and 30% more vancomycin-resistant *Enterococcus* (VRE) infections. The authors concluded that increases in opportunistic infections may have been driven by significantly higher usage of vancomycin, clindamycin, and fluoroquinolone, as vancomycin exposure is associated with VRE, and clindamycin and fluoroquinolones are the antimicrobial classes posing the greatest risk for *C. difficile* [8]. In another study, 31%–51% of vancomycin use was attributed to alternative therapy in patients with penicillin allergy [9].

In patients with severe invasive methicillin-susceptible *S. aureus* (MSSA) infections such as bacteremia and endocarditis, resorting to vancomycin to avoid a purported penicillin allergy may have serious impact on outcomes, given consistent and reproducible clinical evidence pointing to vancomycin's inferior performance in these patient settings [10–16]. For example, in a large retrospective cohort of 5633 Veterans Affairs patients with MSSA bacteremia, patients who received definitive therapy with a β-lactam had 35% lower mortality, and patients receiving cefazolin or an antistaphylococcal penicillin a 43% lower mortality, compared with patients who received vancomycin [16]. Indeed, the 2-fold increased mortality in patients with MRSA bacteremia compared to those with MSSA bacteremia may be largely attributable to the fallback use of vancomycin against MRSA [17].

Based on the preponderance of evidence, vancomycin use should be avoided in the treatment of MSSA bacteremia. Alternatives to vancomycin have emerged in the last 2 decades for the penicillin-allergic patient, with daptomycin being the first US Food and Drug Administration–approved alternative therapy in MSSA bacteremia, showing noninferiority to β-lactams in a prospective randomized trial [18]. A recent study of patients with reported penicillin allergies and MSSA bacteremia compared outcomes of patients that either (1) were given vancomycin without any assessment, (2) received cefazolin if anaphylaxis was ruled out by history, or (3) had a complete allergy evaluation including penicillin skin testing [19]. They found as expected that vancomycin yielded the lowest cure rates (67%) and highest rates of recurrence (15%), in contrast to those who received cefazolin, where cure rates were approximately 84% and relapse only 9%. The vancomycin-treated group also had the highest rates of allergic and other adverse drug reactions. This study makes it very clear that taking a stated penicillin allergy at face value and avoiding it with vancomycin use is providing suboptimal care in MSSA bacteremia [19]. The same researchers showed in a subsequent study of MSSA bacteremia that optimal and adequate antimicrobial therapy was hampered by a history of a penicillin allergy [20].

Further evidence of the negative consequences of purported penicillin allergies continues to accumulate. Compared to patients without allergy, reported penicillin-allergic patients have 50% increased odds of getting a surgical site infection, attributable to more frequent receipt of second-line agents such as vancomycin (35% vs 3%) or clindamycin (49% vs 3%), and less likely receipt of cefazolin (12% vs 92%) [21]. Another large multicenter prospective cohort study found that patients with reported allergies who did not receive preferred β-lactam therapy had an adjusted odds ratio of 3 for an adverse event, compared to those without allergy or those that received an alternative β-lactam agent [22]. In a retrospective study at a Veterans Affairs hospital, patients with a penicillin allergy had a significantly longer time to receipt of first antibiotic dose (236 minutes vs 187 minutes, $P = .03$), and were more likely to receive a carbapenem or fluoroquinolone antibiotic ($P < .00001$), which may have implications on selection of more antimicrobial resistance or *C. difficile* infections [23]. From an economic standpoint, a recent comprehensive meta-analysis showed that reported penicillin-allergic patients had higher outpatient and inpatient drug costs and inpatient hospitalizations that cost on average $1145–$4254 more per patient [24].

In summary, consistent data have emerged pointing toward possible shortcomings in clinical outcomes and medical care costs when utilizing non-β-lactam antibiotics in patients with penicillin allergies. These studies are not definitive and cannot rule out the possibility that penicillin allergy may be a surrogate marker of a suboptimal response to infection. Until more definitive clinical or immunological studies can be done, another approach is to determine if β-lactams offer any additional adjunctive properties that are not seen in other antibiotic classes. These are discussed in the next section.

INDIRECT ANTIMICROBIAL PROPERTIES OF β-LACTAMS: BEYOND THE STANDARD MINIMUM INHIBITORY CONCENTRATION

Delay in therapy as discussed above may be one contributing factor toward inferior outcomes in patients with penicillin allergies [23]. However, significant data have emerged in the last few years indicating that β-lactams display unique antibacterial properties that are not appreciated in our standard in vitro susceptibility testing assays. Antistaphylococcal β-lactams (eg. nafcillin, oxacillin, flucloxacillin) were for many years considered clinically irrelevant against MRSA due to absence of activity in standard minimum inhibitory concentration (MIC) testing in bacteriologic media such as Mueller-Hinton broth. However, these agents have recently been shown to render MRSA more vulnerable to killing by antimicrobial peptides and other components of the innate immune system [25, 26].

These effects have recently been employed in combinatorial treatment regimens against MRSA, wherein reinstitution of various β-lactam drugs with either daptomycin or vancomycin led to more rapid bloodstream clearance and successful salvage of refractory MRSA bacteremia [25–28]. Similar effects were identified with ampicillin-resistant VRE, wherein the addition of ampicillin, which alone demonstrated no activity, markedly potentiated the activity of daptomycin and host innate peptides in the killing of the pathogen [29]. Ceftaroline and other β-lactams exhibit similar properties for sensitizing VRE to cationic peptides and immune clearance [30, 31]. VRE isolates with a daptomycin MIC of 4 mg/L, considered susceptible under the current Clinical and Laboratory Standards Institute breakpoint, have been associated with increases in daptomycin treatment failure in bacteremia, stimulating calls to lower the daptomycin enterococcal susceptibility breakpoint to ≤2 mg/L [32]. β-Lactam plus daptomycin combination therapy restores clinical success rates in VRE bacteremia against isolates with daptomycin MIC of 4 mg/L to rates similar to those seen for isolates with lower MICs [33].

Cationic antimicrobial peptides such as cathelicidins, defensins, and platelet microbicidal proteins (PMPs) are key front-line elements of human innate immune defense against systemic infection [34]. Bacterial strains may evolve resistance to bactericidal activity of these peptides, sometimes as an unintended consequence of exposure to structurally similar pharmaceutical antibiotics that we administer [35], or simply by chronic persistence in vivo whereby they may be exposed to the peptides at sublethal doses, for example, in high-inoculum infections with poor surgical source control [36, 37]. Resistance to these peptides may impact clinical outcomes. For example, PMP resistance in staphylococci and streptococci is associated with endocarditis and metastatic infection [38–40], and MRSA isolates from patients with persistent bacteremia were more resistant to PMP killing than those from resolved bacteremia [41]. It appears that β-lactams, by enhancing killing of *S. aureus*, *Enterococcus* species, and potentially other organisms, provide a means by which bacteremia may be cleared more efficiently by boosting the activity of cationic peptides of the innate immune system or, when used in a combination regimen, potentiation of cell wall–active antibiotics such as daptomycin or vancomycin.

It is beyond the scope of this article to discuss recognition of *S. aureus* and other bacteria by innate immunity; thus, we refer readers to comprehensive reviews on the subject [42]. A poor proinflammatory cytokine response by leukocytes exposed to *S. aureus* is associated with worse outcomes in mice challenged with *S. aureus* [43]. Rose et al examined cytokine expression on the day of clinical presentation in patients with *S. aureus* bloodstream infection, and found that a low interleukin 1β (IL-1β) response was a significant marker for persistent bacteremia, whereas elevated concentrations of IL-10 was a predictor of increased patient mortality [44]. IL-1β is a potent inducer of T lymphocytes and neutrophils and augments the production of several proinflammatory cytokines in response to *S. aureus* and other pathogens [42, 45]. Recent work suggests that β-lactams may enhance *S. aureus* expression of its pore-forming α-toxin [46, 47], modulate *O*-acetyl transferase-mediated lysozyme resistance [48, 49], or influence other exotoxin expression through PBP1 binding [50]. These steps may enhance inflammasome activation and host IL-1β production, thereby promoting more rapid bacterial clearance from the bloodstream. Furthermore, MRSA bacterial cell wall synthesized in the presence of β-lactams exhibits a reduction in cross-linking and generates a stronger IL-1β response by macrophages [51]. Enhanced IL-1β production may exacerbate inflammation and clinical symptomsin certain exotoxin-driven *S. aureus* infections (eg, pneumonia, soft tissue infection). However, scientific data suggests that the β-lactam induction of IL-1β signaling may counteract establishment of infection or enhance clearance of endovascular *S. aureus* infection [52]. Indeed, increased expression of α-toxin, a known IL-1β inducer, attenuates *S. aureus* virulence in a rabbit endocarditis model [53].

Another key adjunctive property of β-lactams in MRSA treatment is synergy with cationic host defense peptides that is not seen with vancomycin [25]. In line with these immunological synergies, MRSA grown in 1/50th MIC of nafcillin showed significant reduction in skin lesions when injected subcutaneously into mice, in contrast to untreated controls or MRSA grown in 1/4th MIC of vancomycin [25]. Compared to cefazolin, use of vancomycin as surgical prophylaxis increases the risk of MSSA surgical infection. Conversely, vancomycin may not outperform cefazolin in MRSA prophylaxis [54], although a meta-analysis on this topic that shows a benefit of vancomycin as surgical prophylaxis in preventing MRSA postoperative infection leaves this topic controversial [55].

Laboratory science is building evidence that β-lactams play an important role as "immunoadjuvants" in addition to antibiotics in *S. aureus* bacteremia. A summary diagram demonstrating the mechanisms of enhancement of immune system killing of *S. aureus* by β-lactams, including what was discussed above [44, 56–59], is depicted schematically in Figure 1. Patients who receive non–β-lactam antibiotics in response to purported penicillin allergy may be missing out on these significant effects that enhance treatment or prevent infection, as reflected in the negative clinical and medical economic data associated with penicillin-allergic patients reviewed above.

It is important to point out that β-lactams are not the "be-all and end-all" of antimicrobial agents with respect to host inflammation. As β-lactams induce α-toxin and other exotoxin expression to enhance IL-1β (a benefit in bacteremia), the same property may generate more local tissue inflammation and thereby more damage and worse clinical outcomes in infection types driven by exotoxin expression, such as pneumonia [60] and soft tissue infection [61]. This rationale is behind the

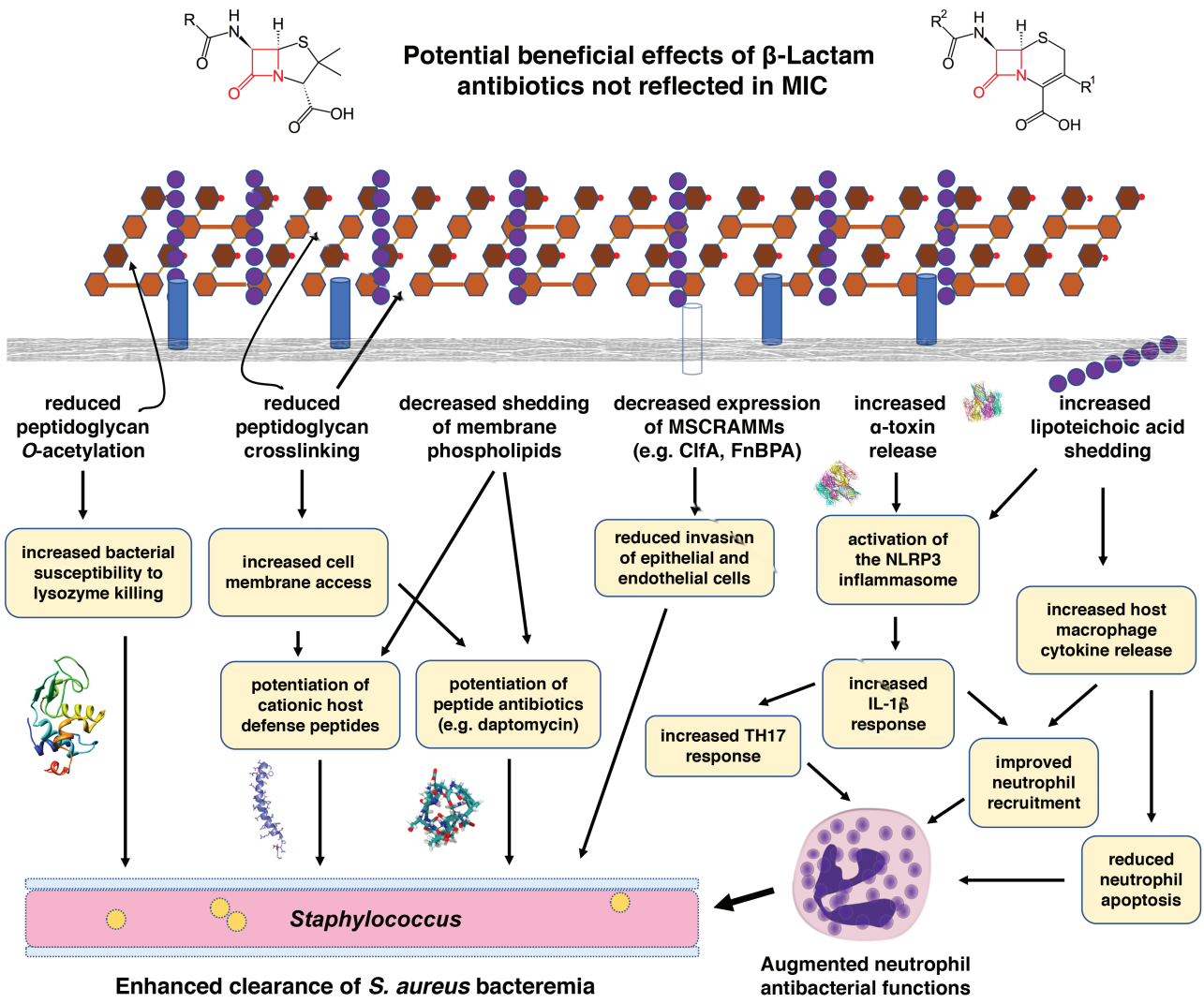

Figure 1. β-Lactams exhibit conservable impacts on the relationship between bacterial pathogens and the human host. This has been studied in detail with *Staphylococcus aureus*, whereby the effects on bacteria render them more vulnerable to clearance by the innate immune system through multiple mechanisms outlined above. Abbreviations: ClfA, clumping factor A; FnBPA, fibronectin binding protein A; IL-1β, interleukin 1β; MIC, minimum inhibitory concentration; MSCRAMMs, microbial surface components recognizing adhesive matrix molecules; TH17, T-helper 17 cell.

recommendation of concomitant β-lactam and clindamycin therapy for extreme examples of these types of infections such as necrotizing fasciitis, presumably whereby the clindamycin reduces superantigen expression induced by the β-lactams. These types of studies make it clear that the assessment of antimicrobial therapy likely needs to extend to including pharmacodynamic interactions not just of drugs between each other, but also drugs with the innate immune system.

ALTERNATIVE β-LACTAM OPTIONS: CROSS-ALLERGIES ACROSS THE β-LACTAM SUBCLASSES

In patients with an unconfirmed penicillin allergy, cross-reactivity to other β-lactams has been a historical concern. While early research incorrectly implied a penicillin-cephalosporin cross-reactivity of up to 10%, this is now recognized to be a gross overestimation [62]. Unfortunately, these false data have populated medical practice, resulting in the propagation of the 10% cross-allergy myth across decades. In contrast, more careful recent studies demonstrate clinically significant immunologically mediated cross-reactivity of <1% [63–67]. These low rates have been incorporated into guidelines within the anaphylaxis practice parameter. They state that approximately 4% of patients who have positive penicillin skin tests also react to cephalosporins, whereas patients who have negative penicillin skin tests can receive cephalosporins without allergy concerns [68].

Penicillins and carbapenems both have a bicyclic core rendering them similar in structure. The bicyclic core is composed of a 5-membered ring, which is attached to the β-lactam ring. Since the inception of the first carbapenem drug approval, there has

been a theoretical concern for cross-reactivity of a drug in this class in a patient with a verified history of a penicillin allergy. As with cephalosporins, early studies overestimated the cross-allergy risk between penicillin, while more recent studies place the risk at 0.9%–11%. Currently, there are experts in the field stating that the avoidance of carbapenem use in patients with a history of penicillin allergy should be reconsidered [69]. In 2015, researchers tested patients with a positive penicillin skin test with 3 different carbapenems (imipenem-cilastatin, meropenem, and ertapenem) in 211 subjects [70]. None tested positive to any of the carbapenems. A subsequent study examining the cross-allergy of a confirmed penicillin immunoglobulin E (IgE)–mediated hypersensitivity to ertapenem found the cross-reactivity was only 1 of 36 (2.8%) to full-dose systemic exposure to ertapenem [71]. These authors concluded that the practice of avoiding carbapenems in patients with β-lactam allergy histories should now be abandoned.

With respect to monobactams (ie, aztreonam), the risk of cross-allergy to penicillin appears to be negligible. A 2016 study tested 214 subjects who had a positive penicillin skin test (T-cell–mediated hypersensitivity) with an aztreonam skin test [71]. No subjects had a positive skin test to aztreonam. One hundred seventy of the patients (all with negative aztreonam skin tests) accepted to be further challenged with systemic exposure. No subjects had clinical signs or symptoms of an adverse drug reaction [72].

Consistent with cephalosporins, immunological studies indicate that the side chain of aztreonam determines cross-reactivity, rather than the monobactam ring itself [73]. Of note, the aztreonam side-chain is identical to the side-chain of ceftazidime. Hence, the risk of cross-reactivity between aztreonam and ceftazidime is predicted to be much higher than the other cephalosporins and penicillin derivatives [73]. Consequently, clinical practice of using aztreonam in patients with a history of penicillin allergy is supported by the joint Task Force on Practice Parameters [68], stating concern only for patients with ceftazidime allergies.

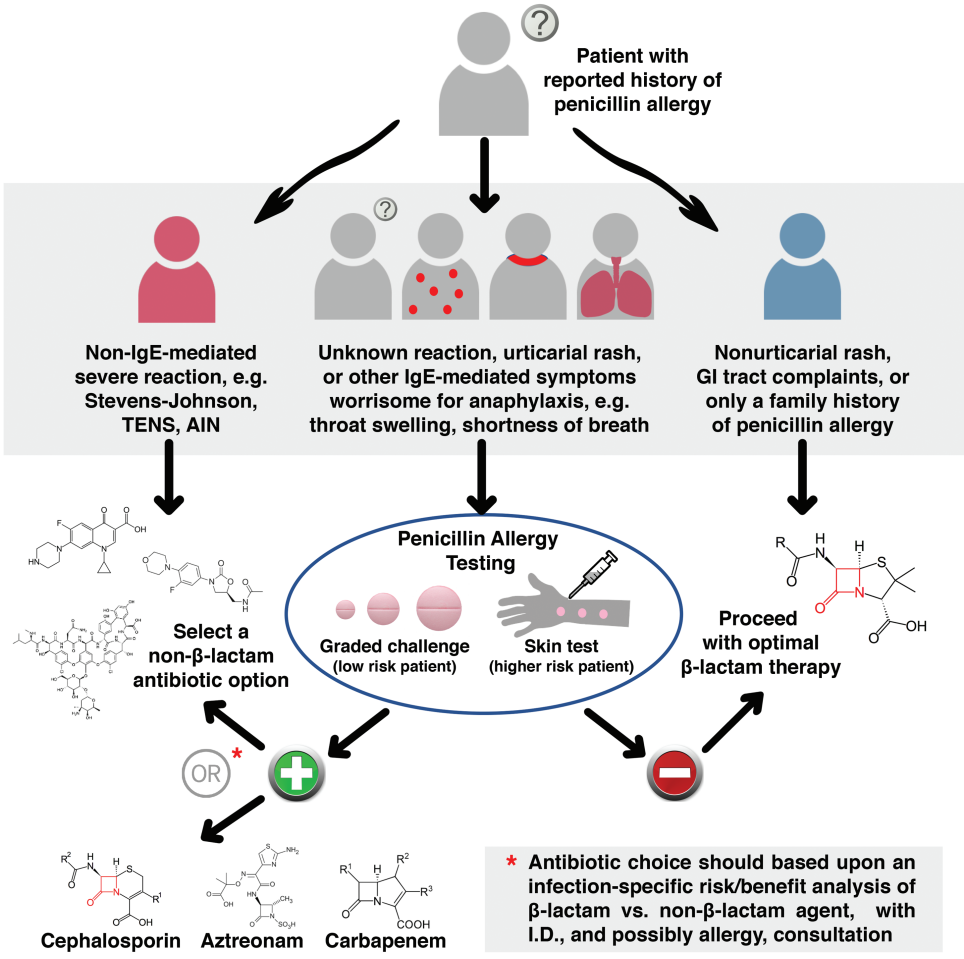

Figure 2. A proposed algorithm for approaching hospitalized patients with purported penicillin allergy, using a combination of detailed clinical history and skin testing. Abbreviations: AIN, acute interstitial nephritis; GI, gastrointestinal; ID, infectious diseases; IgE, immunoglobulin G; TENS, toxic epidermal necrolysis syndrome.

THE ROLE OF PENICILLIN ALLERGY TESTING IN ANTIMICROBIAL STEWARDSHIP

Although it is common for a patient or family member to declare a drug allergy, treating clinicians must verify the allergy by taking a thorough history and, if deemed necessary, test for a type 1 reaction. Often, obtaining a thorough history by interviewing the patient has proven effective in removing the purported allergy from the patient's medical profile [65, 74].

The current reference standard test to confirm acute penicillin-class antibiotic tolerance is an oral amoxicillin 250 mg challenge with 1 hour of observation. Delayed-onset tolerance is confirmed by the lack of a rash over the next 5 days. Direct oral challenges have been safely used in children and adults with low-risk histories [75].

Skin tests may also be used to diagnose a type I (immediate) IgE-mediated drug hypersensitivity, especially in the inpatient setting. However, skin testing, prior to an oral challenge, is often not necessary to safely rule out type I (immediate) IgE-mediated hypersensitivity in individuals with low-risk drug allergy histories. Some clinicians in the acute care setting are opposed to taking the time for confirmation of tolerance testing, because it may delay initiation of antibiotics. In individuals with a low-risk history, taking 1 hour to confirm tolerance may be an hour well spent [63, 76–78].

Based on the evidence favoring β-lactam therapy for some serious infections (eg, *S. aureus* bacteremia), poor outcomes in patients with purported penicillin allergies, and the fact that purported allergies are rarely true allergies, we advocate a combinatorial scheme of a detailed history algorithm supplemented with penicillin allergy testing, as was conducted by Ramsey and Staicu in their recent study [79]. Figure 2 outlines an approach to the hospitalized patient with penicillin allergy requiring antimicrobial therapy. An initial history stratifies patients into those in whom a purported allergy is dismissed by history alone (eg, gastrointestinal complaints, candidiasis), those in whom a documented life-threatening non-IgE-mediated reaction eliminates β-lactam use (eg, Stevens-Johnson toxic epidermal necrolysis syndrome, acute interstitial nephritis), and those in whom penicillin testing can help delineate therapy. For the latter group, a negative allergy test (anticipated for the majority, especially if the urticarial rash history is remote) would place them into the nonallergy group, where they stand to receive the greatest benefit from this intervention.

Complex clinical decision making occurs in patients who test skin positive but have more severe infections where β-lactams have proven advantageous. While those patients would not be challenged with penicillins, except in rare situations where there would be no other therapeutic options and therefore must be dealt with through desensitization, the low likelihood of cross-allergy to other β-lactam groups would have to be weighed against the significant benefit of using this group of drugs. A very common example where this would arise would be the potential choice of cefazolin instead of vancomycin for MSSA bacteremia. The clinical advantages of cefazolin over vancomycin would likely outweigh the <5% risk of cross-allergy, especially in patients with complex infections. Daptomycin would be an alternative that appears to offer similar outcomes to β-lactam therapy, but is currently considerably more costly [18]. Such cases should be handled with the assistance of an infectious disease consultant, and perhaps with further input from an allergy-immunology specialist, especially in light of emerging data that this approach markedly improves outcomes [80, 81].

In sum, a coordinated and resolute approach to de-label false allergies, with the assistance of infectious disease physicians and infectious disease pharmacists, may lead to improved patient outcomes and reduction in healthcare costs [82, 83].

Notes

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