



Beta-lactam Allergy Review: Implications for Antimicrobial Stewardship Programs

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Abstract

Purpose of review Beta-lactam allergies, and specifically penicillin allergies, result in receipt of therapy that is not considered first line in many instances. Being labeled as allergic many times comes via subjective history from the patient. Carrying this label can cause a patient to receive broad-spectrum therapy with increased side effects and resistance. Antimicrobial stewardship programs can play a role in allergy evaluation and intervention based on resources. This review provides an update on beta-lactam allergies and emphasizes incorporation of evaluating these patients as a core tenant of antimicrobial stewardship.

Recent findings Many patients with a listed beta-lactam allergy are not truly allergic and can have the allergy removed with proper evaluation. Patients who have low-risk histories that are unlikely to be IgE mediated can safely be re-challenged. High-risk patients or those with an unknown history can be desensitized or skin tested (if allergic to penicillin). All strategies should result in proper labeling or de-labeling in the electronic health

record. Antimicrobial stewardship programs are recommended to be involved in allergy assessments to create testing and treatment strategies.

Summary Deciding whether an allergic patient is a candidate for re-challenge or graded-challenge, penicillin skin testing, or desensitization is paramount to antimicrobial stewardship programs in conjunction with an allergist, if available.

Introduction

The World Health Organization defines a drug allergy as an immunologically mediated hypersensitivity reaction to a drug in a sensitized person. Allergies to drugs can be further classified by the time in onset of symptoms as immediate or delayed to help classify the probable immunologic mechanism. Examples of drug allergies are anaphylaxis from beta-lactam antibiotics, Stevens-Johnson syndrome from carbamazepine, thrombocytopenia that is heparin-induced, or systemic drug-induced lupus erythematosus from hydralazine [1]. For penicillin specifically, a high prevalence of individuals in the USA report an allergy making this the most common drug allergy reported [2, 3]. Avoidance of penicillins in

patients that present with a self-reported allergy is a growing health concern. There are documented inferior clinical outcomes, as well as increased length of stay and overall care costs, when labeled with a penicillin allergy [4]. Another cause for concern is avoidance of other beta-lactams in these patients. Cross-reactivity to cephalosporins occurs in ~2% of patients, which is much less than previously reported. Allergies specific to carbapenems and aztreonam are uncommon [5••]. This review summarizes beta-lactam allergies and how a focused evaluation and intervention as part of an antimicrobial stewardship program can address these often incorrect labels.

Classification and manifestations

Drug hypersensitivity results from interactions between a pharmacologic agent and the human immune system. Penicillin allergies are the most commonly documented drug allergy in a medical record with a reported prevalence of 9 to 12% that can manifest in a variety of ways [6, 7]. The Gell-Coombs classification is the most common method of determining types of immunologically mediated hypersensitivities. Mechanisms of immune responses to antigen are split into four types of reaction to allow for a better understanding of the pathogenesis of reaction as described in Table 1 [8]. It is comprised of immediate-type reactions mediated by drug-specific IgE antibodies (Type I), cytotoxic reactions mediated by drug-specific IgG or IgM antibodies (Type II), immune complex reactions (Type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (Type IV). Full evaluation of allergy history is imperative as approximately 90% of patients with a history of penicillin allergy are able to tolerate penicillins; this is in part due to the process of penicillin-specific IgE antibodies waning over time that cause patients to outgrow their allergy [10, 11].

Other types of hypersensitivity reactions that occur outside of Gell-Coombs classification include drug-induced autoimmunity and fixed drug eruption. Drug-induced autoimmunity refers to drugs like phenytoin, isoniazid, and sulfasalazine that can induce autoimmune diseases such as lupus due to

Table 1. Gell-Coombs classification table

| Gell-Coombs hypersensitivity reaction type [8, 9] | | | | |
|---|--|---|--|--|
| | Type I (IgE) | Type II (IgG/IgM) | Type III (IgG) | Type IV (T lymphocytes) |
| Mechanism | Drug-IgE complex binds to mast cells to cause degranulation with release of histamine and inflammatory mediators | Drug-IgG/IgM complex binds to antigen on cell membrane to activate the complement cascade and result in destruction of cell by activated phagocytes | Tissue deposition of drug-antibody complexes with complement activation and inflammation | Cell-mediated response that causes antigen-specific T lymphocytes to activate cytokine and inflammatory mediator release |
| Manifestations | Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis | Hemolytic anemia, neutropenia, thrombocytopenia | Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis | Allergic contact dermatitis, maculopapular drug rash, Stevens-Johnson syndrome |
| Timing | Minutes to hours | 5–15 days | 1 to 3 weeks | Variable |

unknown mechanisms; this type of reaction is not seen often with antibiotics. Fixed drug eruptions are characterized by round erythematous macules and plaques on the skin or mucous membrane that can be seen with administration of pseudoephedrine, trimethoprim, tetracyclines, and sulfonamides [12]. Infusion reactions can also occur with drugs such as vancomycin, a reaction colloquially referred to as “red man syndrome.” Red man syndrome refers to pruritus and an erythematous rash that typically involves the face, neck, and upper torso that is associated with rapid infusion of vancomycin [13].

Treatment

Approaches to treatment are based on a prompt triage and evaluation of the patient for an immediate reaction (anaphylaxis) versus a delayed reaction (rash). Anaphylaxis is associated with potential death from cardiovascular and asphyxiation complications and requires immediate medical attention. Prompt discontinuation of the causative medication is required during the acute treatment phase. Patients should be evaluated by cutaneous, respiratory, gastrointestinal, and cardiovascular presentation. Typically, at least 2 organ systems are involved, although only 1 organ system may initially be involved upon presentation. Immediate interventions that should be performed in the emergency department include assessing airway, breathing, circulation, and intravenous access. Intramuscular 0.01 mg/kg epinephrine (max 0.5 mg) every 5 to 15 min is recommended as the first-line management of anaphylaxis [14]. Other adjunctive interventions based on patient-specific presentation include rapid fluid infusion, intravenous epinephrine infusion, bronchodilators,

corticosteroids, antihistamines, and glucagon. Patients should remain on continuous hemodynamic monitoring to assess response to therapy.

Delayed reactions often require prompt discontinuation of therapy and if symptoms do not resolve spontaneously, additional symptomatic therapy may be indicated. Severe cytotoxic or T cell-mediated reactions such as drug-induced hemolytic, thrombocytopenic, or granulocytic cytopenia can be treated with glucocorticoids [15]. Use of glucocorticoids is controversial in advanced stages of erythema multiforme major, Stevens-Johnson syndrome, or toxic epidermal necrolysis due to increased risk of infection and requires clinical evaluation. Antihistamines, glucocorticoids, and/or non-steroidal anti-inflammatory drugs are useful for reactions related to urticaria, joint symptoms, and vasculitis.

Every effort to discontinue or avoid medications that have cross-reactivity with causative agents should be attempted; however, certain instances require use of medications that may cause hypersensitivity and require desensitization. Of note, re-administration of a drug that caused severe non-IgE-mediated reactions such as Stevens-Johnson syndrome, Churg-Strauss syndrome, or exfoliative dermatitis is contraindicated. Desensitization protocols are used to modify a patient's response to a drug to temporarily allow treatment and is only indicated when alternate non-cross-reacting medications cannot be used. This temporary state of tolerance is maintained only as long as the patient continues to take the drug. All procedures to induce drug tolerance involve administration of incremental doses of the drug to render effector cells less effective. Protocols often require intensive care unit admission for close monitoring and allow for labor intensive protocol implementation. For penicillin desensitization, 1/10,000 of the full therapeutic dose with dose increases to twice the previous dose every 15 to 30 min until therapeutic levels are achieved is performed over a course of 4 to 12 h [15]. This process requires many nursing and pharmacy resources for proper implementation.

Evaluation with emphasis on stewardship

While each member of the healthcare team should be aware of the types of allergic reactions and how to treat them, it is important to first evaluate the patient's risk of having a reaction. In 2016, the Joint Commission mandated that all hospitals have Antimicrobial Stewardship Programs (ASPs) as part of their Core Standards [16]. As a result of this requirement, the Infectious Diseases Society of America created a guideline for implementing ASPs in various healthcare settings. These guidelines recommend ASPs be involved in allergy assessments, specifically beta-lactams, and work together with allergists to create testing and treatment strategies [17]; however, not all hospitals with ASPs have access to allergists, thereby requiring resource assessment. While resources may vary depending on the institution, the importance of offering allergy testing is well recognized. In a survey sent to adult and pediatric infectious diseases physicians, 68% agreed that ASPs should be involved in this process to improve antibiotic prescribing [18].

There are a number of ASP-led beta-lactam allergy initiatives described in the literature. These initiatives range from multidisciplinary groups including pharmacists, nurses, infectious diseases physicians, and allergists/immunologists

[19•, 20–22], to leveraging clinical decision support software to guide prescribers when ordering antibiotics for a patient with a penicillin allergy [23–25]. The use of computer decision support software is not widely studied, but may be beneficial in settings where allergists or immunologists are not readily available for evaluation. Telemedicine has been described as part of an allergy assessment when trained allergy nurses or mid-level practitioners are on site, but evaluation by an allergist or immunologist remotely is needed [26]. Also, in order to maximize limited resources, it may be beneficial to identify patients who would most benefit from testing, such as those with methicillin-sensitive *Staphylococcus aureus* bacteremia where mortality is increased when patients receive inferior alternative agents for definitive therapy [27]. While penicillin skin testing is the most reliable method for de-labeling patients with a history of an IgE-mediated reaction, institutions with limited resources and without access to allergy specialists can utilize detailed allergy history interviews to clarify reactions and identify low-risk patients to receive cephalosporins when appropriate [28].

Members of the ASP team are in a unique position to improve upon the allergy history review process when patients are admitted to the hospital. Their understanding of infectious diseases, cross-reactivity, and allergy classifications can lead to a thorough interview of patients and their caregivers regarding their antimicrobial use history. While there are no widely accepted allergy history questionnaires, it is important to obtain a detailed history of the reaction in order to inform prescribing. Details such as the date of the reaction (to the best of the patient's knowledge), the route of administration, and the specific reaction are all important aspects to document when taking an allergy history. Reactions can often be grouped into intolerances (gastrointestinal upset, headache, fatigue), low-risk (family history, unknown, patient denies allergy), moderate-high risk (anaphylaxis, wheezing, angioedema, rash), and high-risk histories (Stevens-Johnson syndrome, serum sickness, hemolytic anemia) [5••, 20, 29]. Through the use of an allergy assessment, many reported adverse reactions can be removed based on intolerances that were initially reported as allergies [30]. Patients can be easily identified as not benefitting from allergy testing with reported blistering rash, nephritis, hemolytic anemia, or joint pain.

There have been significant contributions to the literature in recent years regarding the cross-reactivity between penicillins and other classes of antibiotics such as cephalosporins and carbapenems. Understanding the potentials for cross-sensitivity between these agents can provide opportunities to improve prescribing even in the absence of penicillin skin testing and oral challenges depending on the patient's allergy history. More recent literature, including the work of Romano and colleagues, has explored the prediction of cross-sensitivity based on shared R1 and R2 side chains [31]. This idea supports the safe use of antibiotics in the same class if they have dissimilar side chains, which may be the cause of the allergic reaction. For example, the first-generation cephalosporin cefazolin demonstrates a low cross-reactivity with penicillin due to its unique side chain. Therefore, updated estimates of cross-reactivity between penicillins and cephalosporins are likely less than 2%. In patients with an immediate penicillin allergy, cross-reaction with carbapenems has been shown to be < 1% [32,

33]. However, patients who have a history of positive penicillin skin test should avoid other penicillins [5••].

Stewardship interventions

Penicillins and other beta-lactam agents are the treatments of choice for a variety of organisms and infection types and are recommended as first-line therapies by several guidelines [34–37]. The presence of a documented or self-reported penicillin allergy can necessitate treatments which diverge from clinical guidelines and utilize broad-spectrum and second-line antibiotic regimens. Robust evidence has found these practices can have significant consequences on overall infection management as well as patient outcomes, and can result in increased emergence of antibiotic resistance, increased risk of treatment failure, higher mortality, and increased healthcare costs [38–40]. Proper allergy evaluations as mentioned above are essential for distinguishing severe allergies from mild adverse reactions and preventing needless administration of second-line antibiotics. However, when evaluations are uninformative or true penicillin allergies are confirmed, single or combination use of such antimicrobial stewardship interventions such as oral penicillin challenges, penicillin skin testing, and antibiotic desensitization can be utilized to address the allergy and possibly facilitate penicillin administration. Antimicrobial stewardship programs are recommended to incorporate these services into practice as possible to mitigate the consequences listed above [17]. Selecting the appropriate intervention for a patient will be dependent upon their allergy history [5••]. An algorithm to assist with penicillin allergies is listed in Fig. 1.

Re-challenge and graded challenge

Oral challenges are an effective method to confirm the absence of severe reactions in patients who report mild allergies to penicillin antibiotics. This strategy involves administering oral penicillin or amoxicillin and observing the patient for the development of immediate or delayed reactions of high severity. Penicillin or amoxicillin can be administered at full dose as a challenge, or can be administered as part of a graded challenge. A graded challenge begins with administration of a reduced or diluted dose of the medication, followed by administering increasing doses until a full dose is achieved. Graded challenges may be selected over full-dose oral challenges when a patient's allergy history suggests potential for a moderate reaction type, or in circumstances when a skin test is indicated but unable to be performed [41]. These various types of oral challenges have been safely incorporated as a routine antimicrobial stewardship intervention in diverse patient populations, as exemplified by recent evaluations which have demonstrated that both mild- and immediate-onset reactions following oral challenges occur in only a small percentage of patients [42, 43]. Important for antimicrobial stewardship, patients who tolerate oral penicillin challenges are considered non-allergic and can have the allergy removed from their health record [1, 44]. Removing the penicillin allergy from a patient's electronic health record (EHR) has significant implications for future antibiotic use, as demonstrated by a recent prospective oral challenge trial. In this trial, patients with negative oral challenges were 84.6% more likely to be given a

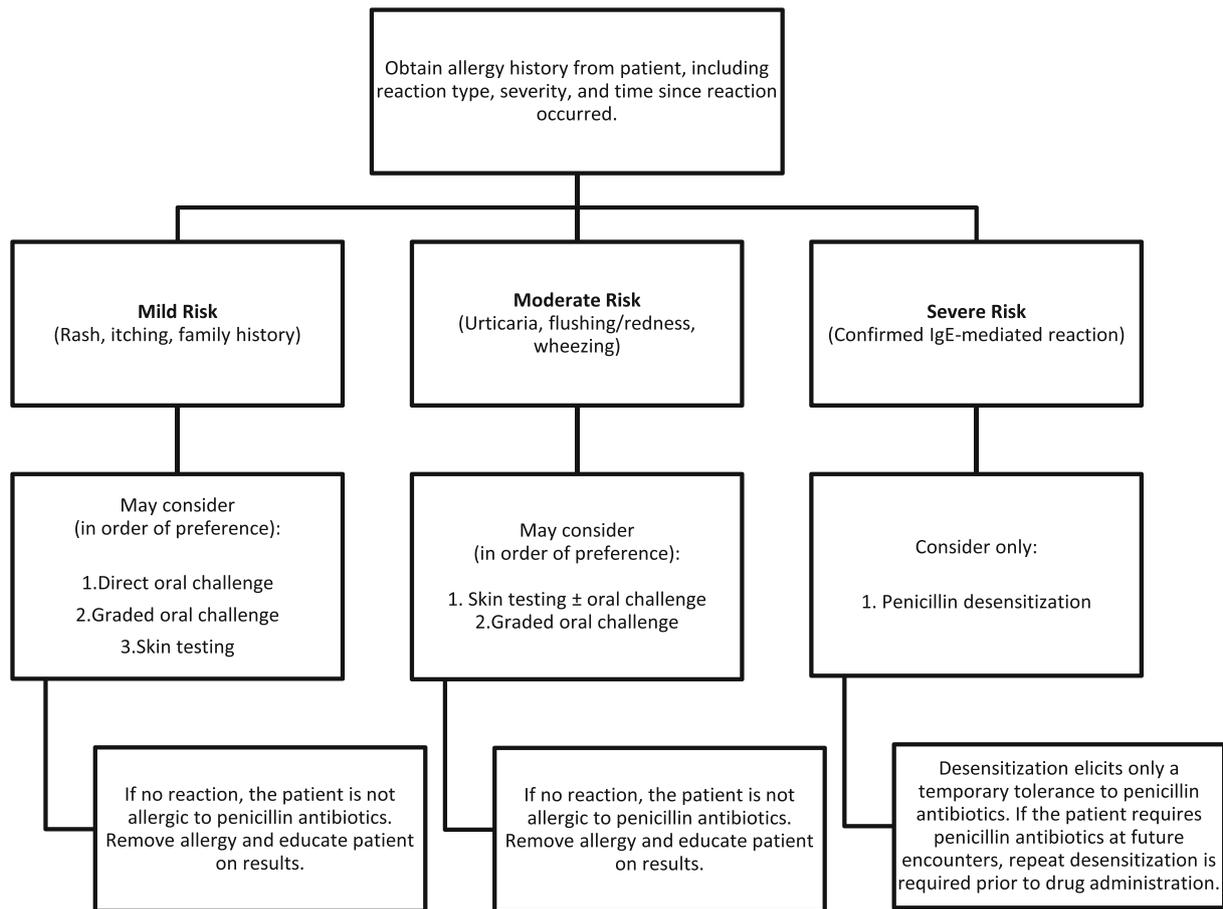


Fig. 1. Penicillin allergy assessment algorithm [5].

penicillin-based antibiotic in the 90-day period after an oral challenge than in the pre-challenge period [42]. Removing the allergy can also result in significantly reduced use of broad-spectrum and more toxic antibiotics [45].

Varying protocols for oral challenges have been described in the literature [42–45]. A single oral dose can be administered following penicillin skin testing to increase the overall specificity of the process [45], or direct oral challenges can be administered singularly as part of a graded challenge or an extended exposure evaluation to monitor for delayed allergic reactions [43, 46, 47]. A testing algorithm and/or risk stratification guide can be implemented to identify low-risk patients who may benefit from oral challenges, and can assist in selecting the most appropriate oral challenge method.

Penicillin skin testing

Penicillin skin testing is the most reliable method to test for IgE-mediated allergic reactions. This test has been successfully incorporated into inpatient, outpatient, and emergency department settings, and is a useful strategy for patients with reported penicillin allergies of moderate severity, or in reported allergies with unknown reactions [45]. The test involves a two-step process with

a scratch and intradermal test, followed by an optional oral penicillin challenge. Each required step utilizes major and minor determinants and, when used appropriately, can have a negative predictive value of over 97% [5••, 45]. The high negative predictive value of this test allows for safe and accurate de-labeling of penicillin allergies in patients with negative results, which can then prompt antibiotic de-escalation to targeted beta-lactam agents [45, 48]. Negative skin tests have been shown to initiate antibiotic de-escalation in $\geq 73\%$ of patients and promote inpatient cost savings of approximately \$300 per patient [3, 47, 49]. Furthermore, patients with negative skin tests can be de-labeled as penicillin allergic and safely receive penicillins and beta-lactam agents at future encounters. The positive antimicrobial stewardship implications associated with this test have led some experts to recommend that all patients with unconfirmed penicillin allergy undergo skin testing [41]. The Infectious Diseases Society of America also recommends that penicillin skin testing be incorporated into standard patient care when feasible [17, 44]. Importantly, administration of this test can be directed by physicians, pharmacists, and nurses in accordance with state laws, further increasing the applicability and feasibility of the test [2•, 5••]. A recent publication described methods for practical implementation of penicillin skin testing and is a useful tool for facilitating long-lasting antimicrobial stewardship [2•].

Penicillin desensitization

Alternative classes of antibiotics may be reasonably considered in patients who demonstrate a severe reaction to penicillin or have a history of severe IgE-mediated hypersensitivity to beta-lactam antibiotics. In select infections, however, penicillin treatment is necessary and warrants antibiotic desensitization. For example, confirmed syphilis in the setting of pregnancy necessitates penicillin for treatment, and the Centers for Diseases Control and Prevention mandate penicillin desensitization in these patients as no other therapy has been shown to be equally efficacious [50–52].

Desensitization is the process by which drug tolerance may be temporarily induced by slowly exposing a patient to increasing oral or intravenous concentrations of penicillin. This method of administration must be performed cautiously over an extended period of time, and often requires patient monitoring in a high level of care environment. Strict protocols on antibiotic dilution and timing of administration are also required and must be executed by trained personnel [5••, 44]. Importantly, desensitization does not rule-out penicillin allergy. After completion of the desensitization process, the patient will return to an allergic state and will require repeat desensitization for future penicillin administrations. Penicillin desensitization enables administration of the most effective and evidence-based therapy, and is subsequently a key component of antimicrobial stewardship.

De-labeling and education

De-labeling and proper education may be the most crucial step in combating the problem of allergy over-reporting and subsequent non-beta-lactam overprescribing. The work done to clarify and challenge allergies can be undone instantly if de-labeling and education steps are not executed. This process

should involve appropriate documentation in the EHR, thorough patient education, and notification of any known providers caring for the patient.

The process of properly labeling and de-labeling allergies will vary depending on the specific system used for the EHR. Many systems now allow for the differentiation of allergy, intolerance, and adverse effects. This function is the simplest way to handle reactions such as nausea, vomiting, or diarrhea, which are not truly allergies but often get documented as such. This differentiation is an important step upon allergy clarification, but if performed at the point of initial allergy, documentation can prevent confusion and ensure optimal antibiotic choices are available to the patient. This is a prime example of nursing partnership in antimicrobial stewardship endeavors. For those patients with true allergic reactions documented, the results of a PST or other method of allergy clarification may show that an allergy is no longer active. De-labeling has proven to be major hurdle, with one study showing that 49% of patients who underwent a PST with negative result still had the allergy documented at the time of discharge [53].

There is some debate over how best to handle the removal of a documented allergy. One option is to delete the allergy altogether. This, however, allows for re-addition of the allergy at a subsequent visit. In fact, a 2013 study showed that 36% of patients who had an allergy removed due to a negative PST had the allergy added back within a year of testing [54]. One strategy to inhibit this re-addition is requiring a reason for removal of the allergy. If a user attempted to re-enter the allergy, the system would send a pop-up alert that the allergy had been previously removed for the documented reason. Many institutions prefer to instead maintain the allergy on the patient's profile, but change the reaction type or add a comment clarifying the allergy and providing any allergy test results. The major downfall of this option is that it typically continues to flag providers when an attempt is made to prescribe a beta-lactam and may therefore lead to an alternative agent being prescribed if the comment is overlooked. Ultimately, the decision should be made for each individual facility by considering EHR abilities and limitations, provider preferences, and risk of allergy re-addition.

A major step that can be taken to minimize the risk of allergy re-addition is thorough patient education. This ideally should be multifaceted and include both verbal and written components. Education before or during the clarification process should focus on why allergy clarification is important and how an inaccurate allergy could impact his or her care. Education following clarification of the allergy should involve repetition of the results, stressing the importance of informing all other healthcare providers of those results, and reemphasizing the impact of allergies on patient care decisions. Many institutions have designed physical materials to send home with the patient to help ensure the results are explained clearly. These materials may be as simple as a printed paper handout or they may be more involved such as a laminated wallet-sized card that the patient can keep on them at all times. The latter has the added benefit of being readily available to show any other healthcare providers the patient visits.

The task of informing providers of allergy test results or clarifications should not rest fully on the patient. The healthcare team performing the test should make an effort to contact all known providers for the patient tested. Results can be sent to the patient's primary care provider in the form of a letter, or if time warrants, via phone call to the provider's office. While informing providers of allergy clarifications is critical to the particular patient being tested, educating

providers as a whole on the intricacies of allergy management can greatly impact antibiotic prescribing. A 2014 study surveyed inpatient practitioners on their knowledge of managing patients with allergies before and after education and provision of an institutional guideline on the subject [55]. Interestingly, 42% of participants reported never having formal education regarding allergies prior to the study. After the education period, the researchers saw an increase in knowledge of PST, knowledge about loss of penicillin allergy over time, and preparedness to distinguish severe allergies.

Conclusion

Beta-lactam allergies are commonly reported issues that providers have to address on a daily basis. Being labeled as allergic to penicillin or cephalosporins often results in receipt of antibiotics that are broad-spectrum or not first-line. Knowledge of different types of reactions, coupled with a proper allergy history from the patient, can lead to reconciling or de-labeling the patient's allergy. Based on the subjective report, a patient can be triaged to re-challenge, graded challenge, penicillin skin testing, or desensitization, if needed. Incorporating this process into an established antimicrobial stewardship program should be encouraged.

Compliance with ethical standards

Conflict of interest

B.J. and C.B. have received research funding from ALK-Abello and have both served as consultants for ALK-Abello. C.M. declares she has no conflict of interest S.M. declares that she has no conflict of interest. E.W. declares that she has no conflict of interest. C.J. declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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