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Beta-Lactam Allergy De-labeling in a Pediatric Hospital

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OBJECTIVE To assess the ability to de-label pediatric patients of their beta-lactam allergy by using a newly implemented institutional protocol and to identify potential barriers to the de-labeling process.

METHODS All patients with reported allergies to prespecified beta-lactam antibiotics were eligible for a beta-lactam allergy interview. Following the interview, patients were grouped into 4 risk categories—no risk, low risk, moderate risk, and high risk—and assessed for intervention eligibility. Potential interventions included de-labeling based on the interview alone or proceeding to an oral amoxicillin challenge with or without penicillin allergy skin testing.

RESULTS Of the 62 patients eligible for beta-lactam allergy interviews, 40% (n = 25) were de-labeled. Among de-labeled patients, 60% (n = 15) were de-labeled on the basis of the interview alone. Additionally, no failures were documented in patients who underwent an oral amoxicillin challenge or penicillin skin testing. Barriers to performing oral amoxicillin challenges or penicillin skin testing included concomitant systemic steroid or antihistamine use, refusal of intervention, and insufficient resources to perform penicillin skin testing.

CONCLUSIONS There was a high frequency of patients de-labeled of their beta-lactam allergies in this study. Increased education to patients, parents, and providers on the de-labeling process, as well as increased personnel available to coordinate and perform de-labeling interventions, may result in more beta-lactam allergy de-labeling.

ABBREVIATIONS ASP, antimicrobial stewardship program; EHR, electronic health record; IgE, immunoglobulin E

KEYWORDS de-labeling; oral amoxicillin challenge; pediatrics; penicillin allergy; penicillin skin testing

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Introduction

Approximately 10% of patients worldwide report allergies to the penicillin class of antibiotics.[1–5] Within this cohort, clinically significant immunoglobulin E (IgE) or T-lymphocyte–mediated reactions occur in less than 5% to 10%.[1–5] IgE-mediated reactions occur relatively quickly after introduction of the offending agent (1–6 hours) and include symptoms such as urticaria, bronchospasm, and anaphylaxis, whereas T-lymphocyte–mediated reactions typically have a delayed onset (days to weeks) and include symptoms such as maculopapular rash or severe dermatologic reactions.[6] In comparison, reactions not representing a true immunologic response include isolated gastrointestinal symptoms or benign rashes and can develop at varying time points subsequent to contact with the offending agent.[6] In addition, IgE-mediated penicillin allergies are known to decrease over time, with 80% of patients with a reported allergy gaining tolerability after 10 years.[1] An actively listed penicillin allergy in the patient's electronic health record (EHR) can also affect major decisions regarding antibiotic therapy, including avoidance of cephalosporins and other first-line agents.[6,7] Owing to the spectrum of activity, tolerability, cost, and supporting data for use of penicillin and other beta-lactam antibiotics, guidelines commonly recommend these agents as first-line therapies for many infectious conditions.[8] Additionally, avoidance of these antibiotics in the setting of a documented allergy has been shown to carry negative consequences.[8] Use of alternative antibiotics can result in increased antimicrobial resistance, increased incidence of adverse events, and increased health care costs.[1,3,6]

Avoidance of the penicillin class and other beta-lactam antibiotics is particularly concerning in the pediatric population. Numerous childhood infections including community-acquired pneumonia, acute otitis media, and streptococcal pharyngitis have recommendations to use these agents as first-line therapy.[6] Additionally, with no deliberate intervention, these documented allergies will persist in the child's EHR and lead to future avoidance of beta-lactam antibiotics as the child ages.[9] Allergy de-labeling, or the removal of potentially inappropriately listed allergies from a patient's medical record via patient interview and often drug challenge, has emerged as a solution to this problem.

An increasing body of literature has consistently shown the utility and safety of penicillin skin testing and oral amoxicillin challenge as methods to facilitate allergy de-labeling in patients with documented non-severe allergies to the penicillin class of antibiotics.[1–9] The success of these de-labeling interventions has made them an important part of antimicrobial stewardship efforts globally, because they align with key antimicrobial stewardship program (ASP) goals including reduced antimicrobial resistance and increased antimicrobial appropriateness.[10] Although the benefits to de-labeling are highly supported throughout literature and recommended in ASP guidelines worldwide, the ideal way to implement de-labeling in clinical practice remains undetermined.[10] Therefore, the goal of this study was to assess the effect of a newly implemented beta-lactam allergy de-labeling protocol at a pediatric community hospital and identify barriers to the de-labeling process. The institutional beta-lactam de-labeling protocol created was primarily pharmacy driven and reviewed by multiple health care disciplines prior to implementation.

Materials and Methods

This was a prospective, observational study conducted at Arnold Palmer Hospital for Children, a 158-bed community pediatric hospital in Orlando, FL, between August 1, 2022, and November 30, 2022. Patients eligible for the de-labeling process were identified via daily chart review of all hospitalized patients admitted with antibiotic allergies as identified in the EHR (Epic), and intervention eligibility was determined after the initial de-labeling interview. Documented allergies to penicillin, amoxicillin, ampicillin, amoxicillin-clavulanic acid, ampicillin-sulbactam, nafcillin, oxacillin, dicloxacillin, piperacillin-tazobactam, aztreonam, all cephalosporins, and all carbapenems qualified for the initial interview. Allergens eligible for an oral amoxicillin challenge with or without penicillin skin testing included penicillin, amoxicillin, ampicillin, amoxicillin-clavulanic acid, ampicillin-sulbactam, nafcillin, oxacillin, dicloxacillin, and piperacillin-tazobactam. Cephalosporin and carbapenem allergies were not eligible for de-labeling via an oral amoxicillin challenge/penicillin skin testing owing to lack of cross-reactivity between penicillins and these other beta-lactam subgroups, as well as lack of data supporting use of oral amoxicillin challenge/penicillin skin testing in this setting.[11,12] Exclusions to the patient/caregiver interview process included critically ill patients receiving vasopressors and/or high-level sedation (i.e., requiring continuous infusion sedative agents) and/or mechanical ventilation. Exclusions to an oral amoxicillin challenge and/or penicillin skin testing included receipt of systemic antihistamine or corticosteroid agents within the last 48 hours, those with "nothing by mouth" status, and patients with current symptoms similar to an IgE or IgE-like reaction.

Allergy interviews were conducted by clinical pharmacists, which included both EHR review prior to the interview followed by patient/caregiver questioning. Specific interview questions are available in the Supplemental Materials section under Supplemental Figure S1. Based on the information gathered during chart review and the interview process, the patient's reported allergy was stratified into a risk category of no risk, low risk, moderate risk, or high risk (see Table 1).

Table 1. Risk Stratification and Intervention Recommendation Pathway Based on Reaction(s)

Risk Stratification	Recommendation
No risk • **Family history only** • **Tolerated the medication without reaction since initial documentation** • **Isolated GI upset** • **Isolated headache or fatigue**	If family history only or has since tolerated without reaction, remove allergy in EHR; If isolated GI upset, headache, or fatigue only, update "allergy" to "intolerance" in EHR
Low risk • **Itching only** • **Non-urticarial rash** • **Remote (>10 yr) history of non-anaphylactic IgE-mediated reaction** • **Unknown reaction without features of IgE**	Oral amoxicillin challenge for qualifying allergens
Moderate risk • **Immediate (within 24 hr) development of urticarial rash** • **Other possible non-anaphylactic IgE-mediated reactions occurring within last 10 yr**	Penicillin skin testing followed by oral amoxicillin challenge for qualifying allergens
High risk • **Immediate (within 1 hr) anaphylaxis requiring hospitalization** • **Steven-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms** • **Serum sickness** • **Acute interstitial nephritis or any organ involvement** • **Drug-induced anemia** • **Blistering rash** • **Joint pain** • **Drug-induced exfoliative dermatitis** • **Acute generalized exanthematous pustulosis** • **Vasculitis** • **Recurrent reaction with re-exposure**	Avoid penicillin and recommend allergist referral outpatient; Inpatient penicillin skin testing may be considered for history of anaphylaxis >5 yr ago

EHR, electronic health record; GI, gastrointestinal; IgE, immunoglobulin E

For patients categorized as "no risk," de-labeling of their allergy could occur on the basis of their interview alone. Patients with low-risk reactions qualified for a nongraded oral amoxicillin challenge. This challenge consisted of a single dose of amoxicillin 250 mg with the patient being monitored by nursing staff over a 1-hour timeframe post dose for development of an IgE-mediated reaction. Patients with moderate-risk reactions were recommended to undergo penicillin skin testing, followed by an oral amoxicillin challenge if skin testing results were negative. Penicillin skin testing was performed by licensed physicians, physician extenders, and/or nurses, who have completed mandatory training and demonstrated competency in penicillin allergy skin testing procedures, per institutional protocol. Penicillin skin testing included an initial skin prick test followed by intradermal testing upon a negative result for skin prick testing. Both Pre-Pen (AllerQuest LLC, Plainville, CT) and penicillin G (diluted to 10,000 units/mL) were used in both the skin prick and intradermal testing. Those patients with high-risk reactions were advised to avoid penicillin and were referred to an outpatient allergy specialist. Allergy interviews and interventions, if applicable, were documented in the patient's EHR upon completion. If a patient was able to be de-labeled of their beta-lactam allergy, education was provided to the patients, caregivers, and providers by pharmacy staff on the removal of this allergy label and its implications on the patient's ability to safely receive beta-lactam antibiotics. Documentation of allergy label removal and the education stated above was also recorded in the patient's EHR. An algorithm describing this process can be found in the Supplemental Figures section under Supplemental Figure S2.

The primary outcome of this study was the frequency of patients de-labeled of their beta-lactam allergy, using the newly implemented beta-lactam allergy de-labeling institutional protocol. Secondary outcomes included allergy risk-assessment stratification, frequency of patient or caregiver refusal of intervention, success rates with oral amoxicillin challenges and penicillin skin testing, effect of de-labeling on the patient's current antibiotic if applicable, and barriers to execution of the de-labeling protocol. Failure was defined as development of an IgE-mediated reaction subsequent to performing the oral amoxicillin challenge and/or penicillin skin testing. Barriers to execution of the protocol were described as any obstacles that arose during prospective data collection that prevented full implementation of the beta-lactam de-labeling process. Data were collected from the EHR and stored in REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN). Descriptive statistics, including median and IQR, were used because the data did not meet the assumption of normality. REDCap and Microsoft Excel (version 2310) were used to assess data.

Results

Sixty-two patients were eligible for beta-lactam de-labeling interviews during the study period. The median age of patients evaluated was 11.0 years (6.0–14.5) and 34 patients (55%) were female. Twenty-four patients evaluated (39%) were currently admitted for an infectious process requiring antibiotic therapy. Among allergens listed in the EHR, penicillin-containing (24%) and amoxicillin-containing (68%) agents were the most common. Reactions most commonly reported to the listed allergens were urticarial (45%) and non-urticarial (31%) rashes. Table 2 provides further pertinent baseline characteristics of study patients. Of the study participants, 25 patients (40%) were successfully de-labeled of their beta-lactam allergy (Table 3). Most de-labeled study participants (60%) were de-labeled with the beta-lactam allergy interview alone, while the other 40% underwent the oral amoxicillin challenge and/or penicillin skin testing. Among patients interviewed, 25 patients (40%) were not eligible for interventions beyond the de-labeling interview, based on the approved institutional protocol. Of patients ineligible for oral amoxicillin

Table 2. Baseline Patient Characteristics (N = 62)

Characteristic	Result
Age, median (IQR), yr	11.0 (6.0–14.5)
Weight, median (IQR), kg	37.1 (19.6–53.7)
Sex, n (%)	
Female	34 (55)
Male	28 (45)
Current admission for infection and receiving antibiotics, n (%)	24 (39)
Reported allergen, n (%)	
Amoxicillin	36 (58)
Penicillin	15 (24)
Amoxicillin/clavulanic acid	6 (10)
Cefdinir	6 (10)
Ceftriaxone	5 (8)
Cephalexin	3 (5)
Other	2 (3)
Reported reaction, n (%)	
Urticarial rash	28 (45)
Non-urticarial rash	19 (31)
Gastrointestinal upset	10 (16)
Other*	5 (8)
Swelling or angioedema	4 (6)
Shortness of breath	2 (3)
Anaphylaxis	1 (2)
Family history	1 (2)
Itching only	1 (2)
Unknown	1 (2)

* Reactions listed as other: mental status change, blurred vision, headache.

Table 3. Results

Outcome	Value
Patients de-labeled of their beta-lactam allergy, n (%)	25 (40)
Allergy interview alone	15 (60)
Oral amoxicillin challenge alone	8 (32)
Penicillin skin testing followed by oral amoxicillin challenge	2 (8)
Risk stratification, n (%)	
No risk	16 (26)
Low risk	24 (39)
Moderate risk	21 (34)
High risk	1 (2)
Failure of oral amoxicillin challenge and/or penicillin skin testing, n (%)	0 (0)
Patient and/or caregiver refusal of intervention, n (%)	5 (8)
Reasons for ineligibility beyond beta-lactam interview, n (%)	
Concomitant antihistamine or systemic steroid use	15 (60)
Current IgE or IgE-like reactions	4 (16)
Cephalosporin allergy	3 (12)
NPO status	2 (8)
Classified as high-risk	1 (4)
De-labeling prompting change in current antibiotic therapy, n (%)	5 of 25 (20)
Barriers to the de-labeling process, n (%)	
Concomitant antihistamine or systemic steroid use	15 (24)
Patient, caregiver, or provider refusal of intervention	8 (13)
Insufficient resources or personnel for penicillin skin testing	4 (7)

IgE, immunoglobulin E

challenge and/or penicillin skin testing, primary reasons included concomitant use of systemic antihistamines or steroid agents within the previous 48 hours (60%), patients with current IgE or IgE-like symptoms (16%), and documented allergy to a cephalosporin agent (12%) (Table 3). In certain patients, de-labeling was stopped owing to various reasons, including preferences of caregivers/providers/patients and logistical problems associated with managing penicillin skin testing. None of the patients who received the oral amoxicillin challenge and/or skin test had an allergic reaction. Of note, only 1 patient in this study was classified as having a high-risk reaction and referred to an outpatient allergist for evaluation. Among patients with barriers to intervention and for those who were not eligible for intervention, outpatient allergist evaluation was recommended. Five study patients (21%) who were de-labeled had antibiotic therapy further streamlined with a beta-lactam.

Discussion

This study supports the implementation of a beta-lactam allergy de-labeling program as an effective means to remove incorrectly reported allergic reactions. The de-labeling interview alone was impactful, which was consistent with previously reported data.[2] Those challenged with oral amoxicillin, with or without prior penicillin skin testing, had no reported IgE-mediated reaction, which is also consistent with current data.[3–5,8,13] This allergy de-labeling may later result in appropriate selection of beta-lactams in cases where they are considered first-line therapies. Comparatively, a study by Steenvoorden et al[13] showed a higher rate of change in current antibiotic treatment subsequent to de-labeling (42% versus 21%). Although the frequency of change was greater, this can be influenced by many factors such as local prescribing patterns, the infection or organism being targeted, and other unique patient factors.[13] This study not only demonstrated active antimicrobial modifications, but also suggests these interventions may have lasting effects on future antimicrobial selection. Despite adult patients having a greater prevalence of documented antibiotic allergy, these labels are most often applied during childhood, a period when febrile respiratory illnesses are increasingly common and antibiotic usage is heightened.[14] Viral illnesses during childhood also occur at an increased rate and literature has shown the development of rashes during the infectious process, with Epstein-Barr virus being an example of a possible causative vector.[1] Because antibiotics are commonly overprescribed during viral illnesses, viral rashes have the potential to be inaccurately documented as antibiotic allergies. Furthermore, patients may have an allergy added to their medical record for things such as family history of an allergy to the offending agent or a non–IgE-mediated adverse effect of the agent. Jones and colleagues[14] concluded that with patients most often receiving these beta-lactam allergy labels in childhood, allergy overdiagnosis and lack of de-labeling interventions are major contributors to the harms associated with avoiding beta-lactam antibiotics in adulthood.

During the implementation of our institutional protocol, a variety of barriers to performing the de-labeling process were identified including patient receipt of concomitant antihistamine or systemic steroid agents, patient, caregiver, or provider refusal of intervention, and/or insufficient resources or personnel to perform penicillin skin testing. Our protocol excluded patients from oral amoxicillin challenges or penicillin skin testing if they had received antihistamine agents or systemic steroids within the last 48 hours, which encompassed a large portion of the patients who were otherwise eligible for these interventions. Other institutional protocols have also excluded similar populations, primarily those receiving antihistaminic agents, while others

do not include these agents in their exclusion criterion.[2,3,8,13,15] Another barrier encountered was refusal to proceed further than the de-labeling interview owing to patient, caregiver, or provider refusal. For most of these instances, hesitation to continue the de-labeling process was due to a concern for clinical deterioration or not to convolute ongoing assessment of their primary hospital problem(s). This concern affected both the ability to proceed with protocol-recommended interventions (i.e., oral amoxicillin challenges or penicillin skin testing) and removal of therapies (i.e., antihistamine agents or systemic steroids) that would make the patient eligible for these interventions. Similar studies have reported patient, caregiver, and provider resistance to performing the de-labeling process.[3,13] Additionally, the availability of appropriately trained personnel to perform inpatient penicillin skin testing was limited, and patients were commonly recommended to seek testing from an outpatient allergist, resulting in many missed opportunities. Numerous other studies evaluating this de-labeling process have reported similar barriers to using penicillin skin testing, including the need for specific allergist training, cost of performing penicillin skin testing, and the wait time for patients to be seen to perform skin testing.[3,8,9,16] Notably, 80% of patients de-labeled beyond the interview stage were done so with oral amoxicillin challenge alone, further highlighting the difficulties surrounding penicillin skin testing.

Other barriers reported in literature not seen in this study included lack of provider education, limitations in allergy documentation and follow-up in the EHR, and perception of intervention feasibility by other members of the health care team.[2,3,13,15] In this study, de-labeling interventions were discussed with providers on an individual basis, allowing for continued education with each potential intervention. This aspect, unfortunately, may not be translatable to a larger institution. Antoon and colleagues[15] addressed the feasibility of a pharmacy-led penicillin allergy de-labeling service through the use of surveys sent out to members of the health care team involved in this process. Incorporation of surveys into this study may have helped with increasing the acceptance and number of de-labeling opportunities. Although not a perceived barrier in our study, the practice model of the institution could impede smooth implementation of a de-labeling protocol, based on aspects such as staffing shortages and clinical time availability to perform de-labeling interventions.

This study was descriptive in nature, which comes with its innate limitations, notably lack of assessment of patient-specific outcomes as well as lack of a comparator group. With this being said, the ability to assess the complete effect of de-labeling these patients of their beta-lactam allergy was limited. The number of patients included in our study is lower than the population sizes in other studies investigating de-labeling of beta-lactam allergies.[3,8,13] Additionally, our institution does not have a pharmacist presence in the emergency department, which is a setting other literature has shown benefit in allergy de-labeling.[3] Patients within our institutional protocol were monitored for 60 minutes after administration of their oral amoxicillin challenge, which is similar to other de-labeling protocols.[1–5] This aspect limited the ability to detect delayed T-cell–mediated reactions, which may take days to weeks to appear after the oral amoxicillin challenge. Ensuring follow-up after this period could potentially help mitigate this limitation.

Finally, the institutional protocol used in this study was limited in its ability to evaluate non–penicillin class allergies beyond the interview stage. With penicillin class antibiotics accounting for a significant portion of documented allergies worldwide (10%)[1–5] and the known cross-reactivity within this class, the first iteration of this protocol was tailored as such. Cross-reactivity among beta-lactams is commonly associated with R1 side-chain similarity, with cross-reactivity between penicillins and cephalosporins historically being reported as ranging from 2% to 10%.[12] In contrast, Macy et al[11] added to the body of literature supporting a lack of clinically meaningful immunologic cross-reactivity between penicillins and cephalosporins. Based on the uncertainty of this cross-reactivity, the oral amoxicillin challenge and penicillin skin testing could only be used reliably in those with documented penicillin class allergies. Looking forward, expanding our protocol to allow for complete de-labeling of all beta-lactam allergies, if clinically appropriate, will contribute to further de-labeling efforts. Although the number of patients de-labeled with this newly implemented protocol is reassuring, there are areas to be addressed, which may result in the process having an even greater effect. Continued education of patients, caregivers, and providers on the importance of de-labeling beta-lactam allergies when appropriate will aid in efforts to de-label patients. Because concomitant antihistamine and systemic steroid use served as a significant barrier to performing de-labeling interventions, revising our current protocol to be more inclusive of those receiving these therapies will allow for increased de-labeling opportunities. Additionally, pharmacist presence in the emergency department may increase the number of patients able to be identified and intervened on for allergy de-labeling.

As indicated above, the inability to perform penicillin skin testing was a barrier in our patients stratified into the moderate-risk category. Mabilat et al[17] recently described a risk stratification strategy that differentiates patients with a reaction of urticarial rash, based on the duration of the rash. In this article, patients having an urticarial rash lasting more than 1 day would be classified as mild risk, while patients having urticarial rash lasting less than 1 day were classified as moderate risk.[17] Additionally, Jones et al[18] suggests a graded oral penicillin or amoxicillin challenge be used in patients with moderate risk allergies when penicillin skin testing in unable to be performed.

Both of these differences relative to our institutional protocol would allow for more oral amoxicillin challenges if incorporated and less need for penicillin skin testing, thereby increasing the opportunity for patients to be de-labeled. Our study was able to show a positive effect with implementation of a beta-lactam allergy de-labeling protocol, and with further improvements to this protocol and education to all parties involved, many of the barriers encountered can be addressed.

Conclusion

Our study demonstrated successful implementation of a beta-lactam de-labeling protocol at a community pediatric children's hospital. Our study was also able to add to the current body of literature supporting de-labeling initiatives by providing a more detailed investigation into possible barriers to implementation, an aspect where the most ideal approach still seems uncertain.[10] Future revisions may include adjusting risk stratification, including alternatives to penicillin skin testing, earlier identification (prior to antihistamine or corticosteroid use), increasing pharmacist presence in critical areas such as the emergency department, and expanding the breadth of beta-lactam antibiotics included in our institutional protocol. All of these changes may allow for increased opportunity for beta-lactam allergy de-labeling and further insight into the ideal implementation strategy for institutions seeking to create de-labeling services.

Article Information

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