

Evaluating Pediatric Penicillin Allergy—The Need to Broaden Indications and Improve Access



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The Infectious Diseases Society of America (IDSA), The Society for Healthcare Epidemiology of America (SHEA), and The Pediatric Infectious Diseases Society (PIDS) define antibiotic stewardship as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration.”¹ In 2015, after former President Barack Obama released an executive order for a National Action Plan for combating antibiotic-resistant bacteria, the National Quality Forum (NQF) committed its support and resources to this initiative. The American Academy of Allergy, Asthma, and Immunology (AAAAI) became an active participant in this effort and released a position statement stipulating that penicillin allergy testing should be routinely performed in patients self-reporting penicillin allergy.² Unfortunately, the vast majority of children with self-reported amoxicillin-associated reaction (AAR) are not referred to an allergist and, thus, much of the penicillin allergy epidemic begins in childhood. Nearly 70,000 pediatric patients present annually to urgent care (UC) and emergency departments (ED).³ For this reason, efforts aimed at evaluating penicillin allergy must include pediatric settings, including acute care.

Given the high utilization of acute care setting for AARs, researchers from Cincinnati Children’s Hospital published companion papers in this issue of the *Journal of Allergy and Clinical Immunology: In Practice*. Guarnieri et al⁴ and Xie et al⁵ characterize pediatric AARs in the acute-care setting and examine predictors of acute care reutilization for the same AARs. The studies evaluated 668 children presenting to EDs/UCs for AARs, with 44% presenting with urticaria, 36% with a maculopapular exanthema, and 11% with a serum sickness–like reaction (SSLR). Onset of symptoms was typically late in the antibiotic course, occurring during days 6 to 8. Notably, 30% of children

experienced associated fever, and 11% had joint involvement. The cohort had a male predominance (57%) with median age of 1.8 years of age. The most common indication for treatment with amoxicillin was otitis media. Approximately 10% of children presented more than once to EDs/UCs owing to progression of symptoms, as compared with 2.6% and 3.1% of children without an AAR who were reevaluated for otitis or streptococcus infection, respectively. Predictors of ED/UC reutilization included male sex, the presence of angioedema, and the presence of joint involvement or gastrointestinal manifestations. Those who reutilized the EDs/UCs were also more often treated with oral corticosteroids, as well as antihistamines and nonsteroidal anti-inflammatory drugs. Importantly, the median time between the 2 EDs/UCs encounters was 19 hours.

There is extensive literature documenting that more than 90% of individuals, including children, who are evaluated for penicillin allergy tolerate the medication without difficulty and can, thus, be successfully delabeled of their allergy. Historically, these evaluations have focused on a history suggestive of immunoglobulin E–mediated reaction and/or cutaneous-only manifestations, while excluding SSLRs. Given the work by Guarnieri et al⁴ demonstrating that 11% of AARs possibly represented an SSLR, it is important to consider whether these AARs may be delabeled to broaden antibiotic stewardship efforts. Alba-Rojas et al⁶ showed very little concordance between the diagnoses of AARs made in EDs/UCs compared with diagnoses at dermatology follow-up. The diagnosis of urticaria showed the greatest diagnostic agreement, but in contrast, SSLR diagnoses were frequently discordant. Coli et al⁷ performed a graded challenge to amoxicillin in 75 children reporting SSLR at a median age of 2 years. When evaluated, 70 patients (93.3%) tolerated the challenge, 2 (2.7%) had immediate symptoms that responded to antihistamines, and 3 (4%) had mild nonimmediate symptoms. These data suggest that even children reporting systemic symptoms of fever and joint pain along with cutaneous manifestations consistent with an SSLR or worrisome symptoms should be considered for penicillin allergy evaluations; this can be done by means of a graded challenge at a very young age with minimal time delay from the initial reaction. Even if children experience an immediate or delayed reaction, these are typically mild and adequately treated with second-generation antihistamines, with very little clinical significance and no evidence of increased health care utilization. It is also worth noting that many children with a history possibly consistent with a SSLR are likely challenged in allergy/immunology offices frequently because of unclear historical reactions.

In addition to potentially broadening criteria for when to consider graded challenge in children reporting AARs, the timing and setting of these evaluations are also important to consider.

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The vast majority of children with an AAR are acutely evaluated in the ED, UC, or by their pediatrician, and only a minority receives referral to an allergist. Widespread implementation of teaching tools to nonallergists encouraging evaluation of AARs may, therefore, be beneficial. A systematic means of referral from the ED/UC setting to an allergist may also improve outpatient evaluation. Timely referrals could also potentially reduce reevaluation visits for the same AARs, which occurred 10% of the time in these studies, because specialists trained in drug allergy could provide targeted education regarding acute symptoms. In the paper by Xie et al,⁵ a Penicillin Allergy Testing Service was established at Cincinnati Children's Hospital. In addition to clinic appointments, by utilizing telemedicine, the Penicillin Allergy Testing Service program was able to offer same or next day counseling on the management of AARs, with possible scheduling of penicillin allergy evaluations at a future date. With the increased growth of integrated health systems and electronic health records, such systematic referrals could be streamlined through automatic referral or best practice alerts. Given the relatively limited number of allergists in the United States, and the fact that access to allergists is limited in regions of the United States,⁸ other specialties can be involved in antibiotic stewardship and penicillin allergy delabeling efforts, and this process can start at the time of ED or UC evaluation.^{9,10}

We commend the companion papers by Guarnieri et al⁴ and Xie et al⁵ evaluating pediatric AARs in the ED/UC setting. These papers bring important features of penicillin allergy to light, demonstrating that AARs impart a heavy burden in the ED/UC setting. Individuals are often labeled with penicillin allergy at a very young age, and despite the majority of reactions being managed with modest medications in the outpatient setting, very few are referred for evaluation by an allergist for potential delabeling. In the spirit of maximizing efforts at antibiotic stewardship, there needs to be improved access to specialists trained to complete penicillin allergy evaluations. We offer that the majority of these evaluations can be safely completed in a young pediatric population through a graded challenge, even in

the setting of systemic manifestations such as fever, arthralgia, angioedema, and respiratory symptoms. Continued progress in access and broadened indications of penicillin allergy evaluation will further promote the enduring effort toward improved antibiotic stewardship.

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