

Distinct Characteristics and Chronology of Amoxicillin-Associated Reactions in Pediatric Acute Care Settings



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What is already known about this topic? Allergy referral population studies report that patients with amoxicillin-associated reactions (AARs) commonly present with maculopapular exanthems, urticaria, or, less frequently, serum sickness-like reactions—with >90% tolerating rechallenges regardless of phenotype.

What does this article add to our knowledge? This paper comprehensively characterizes the chronology, seasonality, and “worrisome” systemic symptoms accompanying AARs at initial presentation—often not seen by allergists—in order to increase diagnostic acumen and confidence in subsequent allergy evaluation and delabeling.

How does this study impact current management guidelines? AARs presenting to acute care settings differ in phenotypic composition from allergy referral populations and among clinical phenotypes, providing foundation for future studies on risk stratification and rechallenge tolerance rates.

BACKGROUND: Amoxicillin-associated reactions (AARs) in children presenting as rashes are common, and recent data suggest that >90% tolerate amoxicillin on re-exposure. However, additional data would help pediatricians and allergists gain confidence in referring and testing children who experienced systemic symptoms perceived as “worrisome,” thus leading to urgent medical evaluations. By characterizing the entire spectrum of AAR symptoms in pediatric patients presenting to emergency department (ED)/urgent care (UC) settings, we sought to increase our diagnostic acumen to guide subsequent allergy evaluations.

OBJECTIVE: To fully characterize clinical features of rash and systemic symptoms in children presenting to the ED/UC with AARs.

METHODS: A retrospective chart review of children seen in the ED/UC from July 1, 2015, to June 30, 2017, was conducted. Clinical features, chronology, and seasonality were detailed, and cases were classified into 3 previously described AAR phenotypes: maculopapular exanthem (MPE), urticaria, and serum sickness-like reactions (SSLRs), if they experienced joint symptoms.

RESULTS: Children ($n = 668$; median age: 1.8 years) presented to the ED/UC with urticaria (44%), MPE (36%), and SSLRs (11%) typically on days 7 to 10 of amoxicillin. Although children with SSLRs were more frequently treated with corticosteroids (28%, $P < .0001$) and exhibited higher rates of “worrisome” features (fever, angioedema, or gastrointestinal symptoms; 73%, $P < .0001$), delayed-onset systemic symptoms were identified frequently in all 3 groups. ED/UC reutilization was unexpectedly high with 66 children (10%) returning to the ED/UC for re-evaluation.

CONCLUSION: “Worrisome” symptoms are common in children presenting to the ED/UC with AARs. Future studies are needed to determine the impact on subsequent referral and allergy testing. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2951-7)

Key words: Drug allergy; Drug rash; Penicillin; Amoxicillin; Pediatric; Emergency department; Urgent care

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Concern for antibiotic allergy is a common complaint in pediatric health care with penicillins representing the most frequently implicated drug class.¹ Up to 10% of the United States population is labeled as penicillin allergic, suggesting that at least 5 million children share this label.¹⁻³ As amoxicillin ± clavulanate remains first-line treatment for many common pediatric infections, including otitis media (OM) and group A streptococcal pharyngitis (GAS), amoxicillin represents

*Abbreviations used**AARs*-Amoxicillin-associated reactions*ED*-Emergency department*EM*-Erythema multiforme*EMLRs*-Erythema multiforme–like rashes*GAS*-Group A streptococcal pharyngitis*GI*-Gastrointestinal*ICD-10*-International Statistical Classification of Diseases—10th Revision*IQR*-Interquartile range*MPE*-Maculopapular exanthema*OM*-Otitis media*SSLR*-Serum sickness–like reaction*UC*-Urgent care

approximately 65% of the implicated β -lactam antibiotic allergies among children.⁴

Children with amoxicillin-associated reactions (AARs) typically present to the general pediatrician's office, urgent care (UC), and/or the emergency department (ED) for initial evaluation. Although some of these children may be referred to an allergist for further evaluation, a significant portion are not—with previous retrospective studies suggesting that 50% to 94% of those seen in primary care settings for penicillin allergy are not referred.^{5–8} The population that is referred may select for AARs that are more severe—providing a stronger impetus for allergy referral and caregiver follow-through—or, alternatively, may exclude those with the most severe presentations given potential reticence to rechallenge. Unfortunately, allergists do not typically see patients with AARs in real time and thus miss exposure to the acute presentations of these reactions, which helps to build clinical pattern recognition and subsequent confidence in allergy delabeling.

The current allergy literature describes 3 identifiable clinical phenotypes for children with AARs who have been referred for allergy testing—maculopapular exanthem (MPE), urticaria, and serum sickness–like reaction (SSLR)—based on rash and the presence of joint involvement. Recent literature suggests that all 3 phenotypes are associated with a low rate (<10%) of confirmed allergy.^{4,9–11} However, because there is a dearth of literature characterizing the full clinical presentation of AARs—especially in the context of chronology, seasonality, and accompanying “worrisome” features, such as fever, angioedema, and gastrointestinal (GI) symptoms—the presence of certain characteristics that have not been well described may wrongly influence clinicians' inclination to pursue allergy referral and testing. For example, a clinician may be hesitant to recommend allergy evaluation for a patient who presented to the ED/UC with angioedema due to concern that this finding represents “true” allergy. Mechanistically, an early-onset urticarial rash may be assumed to be IgE-mediated, whereas a delayed reaction may be attributed to immune complex formation as previously described in serum sickness;^{12–14} conversely, a patient presenting with MPE may be offered amoxicillin again in the primary care office under the assumption that the rash was simply a viral exanthem. In reality, the timing and frequencies of AAR symptoms and their underlying pathophysiologic mechanisms remain unknown. Consequently, a more comprehensive understanding of the presentations of AARs will better inform clinical decision-making.

As caregivers of pediatric patients frequently have difficulty recalling details of the reaction history at the time of allergy consultation months to years later, we reasoned that this information would be best extracted from initial clinical encounters for AARs rather than reported symptoms at the time of allergy evaluation. Consequently, we designed a retrospective chart review of patients with AARs seen in the pediatric ED/UC with the goals of describing salient clinical features at the time of presentation, including chronology of the 3 frequently described clinical phenotypes and additional “worrisome” symptoms, such as fever, angioedema, joint involvement, and GI symptoms, to determine whether there are meaningful differences across these phenotypes and/or variance from allergy referral populations.

METHODS

Design, setting, and participants

A retrospective chart review was conducted on pediatric patients (age ≤ 18 years) presenting with AARs to Cincinnati Children's Hospital Medical Center ED or UC between July 1, 2015, and June 30, 2017. The Epic (Verona, Wis) Clarity electronic medical record database was used to identify clinical encounters with at least 1 of 11 relevant International Statistical Classification of Diseases—10th Revision (ICD-10) diagnostic codes through a stepwise process (see Online Repository text and Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The relevant ICD-10 diagnostic codes included T80.69 (serum sickness/SSLR), L51 (erythema multiforme [EM]), T78.40X (allergic reaction/hypersensitivity reaction), L50.0 (allergic urticaria), L50.8 (other urticaria), L50.9 (urticaria, unspecified), R21 (rash), T36.0X5 (adverse effect of penicillin), T88.7XX (adverse drug event), L27 (drug rash), and T88.6XX (anaphylaxis to drug). The search yielded a total of 2014 unique patients. Severe cutaneous adverse drug reactions were excluded, resulting in exclusion of 1 case of Stevens-Johnson syndrome. A chart review was conducted independently by the first and second authors as pediatric residents. The senior author (faculty allergist/immunologist) reviewed a subset of the cases for confirmation, and a final database was assembled with reactions attributed to amoxicillin $\pm$ clavulanate. In addition, deidentified data were obtained from all ED/UC encounters with OM or GAS as final ICD-10 diagnostic codes within the study time period—particularly focusing on age and seasonality—to serve as a surrogate for the population of children prescribed amoxicillin $\pm$ clavulanate.

Patient classification and measures

Demographic and clinical variables were collected, including sex, age at presentation, indication for antibiotic use, month of reaction, day of onset post-antibiotic initiation, clinical features (including rash morphology and associated systemic symptoms), oral corticosteroid treatment, and ED/UC reutilization. On chart review, there were notable discrepancies between clinical characteristics documented by ED/UC providers and ICD-10 diagnostic code assigned. Consequently, we elected to classify the data into 4 subsets reflecting distinct AAR clinical phenotypes: (1) MPE, (2) urticaria, (3) SSLR, and (4) other rash/resolved rash, based on objective physical examination documentation by the ED/UC provider.

SSLR was designated by any reaction with objective joint involvement documented on examination—defined as pain or swelling localized to the joint, limited range of motion, or refusal to bear weight—regardless of rash morphology or the presence of fever. If there was no joint involvement, the reaction was categorized by rash morphology (Figure 1). Rashes were classified as MPE

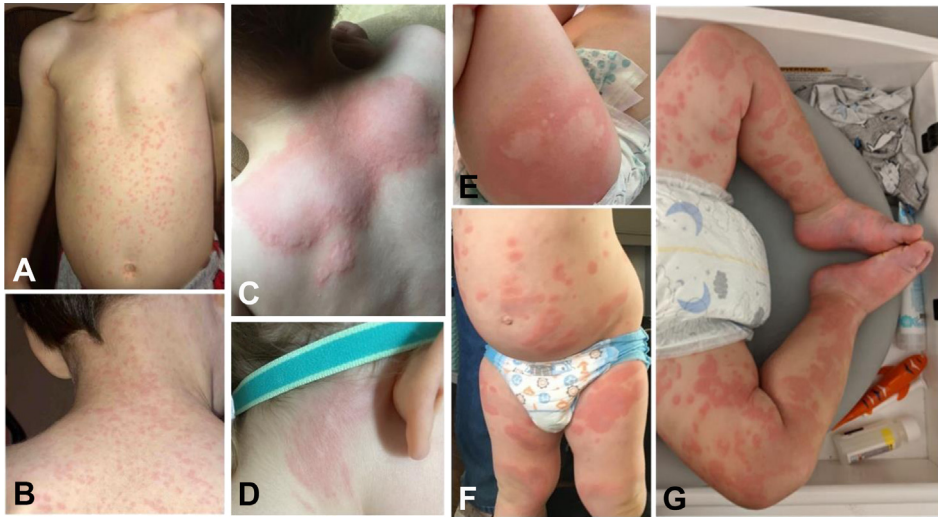


FIGURE 1. Amoxicillin-associated rash morphology. (A, B) Maculopapular exanthem, characterized by diffuse macules and papules with areas of coalescence. (C-E) Urticaria, characterized by erythematous, circumscribed plaques with central clearing. (D) Dermatographism may be noted. (F, G) Erythema multiforme-like rash (EMLR) with coalescent edematous targetoid outer rings and dusky/ecchymotic-appearing centers. EMLR differs from EM in its absence of central necrosis or blistering and trunk predominance.

TABLE I. Comparison of the salient demographic, chronological, and clinical characteristics of children with amoxicillin-associated reactions presenting to the acute care setting across the 3 described phenotypes

Characteristics (n = 606)	Clinical category			P value
	MPE (n = 241)	Urticaria (n = 291)	SSLR (n = 74)	
Male	138 (57)	171 (59)	45 (61)	.85*
Age, median (quartiles) (y)	1.4 (0.9, 4.3)	1.8 (1.5, 2.0)	2.5 (1.7, 5.0)	.007†
Day of antibiotic exposure, median (quartiles)	6 (3, 8)	7 (5, 10)	8 (7, 10)	<.0001†
Reactions in winter season (December 1-March 31)	90 (37)	144 (49)	35 (47)	.017*
Presenting systemic features				
Fever	61 (25)	88 (30)	35 (47)	.0015*
Angioedema	15 (6)	64 (22)	38 (51)	<.0001*
Facial only	11	23	4	
Acral only	4	28	23	
Facial + Acral	0	13	11	
GI symptoms	18 (8)	27 (9)	12 (16)	.078*
Oral corticosteroid treatment	12 (5)	54 (19)	21 (28)	<.0001*
Patients with ≥2 ED/UC visits	7 (3)	36 (12)	19 (26)	<.0001*

Data are presented as n (%), unless otherwise indicated.
Bolded P values are statistically significant.
ED, Emergency department; GI, gastrointestinal; MPE, maculopapular exanthem; SSLR, serum sickness-like reaction; UC, urgent care.
*Pearson χ^2 test.
†Kruskal-Wallis test.

(Figure 1, A and B) if documented as macular and/or papular and as urticaria (Figure 1, C-E) if described as “hives,” “wheals,” “welts,” “serpiginous” rash, or “targetoid” lesions with “central clearing.” Any rash morphology that did not fit the above descriptions was assigned to an “other/resolved rash” subset. For example, if the rash was described as targetoid lesions with central blistering or necrosis or documented explicitly as “erythema multiforme” or “EM” in the provider’s examination, these rashes were considered to represent true EM and were included in the “other rash” subset. Annular or targetoid rashes without the central blistering or necrosis of typical EM are better characterized as EM-like rashes (EMLRs) (Figure 1, F and G).¹⁵ For the purposes of this study, EMLRs were included in

the urticaria subset. If the rash was reported by caregivers but not present at the time of the ED/UC encounter, it was classified as a “resolved rash.” The other/resolved rash subset represented 9% of the total and was excluded from comparative analyses to focus on the features in the 3 classically described phenotypes.

Within each subset, data were collected on the presence of systemic features, including fever (caregiver-reported or documented in ED/UC encounter vitals), angioedema (documented in ED/UC provider’s physical examination), and GI symptoms, including nausea, vomiting, diarrhea, and/or abdominal pain that started in conjunction with or after rash onset (caregiver-reported). Associated angioedema was further subdivided into 3 categories by

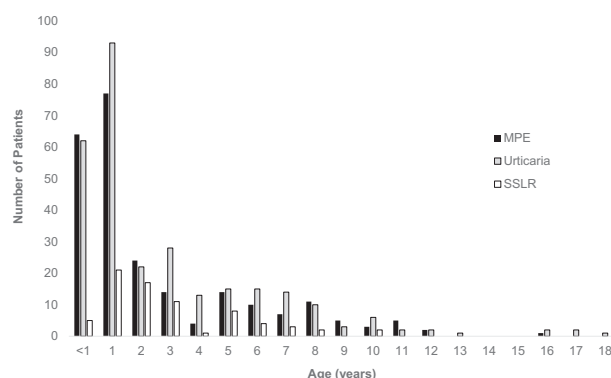


FIGURE 2. Age of patients with amoxicillin-associated reactions. Age represents the patient's age at the first emergency department/urgent care encounter. Clinical phenotypes represent subsets for those classified with maculopapular exanthem (MPE), urticaria, or serum sickness-like reaction (SSLR), with the majority of all phenotypes presenting by 3 years of age.

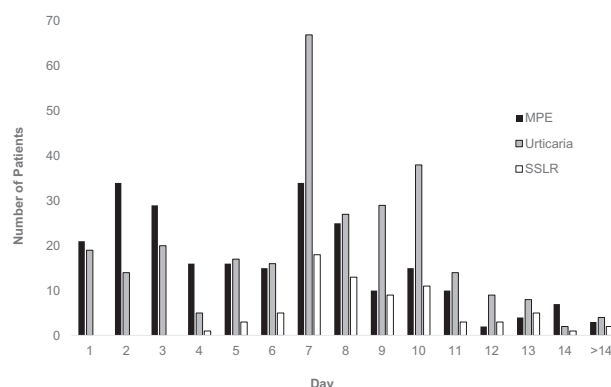


FIGURE 3. Day of symptom onset after initiating amoxicillin ± clavulanate. Day represents the day of first symptoms after initiating the antibiotic. Day 1 represents the day of the first dose.

distribution—facial, involving the periorbital region, cheeks, or lips; acral, involving the distal extremities (hands and feet), genital region, or ears; or both facial and acral.

In addition, oral corticosteroid treatment was regarded as any oral corticosteroid prescribed by the ED/UC provider or primary care physician during the AAR course. ED/UC reutilization was defined as returning to the ED/UC for a chief complaint of new, persistent, or worsening rash and/or systemic symptoms before AAR resolution. No time limit was placed on reutilization within the study time period.

Statistical analysis

Comparative analyses among the 3 phenotypes were conducted for sex, age at presentation, occurrence in winter season (defined as December 1–March 31, consistent with the hospital's designated influenza season), day of onset post-antibiotic initiation, associated systemic features, oral corticosteroid treatment, and ED/UC reutilization. Categorical variables were described using frequencies with percentages and tested by the Pearson χ^2 test. The Kruskal-Wallis test was used for continuous variables and described using median,

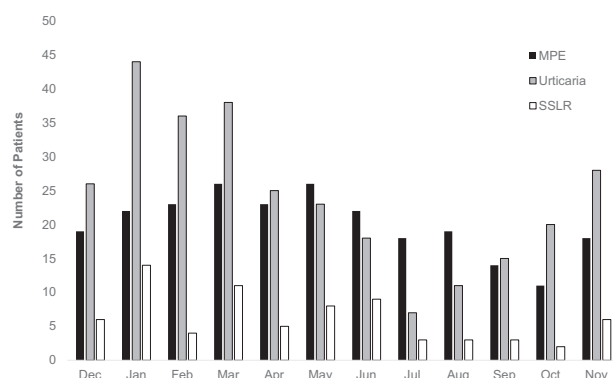


FIGURE 4. Month of amoxicillin-associated reaction. Month of reaction represents the month of the first emergency department/urgent care visit.

25th, and 75th percentiles. No multiple testing adjustments were done.

RESULTS

Overall sample characteristics

A total of 668 patients with reactions attributed to amoxicillin ± clavulanate were identified. Fifty-seven percent ($n = 383$) were male—differing from the typical female predominance in the adult drug allergy literature.^{16–18} The median age was 1.8 years (interquartile range [IQR]: 1.0–5.0 years). The most common indications for antibiotic use were OM ($n = 439$, 66%), GAS or scarlet fever ($n = 127$, 19%), pneumonia or bronchitis ($n = 37$, 6%), and sinusitis ($n = 34$, 5%), with some patients having multiple indications. The median time of AAR onset was day 7 post-antibiotic initiation (IQR: 4–9 days), and none presented with immediate-onset symptoms consistent with anaphylaxis. Approximately half of all patients ($n = 326$) had at least 1 systemic feature, including 30% ($n = 203$) with fever, 20% ($n = 133$) with angioedema, 11% ($n = 74$) with joint involvement, and 9% ($n = 62$) with GI symptoms. In addition, 14% ($n = 93$) were prescribed oral corticosteroids, and 10% ($n = 66$) returned to the ED/UC for at least 1 additional encounter for continued, worsening, or new complaints related to the same AAR. The median time to the second encounter was 19 hours (IQR: 12–34 hours, range: 1.9–314.2 hours).

Clinical phenotype subsets

After patient classification by previously described clinical phenotypes (detailed in the Methods section), the study sample consisted of 241 patients (36%) with MPE, 291 (44%) with urticaria, 74 (11%) with SSLR, and 62 (9%) with other/resolved rash. Additional information on case classification by the ICD-10 diagnostic code is provided in this article's Online Repository at www.jaci-inpractice.org (Online Repository text and Table E1).

Clinical phenotype comparison

Clinical features were compared across the subcohort of 606 patients with MPE, urticaria, or SSLR phenotypes. There was a consistent male predominance with 57% in the MPE subset, 59% in the urticaria subset, and 61% in the SSLR subset ($P = .85$) (Table I). The overall pattern of age at presentation was also similar across all 3 phenotypes with the majority presenting at <3 years of age (Figure 2). However, the median age

TABLE II. Comparison of classical amoxicillin-associated reaction clinical phenotype composition in our cohort with previously published pediatric cohorts from allergy referral populations

Clinical phenotype, % (n)	Study population			
	Study cohort (n = 668) <i>United States</i>	Ponvert et al ⁴ (n = 1431) <i>France</i>	Mill et al ⁹ (n = 818) <i>Canada</i>	Ibáñez et al ¹⁰ (n = 734) <i>Spain</i>
Maculopapular exanthem	36% (241)	18% (264)	Approx 30%*	56% (411)
Urticaria	44% (291)	71% (1013)	Approx 65%*	39% (286)
Serum sickness–like reaction	11% (74)	2% (23)	Approx 3%*	Approx 1% (6)†
Anaphylaxis	0	7% (100)	0	0

*Proportion in each category not clearly specified. Estimated from data presented in Figure 2 of Mill et al.⁹

†Patients with serum sickness reactions were excluded from testing; however, number reported represents those with joint involvement in Ibáñez et al¹⁰ as an estimate of serum sickness–like reactions.

at presentation was significantly older for SSLR at 2.5 years (IQR: 1.7–5.0 years) versus 1.8 years (IQR: 1.5–2.0 years) for urticaria and 1.4 years (IQR: 0.9–4.3 years) for MPE ($P = .007$) (Table I). A review of age data from all ED/UC visits for OM and GAS during the study time period showed that the age distribution of AARs paralleled the ages of all patients presenting to the ED/UC with these diagnoses—generally after the OM trend in toddler- and preschool-aged children with a subsequent increase around the GAS peak at 5 to 7 years of age (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org).

Symptom onset largely occurred during the antibiotic course with only slight differences between phenotypes—namely, a median onset of day 6 for MPE, day 7 for urticaria, and day 8 for SSLR ($P < .0001$) (Table I). Notably, the onset of MPE demonstrated a bimodal distribution with children either presenting within the first few days of treatment with a distinct peak at day 2, or around day 7 similarly to children with urticaria or SSLR. Of note, all children with SSLR presented as late onset with no reactions occurring before day 4 (Figure 3).

Nearly half of patients with urticaria (49%) and SSLR (47%) presented during the winter viral season from December 1 to March 31, whereas significantly fewer cases of MPE (37%) presented during this time ($P = .017$) (Table I). Overall, AARs presented more frequently in the winter months; however, when they did occur in the late spring or summer months, patients were more likely to present with MPE (Figure 4). On comparison of the seasonality of AARs in our cohort with that of OM and GAS, the frequency of AARs generally paralleled the frequency of OM and GAS, with the exception of higher numbers of AARs in the summer (June–August) relative to lower frequencies of OM and GAS during the same months (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

Characterization of potentially “worrisome” symptoms across phenotypes showed that those with SSLR experienced systemic symptoms (fever, angioedema, and/or GI symptoms) at any point most frequently (73%) compared with 47% of those with urticaria and 34% of those with MPE. On evaluation by individual symptom, the distribution of fever and angioedema differed significantly across phenotypes (Table I). Fever was present in 47% of those with SSLR, 30% with urticaria, and 25% with MPE ($P = .0015$). Angioedema was present in 51% of cases with SSLR, 22% with urticaria, and 6% with MPE ($P < .0001$). Of the AARs with angioedema, those with SSLR and urticaria were more likely to have acral angioedema—comprising 61% and 44% in these subsets, respectively—whereas those with MPE were more likely

to have facial angioedema (73%). Although not a well-described feature in allergic drug reactions, new-onset GI symptoms (including nausea, vomiting, abdominal pain, or diarrhea) presented concurrently with rash in 16% of those with SSLR, 9% with urticaria, and 8% with MPE ($P = .078$) (Table I).

We then evaluated 2 features that spoke to provider and/or caregiver “worry”: prescription of oral corticosteroids and ED/UC reutilization. SSLR was treated with oral corticosteroids most frequently (28%), followed by urticaria (19%), then MPE (5%) ($P < .0001$). When evaluating patients based on the recognized clinical criteria, children who eventually developed symptoms consistent with SSLR reutilized the ED/UC most frequently, with 26% having multiple visits compared with 12% of those with urticaria and 3% of those with MPE ($P < .0001$) (Table I). The timing and clinical features that contributed to ED/UC reutilization are described in our companion paper by Xie et al.¹⁹ Likewise, those with SSLR were hospitalized more frequently with 5% of cases being admitted versus 2% with urticaria and <1% with MPE.

DISCUSSION

This study is the first, to our knowledge, to extensively characterize the presenting clinical features of AARs from a pediatric ED/UC population. We focused on this population as we theorized that there would be substantial differences in phenotypic composition compared with pediatric allergy referral populations. Our cohort, in comparison to those from 3 large studies on pediatric penicillin allergy testing (Table II), was notable for an increased proportion of MPE and reduced proportion of urticaria compared with the French (Ponvert et al)⁴ and Canadian (Mill et al)⁹ studies. We also noted a substantially increased frequency of SSLR (11%) in comparison to all 3 studies (1%–3%). Of note, the Spanish (Ibáñez et al)¹⁰ study did not explicitly specify a proportion of SSLR but did report that 1% presented with joint involvement—the cardinal feature of SSLR.^{10,13,20–22}

In addition, we found that children with SSLR exhibited higher rates of what may be considered “worrisome” features—including fever, angioedema, GI symptoms, oral corticosteroid treatment, and ED/UC reutilization—compared with other rash phenotypes. It is possible that these features lead to family hesitancy to pursue allergy testing and/or provider misperception that children with SSLR should avoid the presumed drug trigger indefinitely. Both biases may contribute to a lack of allergy evaluations in these children, reducing the proportion of children with a history of SSLR in allergy referral populations.^{4,20,21}

Although avoidance of penicillin is recommended for patients with severe nonimmediate reactions to amoxicillin, a review of more recent data indicates that children who experienced SSLR may safely undergo subsequent drug provocation challenges.^{13,23} Notably, Delli Colli et al¹³ found that among a cohort of 75 children with suspected SSLR, most of which were attributed to amoxicillin, 93.3% tolerated a graded drug provocation challenge—comparable to children with less severe reaction histories—though 25% did report mild macular/papular rash on subsequent antibiotic use. In addition, SSLR presentations have been seen in patients without preceding drug exposure, suggesting an alternative mechanism—such as virally induced—and further supporting re-evaluation by an allergist.^{13,22} Given these findings and the higher incidence of SSLR in our cohort, interventions aimed at promoting allergy referrals from the acute care setting are necessary to facilitate delabeling and reduce unnecessary avoidance of penicillins.

Furthermore, our comprehensive characterization of the varying clinical features and chronology of the 3 distinct AAR phenotypes may provide clues regarding differing underlying immunopathology driving AARs. Findings such as the bimodal pattern for day of reaction onset in those with MPE may also suggest varied immunopathology even within the subset. Traditionally, timing of reaction has been used to distinguish presumed immunopathology—with urticarial and more immediate-onset reactions thought to signify an IgE-mediated process and nonimmediate reactions considered to be more likely T-cell-mediated.^{12,24} However, in our cohort, urticarial rashes were late-onset—peaking between days 7 and 10—and appearing to be more closely related to SSLR in timing, seasonality, and systemic symptoms. In addition, the earlier peak of onset around day 2 for MPE may reflect the influence of an underlying virus, which can manifest with a rash and systemic symptoms unrelated to the drug, or potentially due to a drug-virus interaction.

Similarly, differences in seasonality may further indicate underlying viral influences for certain AAR phenotypes. Enterovirus infections, for example, tend to peak in the summer months and commonly manifest with viral exanthems—typically MPE.^{25,26} Accordingly, a higher number of AARs presented during the summer months relative to the number of all ED/UC visits for OM and GAS during the same time period, with MPEs emerging as the predominant rash phenotype from May through August in our cohort. In contrast, winter viruses, such as influenza, adenovirus, respiratory syncytial virus, rhinovirus, and parainfluenza, are known to manifest with viral-induced urticaria.²⁷ Seasonally, AARs in our cohort presented with urticaria more frequently in the winter months compared with MPE. Given the demonstrated propensity of AARs to present with MPE in the summer months and urticaria in the winter months, the viral landscape throughout the year may influence phenotypes of reactions attributed to amoxicillin.

This study also demonstrates that AARs disproportionately present in the younger ages, particularly <3 years, likely given that a large proportion of children are first introduced to amoxicillin at a young age and subsequently avoid penicillins after a presumed reaction. Consequently, this young age group should be targeted for penicillin allergy delabeling efforts, inclusive of those with SSLR.

The major limitation of this study was identifying cases by ICD-10 codes. Although a broad selection of ICD-10 diagnostic

codes was used in an attempt to fully capture the population of interest, it is possible that cases with alternate diagnostic codes were missed. Reliance on provider documentation represents another limitation of our study, though our classification with standardized inclusion criteria for each phenotype subset sought to reduce the bias of provider-specific variance in diagnosis. In addition, the SSLR subset data may have differed if the inclusion criteria for the subset were more stringent, such as requiring associated fever. The study is also inherently limited by the retrospective design, although reviewing acute care providers' documentation to ascertain patients' clinical features on initial presentation reduces referral and recall biases compared with previously studied populations.

In conclusion, our study demonstrates that the phenotypic composition of AARs presenting to pediatric acute care settings differs from that of previously published AARs in allergy referral populations. We suspect that the presence of features attributed to SSLR and/or other “worrisome” features noted in our cohort are likely deterrents for subsequent allergy referral and testing for patients and providers alike. Although the immunopathology of these differences has yet to be elucidated, this study serves as a foundation to aid clinicians in pattern recognition of AARs, increase confidence in counseling patients and caregivers, and promote allergy referral and delabeling in a very young pediatric population. Interestingly, prior studies have suggested that certain associated features—such as angioedema—convey increased risk of positive penicillin allergy testing in adult patients.²⁸ Further prospective studies are needed to evaluate whether these distinct AAR phenotypes and associated clinical features correlate with meaningful differences in drug provocation challenge outcomes in the pediatric population, as rechallenge tolerance data derived from allergy referral populations may not be generalizable to this population.

Finally, we noted differences in the likelihood of hospital reutilization—an important outcome, which can result in significant financial and psychosocial burdens for the family and resource expenditure for the hospital system. In our companion paper (Xie et al), we examine clinical features associated with risk for ED/UC reutilization to assist clinicians in counseling patients and caregivers, managing expectations, and implementing interventions to prevent unnecessary health care reutilization.¹⁹

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ONLINE REPOSITORY

SUPPLEMENTAL METHODS

Identification of children presenting with amoxicillin-associated reactions (AARs) in the electronic medical record

Selection of the relevant International Statistical Classification of Diseases—10th Revision (ICD-10) diagnostic codes was achieved through a 3-step process, as detailed in [Figure E1](#). Initial codes selected included T78.40X (allergic reaction/hypersensitivity reaction), T80.69 (serum sickness/serum sickness–like reaction [SSLR]), and L51 (erythema multiforme [EM])—as the latter 2 are commonly attributed to antibiotics. Encounters involving AARs were identified, and additional ICD-10 diagnostic codes for those encounters were reviewed. On review, the codes L50.0 (allergic urticaria), L50.9 (urticaria, unspecified), and R21 (rash) were noted to be additional diagnostic codes for these encounters and relevant to the AAR, so a second round of data collection was conducted using these ICD-10 diagnostic codes. Similarly, encounters involving AARs were identified and additional diagnostic codes for those encounters were reviewed, prompting a third round of data collection using the ICD-10 diagnostic codes L50.8 (other urticaria), T36.0X5 (adverse reaction to penicillin), T88.7XX (adverse drug event), and L27 (drug rash). The diagnostic code T88.6XX (anaphylaxis to drug) was additionally included in an attempt to capture any anaphylactic AARs, though this code produced no encounters for AARs within the study time period.

Of note, the ICD-10 code for “amoxicillin allergy” or “penicillin allergy” is Z88.0—a Z code, which represents a “status” rather than a “diagnosis.” When we searched for patient encounters using this code as an ED diagnosis, there were only 2 patients identified. This reflects that our emergency department/urgent care physicians do not typically “diagnose” penicillin allergy, instead listing the diagnoses above. Consequently, this code was not used as a primary diagnostic code for identifying encounters in our review.

Diagnostic code AAR relevance rates

In the data collection process, the ICD-10 diagnostic codes T36.05 (adverse reaction to penicillin), T88.7X (adverse drug event), and L50.0 (allergic urticaria) yielded the highest percentage of relevant cases with 100%, 93%, and 91%, respectively, yielding reactions presumed to be amoxicillin associated. Of note, initial data collection for the ICD-10 diagnostic codes L51 (EM), T80.69 (serum sickness/SSLR), and T78.40X (allergic reaction) was performed without restricting results to encounters containing “amox” or “Augmentin” in any of the encounter notes, whereas all subsequent data collections used this specification to increase yield relevance—consequently affecting relevance rates ([Table E1](#) and [Figure E1](#)).

Eighty percent of the relevant 234 cases that had been assigned an ICD-10 diagnostic code of R21 (rash) were classified into the maculopapular exanthem (MPE) subset with 18 (8%) classified as urticaria, 4 (2%) as SSLR, and 25 (11%) as other/resolved rash. The majority (88%-95%) of the relevant cases with any of the urticaria diagnoses (L50.0: allergic urticaria, L50.8: other urticaria, L50.9: urticaria, unspecified; n = 151 total) were classified into the urticaria subset with a small proportion (4%-6%) classified as SSLR. Of the 70 relevant cases with the ICD-10 diagnostic code T78.40X (allergic reaction), 30 (43%) were classified as MPE, 31 (44%) as urticaria, 3 (4%) as SSLR, and 6 (9%) as other/resolved rash. Of the 95 relevant cases that had been assigned the L51 (EM) ICD-10 diagnostic code, only 18 (19%) had documented evidence of true EM rash (with central blistering or necrosis)—1 of which was classified as SSLR and the remaining 17 were classified as other/resolved rash. Of the additional relevant L51 cases, 60 (63%) were classified as urticaria, 6 (6%) as MPE, and 11 as SSLR for a total of 12 (13%) with SSLR. For the 101 relevant cases with the T80.69 (serum sickness/SSLR) diagnostic code, 50 (50%) were classified as SSLR with 40 (40%) reclassified as urticaria, 5 (5%) as MPE, and 6 (7%) as other/resolved rash—the latter 3 signifying no joint involvement ([Table E1](#)).

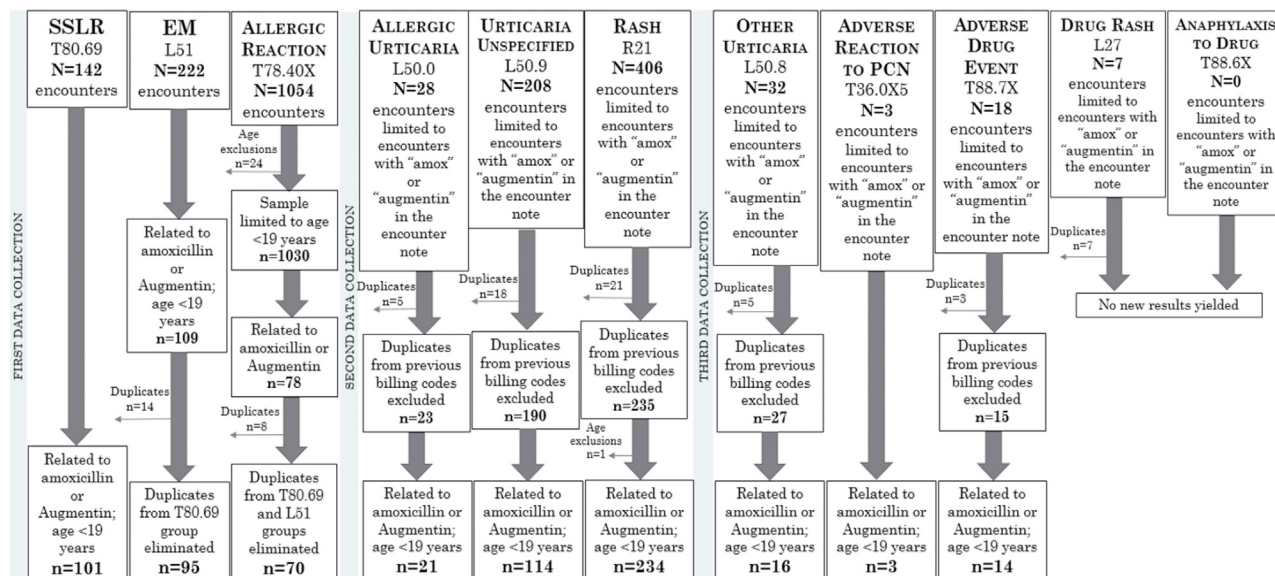


FIGURE E1. Phases of data collection using relevant International Statistical Classification of Diseases—10th Revision (ICD-10) diagnostic codes. Cases with encounter age ≥ 19 years were excluded. Encounters retrieved in a later data collection phase that had previously been identified in an earlier phase due to having multiple of the relevant ICD-10 codes were eliminated as duplicates.

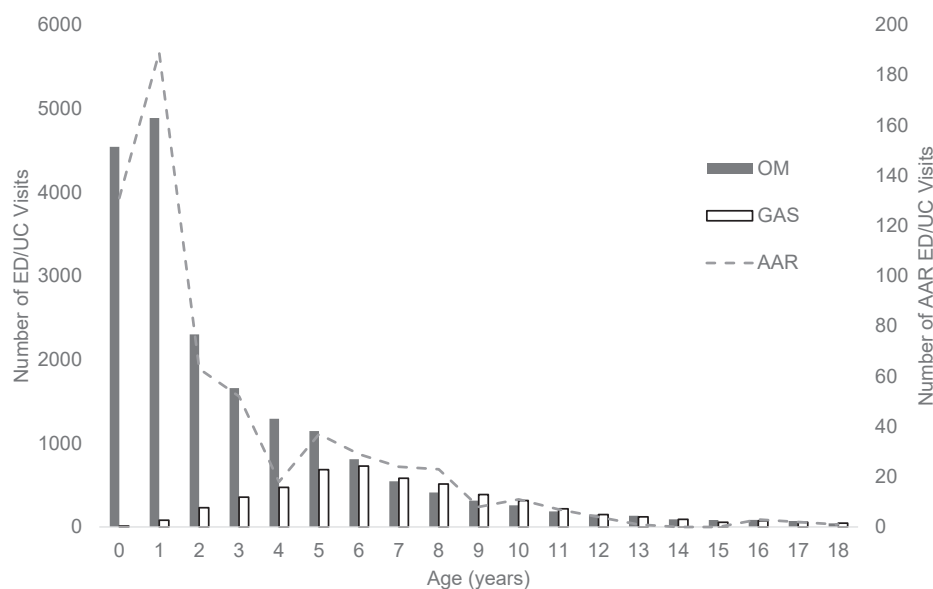


FIGURE E2. Age distribution of patients presenting to the ED/UC with an amoxicillin-associated reaction in comparison to those presenting to the ED/UC for otitis media or group A streptococcal pharyngitis—2 of the most common indications for amoxicillin $\pm$ clavulanate—during the study time period.

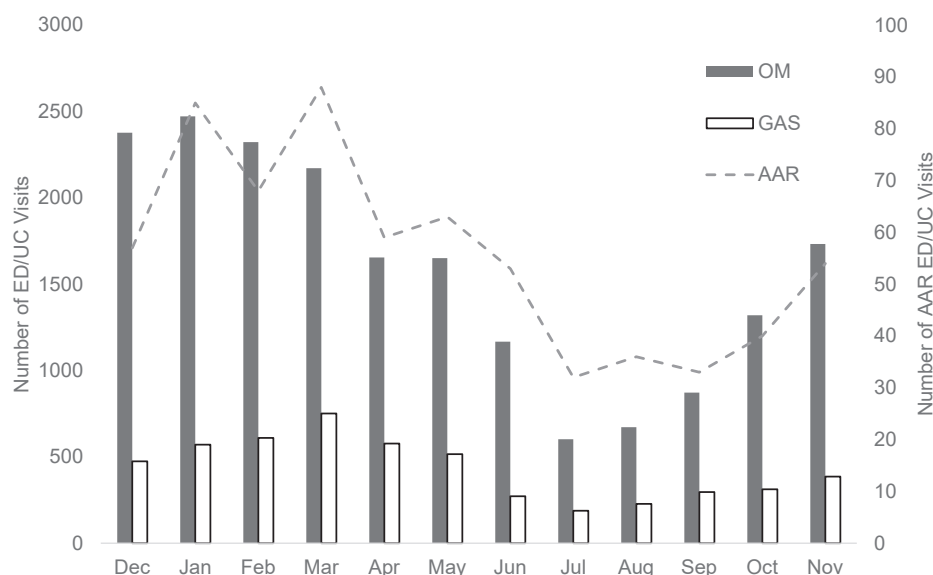


FIGURE E3. Amoxicillin-associated reaction seasonality, represented by month of initial ED/UC presentation, in comparison to seasonality of visits for otitis media and group A streptococcal pharyngitis during the 2-year study time period.

TABLE E1. Reactions identified by the ICD-10 diagnostic code, association with amoxicillin ± clavulanate, and classification by clinical phenotype

ED/UC ICD-10 diagnostic code	Amoxicillin associated (relevance rate)‡	Classification			
		MPE (n = 241)	Urticaria (n = 291)	SSLR (n = 74)	Other/resolved rash (n = 62)
R21: rash (n = 385)*	234 (61)	187 (80)	18 (8)	4 (2)	25 (11)
L50.0: allergic urticaria (n = 23)*	21 (91)	0	20 (95)	0	1 (5)
L50.8: other urticaria (n = 27)*	16 (59)	1 (6)	14 (88)	1 (6)	0
L50.9: urticaria, unspecified (n = 190)*	114 (60)	0	105 (92)	4 (4)	5 (4)
T78.40X: allergic reaction (n = 1054)	70 (7)	30 (43)	31 (44)	3 (4)	6 (9)
T36.0X5: adverse reaction to PCN (n = 3)*	3 (100)	3 (100)	0	0	0
T88.7X: adverse drug event (n = 15)*	14 (93)	9 (64)	3 (21)	0	2 (14)
L51: erythema multiforme (n = 223)	95 (43)	6 (6)	60 (63)	12 (13)	17 (18)
T80.69: SSLR (n = 142)	101 (71)	5 (5)	40 (40)	50 (50)	6 (7)
L27: drug rash (n = 0)*,†	0	0	0	0	0
T88.6X: anaphylaxis to drug (n = 0)*	0	0	0	0	0

Data are presented as n (%).

ED, Emergency department; ICD-10, International Statistical Classification of Diseases—10th Revision; MPE, maculopapular exanthem; PCN, penicillin; SSLR, serum sickness–like reaction; UC, urgent care.

*Data collection limited by encounter notes containing “amox” or “Augmentin.”

†Produced no new results but was an additional code on 7 of the previously retrieved cases.

‡Represents percentage of all cases identified for that diagnostic code that had symptoms attributed to amoxicillin ± clavulanate.