Pediatric Drug Allergy

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KEYWORDS

- Drug • Antibiotic • Nonsteroidal anti-inflammatory drug • Hypersensitivity • Allergy
- Pediatric • Children

KEY POINTS

- Self-reported drug allergies are common among children and these labels carry significant clinical and economic implications.
- Most self-reported drug allergies are not confirmed by a diagnostic workup.
- Direct challenge tests can be safely and effectively used to evaluate penicillin derivative allergies in children.
- The best diagnostic approaches for patients presenting with the most severe cutaneous adverse reactions are unknown.
- Evidence on the best diagnostic approaches in cases whereby the culprit drug may be protopathic and not truly implicated are unknown.

Abbreviations	
NSAID	non steroidal anti-inflammatory drug
SSLR	serum sickness-like reaction
SJS	stevens-Johnson syndrome
AGEP	acute generalised exanthematous pustulosis
SCAR	severe cutaneous adverse reaction
DRESS	drug reaction with eosinophilia and systemic symptoms
SPT	skin prick test
IDT	intradermal test
sIgE	specific IgE test
NPV	negative predictive value
PPV	positive predictive value
TEN	toxic epidermal necrolysis

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ADR	adverse drug reaction
PT	patch test
LTT	lymphocyte transformation test

INTRODUCTION

True drug allergies are relatively rare among children; however, children are often incorrectly labeled at the time of an acute viral infection. Urticaria or a delayed exanthem associated with an antibiotic is rarely followed-up in children with an appropriate diagnostic workup. Drug allergy labels are common and have significant associated cost and health implications.[1,2] The prevalence of self-reported drug allergies among children ranges from 2.9% to 16.8%, whereas as few as 4% of these suspected drug allergies are confirmed after appropriate diagnostic work-up.[3] Antibiotics and NSAIDs account for the majority of reported drug allergies in children.[4] In the following sections, we will review current data related to the prevalence, diagnosis, and management of common pediatric drug allergies.

BETA-LACTAM ANTIBIOTICS
Prevalence, Cross-Reactivity, and Natural History

Beta-lactams are among the safest, most effective, and widely used antibiotics for treating community and hospital-acquired pediatric infections. The prevalence of self-reported penicillin-class and cephalosporin allergy among children range from 5% to 10% and 0.5% to 1.1%,[5,6] respectively, but true allergies to beta-lactams are rare. A recent study established that among the 1914 children assessed for suspected amoxicillin allergy only 5.4% (2.2% immediate and 3.2% nonimmediate) had a true allergy.[7] Among children with confirmed penicillin class allergies, cross-reactivity to cephalosporins with dissimilar R1 side chains is low (approximately 2%), but cross-reactivity increases with R1 side chain similarity.[8] The prevalence of confirmed cephalosporin allergy among children evaluated for a suspected allergy ranges from 14.3% to 28.9%.[9–11] Additionally, data suggest that in children, true beta-lactam allergy typically resolves in children by adulthood. Among children with a history of positive direct ingestion challenge to beta-lactams, 89% tolerated a subsequent direct ingestion challenge after a mean of 3.5 years after the initial evaluation.[12] Given these findings, it is suggested that the majority of children presenting

Fig. 1. (*A*) Child presenting with urticaria after amoxicillin challenge. (*B*) Child presenting with maculopapular rash after cefixime challenge.

with benign skin rashes should not avoid future treatment even in the absence of drug challenges.

Presentation

In children, reactions to beta-lactams most commonly occur between 1 and 3 years of age, with amoxicillin being the most frequent culprit, followed by third-generation cephalosporins,[7,13] likely due to their relative usage in children. Nonimmediate reactions (occurring more than 1 hour after exposure) to beta-lactams are more common than immediate reactions.[7,11,13] Among patients presenting with a suspected drug allergy, the most common symptoms are urticaria (Fig. 1A) and maculopapular rashes (Fig. 1B), followed by angioedema and gastrointestinal symptoms (vomiting and diarrhea). One study of 1431 pediatric patients documented that 7% of patients with a suspected allergy to beta-lactams reported anaphylaxis to the culprit drug, and of these reactions, 50% were confirmed as true allergy based on skin testing and challenge.[14] In most patients, symptoms from suspected beta-lactam allergies resolve within 3 days of onset, whereas in approximately 10% to 20% symptoms persist for more than 7 days.[7,13]

Serum-sickness-like reaction (SSLR) is a subtype of nonimmediate reaction presenting with arthralgia and a rash (often with hemorrhagic components) with or without fever (Fig. 2). SSLRs are benign and often occur several days to weeks after starting antibiotic treatment. SSLRs are reported to occur more often in children,[15] are more common after treatment with cefaclor versus amoxicillin,[16] and occur in approximately 1% to 2% of patients with suspected drug allergy.[14]

Beta-lactams trigger up to 30% to 40% of all severe cutaneous adverse reactions (SCARs) in children, the most common reaction being Stevens–Johnson syndrome (SJS).[17,18] Penicillin derivatives are reported to cause the majority of pediatric acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS).[19] However, the proportion of cases of SCARs attributed to beta-lactams may be confounded by protopathic bias, whereby beta-lactams are administered at the onset of SCAR symptoms and are misattributed as the cause.[20]

Approach

When assessing a patient with a suspected beta-lactam allergy, antibiotic treatment should be ceased and an alternative antibiotic with a low risk of cross-reactivity should be prescribed. A thorough history should be taken to establish the nature of the

Fig. 2. Child presenting with serum sickness-like reaction after amoxicillin treatment.
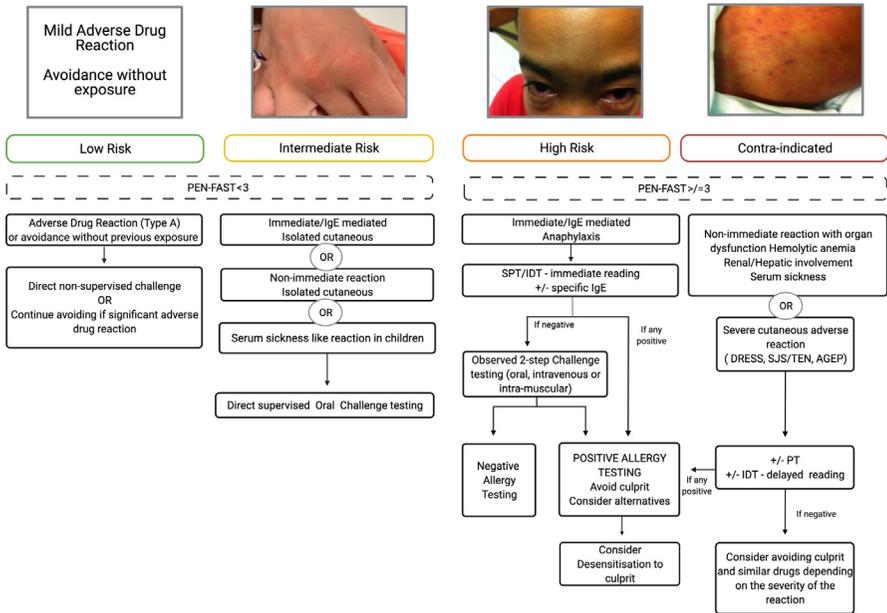
Fig. 3. Algorithm for diagnostic approach in pediatric patients with suspected beta-lactam allergy. Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; IDT, intradermal testing; PT, patch testing; SJS, Steven-Johnson syndrome; SPT, skin prick testing; TEN, toxic epidermal necrolysis; Note 1: Delayed reactions are defined as reactions that occur more than 1 hour after drug administration. Note 2: In severe cutaneous adverse reactions and serum sickness reaction, drug provocation is contraindication, and the culprit drug should be avoided.

reaction (immediate/nonimmediate and allergic/hypersensitivity) and the likelihood of the antibiotic being the cause. History taking should assess the timeframe of the reaction, past exposure/reactions to the antibiotic, indication for antibiotic prescription, symptoms of the reaction, and concurrent medication use.[21] As most drug reactions involve a rash, the skin should be evaluated to assess the morphology of the rash (macular and/or papular vs urticarial vs vesicular/bullous). Recently, the PEN-FAST approach was developed and validated in adults to identify low-risk penicillin hypersensitivities reactions amenable to direct delabeling or direct oral challenge; however, this has not been validated in children.[22] A high index of suspicion for SCARs and SSLRs should be maintained for patients presenting with systemic symptoms and/or severe cutaneous symptoms. The recommended approach to the diagnosis of a beta-lactam allergy is summarized in **Fig. 3**.

Diagnosis

There has been a recent paradigm shift in the diagnosis of beta-lactam allergy, mainly amoxicillin, in children not presenting with anaphylaxis or SCARs. Several studies support the safety and diagnostic value of the direct ingestion challenge (without prior skin or blood tests).[7,13,23] Classically, skin prick tests (SPT) and intradermal tests (IDT) using various antigenic determinants of penicillin, and, infrequently, specific IgE tests (sIgE) have been used in the diagnosis of pediatric drug allergies. Despite the high specificity and negative predictive value (NPV) of these tests, recent pediatric studies suggest poor sensitivity and low positive predictive value (PPV), which limits their

Table 1
Diagnostic properties of available tests for suspected beta-lactam and non–beta-lactam allergies in children

Drug	Test	Patients Evaluated with the Test and Gold Standard	Index Reaction Timing	Author, Year	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Amoxicillin/ Penicillin	SPT	732	Nonimmediate and Immediate	Ibáñez et al,[107] 2018	9.1	98.3	20.0	95.8
Amoxicillin/ Penicillin	SPT (Penicillin G only)	562	Nonimmediate and Immediate	Picard et al,[30] 2014	-	-	-	95.2
Amoxicillin/ Penicillin	SPT	337	Nonimmediate	Barni et al,[108] 2015	8	99.7	-	-
Amoxicillin/ Penicillin	SPT	168	Immediate	Celik et al,[109] 2020	-	-	-	92.2
Amoxicillin/ Penicillin	IDT	732	Nonimmediate and Immediate	Ibáñez et al,[107] 2018	0.0	100.0	-	95.0
Amoxicillin/ Penicillin	IDT	77	Nonimmediate	Caubet et al,[26] 2010	50	91.8	25	97.1
Amoxicillin/ Penicillin	sIgE	732	Nonimmediate and Immediate	Ibáñez et al,[107] 2018	2.9	99	12.5	95.3
Amoxicillin/ Penicillin	SPT and IDT	17	Nonimmediate and Immediate	Mill et al,[13] 2016	5.9	-	-	-
Amoxicillin/ Penicillin	Ingestion challenge	55	Nonimmediate and Immediate	Mill et al.[13] 2016	-	100	100	89.1
Amoxicillin/ Penicillin	Ingestion challenge	265	Nonimmediate and Immediate	Exius et al,[7] 2021	-	-	-	85.3
Cephalosporin	SPT and IDT	136	Nonimmediate and Immediate	Touati et al,[9] 2021	-	-	-	91.9
Cephalosporin	SPT and IDT	96	Nonimmediate and Immediate	Romano et al,[27] 2008	72.1	-	-	-

Table 1
(continued)

Drug	Test	Patients Evaluated with the Test and Gold Standard	Index Reaction Timing	Author, Year	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cephalosporin	IDT	11	Nonimmediate	Caubet et al,[26] 2010	100	88.9	33.3	100
Cephalosporin	sIgE	23	Immediate	Mori et al,[10] 2019	20	95.6	50	84.6
Cephalosporin	Ingestion challenge	6	Nonimmediate and Immediate	Attari et al.[29] 2019 (Conference Abstract)	-	-	-	83.3
Clarithromycin	SPT	89	Nonimmediate and Immediate	Suleyman et al,[62] 2021	-	73.9	-	92.1
Azithromycin	SPT	6	Immediate	Barni et al.,[54] 2015	-	-	75	50
Clarithromycin	SPT	32 (nonimmediate) and 19 (immediate)	Nonimmediate and Immediate	Barni et al,[54] 2015	-	-	-	94 (nonimmediate) and 100 (immediate)

diagnostic value (**Table 1**). No standardized protocol exists for direct ingestion challenge in children; however, amoxicillin challenges have been used successfully using 10% of the therapeutic dose followed by a 90% of the therapeutic dose 20 minutes later, with a subsequent 1-hour observation period.[7,13] Two large pediatric studies using amoxicillin challenge reported only mild reactions.[7,13] Both these studies assessed the NPV of the direct ingestion challenge and determined it to be 85.3% to 89.1%.[7,13] Moreover, one of these studies determined that the PPV of the direct ingestion challenge was 100% (95%CI: 86.3%, 100.0%) and that the specificity was 100% (95%CI: 90.9%, 100.0%).[13] More recently, a study on children presenting with SSLRs after amoxicillin treatment revealed that direct ingestion challenge may be an appropriate strategy in these cases.[24] Of the patients challenged, 2.7% reacted immediately (within 1 hour) and 4.0% had a nonimmediate reaction.[24] Among the 43 patients successfully contacted, 20 reported subsequent culprit antibiotic use, of whom 25.0% had a subsequent mild reaction (macular/papular rash) not in keeping with the original SSLR.[24]

Unlike penicillin, no commercially standardized reagents exist for cephalosporin skin testing. For parenteral forms, dilution of native cephalosporins into nonirritating concentrations is suggested.[25] There are currently no skin tests based diagnostic strategies for oral cephalosporins that are not available in a parenteral formulation. The data on the diagnostic properties of skin tests and sIgE in the diagnosis of cephalosporin allergies are limited (see **Table 1**). Current data may suggest that skin tests have much better sensitivities in the diagnosis of cephalosporin than penicillin allergies (sensitivity: 72.1%–100%).[26,27] In contrast, a large study of adults and adolescents found the sensitivity of IDT in the diagnosis of immediate cephalosporin allergy to be 0%.[28] However, this study is confounded by the restricted range of cephalosporins tested and the study design, which tested participants for cephalosporin allergy without a history of reaction to cephalosporins. Scarce data on direct ingestion challenge for the diagnosis of a cephalosporin allergy in children are available. A conference abstract reported that among 89 children with suspected cephalosporin allergies undergoing direct ingestion challenge, only 6.7% reacted and all reactions were mild and limited to the skin.[29] Of the 42 patients with negative cephalosporin challenge who responded to the follow-up questionnaire, 6 reported subsequent cephalosporin use and one of which had a mild reaction.[29] Further studies on large patient populations are necessary to validate the diagnostic properties and safety of direct cephalosporin challenges.

For patients with a history of anaphylaxis or SCAR to beta-lactams, direct ingestion challenge is contraindicated. A negative skin test should be elicited before direct ingestion challenge in patients with a history of anaphylaxis to beta-lactams.[21,30]

Management

Because of low cross-reactivity between penicillin derivatives and cephalosporins, most cases of true penicillin allergy can safely be administered cephalosporins with dissimilar side chains.[31] In one study of 30 children with nonimmediate allergies to penicillin, all patients tolerated cephalosporin on challenge.[32] In these patients, third generation cephalosporins are often recommended.[33] For patients with immediate reactions to penicillin, some studies suggest that skin testing with second/third generation cephalosporins with dissimilar side chains should precede antibiotic challenge.[33–35] Other studies indicate that a structurally dissimilar cephalosporin, such as cefixime, could be used safely with no prior skin test in children with confirmed amoxicillin allergies.[13] There is an increased risk for reactions (10%, involving mild cutaneous reactions) with first generation cephalosporins containing similar side

chains, such as cephalexin.[7] Alternatively, in children with a cephalosporin allergy, without a known history of penicillin allergy, penicillin can be safely administered following a negative cephalosporin skin test and negative cephalosporin challenge.[36] While most patients with cephalosporin and/or penicillin allergies can safely be prescribed aztreonam,[21] patients allergic to ceftazidime should avoid aztreonam without specific allergy testing due their identical side chains.[37] Penicillin allergic patients may also undergo carbapenem challenges, as there is low cross-reactivity between these antibiotic types.[21,38] In a study of 104 adolescent and adult patients allergic to penicillin, one patient had a positive IDT to meropenem, and the remaining patients with negative skin tests tolerated meropenem challenge.[38] Alternatives to beta-lactams depend on the type of infection being treated but for common community-acquired infections could include azithromycin or clindamycin for IgE-mediated reactions. Since resistance is common among community-acquired infections delabeling beta-lactam allergy is an important antimicrobial stewardship strategy in children that has positive benefits into adulthood.[39] Cefdinir has been suggested as an alternative for non-IgE mediated reactions to penicillin; however, the cross-reactivity between cefdinir and penicillin for IgE-mediated reactions would be less than 2%.[40] These alternative medications are associated with a 2- to 5-fold cost increase compared with amoxicillin providing an additional incentive for penicillin testing and delabeling approaches in childhood.[39]

Desensitization provides temporary antibiotic tolerance by diminishing the immune response to a given medication and may be used when alternative antibiotics are contraindicated, unavailable, and/or less effective. These situations occur most often in patients with life-threatening infections whereby a beta-lactam is the drug of choice or multidrug-resistant infections and/or chronic conditions.[41]

Desensitization has been proposed for suspected IgE-mediated reactions, as well as nonsevere type IV reactions.[42] Contraindications include type II hypersensitivity reactions, type III reactions, and SCARs.[42] Importantly, a careful risk/benefit analysis should be performed before performing desensitization.

Studies and standardized protocols on pediatric desensitization are lacking. Given the paucity of the data, adult protocols are frequently adapted for use in children. The penicillin desensitization protocol published by Sullivan and colleagues is the most widely used or adapted protocol in clinical practice.[43] This protocol involves an initial dose of penicillin beginning at 1/10000 to 1/1000 of the target therapeutic dose, and doses are doubled at 15- to 20-min intervals.[41] Oral desensitization for penicillin has been suggested to be safer and is favored for children.[41] A study on oral penicillin desensitization in 24 adults and 2 children successfully desensitized 25 out of 26 participants.[44] Cessation of protocol occurred in a 15-year-old participant with cystic fibrosis and severe pulmonary disease due to gradual worsening of wheezing. Sparse data exist describing successful desensitization to non–penicillin beta-lactams in children.[45]

Importantly, desensitization should be performed by well-trained specialists in a setting equipped to treat adverse reactions (e.g., anaphylaxis). There is a need for more data on its safety and efficacy in the pediatric population. Given that most drug allergies are desensitized empirically and not based on a positive skin test, it is recommended that patients follow-up with an allergist for further testing and potential delabeling 6 weeks either following the procedure or completion of therapy.

Impact of Drug Allergy Label on Cost and Care in Children

Antibiotic allergy labels in the pediatric population are associated with adverse health and economic outcomes. In a study of 1718 hospitalized children, those labeled as penicillin-allergic had a longer duration of hospital stay and a higher comorbidity index

compared with control patients.[46] Another study determined that beta-lactam allergic patients were more likely to receive broad-spectrum antibiotics compared with nonallergic patients.[47] Broad-spectrum antibiotics may be less effective, have more side effects, and contribute to antibiotic resistance.[21]

Drug allergy labels increase the cost of care for both patients and health care systems. Treatment with alternative antibiotics is more expensive than the standard of care. The use of alternative antibiotics among 48 pediatric patients was found to be associated with an average additional cost of $326.50 CAD per patient compared with beta-lactam standard-of-care.[48]

Drug Allergy Delabeling

Appropriate diagnostic workup is essential in preventing erroneous drug allergy labeling. However, both pediatric emergency medicine and primary care providers were found to infrequently refer children for detailed penicillin allergy assessment.[49]

Following a negative challenge, the beta-lactam allergy label should be entirely removed from a patient's medical record. However, failure to adequately update medication allergy records has been estimated to occur in more than one in 5 patients,[50] which impedes future beta-lactam prescriptions.

Patients who tolerate beta-lactam challenges, as well as their families, should be educated that they are not allergic to the medication and can safely take it in the future. Picard and colleagues report that 18% of parents are reluctant to give their children penicillin despite removal of the allergy label due to fear of subsequent reaction.[51] Several strategies have been proposed to improve the efficacy of delabeling beta-lactam allergies. A study of an extended versus a short ingestion challenge protocol (7 days vs 1 day) for suspected beta-lactam allergy in adults demonstrated increased beta-lactam usage at follow-up in patients on the extended protocol.[52] Further, Jeimy and colleagues have proposed written instructions to reiterate a patient's successful challenge and educate on anaphylaxis.[21] Taken together, a thorough evaluation, proper documentation, and patient education may improve drug allergy delabeling and mitigate the negative impacts of a drug allergy label.

NON–BETA-LACTAM ANTIBIOTICS
Prevalence of Hypersensitivity Among Children

Non–beta-lactam antibiotics, mainly macrolides, are often used in clinical practice to treat children for a variety of infections. The prevalence of self-reported macrolide allergy is low and ranges from 0.3% to 0.8% in children.[5,33] Sulfonamide antibiotics can be prescribed to treat urinary tract infections, as prophylaxis therapy for acute otitis media, and for the prevention of meningococcal infections. Due to its known toxicity, sulfonamides are not recommended for children below the age of 2 months.[53] The self-reported allergy prevalence of these antibiotics among children ranges from 0.5% to 2.7%.[5]

Other non–beta-lactam antibiotic allergic reactions reported in children include fluoroquinolones, tetracyclines, clindamycin, aminoglycosides, glycopeptides, and nitroimidazoles. The prevalence of self-reported allergic reactions for fluoroquinolones and tetracyclines among children was 0.004% to 0.04% and 0% to 0.3%, respectively.[5] There are limited data on the prevalence of allergic reactions to all other antibiotics due to their infrequent prescription and application in the pediatric population.

Presentation

Allergic reactions to macrolides can present as either immediate or nonimmediate reactions. Among nonimmediate reactions to clarithromycin, the majority (over 90%)

Fig. 4. Maculopapular exanthema in a child with a positive challenge to azithromycin.

present with cutaneous manifestations, such as urticaria, angioedema, and/or maculopapular rash (Fig. 4).[54] Immediate reactions to clarithromycin also commonly present as cutaneous manifestations, with a smaller proportion reporting gastrointestinal symptoms.[54] Anaphylaxis to clarithromycin is rare, reported to be one case per one million per year in pediatric studies.[55] Nonimmediate reactions to azithromycin present similarly to nonimmediate reactions to clarithromycin listed above; however, immediate reactions have been reported to be more severe. In a comparative study of azithromycin versus clarithromycin, it was found that among children presenting with immediate reactions to azithromycin, half had history of anaphylaxis.[54]

Allergic reactions to sulfonamide antibiotics can present as a variety of reaction severities and can be immediate or nonimmediate.[56] Cutaneous manifestations, including maculopapular rash and fixed drug eruption, are the most common presentations.[57] More severe presentations can include cell-mediated reactions such as DRESS, SJS, or toxic epidermal necrolysis (TEN).

Allergic reactions to other antibiotics, such as fluoroquinolones and tetracyclines, occur mostly among those with chronic diseases.[6] Similarly, allergic reactions to aminoglycosides and glycopeptides (vancomycin, teicoplanin) are infrequent in children but can include both immediate and nonimmediate reactions, including anaphylaxis.[58,59] Vancomycin is now the most common antibiotic associated with DRESS in many series.[60]

Approach and Diagnosis

The therapeutic approach following a suspected allergic reaction to non–beta-lactam antibiotics includes avoidance of the culprit drug and assessment by a specialist to properly identify a true hypersensitivity reaction.[61] For non–beta-lactam antibiotics, validated skin tests are not available; therefore, an ingestion challenge is frequently required.

Studies assessing the validity of skin tests to diagnose macrolide allergy report that predictive values of SPT are highly variable and are much lower and less accurate compared with beta-lactam antibiotics (see **Table 1**). In a recent study of 160 children with suspected clarithromycin allergy, the specificity of SPT was 73.9% (95%CI: 64.7%, 81.8%) and sensitivity was negligible. The NPV was 92.1% (95%CI: 60.3%, 77.6%) and PPV was negligible.[62] This is in line with a study by Mori and colleagues, assessing clarithromycin allergy in children, which reports a sensitivity and specificity of 75% and 90%, respectively.[63] Predictive values for azithromycin have been assessed by Barni and colleagues, reporting a PPV of 75% and an NPV of 50%, which is much lower compared with clarithromycin.[54] It has been demonstrated that SPT results were not compatible with ingestion challenge results, emphasizing the important role of the ingestion challenge in diagnosing macrolide allergy. There are no studies assessing the predictive values for the ingestion challenge of macrolides in children.

Similarly, skin tests and in vitro tests for sulfonamide antibiotic allergy are reported to be unreliable.[64] Undergoing a direct ingestion challenge should be considered on an individual basis based on patient need and risk-benefit ratio. Recent data support the use of an ingestion challenge as an effective mechanism to delabel sulfa antibiotic allergy[64,65].

It was suggested that SPT and IDT for fluoroquinolones and tetracyclines are associated with high risk for false-positive results due to the potential for mast cell activation.[66] Hence, the ingestion challenge for quinolones and tetracyclines is currently the most appropriate diagnostic tool.

Management

The management of macrolide antibiotic allergy includes avoidance of the culprit drug. Macrolides are unlikely to be cross-reactive; however, there are few published case reports describing cross-reactivity among different macrolides, possibly due to similarities in the chemical structure.[66] Cross-reactivity among the macrolides is less commonly reported than other antibiotic categories, such as beta-lactams.[33] Desensitization to macrolide hypersensitivity has been shown to be successful in a few cases.[66]

Sulfonamide antibiotic allergy management involves immediate withdrawal of the culprit drug and prescription of a safe alternative. While there is limited evidence on the cross-reactivity between sulfonamides, it seems unlikely that sulfonamide antimicrobials and sulfonamide nonantimicrobials would cross-react due to differences in chemical structure.[64] Desensitization is possible among patients with mild reactions and is especially indicated among patients with human immunodeficiency virus who require prophylactic sulfonamides. Multiple different protocols have been published, with the majority updosing over the span of several days.[66] Desensitization for patients with anaphylaxis is rare. However, there has been one successful published protocol to date.[64] When possible, attempts should be made to delabel the patient of sulfa antibiotic allergy.[65]

For other non–beta-lactam antibiotics, there is lack of data on potential cross-reactivity. The safest approach among patients with tetracycline hypersensitivity is to change to an alternative drug with a similar antibiotic spectrum.[67] Desensitization protocols have been described for patients allergic to tetracycline.[67] Cross-reactivity among fluoroquinolones has been demonstrated in a handful of published case reports.[66] Given that there is some evidence, other fluoroquinolone antibiotics should be avoided. Desensitization is also a management option for patients with hypersensitivity to fluoroquinolones; however, many of these can also be delabeled using ingestion challenge.[66] Fluoroquinolones often cause hives and symptoms that mimic IgE-mediated reactions; however, they are known to interact with MRGPRX2 and cause non–IgE-mediated mast cell activation. If the latter, antihistamines are helpful to allow continued dosing.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS
Presentation

Following antibiotics, NSAIDs are one of the most common reported causes for adverse drug reaction (ADR) in children, with a self-reported prevalence of 0.7%[68] In a cohort of 211 Thai children with a median age of 4, NSAIDs were considered causal in 4.7% of ADR,[69] while in a cohort from Latin America that included 862 patients (178 children), NSAIDs represented the majority of culprit agents at 52.3% with an increase incidence in children and adults compared with an elderly population.[70] Differences in prevalence may be attributed to a difference in populations, differences in existing types of prescribed and over-the-counter used NSAIDS and/or due to differences in diagnostic strategies.[71]

The most commonly implicated NSAID is ibuprofen.[72–76] The main identified risk factors for NSAID hypersensitivity are older age, atopy, chronic urticaria, a previous anaphylaxis history, the number of concomitant drugs, and a family history of NSAID allergy.[72,75–82]

Approach and Diagnosis

Because of the low accuracy of the available skin testing for NSAIDs, various authors do not employ these investigational tools.[74,76,83] In general, SPT has been described with approximately 5% to 33% positivity rate.[70,73,75,80,81,84,85]

Ingestion challenge remains the gold standard for NSAID assessment allowing to confirm or rule out the allergy. The rate of positive ingestion challenge reported in the literature varies from 11%[74,80] to 30%[70,72,73,75,81,85] for the majority of the studies. There is no consensus among the different studies regarding the number of steps required for ingestion challenge with some studies indicating only a maximum of steps performed for drug challenge (e.g., less than 5 escalating steps).[72,73,86] Furthermore, a negative drug challenge might not necessarily predict tolerance as reported in some pediatric cohorts whereby 4% to 12% of the patients described a reaction following a negative challenge test,[86,87] allowing the calculation of an NPV of 96.3%.[87] Following allergy confirmation to a COX-1 NSAID, alternative agents can be considered such as acetaminophen (at <1 g/d, when it has minimal COX-1 inhibition[88]) as well as COX-2 agents.[89] Following this literature review, we believe that a direct ingestion challenge in children in a well-supervised and equipped setting is the preferred diagnostic strategy.

SEVERE CUTANEOUS ADVERSE REACTIONS IN CHILDREN
Presentation

In the pediatric population, the most common SCAR phenotypes were reported are SJS/TEN,[19,70,74,83,90–95] DRESS,[19,92,93,96–98] and AGEP.[92,93,97] Some reports suggest, however, that SCARs are less prevalent and have a better prognosis being less associated with comorbidities in the pediatric population compared with an adult population.[70,92,95,96]

The main reported culprit drugs for SJS/TEN in children are antibiotics such as beta-lactams and sulfonamides[19,74,90,92,95,99,100] followed by anticonvulsant drugs such as phenobarbital, carbamazepine, and phenytoin.[90–92,95] Besides drugs, *Mycoplasma pneumoniae,* cytomegalovirus, and adenovirus were considered causal in pediatric cases of SJS/TEN.[19,90,92,93,101] While the literature described a mortality of up to 5% for SJS and up to 35% for TEN,[93,95] in some pediatric cohorts this was reported at 1.5%[90]–2.9%.[92] Antibiotics such as amoxicillin-clavulanate,[92,93] vancomycin,[74] and antiepileptics[93] such as phenytoin,[19] carbamazepine[92,96] are then main culprits

associated with DRESS syndrome in children. Antibiotics, such as amoxicillin, were the most commonly suspected cause of AGEP in the pediatric population.[92]

Because of the increased prevalence of infections and inflammatory manifestations such as Kawasaki disease in children, the diagnosis of SCAR may be challenging.[96] During the acute phase, skin biopsy can help confirm the diagnosis.[92] In terms of acute management, similar to adults, besides adequate bedside care, SJS/TEN is often treated with systemic corticosteroids and intravenous immunoglobulins.[92,93,95] DRESS and AGEP are treated with drug withdrawal and oral antihistamines with some of the DRESS cases also receiving systemic corticosteroids[93] and intravenous immunoglobulins.[92,96]

Approach and Diagnosis

Six months after the complete resolution of the skin condition, these reactions can be evaluated in the allergy clinic by IDT and patch testing (PT) as well as immunologic assays such as the lymphocyte transformation tests (LTT), enzyme-linked ImmunoSpot, and flow cytometric lymphocyte activation tests.[19,93,102,103] PT has been used in various pediatric studies with concentrations of 5%, 10%, 20%, 30%, and 50% in petrolatum (e.g., beta-lactams such as benzyl-penicillin, ampicillin, amoxicillin, and anticonvulsants such as carbamazepine, phenobarbital, and lamotrigine).[73,83,92,93] Various pediatric reports showed positive PT results in cases of SJS[74] as well as positive PT and delayed IDT for DRESS.[74,104] However, in larger cohorts, PT has shown poor sensitivity in children (<5%).[73] Further studies are required to establish the validity of PT in the pediatric population. IDT with delayed reading is rarely described in the pediatric population.[93] Similar to the adult population, delayed IDT was positive in DRESS.[93] In cases of SCAR, ingestion challenge is considered contra-indicated. However, recent reports questioned this practice allowing rechallenge in specific situations in resource-poor settings whereby there are no alternative drugs.[105]

In terms of *in vitro* testing, reports are limited to case reports and case series. For example, LTT was a valuable tool in various pediatric reports such as a case of phenytoin associated with DRESS,[19] a case of amoxicillin and ibuprofen associated TEN.[19] A large pediatric cohort demonstrated 12/15 (80%) positive LTT in a cohort of varied phenotypes including DRESS and SJS/TEN.[93]

Genetic associations have been established that have both a preventive and diagnostic role. In a Thai pediatric population, an association has been described between carbamazepine-induced SJS/TEN and HLA-B*1502.[90] This has led to preventive genotyping before treatment with carbamazepine in these regions. As more genetic associations are described in association with SCAR, HLA testing may become increasingly useful for screening testing and diagnosis.

SUMMARY

In the last decade, there has been a paradigm shift in the diagnosis of drug allergy, mainly penicillin derivatives, in the pediatric population. Cases of reported nonsevere reactions (defined as the presence of rash with no vesicles/bullous lesions and no mucosal involvement) to penicillin derivatives should be assessed with a direct ingestion challenge.[106] However, there is still a lack of sufficient evidence regarding the best diagnostic approach for non–beta-lactam antibiotics and NSAIDs, and scarce data on the best diagnostic tests for SCAR. Our review will assist allergists and physicians treating children to appropriately diagnose and manage drug allergy. Appropriate diagnosis is crucial to prevent mislabeling, increase the use of appropriate first-line antibiotics, and decrease the use of alternative broad-spectrum antibiotics.

CLINICS CARE POINTS

- Drug allergy labels in children are costly and are correlated with adverse health outcomes.
- Children presenting with adverse drug reactions potentially allergic in nature should be assessed by an allergist, as true drug allergies are uncommon.
- Cases of nonsevere reactions to penicillin derivatives can be appropriately assessed by a direct ingestion test.
- In cases of negative diagnostic workup for drug allergy, patient/parent education, and medical record delabeling are crucial.
- In cases of positive diagnostic workup for drug allergy, the use of that drug is contraindicated, and an appropriate alternative or, in certain cases, desensitization can be considered.

DISCLOSURE

The authors have nothing to disclose.

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