Antibiotic Allergy in Children: More than Just a Label

Elissa Abrams^a Elena Netchiporouk^b Barbara Miedzybrodzki^c
Moshe Ben-Shoshan^c

^aDepartment of Pediatrics, Section of Allergy and Clinical Immunology, University of Manitoba, Winnipeg, MB, Canada; ^bDivision of Dermatology, McGill University, Montréal, QC, Canada; ^cDivision of Allergy Clinical Immunology and Dermatology, Department of Pediatrics, Montreal Children's Hospital, McGill University, Montréal, QC, Canada

Keywords

Antibiotic allergy · Pediatrics · Drug allergy · Skin test · Drug challenge

Abstract

Within the broad category of adverse drug reactions in children, there has been a recent focus specifically on the evaluation of children with antibiotic allergy, in particular, beta-lactam allergy. The potential consequences of being labeled beta-lactam allergy are increasingly recognized. Appropriate evaluation of children with suspected reactions to antibiotics is essential as it is increasingly being recognized that the label of “penicillin allergy” is associated with adverse health and economic outcomes. This review will focus on the 3 main classes of antibiotics reported to cause allergic reactions in children: beta lactams (penicillin derivatives and cephalosporins), macrolides, and sulfonamides. This article is a narrative review of the prevalence, diagnosis, and management of different types of antibiotic allergies in children. Our review reveals that antibiotic allergy is often overreported and not appropriately diagnosed in the pediatric age groups. There is a recent shift in the diagnostic paradigm from the use of skin tests and if negative challenges to the

use of challenge only in the pediatric age group. Larger studies to establish the usefulness and safety of this new approach as well as updated guidelines are needed.

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Background

Adverse drug reactions (ADRs) are common in children, with higher incidences in the inpatient versus the outpatient population. A systematic review of ADRs in pediatric patients (17 prospective studies) reported the overall incidence of ADRs in the inpatient setting was 9.53% (95% CI 6.81–12.26%) compared to 1.46% (95% CI 0.7–3.3%) in the outpatient setting [1]. Severe reactions accounted for 12.29% (95% CI 8.43–16.17%) of these reactions; the rate of hospital admissions due to ADRs was 2.09% (95% CI 1.02–3.77%). An international prospective observational cohort ($n = 1,278$) of pediatric hospital admissions noted the incidence of ADRs at 16.5% (95% CI 14.5–18.7%) with rates varying dramatically between

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countries [2]. It has been noted that ADRs in children constitute a “significant public health problem” with lower incidences reported in national databases than in studies of hospitalized children and outpatients and a call to improve the submission of reports to national reporting systems [3].

Within the broad category of ADRs in children, there has been a recent focus specifically on the evaluation of children with antibiotic allergy, in particular, beta-lactam allergy, as amoxicillin is the most common medication prescribed in children [4] and a common reported culprit of ADRs. It has been noted that as many as 6% of children are labeled as beta-lactam allergic [5]. In a meta-analysis, it was reported that the prevalence of immediate reactions to penicillin derivatives in patients reporting a β -lactam hypersensitivity was 1.98% (95% CI 1.35–2.60) in the pediatric group, 7.78% (95% CI 6.53–9.04) in the adult group, and 2.84% (95% CI 1.77–3.91) in the combined group, as tested in various studies, using skin tests and oral challenges [6]. Self-reported other antibiotic allergies are less frequent and constitute largely the macrolide family of antibiotics [7] and sulfonamides (e.g., trimethoprim-sulfamethoxazole) [8].

Various risk factors have been described for ADRs. A study of suspected drug allergy reactions in 97 children noted a family history of drug allergy to be significantly related to confirmed allergic drug reactions [9]. HLA-B, HLA-C, and HLA-DRB1 genotypes have been recently found strongly associated with immediate and delayed reactions to beta-lactam in children [10]. In contrast to other allergic conditions, age, sex, and atopy are not significant risk factors for ADRs [11]. Other risk factors include immunosuppression, cystic fibrosis, previous exposure to the implicated medication, prolonged dose and duration of medication, route of administration (with parenteral and cutaneous routes more sensitizing), and concurrent viral infection (up to 100% of children and adolescents with Epstein Barr virus with rash if on amoxicillin) [12]. Given the societal burden and challenges related to diagnosis and management, this review will focus on the 3 main classes of antibiotics reported to cause allergic reactions in children: beta lactams (penicillin derivatives and cephalosporins), macrolides, and sulfonamides.

Classification

The World Health Organization defines an ADR as “all intended pharmacologic effects of a drug except therapeutic failures, intentional over-dosage, abuse of the

drug, or errors in administration” [13]. ADRs are categorized into predictable and unpredictable reactions [14]. Predictable reactions (overdose, side effects, drug interactions) are defined as occurring in otherwise healthy children, related to known pharmacologic actions of the medication, and usually dose dependent in nature [14]. In contrast, unpredictable reactions occur in susceptible children, are not related to pharmacologic actions of the medication, and are not dose dependent [14]. Unpredictable reactions can be further subdivided into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions.

Drug allergy accounts for about 5–10% of all ADRs [15]. There is no current international consensus on the classification of drug allergic reactions [16]. A common definition is to categorize reactions as either immediate (reaction within an hour after drug administration) or nonimmediate (reaction more than an hour after drug administration; often days to weeks later) [17, 18], although other classification systems exist. These reactions can also be classified based on the Gell and Coombs traditional classification system as type I (immunoglobulin [IgE]-mediated), type II (cytotoxic), type III (immune complex), and type IV (delayed hypersensitivity) [14, 19].

Pathogenic Mechanisms of Antibiotic Allergy

Immediate reactions occur within an hour after drug administration and are considered IgE-mediated (Gell and Coombs type I) [14, 19, 20]. Clinical manifestations include any combination of cutaneous symptoms (erythema, urticaria, angioedema), respiratory symptoms (shortness of breath, cough, wheeze), gastrointestinal symptoms (severe abdominal pain, profuse vomiting, or diarrhea), or cardiovascular symptoms (hypotension or end-organ dysfunction such as hypotonia, syncope, incontinence) [19, 21, 22]. The most common clinical presentation is isolated cutaneous symptoms.

Anaphylaxis is a potentially fatal IgE-mediated reaction and is defined when the allergic reaction involves at least 2 organ systems or if hypotension develops after exposure to a known allergen [23]. Anaphylaxis can be biphasic in nature in up to 20% of the time (a second reaction several hours to 72 h after resolution of clinical symptoms) [24].

In general, immediate reactions require a sensitizing dose prior to clinical reactivity so reactions are only observed with second (or further) course of the medication, unless doses are missed with the first course [25]. A modified classification suggests that IgE-mediated reactions

can occur up to 6 h after drug administration (immediate) and up to 4 days after last exposure [26]. However, more recently, it was reported that some of the reactions defined as immediate are actually mediated through direct mast cell activation due to certain antibiotics (antifungal agents, aminoglycosides, and sulfonamides) that have large amounts of tertiary amine and secondary amine groups with easily protonated nitrogen atoms. These antibiotics will cause mast cell degranulation through binding to the human G-protein-coupled receptor (Mrg-prX2). These reactions are often referred to as pseudo-allergic reactions [27, 28].

Nonimmediate reactions (Gell and Coombs type IV) occur more than an hour after drug administration although typically occur several days, or even weeks, later [14, 19]. The pathophysiology of nonimmediate reactions is not completely defined but is thought to be caused by a delayed T-cell-dependent mechanism. The most common clinical presentation of a nonimmediate reaction is isolated cutaneous symptoms such as a maculopapular exanthem or delayed urticaria/angioedema [14, 19]. An isolated maculopapular exanthem accounts for about 90% of all cutaneous drug reactions, and the majority of these exanthems are benign in nature [29, 30]. Within nonimmediate reactions, there is a subcategory of serious cutaneous adverse reactions (SCARs) that include fixed drug eruption, serum sickness-like reaction (SSLR), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS).

Gell and Coombs type II and III reactions are not part of the immediate versus nonimmediate classification and include cytotoxic reactions (type II; drug-induced anemia or thrombocytopenia) and immune complex reactions (type III; serum sickness, vasculitis) [14, 19].

In general, it is thought that an immune response to a drug requires that the drug (if molecular weight is <1,000 Daltons) covalently binds to a hapten protein in order to stimulate an immune response. More recently, the P-I concept (pharmacologic interaction with immune receptors) has been proposed which postulates that even in the absence of a hapten some drugs can bind directly through noncovalent bonds to T-cell receptors or to certain HLA molecules and directly stimulate an immune response [31]. It is also proposed that in order to elicit an immune response the presence of a small-molecular drug capable of interacting with HLA or an HLA-presented peptide is not sufficient and that cross recognition of a different epitope (e.g., from a pathogen) is required to activate the effector T cells in order to produce the observed clinical symptoms (heterologous im-

munity) [20]. Indeed evidence of associations between co-trimoxazole-induced SJS/toxic epidermal necrolysis (TEN) and HLA alleles including HLA-B * 15:02, HLA-C * 06:02, and HLA-C * 08:01 was reported [32] and for amoxicillin clavulanic acid associations were reported with *DRB1* * 15:01-*DRB5* * 01:01-*DQB1* * 06:02e [33, 34] and *HLA-A* * 02:01 [35].

Diagnosis

History and Clinical Presentation

Establishing the diagnosis of antibiotic allergy requires corroboration of clinical history and confirmatory tests. The most essential component in the diagnosis of drug allergy in children is the history. It is important to establish the timeframe of the reaction, including time of onset in relation to the medication intake and the duration of symptoms. As most reactions are cutaneous in nature, it is important to note the morphology of skin lesions (e.g., maculopapular (Fig. 1a), urticarial (Fig. 1b), or with evidence of blistering and skin detachment) as well as inquire about associated systemic symptoms. Questions should also include which medications were used at the time (including pain medications such as nonsteroidal anti-inflammatories, which can also cause allergic reactions) and whether these medications were used before (as most allergic reactions require a period of prior sensitization). There is a validated Naranjo Adverse Drug Reaction Probability Scale which ranks the likelihood of “true” drug allergy, although it is not commonly used in clinical practice and has not been validated specifically in the pediatric population [36].

It is worthwhile noting that while history is paramount, studies suggest that patients and families reported histories have low accuracy in the diagnosis of drug allergy [37]. While in some cases the pattern of the rash is highly suggestive of the pathogenesis, it is often challenging especially in pediatrics to distinguish between a viral induced rash and a drug-induced reaction. Maculopapular rashes are often caused by viruses and are clinically indistinguishable from a delayed hypersensitivity reactions. Further, viral infection is reported to be the most common cause of acute urticaria in children [38]. Determining the culprit of the rash is particularly challenging when there is a combination of rash (often hemorrhagic) and joint symptoms. SSLR (serum sickness-like reaction) is defined when large erythematous, urticarial plaques with dusky to ecchymotic centers, often associated with hand and foot swelling, develop 7–21 days after medica-

Fig. 1. a Maculopapular exanthem in an 8-year-old girl with a positive nonimmediate oral challenge to amoxicillin. **b** Urticaria in 6-month-old infant with a positive nonimmediate challenge to amoxicillin.

Fig. 2. a Serum sickness like reaction in a 1-year-old infant. Milder reaction was provoked by challenge. **b** Urticaria multiforme – challenge to amoxicillin negative and subsequent use tolerated. **c** Fixed drug eruption (provoked by ceftriaxone and established through challenge).

tion exposure (Fig. 2a). In addition to the characteristic cutaneous manifestations, patients with SSLR may have fever, malaise, lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, myalgias, headaches, and a self-limited symmetric arthritis [39]. The prognosis of SSLR is excellent with symptoms resolution usually within a few weeks after stopping the culprit drug [40]. In contrast, viral infections can be associated rarely with a similar rash called “urticaria multiforme” that resembles acute urticaria (Fig. 2b). However, in cases of urticaria multiforme versus SSLR, the rash presents faster (1–3 days following

an acute viral illness). Similar to SSLR this is a self-limited condition with favorable long-term prognoses [41].

In contrast, severe cutaneous ADRs are characterized by a distinct clinical presentation. These reactions are rare (1–5/1,000,000), but could be life threatening. These include drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). Antibiotics, mainly beta lactams, were reported as the main cause of these severe reactions in children [42].

SJS/TEN is the most severe of all SCARs and is characterized by a prodrome of fever and malaise rapidly followed by a centrifugal painful and dusky exanthem. The characteristic features of the rash include pain, skin detachment, and mucosal involvement. Targetoid papules may be seen, but in contrast to the benign erythema multiforme targets, those are 2 colors and flat. Involved non-blistered skin often sloughs with direct lateral pressure (Nikolsky sign) [43]. In addition to skin, other organs with epithelial lining may be involved, and ineffective skin barrier may lead to sepsis and fluid and electrolyte abnormalities [19]. SJS and TEN are thought to be the same disease across a spectrum of severity defined by the percentage of skin detachment related to the body surface area comprising SJS (<10%), SJS/TEN overlap (10–30%), and TEN (>30%) [19]. Treatment consists of discontinuation of the culprit drug and supportive care (wound care, infection surveillance, fluid and nutrition status, electrolyte balance, renal and airway function, and adequate pain control) [44]. SCORE of TEN (SCORTEN) is the clinical scoring system that is commonly used to predict in-hospital mortality in adults and is based on the percentage of skin detachment and physiologic alterations, while it helps to predict morbidity in children, its use in pediatrics has not been validated [45].

DRESS, which is also named as drug-induced hypersensitivity syndrome, usually presents with fever, rash, and internal organ involvement [19]. Viral reactivation of herpesvirus 6 and 7 has been suggested to play a role in the disease pathogenesis through the expansion of the drug-specific T cell repertoire [46]. In contrast to other delayed eruptions that begin 1–2 weeks from medication intake, DRESS typically occurs later (2–6 weeks after) and shows a protracted course [47]. Skin eruption in patients with DRESS shares some common features with the benign delayed hypersensitivity eruption. Clinical features most helpful in differentiating the two include facial edema, fever, lymphadenopathy, malaise, and presence of systemic involvement (e.g., >2-fold elevation in serum alanine transferase, increased creatinine, and/or proteinuria) [19]. Atypical lymphocytosis is reported in 27–67% of the patients, and eosinophilia is reported in 66–95%. Systemic corticosteroids are the mainstay treatment for patients with DRESS [48].

AGEP is another example of a delayed hypersensitivity reaction where T-cells play pivotal role [49]. Drug-specific T-cells produce large amounts of neutrophil-stimulating chemokine CXCL8 (IL-8) explaining infection mimicking clinical features of AGEP. It is characterized by a sudden onset of numerous, sterile,

nonfollicular pustules on a background of diffusely erythematous skin accompanied by fever and leucocytosis [49]. It often starts in flexural areas and occurs within days of exposure to the culprit. A recent study showed that the median lag time to eruption is 1 day for antibiotics and 11 days for other culprit drugs [19]. Full recovery is usually expected within 1–2 weeks after withdrawal of the trigger. Topical corticosteroid may be used and has been correlated with a decreased median duration of hospitalization [48].

Finally, fixed drug eruption (Fig. 2c) recurs in the same area when the culprit drug, mainly NSAIDs/antibiotics, is given [19]. Annular, dusky to violaceous, edematous plaques develop within 30 min to 8 h of drug exposure and resolve within 1 week leaving characteristic macular hyperpigmentation [19]. Mucosa (lips and genitalia) as well as acral skin are the most common locations [50]. Fixed drug eruptions have been described in the pediatric population in association with different classes of antibiotics including penicillin derivatives [51], macrolides [52], and sulfonamides [53].

Confirmatory Tests

Laboratory tests are supportive but not confirmatory in any drug allergic reaction. If history is consistent with a possible IgE-mediated (immediate) reaction, the National Institute for Health and Care Excellence recommends obtaining a serum tryptase level (a marker of mast cell activation) as an elevated serum tryptase is specific for anaphylaxis, especially if a repeat tryptase when the reaction resolves is normal [54]. However, this recommendation is based on low quality evidence from observational studies, and this recommendation is not consistent across guidelines, as other cells (such as basophils) may play a role in immediate reactions [55]. For nonimmediate reactions, in particular, SCARs, supportive laboratory investigations may include liver enzymes, renal function, and complete blood count [19].

Skin Testing

For immediate reactions, validated skin testing reagents only exist for penicillin and not for any of the other antibiotics, nor for any other low-molecular-weight medications [19, 54]. If the history is consistent with a possible immediate reaction to either penicillin or amoxicillin multiple guidelines recommend skin testing (epicutaneous followed by intradermal) as first-line investigation, followed by a drug provocation test (DPT) if negative [19, 26]. It is recommended that skin testing be undertaken with the major (penicilloyl)polylysine) and

minor (penicillin G, penicilloate and/or penilloate) determinants as well as ampicillin although not all the minor determinants are routinely available for testing [19].

Skin testing is safe but is noted to be both “unpleasant” and difficult to undertake in younger children [26, 56, 57]. Skin testing has a high negative predictive value of up to 98% in the diagnosis of penicillin allergy, although most of these studies are in the adult population, and apply to penicillin but not to amoxicillin [58, 59]. In addition, multiple studies have noted the positive predictive value of skin testing to be poor, in the range of 20% in children [60]. Further, it is reported that in 80% of cases the skin tests may be false positives and that the sensitivity is lower than 10% [60, 61].

Drug Provocation Test

There have been several recent studies evaluating the role of DPT in the absence of prior skin testing in children with a history of immediate reactions to penicillins and have found this to be both safe and effective. In a study of 818 children by Mill et al. [61] with suspected amoxicillin allergy who were evaluated by DPT in the absence of pre-emptive skin testing only 2.1% of children had an immediate reaction, all of which were mild cutaneous self-resolving reactions. A study of 155 school-aged children with suspected penicillin allergy found DPT to be similarly safe with only 2.6% of children having immediate reactions, all of which were mild cutaneous self-resolving reactions [62]. As a result, there has been a move in some allergy circles to consider DPT in the absence of pre-emptive skin testing in the evaluation of penicillin and amoxicillin allergy, especially if the reaction was a mild immediate reaction (i.e., limited to the skin) [63, 64].

Nonirritating concentrations of cephalosporins, as well as some other common antibiotics, have been published although this testing is not standardized, and a negative skin test does not rule out allergy as the predictive values of this testing are unknown [19]. In vitro serum-specific IgE assays are available for some common antibiotics such as penicillin and amoxicillin, but their sensitivity and specificity are not well described (although in general the specificity is thought to be higher than the sensitivity) [14, 19]. In general, there is thought to be little utility to in vitro serum-specific IgE assays although some guidelines do recommend their inclusion in the evaluation of penicillin allergy if skin testing is negative despite a convincing history of immediate clinical reactivity [65]. Further, in the case of oral cephalosporins (e.g., cefprozil) that are most commonly used in children, skin tests are limited to prick tests and hence are unlikely to be useful.

For antibiotics other than the beta-lactam antibiotics, validated skin testing is not available and in the context of an immediate reaction a drug provocation is the only available test. In general, it is recommended that a graded challenge be performed in the context of a low likelihood of drug allergy (such as if the immediate reaction was a remote reaction, or an isolated cutaneous reaction) [15]. There are only two studies assessing the use of skin tests for the diagnosis of macrolide allergy in children. In the first study, a skin test (SPT and ID) with intravenous clarithromycin was reported to have a sensitivity of 75% and specificity of 90% with a positive predictive value of 33% [66]. The second study revealed a sensitivity of 0% and PPV of 0% [67].

For mild nonimmediate reactions to penicillin or amoxicillin guidance less resolved on the role of skin testing prior to DPT and in fact the British Society of Allergy and Clinical Immunology as well as a recent report from the American Academy of Allergy Asthma and Immunology and the World Allergy Organization have recommended that DPT be considered without pre-emptive skin testing in children with mild nonimmediate reactions to either amoxicillin or penicillin [26, 68]. Skin testing has very low sensitivity (although high specificity) in the diagnosis of nonimmediate reactions to penicillins. A retrospective review of 352 children with a history of nonimmediate reactions to amoxicillin found the sensitivity and specificity of skin testing to be 8 and 99.7% (respectively) [69]. In addition, the DPT has been shown to be both safe and effective in the diagnosis of nonimmediate reactions to penicillins. In the study by Mill et al. [61], the DPT had a negative predictive value of 89.1 in the diagnosis of nonimmediate reactions to penicillins and was safe (3.8% nonimmediate mild cutaneous self-limiting reactions).

For severe adverse cutaneous reactions, skin testing and DPT are contraindicated with the possible exception of SSLRs, where emerging studies have noted DPT to be safe in children. However, further studies are required to confirm the safety of this approach [61, 70].

Other Investigations

For some mild nonimmediate reactions such as fixed drug eruption, AGEP, and maculopapular exanthem skin patch testing has shown some clinical utility in diagnosis [71]. In North America, patch testing is contraindicated in the context of a severe cutaneous adverse reaction although in Europe patch testing has been used for more severe nonimmediate reactions [72–74].

The basophil activation test (examining basophilic stimulation with a drug allergen and subsequent CD63 or

Table 1. Management strategies for main antibiotic allergies in children

	Beta-Lactam	Macrolide	Sulfonamide
Standardized desensitization protocol	Yes – rapid drug desensitization [77–79]	No	No
Comments	A flexible protocol with 4–16 steps (typically 12) and escalating the dose 2–2.5 times every 15 min is applied. Usually the starting concentration of the solution in a 4 bags/16 steps protocol is 1/1,000 to 1/100 in a 3 bags/12 steps protocol, reaching the target dose at the end of the procedure. Oral penicillin desensitization should always be performed when possible prior to parenteral penicillin use in the setting of confirmed IgE-mediated hypersensitivity	Rechallenges often negative and single dose rechallenges (with 5 days at home observation) are as effective as multidose rechallenges in the setting of benign delayed rashes [20]	Described for nonimmediate reactions. Rechallenges often negative and single dose rechallenges (with 5 days at home observation) are as effective as multidose rechallenges in the setting of benign delayed rashes [20]
IgE, immunoglobulin.			

CD203c expression) is showing promise in the diagnosis of immediate drug allergy but is not standard of care yet [75, 76]. The lymphocyte transformation test is another emerging test with selected commercial assays now available but little literature exists on its utility to date [77].

Management

General

Management generally requires avoidance of any medication that has caused an allergic reaction. For immediate reactions (especially to beta-lactam antibiotics) as well as mild nonimmediate reactions allergy referral would be recommended to rule out (or rule in) drug allergy. A MedicAlert bracelet is recommended for any child with confirmed drug allergy.

In the case of confirmed IgE-mediated allergy, avoidance is recommended and if future use is required, desensitization can be considered. Induction of desensitization is a process that allows a child to temporarily use a medication they are allergic to safely, by temporarily modifying the immune response to the medication while the child remains on the medication [15]. In general, it is only indicated in a situation where no alternative noncross-reacting medication is available. In general, induction of drug desensitization is only indicated for immediate (or mild non-immediate) reactions and is contraindicated for severe cutaneous adverse reactions [19]. Induction of desensitization protocols has been published for multiple antibiotics (Table 1) [19]. The procedure always involves incremental

doses of the implicated medication over time (hours to days) in a setting prepared to treat anaphylaxis [19].

Cross-Reactive Medications

It is thought that cross-reactivity between cephalosporins and penicillins is very low, and cephalosporin allergy is much less common than penicillin allergy [78]. It has been recommended that second and third generation cephalosporins could be safely used in a child with a history of penicillin allergy, as long as the allergic reaction was not life threatening [79]. Alternative consideration could be given to cephalosporin skin testing (while not validated) or a graded challenge to cephalosporins in a child with a history of penicillin allergy [19]. In a child with a history of a reaction to a cephalosporin, either testing or graded challenge to penicillin would be recommended prior to its administration [19]. Less is known about cross-reactivity among non-beta-lactam antibiotics (such as macrolides or aminoglycosides) [19].

The Importance of Delabeling Penicillin Allergy in Children

Evaluation of children with suspected reactions to penicillin antibiotics is essential as it is increasingly being recognized that the label of “penicillin allergy” is associated with adverse health and economic outcomes. This is most poignantly the case with penicillin antibiotics as the majority of children who are labeled as allergic are found to be tolerant after allergy evaluation [5, 80, 81], and penicillin antibiotics are among the most common medication prescribed in children [82, 83].

The label of penicillin allergy is associated with the prescription of alternative, broader spectrum antibiotics, which have a high risk of adverse effects as well as increase the risk of antibiotic resistance [84–86]. The use of broad-spectrum antibiotics is associated with increased duration of hospitalization and higher health care costs [87–90]. As a result, there have been a number of national and international initiatives with the aim of delabeling children with “penicillin allergy” including inpatient and outpatient programs [91, 92], emergency department-led programs [93], and pharmacy-led programs [94, 95].

Prognosis

Prognosis has been best described for penicillin antibiotics in the context of immediate or mild nonimmediate reactions. Multiple studies have shown that the natural history of immediate or mild nonimmediate reactions to penicillin antibiotics is a high rate of resolution over time (up to 80% at 10 years), which may be even higher for amoxicillin in children than for other penicillin antibiotics (up to 100% within 5 years) [14, 26, 96]. Less is known about the natural history of reactions to other medications. In addition, the natural history of severe adverse cutaneous reactions has not been well described.

Conclusion

Our review reveals that antibiotic allergy is often over-reported and not appropriately diagnosed in the pediatric age groups. There is a recent shift in the diagnostic paradigm from the use of skin tests and if negative challenges to the use of challenge only in the pediatric age group. Larger studies to establish the usefulness and safety of this new approach as well as updated guidelines are needed. For those with confirmed immediate allergy, there are effective desensitization protocols for the main classes of antibiotics although the main treatment for those with severe reactions (e.g., Steven Johnson and TEN) remains strict avoidance.

The patients have given their consent for their photos to be published.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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