

Non- β -Lactam Antibiotic Hypersensitivity Reactions

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abstract

OBJECTIVES: Antibiotics are among the most common prescriptions in children, and non- β -lactam antibiotics (NBLAs) account for almost half of those prescribed in Australian pediatric hospitals. Despite this, data on NBLA hypersensitivity in children are limited. This study describes reported hypersensitivity reactions to NBLAs in children and the results of allergy evaluation.

METHODS: Children with a suspected NBLA allergy who had skin testing and/or an intravenous or oral challenge test (OCT) between May 2011 and June 2018 were included. Patients were excluded if they were >18 years old or did not complete the allergy evaluation for any reason other than allergic reaction.

RESULTS: Over the 7-year study period, 141 children had 150 allergy evaluations of 15 different NBLAs. The median time from the initial reported reaction to allergy evaluation was 1.9 (range 0.1–14.9) years. Overall, 27 of the 150 (18.0%) challenge tests to NBLAs had positive results, with the rate of positive OCT results being highest for trimethoprim-sulfamethoxazole (15 of 46; 32.6%) and macrolides (8 of 77; 10.4%). Although 4 children reported initial anaphylactic reactions, no patients had severe symptoms on rechallenge or required adrenaline. Of the challenges that had positive results, the majority of children (23 of 27; 85.2%) had symptoms on repeat challenge similar to those that were initially reported.

CONCLUSIONS: Overall, 8 of 10 children with NBLA allergy could be delabeled. On average, patients waited 1.9 years to be rechallenged. Timely access to allergy evaluation to delabel these patients is needed to preserve first-line antibiotics.

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DOI: <https://doi.org/10.1542/peds.2019-2256>

Accepted for publication Oct 17, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

WHAT'S KNOWN ON THIS SUBJECT: Non- β -lactam antibiotics are commonly prescribed in the pediatric population; however, data on the risk of hypersensitivity reactions are largely unknown.

WHAT THIS STUDY ADDS: This large retrospective study suggests that ~1 in 5 children with a reported non- β -lactam antibiotic allergy had a true allergy, with trimethoprim-sulfamethoxazole and macrolide antibiotics being the most frequently implicated. Timely access to allergy evaluation is recommended.

To cite: Grinlington L, Choo S, Cranswick N, et al. Non- β -Lactam Antibiotic Hypersensitivity Reactions. *Pediatrics*. 2020;145(1):e20192256

Adverse drug reactions to anti-infective agents are reported in up to one-third of the pediatric population.^{1,2} This has been shown to impact costs to the health system through the prescription of more expensive drugs as well as the use of second-line broad-spectrum antibiotics.³⁻⁵ Extensive pediatric data exist on drug hypersensitivity reactions to β -lactam antibiotics; however, studies of hypersensitivity to non- β -lactam antibiotics (NBLAs) are limited. In a previous pediatric study of NBLA allergies, 4.7% of children evaluated by using an intradermal test (IDT) and/or oral challenge test (OCT) had a confirmed allergy. However, the rate of NBLA allergies was 15.6% when those children who were diagnosed solely on the basis of history were included, with macrolides and sulfonamides being the most frequently implicated.⁶

Of all antibacterial prescriptions in 8 Australian hospitals in 2015, 33.0% were for NBLAs.⁷ Despite this, there is a current paucity of data on the clinical presentation and frequency of true NBLA allergies in children. Furthermore, for some NBLAs, such as sulfonamides, an inappropriate label of a drug allergy often results in the exclusion of a broad range of other sulfur-containing drugs (such as cyclooxygenase-2 inhibitors and loop and thiazide diuretics) despite the unlikely cross-reactivity with nonantibiotic sulfonamide medications.^{8,9} We therefore reviewed the clinical presentation and results of allergy evaluation procedures for all children who presented to a tertiary pediatric hospital with a suspected NBLA allergy.

METHODS

This was a retrospective study of children ages 0 to 18 years at a tertiary pediatric hospital in Melbourne, Australia, over a period of

TABLE 1 Classification System for Allergic Reactions

	Immediate	Nonimmediate
Severe	Respiratory compromise (including wheeze and bronchospasm) Angioedema Anaphylaxis Extensive urticaria Arrhythmia or cardiovascular collapse Hypotension or symptoms of end-organ hypoperfusion	Severe cutaneous adverse reactions Mucosal lesions Serum sicknesslike reaction Exfoliative dermatitis or extensive skin desquamation Cytopenia Organ involvement (eg, acute interstitial nephritis)
Nonsevere	Isolated urticaria or mild rash Persistent gastrointestinal symptoms and signs (including vomiting and abdominal cramps)	Itching Isolated exanthem (maculopapular eruption or unknown childhood history)

7 years and 1 month (between May 2011 and June 2018). We included children who had a suspected NBLA allergy and had a skin test (including skin prick test [SPT] or IDT) and/or intravenous test or OCT during the study period. Data were entered into a Research Electronic Data Capture database.

The Royal Children's Hospital Melbourne is a tertiary pediatric referral center and runs the only pediatric drug allergy service in Victoria, Australia. Patients are reviewed in an outpatient clinic before admission to the day medical unit for skin testing and/or intravenous tests or OCT if indicated.

The outpatient review includes a detailed clinical history from the parents or caregivers of the reported reaction including the prescribed antibiotic and formulation, concomitant medications, indication for treatment, age at the time of reaction, nature and timing of the onset of symptoms, and management. Coexisting medical conditions and family history of atopy are also routinely recorded.

Patients were classified as having an immediate reaction or nonimmediate reaction on the basis of the timing of symptoms. An immediate reaction was defined as symptoms developing within 1 hour after drug administration.^{4,10,11} Nonimmediate reactions were those that occurred

1 hour or more postadministration.^{4,11,12} Symptoms were further classified as severe or nonsevere (Table 1).¹² Patients who had symptoms suggestive of an immediate severe immunoglobulin E (IgE)-mediated allergy and/or anaphylaxis (involvement of ≥ 2 organ systems and/or hypotension) had skin testing before intravenous tests or OCT. All patients were advised to avoid antihistamines for 7 days before any testing.

Standard drug test volumes and concentrations were used for both SPT and IDT, with isotonic saline and histamine at 10 mg/mL being used as positive and negative controls, respectively.¹³⁻¹⁵ After SPT, mean wheal diameter was recorded at 15 and 20 minutes for the histamine and allergen, respectively, with a diameter of ≥ 3 mm being considered a positive result.¹⁶ IDT for patients with a negative SPT result involved intradermal injection of 0.02 mL of test allergen at concentrations of 1/100th initially, followed by 1/10th of the maximum recommended dose.¹⁶ A wheal and flare were measured and recorded at time 0 and 20 minutes, with an increase in wheal diameter of ≥ 3 mm being considered positive.¹⁶

The inpatient oral and intravenous challenge protocols are described in Tables 2 and 3, respectively. Patients who were thought to have rate-related allergic-type symptoms

TABLE 2 Inpatient Oral NBLA Challenge Protocol

Time, Min	Dose
0	1/100th of top dose
45	1/10th of top dose
90	Top dose

secondary to an intravenous NBLA were given a graded infusion in which the full dose was given over 4 to 6 hours, starting at a slow rate and increasing every 30 minutes. Patients were observed for 3 hours after the top dose, after which the antibiotic was continued at home for 3 to 5 days (Table 4). The top dose was defined as the maximum appropriate dose as recommended by the *Australian Medicines Handbook*.¹⁷ Patients were provided with instructions to contact the hospital if any allergic symptoms developed and were followed up with via a phone call or outpatient clinic review. Any reactions on rechallenge were classified as previously outlined for the initial reaction (Table 1).

RESULTS

During the study period, 141 children with 150 suspected NBLA allergies were evaluated (Tables 5 and 6). In total, 149 oral or intravenous challenges were completed, with 4 having skin testing done before the challenge. One patient who had a positive IDT result did not proceed to an intravenous challenge. Fifteen different antibiotics were tested, with 9 children being challenged with 2 NBLAs. Of these 141 children, 80 (56.7%) were boys with a median age at the time of challenge of 7.8 (range 1.2–17.6) years. The median number of challenges per child was 1 (range

TABLE 3 Inpatient Intravenous NBLA Challenge Protocol

Times, Min	Dose
0	1/100th of top dose
60	1/10th of top dose
120	Top dose as either a push or graded infusion

TABLE 4 Home Continuation Regimen for Oral NBLA

Antibiotic Frequency	Days Challenged
Daily	Days 2–7: top dose daily
Twice daily	Day 2: top dose daily Days 3–7: top dose twice daily
3 times daily	Day 2: top dose daily Day 3: top dose twice daily Days 4–7: top dose 3 times daily
4 times daily or until course is completed	Day 2: top dose daily Day 3: top dose twice daily Day 4: top dose 3 times daily Days 5–7: top dose 4 times daily or until course is completed

1–2), and the median time from reported reaction to testing was 1.9 (range 0.1–14.9) years.

The NBLAs to which an allergy was suspected were macrolides (77 of 150; 51.3%), trimethoprim-sulfamethoxazole (TMP-SMX) (46 of 150; 30.7%), fluoroquinolones (6 of 150; 4.0%), metronidazole (6 of 150; 4.0%), clindamycin (6 of 150; 4.0%), nitrofurantoin (3 of 150; 2.0%), glycopeptides (2 of 150; 1.3%), trimethoprim (2 of 150; 1.3%), gentamicin (1 of 150; 0.7%), and doxycycline (1 of 150; 0.7%; Table 6). Of these, 70 (46.7%) reported an immediate reaction, 76 (50.7%) reported a nonimmediate reaction, and for 4 patients, the timing of symptoms in relation to drug administration was not documented. Of the 70 patients with reported immediate reactions, 23 (32.9%) were taking concomitant medications at the time.

The overall median age at the time of the reported reaction was 5 (range 0.1–17.0) years. However, 17.3% (26 of 150) could not recall the age at which the initial reaction occurred. Symptoms of reported initial reactions were predominantly cutaneous (135 of 150; 90.0%), including urticaria (69 of 135; 51.1%), nonspecific rash (38 of 135; 28.1%), maculopapular eruption (27 of 135; 20.0%), and erythema multiforme (1 of 135; 0.7%). Other reported symptoms included angioedema (20 immediate and 13

nonimmediate) and suspected anaphylaxis in 4 patients (characterized by 1 or more of the following: hypotension, respiratory compromise, involvement of the skin-mucosal tissue, and/or persistent gastrointestinal symptoms) requiring adrenaline. All 4 patients were concomitantly treated with multiple medications, and 3 were inpatients at the time, 1 of whom did not have skin testing done before an oral challenge because it was presumed that the hypotension was related to a surgical procedure. For the 109 patients for whom data on concurrent infection were recorded, 64 (58.7%) had symptoms suggestive of a viral illness.

Four patients had skin testing done for suspected severe IgE-mediated reactions before consideration of OCT. Three of these patients required adrenaline for anaphylaxis on initial exposure to metronidazole, vancomycin, or gentamicin, and 1 patient developed a severe reaction to TMP-SMX with perioral angioedema and respiratory compromise. One patient had a borderline-positive IDT result (7×9 mm at 20 minutes) for gentamicin and did not proceed to a challenge test. The remaining 3 patients had negative SPT and/or IDT results for TMP-SMX, metronidazole, and vancomycin with subsequent negative oral or intravenous challenge results.

TABLE 5 Patients With Immediate Severe Reactions on Rechallenge

Patient	Antibiotic	Severity	Initial Symptoms	Challenge Result	Challenge Symptoms
75	Bactrim	NIR nonsevere	Diarrhea, vomiting, and abdominal cramping	IR severe	Angioedema of the face, leg weakness, red conjunctiva, and abdominal cramping
161	Bactrim	NIR nonsevere	Generalized urticaria	IR severe	Chest tightness, generalized arthralgia and myalgia, red conjunctiva and photophobia, vomiting, abdominal cramps, and shortness of breath
142	Erythromycin	IR severe	Angioedema of the tongue and lips	IR severe	Angioedema of the tongue and lips
168	Teicoplanin	IR severe	Lethargy with generalized urticaria	IR severe	Itchy throat and persistent cough

IR, immediate reaction; NIR, nonimmediate reaction.

Overall, 26 of the 149 (17.4%) challenge results for NBLAs were positive and 123 (82.6%) were negative. The frequency of positive reactions was highest for TMP-SMX (15 of 46; 32.6%) and macrolides (8 of 77; 10.4%), all of which were to erythromycin. Of the 26 positive challenge results, 10 were classified as IgE-mediated hypersensitivity reactions, 4 of which were severe and 6 were nonsevere (Table 6). In addition, there was 1 patient who had a positive IDT result for gentamicin and was not challenged. TMP-SMX caused the majority of immediate reactions on rechallenge (7 of 10; 70.0%), followed by erythromycin (2 of 10; 20.0%) and teicoplanin (1 of 10; 10.0%). Patients had varying combinations of symptoms, including persistent gastrointestinal symptoms (6 of 10; 60.0%), urticaria (4 of 10; 40.0%), respiratory compromise (4 of 10; 40.0%), symptoms of end-organ hypoperfusion (3 of 10; 30.0%), and angioedema (2 of 10; 20.0%). Immediate reactions were treated with oral antihistamines in 7 of 10 patients. No patients had anaphylaxis.

Of the 69 reactions for which immediate symptoms were initially reported, 11 (15.9%) had a positive or equivocal challenge test result, of which 5 (45.5%) had immediate symptoms. For the 76 challenges for which nonimmediate reactions were reported, 15 (19.7%) had positive or equivocal challenge test results, of which 5 were immediate and 10 were nonimmediate. All 4 patients who

could not recall the timing of their initial reaction had negative OCT results. One patient was challenged with 2 antibiotics from the same class and had a positive OCT result for erythromycin and a subsequent negative OCT result for roxithromycin. One patient who had a positive challenge for TMP-SMX suspension had a negative challenge result for the tablet formulation.

For the 16 patients with a positive nonimmediate reaction on rechallenge, TMP-SMX was the most common causative agent (8 of 16; 50%), followed by erythromycin (6 of 16; 37.5%), ciprofloxacin (1 of 16; 6.3%), and clindamycin (1 of 16; 6.3%). Nonimmediate reactions were nonsevere in the majority (9 of 16; 56.3%), with cutaneous (13 of 16; 81.3%) and/or gastrointestinal (9 of 16; 56.3%) symptoms being the most frequently reported. One patient receiving erythromycin reported angioedema of the larynx and lips on the fourth day of the oral challenge that resolved with oral antihistamines. The majority of patients experienced recurrence of symptoms within the first 2 days of the challenge (11 of 16; 68.8%).

DISCUSSION

Antibiotics are the most commonly prescribed medications in children.^{7,18,19} The Antimicrobial Use and Resistance in Australia 2017 report found that 51.0% of all children aged 0 to 4 years received at

least 1 antimicrobial medication in 2015.⁷ β -lactam antibiotics were the most frequently dispensed antibiotics across all ages; however, NBLAs accounted for a significant proportion, with macrolides accounting for 13.0%, followed by tetracyclines (8.0%), TMP-SMX (5.0%), nitroimidazoles (3.0%), and fluoroquinolones (1.0%).⁷ Despite this, there are few guidelines on how to manage NBLA allergies. The reported rates of confirmed hypersensitivity reactions to NBLAs are highly variable and range from 0.2% to 27.2% in the pediatric population. This variability is likely due to the different NBLAs investigated and the various study methods used (eg, retrospective cohort study versus parental questionnaire).^{6,20–23} In our study, 18.0% of children had a positive NBLA reaction on rechallenge, which is similar to that previously reported.⁶ Whereas the median time from reported reaction to testing was 1.9 years in our population, the delay in confirmation or exclusion of drug allergy extended up to 14.9 years. Although there are no data on the most appropriate timing of drug challenges in children, ideally, testing should occur promptly after an initial reaction.

Antibiotic-allergy labeling can have significant implications for the patient, hospital, and health care system.^{24–27} To date, there have been no studies looking specifically at the health economic impact of NBLAs.

TABLE 6 NBLA Oral and Intravenous Challenge Results

Reaction Type		IDT		Challenge Result				Final Diagnosis After Immune Evaluation
Initial Reaction	Result	Immediate Reaction		Nonimmediate Reaction		Negative		
		Severe	Nonsevere	Severe	Nonsevere			
Macrolides (<i>n</i> = 77)								
Immediate	No IDT							IR, 2 of 77 NIR, 6 of 77 Negative, 69 of 77
IR severe (<i>n</i> = 16)		1 of 16	—	—	—	—	15 of 16	
IR nonsevere (<i>n</i> = 20)		—	—	—	1 of 20	1 of 20	18 of 20	
Nonimmediate								
NIR severe (<i>n</i> = 11)		—	1 of 11	—	—	1 of 11	9 of 11	
NIR nonsevere (<i>n</i> = 29)		—	—	—	2 of 29	1 of 29	26 of 29	—
Insufficient information on timing								
Nonsevere (<i>n</i> = 1)		—	—	—	—	—	1 of 1	—
TMP-SMX (<i>n</i> = 46)								
Immediate	Negative, 1 of 16							IR, 7 of 46 NIR, 8 of 46 Negative, 31 of 46
IR severe (<i>n</i> = 7)		—	1 of 7	—	1 of 7	—	5 of 7	
IR nonsevere (<i>n</i> = 9)		—	2 of 9	—	—	1 of 9	6 of 9	
Nonimmediate								
NIR severe (<i>n</i> = 8)		—	1 of 8	—	1 of 8	1 of 8	5 of 8	
NIR nonsevere (<i>n</i> = 19)		2 of 19	1 of 19	—	2 of 19	2 of 19	12 of 19	—
Insufficient information on timing								
Nonsevere (<i>n</i> = 3)		—	—	—	—	—	3 of 3	—
Fluoroquinolones (<i>n</i> = 6)								
Immediate	No IDT							NIR, 1 of 6 Negative, 5 of 6
IR severe (<i>n</i> = 4)		—	—	—	—	1 of 4	3 of 4	
IR nonsevere (<i>n</i> = 1)		—	—	—	—	—	1 of 1	
Nonimmediate								
NIR severe (<i>n</i> = 0)		—	—	—	—	—	—	
NIR nonsevere (<i>n</i> = 1)		—	—	—	—	—	1 of 1	—
Glycopeptides (<i>n</i> = 2)								
Immediate	Negative, 2 of 2							IR, 1 of 2 Negative, 1 of 2
IR severe (<i>n</i> = 2)		1 of 2	—	—	—	—	1 of 2	
IR nonsevere (<i>n</i> = 0)		—	—	—	—	—	—	—
Metronidazole (<i>n</i> = 6)								
Immediate	No IDT							Negative, 6 of 6
IR severe (<i>n</i> = 4)		—	—	—	—	—	4 of 4	
IR nonsevere (<i>n</i> = 0)		—	—	—	—	—	—	
Nonimmediate								
NIR severe (<i>n</i> = 2)		—	—	—	—	—	2 of 2	
NIR nonsevere (<i>n</i> = 0)		—	—	—	—	—	—	—
Nitrofurantoin (<i>n</i> = 3)								
Nonimmediate	No IDT							Negative, 3 of 3
NIR severe (<i>n</i> = 3)		—	—	—	—	—	3 of 3	
NIR nonsevere (<i>n</i> = 0)		—	—	—	—	—	—	—

TABLE 6 Continued

Reaction Type		IDT	Challenge Result				Final Diagnosis After Immune Evaluation
Initial Reaction	Result	Immediate Reaction		Nonimmediate Reaction		Negative	
		Severe	Nonsevere	Severe	Nonsevere		
Clindamycin (n = 6)							
Immediate	No IDT						
IR severe (n = 2)		—	—	—	1 of 2	1 of 2	NIR, 1 of 6
IR nonsevere (n = 1)		—	—	—	—	1 of 1	Negative, 5 of 6
Nonimmediate							
NIR severe (n = 1)		—	—	—	—	1 of 1	—
NIR nonsevere (n = 2)		—	—	—	—	2 of 2	—
Trimethoprim (n = 2)							
Immediate	No IDT						
IR severe (n = 1)		—	—	—	—	1 of 1	Negative, 2 of 2
IR nonsevere (n = 1)		—	—	—	—	1 of 1	
Gentamicin (n = 1)							
Immediate	Positive, 1 of 1						
IR severe (n = 1)		—	—	—	—	—	IR, 1 of 1
IR nonsevere (n = 0)		—	—	—	—	—	
Doxycycline (n = 1)							
Immediate	No IDT						
IR severe (n = 1)		—	—	—	—	1 of 1	Negative, 1 of 1
IR nonsevere (n = 0)		—	—	—	—	—	

IR, immediate reaction; NIR, nonimmediate reaction; —, not applicable.

However, 1 retrospective study of 51 582 patients found that when compared with adults without an allergy label, those with a penicillin allergy had increased length of stay, increased use of second-line antibiotics, and higher rates of *Clostridium difficile* infection.²⁵ Furthermore, increased rates of infection with resistant bacteria, including vancomycin-resistant *Enterococcus* spp. and methicillin-resistant *Staphylococcus aureus*, have been associated with an antibiotic-allergy labeling.²⁵ Increased mortality rates and intensive care admissions have also been documented.²⁴ The clinical and economic costs to the hospital system as a result of a patient having an antibiotic allergy ranged from no difference to \$609 per patient compared with those without an allergy.²⁸ These results have prompted hospital stewardship programs to incorporate the assessment and testing of reported antibiotic allergies to optimize antibiotic prescribing.^{25,26} Our results highlight that through drug allergy testing evaluation in children, 8 out of 10 children with an NBLA allergy could be delabeled, therefore preserving first-line antibiotics for these patients.

Current guidelines on antibiotic-allergy testing in children are highly variable, especially for NBLAs. Graded OCTs are the gold standard and are safe and effective in delabeling antibiotic allergies; however, the utility of skin testing for both immediate and nonimmediate reactions is controversial.^{10,29,30} One study of 64 children who reported cutaneous reactions to clarithromycin underwent skin testing before an OCT, with all patients having a negative SPT result and 10 having a positive IDT result (1 at 0.05 mg/mL and 9 at 0.5 mg/mL). Of these 10 patients, 3 had a positive OCT result (sensitivity 75.0%). Of note, 54 of 60 children who had negative IDT results also had negative OCT results

(specificity 90.0%).³¹ More recently, a study of 45 children with a reported allergy to clarithromycin (9 immediate and 36 nonimmediate reaction) found that of 20 children who had an IDT (up to 0.05 mg/mL) before an OCT, 9 had a positive result, all of whom subsequently had negative OCT results.³² The authors concluded that skin testing was poorly predictive of a positive OCT result (positive predictive value 0%, negative predictive value 82.0%, sensitivity 0%, and specificity 50.0%).³² Given that skin testing is poorly predictive of a repeat reaction, further studies have supported the approach of skin testing only in patients who describe severe reactions (immediate or nonimmediate) and those with an unclear history before an OCT on the basis of clinical judgment (ie, the clinician feels that the risk of a severe hypersensitivity reaction is likely on reexposure to the antibiotic).^{4,10,12} All other patients would proceed to an OCT without previous skin testing.

Studies have shown that despite patients having a negative challenge result for a suspected antibiotic, ongoing avoidance of the drug continues.^{5,27} This, in part, is due to failure to remove the drug allergy label from patient files, which results in unnecessary avoidance of the antibiotic.³³ Another reason for ongoing drug avoidance is poor communication between different health practitioners and patients.^{5,27,33} In our study, a copy of the discharge summary outlining the test result was sent to the referring doctor and the patient whenever possible. Despite these efforts, 2 studies suggested that patients may continue to unnecessarily avoid the

medication because of ongoing concern of a potential repeat reaction by the patient or primary care physician.^{5,27}

Data on the potential for cross-reactions between and within NBLA classes are limited, especially in children. Studies of adult populations examining cross-reactivity between macrolide antibiotics have suggested that the overall risk is low given the difference in the sizes of the lactone ring.^{30,34–38} A study in children concluded that azithromycin was more allergenic than clarithromycin; however, it should be noted that those with positive skin test results did not proceed to OCT, and patients tested with azithromycin had more positive skin test results (possibly due to the skin test concentration used or the properties of the drug itself producing more irritation).^{15,39} Our study included 1 patient who had a positive OCT result for erythromycin but tolerated roxithromycin. In clinical practice, it is reasonable to consider an oral challenge to an alternative antibiotic within the same class, especially if the OCT is equivocal. For sulfonamide antibiotics, the risk of cross-reactivity with nonantibiotic sulfur drugs appears low given the significant difference in chemical structure.^{9,40} Despite this, often all sulfur drugs are avoided when a patient is suspected of having a sulfonamide antibiotic allergy.^{9,41} In our study, 15 of 46 (32.6%) patients had a positive reaction to TMP-SMX, a sulfonamide antibiotic. These patients were instructed to avoid both oral and topical forms of sulfonamide antibiotics only.

A limitation of this study is its retrospective design, and not all patients who reacted to NBLAs within this time were referred (or seen) in the outpatient clinic. An accurate and thorough documented history was limited by poor parental recall and variability of detail among clinicians in their written records. In addition, not all patients were reviewed as an outpatient after the home challenge. Patients who did not present for follow-up were deemed to have a negative result on the basis of the instructions outlined in the discharge summary to represent if the patient or family were concerned.

CONCLUSIONS

This is the largest study of NBLA allergies in children and found that ~1 in 5 children with a reported NBLA allergy had a true allergy. Allergies to TMP-SMX and macrolides were the most frequent. Our study also highlights the significant delay in the testing and delabeling of NBLA allergy in children. Improved access to standardized and reliable allergy testing protocols to delabel children are urgently needed. Further studies on the risk of potential cross-reactivity within NBLA classes are needed, although biochemically, the risk of cross-reactivity appears low.

ABBREVIATIONS

IDT: intradermal test
IgE: immunoglobulin E
NBLA: non- β -lactam antibiotic
OCT: oral challenge test
SPT: skin prick test
TMP-SMX: trimethoprim-sulfamethoxazole

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics originally published online December 3, 2019;

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Pediatrics originally published online December 3, 2019;

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