

Pediatric Drug Allergies

Updates on Beta-Lactam, Nonsteroidal Anti-Inflammatory Drug, and Chemotherapeutic Reactions



Shazia Lutfeali, MD, David A. Khan, MD*

KEYWORDS

- Pediatric drug allergies • Hypersensitivity reactions • Beta lactam antibiotics
- Non-beta lactam antibiotics • Nonsteroidal anti-inflammatory drugs
- Chemotherapeutics

KEY POINTS

- Beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs remain the most common causes of pediatric drug hypersensitivity, although only a minority of reactions is generally confirmed as true drug allergy.
- Diagnosis typically requires drug challenges because of the lack of standardized and widely available in vivo and in vitro testing.
- An understanding of pediatric drug allergies as well as methods to diagnose true drug allergies is important.

INTRODUCTION

Adverse drug reactions are frequently reported in pediatric patients. A 2012 systematic review found that the overall incidence of adverse drug reactions reached up to 16.8% in hospitalized children and up to 11.0% in outpatient children.¹ Drug allergic reactions account for a lower percentage of all adverse drug reactions, and after evaluation only a minority of presumed drug allergy is confirmed as true drug allergy.^{2,3} For instance, penicillin allergy testing performed in pediatric populations successfully removes penicillin allergy labels from about 96% of patients.⁴ Drug allergy labels in children are associated with adverse clinical outcomes; specifically, antibiotic allergy labels correlate with significant alternate antibiotic use and longer hospital stays.⁵ Therefore, an understanding of pediatric drug allergies as well as methods to diagnose

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Department of Internal Medicine, Division of Allergy & Immunology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8859, USA

* Corresponding author.

E-mail address: dave.khan@utsouthwestern.edu

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true drug allergies is important. In this review article, the authors discuss pediatric drug allergies with emphasis on the most common culprits, beta-lactam (BL) antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). Also included are brief sections on desensitization considerations.

In the pediatric population, BL antibiotics are the most commonly involved drug group followed by NSAIDs and non-BL antibiotics.

PREVALENCE

The most common drugs implicated in pediatric drug hypersensitivity reactions are BL antibiotics and NSAIDs, followed by non-BL antibiotics. As in adults, the most common manifestations are cutaneous, although true drug hypersensitivity is less likely to be confirmed in pediatric than in adult patients.⁶⁻⁸ In addition, although drug reactions are more common in adult women than men,⁹ in children, the gender distribution seems approximately equal.^{2,5} Of note, the occurrence of pathogen-induced cutaneous symptoms, which may be mistaken for drug reaction, is an important consideration. A 2011 study of children presenting to the emergency department with maculopapular or urticarial rash in the setting of BL antibiotic use found that when later challenged to the culprit drug, only 6.8% of children had reproducible rash. Most children resulted positive for viral studies, highlighting the relevance of viral exanthem in these situations.¹⁰ There is also a known association of rash in the setting of amoxicillin administration during Epstein-Barr virus (EBV) infection. Interestingly, however, a recent study showed that of the 18.6% of EBV-infected patients who developed rash, approximately half were treated with antibiotics, implying that EBV-associated rash in the setting of antibiotic use may be less common than previously thought.¹¹

CHARACTERIZATION OF HYPERSENSITIVITY

Drug allergic reactions in general can be classified as immediate or nonimmediate. Immediate reactions usually occur within 1 hour of drug intake (but may occur up to 6 hours after drug exposure) and are typically mediated by immunoglobulin E (IgE) antibodies; they commonly present as urticaria or anaphylaxis.¹² Nonimmediate reactions usually occur days later (but can occur earlier) and are typically T cell mediated. They may present as maculopapular, delayed onset urticaria, other rashes, or rarely, as a severe cutaneous adverse reaction (SCAR). The immunopathogenesis of SCAR is complex and is beyond the scope of this review but has been recently reviewed elsewhere.¹³

PENICILLIN AND OTHER BETA-LACTAM ANTIBIOTICS

Traditionally, diagnostic guidelines for addressing penicillin allergy have been similar in children and adults. However, given the difficulty of adhering to these protocols in children (ie, time required for testing, painful intradermal injections), the benign and typically delayed nature of most reactions,³ the natural history of waning antibiotic sensitivity over time,¹⁴ and consideration that diagnostic protocols in adults may not have equal diagnostic accuracy in children, recent studies have addressed the utility of standard protocols with skin testing versus direct antibiotic challenge, particularly in low-risk patients.

Single-Day Challenge

Although several smaller studies in children had previously evaluated the role of direct drug challenge without skin testing in children, the first large prospective study was

conducted by Mill and colleagues.¹⁵ They performed a prospective study of 818 children with histories of suspected amoxicillin allergy. Only children with SCAR were excluded. Children with anaphylaxis were not excluded, but none were enrolled. All children underwent a graded oral challenge with 10% of the therapeutic dose of amoxicillin followed 20 minutes later by 90% of the therapeutic dose and were observed for at least 1 hour. Among the 818 children challenged with amoxicillin, 94.1% tolerated the challenge with 2.1% having immediate (<1 hour) reactions and 3.8% having delayed reactions. Immediate reactions occurred in 17 children, were all mild, and consisted of hives only. Skin testing was performed 2 to 3 months later and only 1 of 17 had a positive penicillin skin test. In addition, children with histories of serum sickness-like reactions also safely underwent challenge using this protocol with no severe reactions occurring.

Ibanez and colleagues¹⁶ subsequently assessed penicillin allergy in 732 children with histories of nonsevere reactions. Drug provocation tests were administered regardless of skin testing and serum-specific IgE results. Only 4.8% of patients were found to be penicillin allergic, compared with higher rates of penicillin allergy (7.9%–16.7%) in prior studies in which drug provocation tests were only performed in cases of negative skin and serum-specific IgE testing.^{6,17,18} The investigators concluded that penicillin protocols, which have known accuracy in adults,⁹ may not be equally diagnostic in children and may actually result in overdiagnosis. High specificity and low sensitivity for intradermal and specific IgE testing were seen; specificity for intradermal testing and specific IgE resulted at 98.3% and 99%, respectively, whereas sensitivity resulted very low at 9.1% and 2.9%. Interestingly, none of the 5.2% of patients with histories of immediate index reactions were shown to have true penicillin allergy via drug provocation test. Also of note, cefuroxime was tolerated by all but one of the penicillin-allergic patients who were administered cefuroxime challenge.

Confino-Cohen and colleagues¹⁹ evaluated direct challenge in 642 patients with histories of nonimmediate reactions, which included 435 children. They also performed skin tests and drug provocation regardless of test results. Despite a relatively high rate of positive or equivocal skin tests (5.2% and 32.4%), 96.1% of these patients tolerated the first day graded challenge. **Table 1** summarizes these studies.

Prolonged Challenge

Despite the delayed nature of most pediatric BL reactions, delayed intradermal testing and patch testing have been shown to be of limited diagnostic utility.^{6,24} A few studies have addressed the value of prolonged oral provocation challenge in diagnosing nonimmediate BL hypersensitivity (see **Table 1**).

Mori and colleagues²⁰ showed an increase in detection of nonimmediate reactions from 35.7% to 100% with use of prolonged 5-day challenges in a European pediatric cohort of 200 patients with suspected amoxicillin allergy. In the aforementioned study by Confino-Cohen and colleagues,¹⁹ they also found increased detection of nonimmediate reactions; an additional 6.1% of cohort patients developed mild delayed reactions during prolonged 5-day challenge compared with 1-day challenge. No significant correlation was seen with skin testing results, and the investigators concluded that the penicillin allergy label could safely be removed using supervised graded challenge followed by ambulatory prolonged 5-day total oral challenge, without preceding skin test.

Recently, Labrosse and colleagues²³ assessed safety and efficacy of the 5-day challenge in diagnosing BL allergy and also implications for future BL antibiotic use. One hundred thirty Canadian participants with histories of nonsevere reactions (most of which were delayed) underwent blinded skin testing and graded drug provocation challenge

Table 1 Penicillin challenge studies without prior skin testing, or regardless of skin testing results			
Penicillin Direct Challenge Studies		Penicillin Extended Challenge Studies	
Study	Outcomes	Study	Outcomes
Mill et al, ¹⁵ 2016	Of 818 pediatric patients, 5.9% developed mild reactions	Mori et al, ²⁰ 2015	Of 200 pediatric patients given 5-d provocation tests, 9.6% developed reactions
Confino-Cohen et al, ¹⁹ 2017 ^a	Of 617 pediatric patients, 5.3% developed reactions	Vezir et al, ²¹ 2016	Of 119 pediatric patients given 5-d provocation tests, 3.4% developed urticarial reactions
Ibanez et al, ¹⁶ 2018	Of 732 pediatric patients, 4.8% developed nonsevere reactions	Confino-Cohen et al, ¹⁹ 2017 ^a	Of 491 pediatric patients given complete/partial 5-d provocation tests, 6.1% developed mild reactions
Iammatteo et al, ²² 2018	Of 155 patients ≥7 y old, 2.6% developed mild reactions	Labrosse et al, ²³ 2018	Of 130 patients given 5-d provocation tests, 6.2% developed positive/ equivocal reactions

Most studies enrolled patients with non-severe reactions histories.

^a References the same study.

with amoxicillin, regardless of skin testing results. Those patients with initial challenges underwent home amoxicillin administration for a total 5-day course. Patients who were ultimately diagnosed as nonallergic were contacted 2 years later to assess subsequent amoxicillin usage and tolerance, and data were compared with a prior similar group who had received a single-dose graded drug provocation challenge with oral penicillin. Of the study participants, 3 patients had a positive immediate challenge, 3 patients had a positive nonimmediate challenge (all of which were mild cutaneous reactions, suggesting safety of this ambulatory approach), and 2 were equivocal. Of note, parental anxiety was also assessed, and it was determined that almost half of the parents had been very or extremely frightened by their child’s initial allergic reaction. Overall, the 5-day drug provocation test resulted in a significant 24.1% decrease in future penicillin avoidance compared with classical single-dose drug provocation challenge performed for 1 day in the historical cohort. The investigators concluded that 5-day challenge ensures better compliance with future penicillin use.

Discussion

Overall, these recent data specific to amoxicillin or penicillin allergy in children suggest that direct provocation without preceding skin testing appears to be safe and effective. This approach has not been evaluated for those rare children with anaphylactic reactions. Whether prolonged challenges are necessary is still a matter of debate. The length of prolonged challenge (5 days) appears reasonable, because prior studies have reported mean reaction delays of 3.8 days and 5.8 days.^{6,24} However, as previously discussed, these reactions tend to be benign, and it is unclear whether accurately diagnosing a small additional percentage of patients with delayed drug hypersensitivity warrants subjecting all patients to prolonged antibiotic courses, with potential adverse effects. In an era of antimicrobial stewardship, full therapeutic courses of antibiotics without need are problematic. In addition, reactions elicited

during prolonged challenges may in fact be due to delayed reactions after the first dose. Garcia Rodriguez and colleagues²⁵ recently proposed a modified protocol in which subjects underwent supervised challenge followed by a home observation period of at least the time elapsed between first dose and symptoms of the index reaction. Children who did not develop a reaction continued with prolonged ambulatory challenge. Alternatively, adequate cumulative dose may be more relevant than the timing of exposure.

Although prolonged challenges do appear to increase future use of penicillin antibiotics, which is ultimately the goal of addressing penicillin allergies, the main reason to adopt this approach seems to be for parental and provider reassurance. For instance, 1 study showed that even after their children had undergone negative penicillin skin testing and drug challenge, 18% of parents still refused penicillin-class antibiotics because of fear of adverse reaction.²⁶ It remains to be seen whether this objective can be accomplished to the same extent in the pediatric population via better education and effective interventions.

SPECIAL CONSIDERATIONS

Children with cystic fibrosis are generally thought to have a higher prevalence of hypersensitivity reactions to one or more antibiotics, especially BLs, which may be due in part to frequent exposure.²⁷ At least 1 study, though, has shown the opposite finding.²⁸

DESENSITIZATION CONSIDERATIONS

Desensitization is defined as temporary induction of tolerance that can be maintained by continuous exposure to the medication. In the case of penicillin and BL allergy, desensitization is an option in those with histories of immediate reactions and positive skin tests and/or drug provocations. Desensitization may be considered when no alternative treatment exists for optimal therapy, and published data for BL and other antibiotic desensitizations in children largely involve the cystic fibrosis population. In general, proposed desensitization protocols for pediatric patients are similar to those used in adults but differ in the final dose administered. When possible, the oral route is preferred, and one of the most widely used protocols for penicillin has been published by Sullivan and colleagues.^{29,30} IV protocols are also available³¹ and can be adapted for pediatric patients. Successful desensitization to nonpenicillin BL antibiotics has also been performed.³²

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are the other common cause of pediatric drug hypersensitivity.³³ Along with antibiotics, NSAIDs account for most adverse drug reactions among outpatient children.¹ Similarly to antibiotics, NSAID hypersensitivity is less likely to be confirmed in children than adults, and viral infections are an important confounding factor.³⁴ Recent studies have shown rates of 16.9% to 24% of confirmed NSAID hypersensitivity via drug challenge,^{35,36} although prior studies have reported higher rates. Unlike adult patients with NSAID hypersensitivity, in younger children, boys are as frequently if not more frequently involved.^{36,37}

Classifications and Hypersensitivity Mechanisms

NSAIDs can induce hypersensitivity reactions via immunologic and nonimmunologic mechanisms (Table 2). In general, reactions are classified as selective to a particular

Table 2 Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs		
	Hypersensitivity Reactions to NSAIDs	
	Selective (Cross-Tolerant)	Nonselective (Cross-Intolerant)
Type of reaction	Single NSAID-induced urticaria/angioedema or anaphylaxis	NERD
	Single NSAID-induced delayed hypersensitivity reaction	NECD
		Multiple NSAID-induced urticaria and angioedema
Possible mechanism of action	IgE mediated (immediate) or T-cell mediated (delayed)	COX-1 inhibition
Skin testing useful?	Limited to no data available, except for propyphenazone	No

drug or NSAID subclass or nonselective (cross-intolerant). Of these, the nonselective reactions are more frequent. One study showed a distribution of 58% nonselective reactions and 42% selective reactions in children; ibuprofen was the culprit drug in most of both nonselective and selective reactions.³⁸ Atopy and older age at first reaction are recognized risk factors for NSAID hypersensitivity.³⁵

Nonselective or cross-intolerant reactions are triggered by more than 1 subclass of NSAIDs and encompass NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD) in patients with chronic idiopathic urticaria, and multiple NSAID-induced urticaria and angioedema in otherwise healthy patients.³⁹ The latter commonly presents as isolated periorbital edema in children. Nonselective reactions occur when COX-1 inhibition plus an intrinsic defect in arachidonic acid metabolism leads to leukotriene generation and release of mast-cell and eosinophil-derived mediators.³³ Selective NSAID hypersensitivity reactions may be immediate or delayed. Immediate reactions are most likely mediated by specific IgE antibody, although identification of these antibodies is difficult via either skin testing or specific IgE assays with the exception of the NSAID propyphenazone, whereby positive skin tests and specific IgE have been reported in most of the studied individuals.⁴⁰ Selective delayed-type reactions are likely due to specific T-cell responses and can manifest in a variety of ways, including cutaneous reactions (eg, fixed drug eruptions), aseptic meningitis, and pneumonitis. Not all patients fit easily into these criteria and are often referred to as having a blended or mixed reaction as one that does not strictly meet criteria outlined by the aforementioned classification.³⁹

The need for a pediatric-specific classification guideline for NSAID hypersensitivity reactions has been recognized. Cousin and colleagues³⁵ attempted to classify 635 pediatric patients with confirmed NSAID hypersensitivity according to the European Network on Drug Allergy (ENDA) classification, which does not differentiate between age groups. They found that 44% of patients did not fall strictly into 1 of the 5 categories outlined by the ENDA, and that no patient exhibited features strictly corresponding to NERD. The ENDA/European Academy of Allergy and Clinical Immunology recently released a consensus document with a proposed pediatric classification with distinct criteria for children younger than 10 years and 10 years of age to adolescence. The classification attempts to emphasize differences between NSAID hypersensitivity reactions between different age groups, with reactions in younger children typically being nonimmunologic, nonselective, and frequently occurring in the setting of confounding factors, such as viral illnesses. The proposed

classification for older children is similar to the adult classification and takes into account the importance of anaphylactic reactions in this age group.³³

Diagnosis

Diagnosis of NSAID-induced hypersensitivity is often difficult for several reasons, including presence of confounding factors (such as infection or concurrent use of other drugs), lack of established in vivo or in vitro diagnostic methods, and unclear natural history of NSAID allergy and effect of age.³³ As with antibiotics, the gold standard for diagnosis is the drug provocation test. Protocols vary based on the type of reaction to NSAIDs. Skin testing is not considered useful in nonselective reactions, because of the nonimmunologic nature of these reactions. There are also little to no data on skin testing with selective NSAID-induced delayed reactions. As mentioned previously, skin testing may be useful for reactions to propyphenazone. In contrast, most children skin tested with metamizole are negative.^{41,42} However, at this time, skin testing is not recommended for most common NSAIDs because nonirritating concentrations are unknown, there is a lack of parenteral agents, and negative predictive values have not yet been established. In vitro studies are not widely available, and their diagnostic and predictive values also have yet to be validated, particularly in children.⁴³

Nonselective Reactions and Tolerance of Alternative Agents

Although the natural history of nonselective reactions is unknown, it is thought that some patients may develop tolerance over time, especially patients with chronic urticaria because chronic urticaria remits. Therefore, periodic reevaluation is warranted. Acetaminophen/paracetamol at standard doses is generally considered safe in patients with nonselective reactions, although drug challenge may be advisable.³⁸ One study looked at the incidence of aspirin hypersensitivity (using a maximum cumulative dose of 500 mg aspirin) in children and adolescents with chronic urticaria, which was found to be 22%. All patients were able to tolerate acetaminophen/paracetamol.⁴⁴ Another study found that all participants with confirmed COX-1 inhibitor hypersensitivity, diagnosed via drug challenge to aspirin and the culprit NSAID, were able to tolerate acetaminophen/paracetamol as well as etoricoxib, a selective COX-2 inhibitor. Most study participants were able to tolerate meloxicam, a preferential COX-2 inhibitor.^{37,45}

Special Considerations

In general, use of NSAIDs has been correlated with asthma exacerbations in children. Lo and colleagues⁴⁶ showed an association between short-term use of ibuprofen, aspirin, and diclofenac and increased rates of asthma exacerbations resulting in asthma-related hospitalizations. Debley and colleagues⁴⁷ found a prevalence rate of 2% ibuprofen-sensitive asthma in a study of school-aged children with mild to moderate asthma. NSAIDs have also been implicated in the occurrence of food-associated and/or exercise-induced anaphylaxis, more so in adolescents.⁴⁸

Desensitization Considerations

In adults, aspirin-exacerbated respiratory disease (AERD)/NERD is one of the primary indications for aspirin desensitization. This condition rarely manifests before the third decade of life; however, there have been case reports as well as a small study with children as young as 8 years old and adolescents diagnosed with AERD/NERD.^{49–51} In 1 report, a 16-year-old female adolescent with recurrent polyps underwent aspirin desensitization as per the adult protocol proposed by Lee and Stevenson⁴⁵ and experienced long-term clinical benefit on a daily 300-mg dose of

aspirin.⁵⁰ In another report, an 8 year-old girl and a 12-year-old girl underwent successful aspirin desensitization via intranasal ketorolac challenge and desensitization followed by aspirin desensitization and ultimately tolerated 650 mg aspirin twice daily, although aspirin was subsequently discontinued in the younger patient owing to debilitating urticaria.^{51,52} As the pediatric AERD/NERD population has recently been recognized, the efficacy of high-dose aspirin in these patients has not been investigated. Aspirin is generally avoided in pediatrics because of concern for Reye syndrome; the chief exception is Kawasaki disease, which typically presents in young children. Review of the literature does not reveal cases of Kawasaki disease in which aspirin desensitization was necessary. In cases of pain or inflammatory conditions in which NSAIDs/acetylsalicylic acid are not tolerated, it appears that alternative agents are frequently used.

NON-BETA-LACTAM ANTIBIOTICS

Hypersensitivity reactions to non-BL antibiotics, such as aminoglycosides, fluoroquinolones, and macrolides, are rare compared with BL antibiotics. Diagnosis of IgE-mediated allergy to these drugs is difficult due to limited knowledge about relevant metabolites and allergenic determinants. Nonirritating skin test concentrations have been published, but for the most part have not yet been validated in children.^{53–55} In addition, the negative predictive values for these tests is unknown. In general, non-BL antibiotics are uncommon causes of anaphylactic reactions.⁵⁴

Most pediatric studies on non-BL antibiotics consist of case reports or small series of patients.⁵⁵ Guvenir and colleagues⁵⁶ recently addressed hypersensitivity to non-BL antibiotics in children using intradermal concentrations that have previously been published in adults; of the 85 patients with nonsevere reaction histories who underwent testing, non-BL hypersensitivity was confirmed in 4.7%. Those patients with a history of anaphylactic reactions or recent antihistamine ingestion underwent desensitization in lieu of testing.

SULFONAMIDE ANTIBIOTICS

In general, reactions to sulfonamides rarely manifest as IgE-mediated reactions and more frequently present as delayed hypersensitivity reactions, some of which can be life-threatening SCARs, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).⁹ A pooled analysis of 2 multicenter case-control studies showed that sulfonamide antibiotics were identified as 1 of 4 drugs most commonly associated with SJS/TEN in patients less than 15 years of age.⁵⁷ Skin testing with nonirritating concentrations can be used for immediate reactions, and delayed intradermal testing and/or patch testing can be used for nonimmediate reactions.^{55,56} The drug provocation test is the gold standard for diagnosis but is contraindicated in patients with severe reaction histories.⁵⁵ Although alternate therapy is preferred, continuation of therapy ("treating through") with or without addition of antihistamines, steroids, or other medications may be an option for those who require sulfonamide therapy (eg, those with human immunodeficiency virus [HIV] and *Pneumocystis jirovecii* pneumonia) and have a history of mild cutaneous eruptions without mucosal involvement.⁵⁸ The role of desensitization in non-IgE-mediated reactions is unclear. Numerous reports of successful desensitizations for sulfonamide antibiotics exist, including in pediatric patients, particularly those with HIV.^{59,60} However, studies in adults comparing drug reaction rates immediately following sulfonamide drug provocation versus drug desensitizations have shown similar tolerability.^{61–63}

MACROLIDES

In general, hypersensitivity reactions to macrolides are reported less frequently than sulfonamides.⁵⁵ In a study of adult and pediatric patients with a history of macrolide hypersensitivity, none of the confirmed reactions occurred in pediatric patients.⁶⁴ Clarithromycin is probably the best studied; the rate of confirmed hypersensitivity in children is low and may range from 2.1% to 6%.^{56,65} Skin testing to clarithromycin has shown variable reliability, and different studies have used different nonirritating concentrations.⁶⁵ Based on this, many experts do not recommend skin testing for evaluation of macrolide allergy.⁶⁶ Anaphylaxis to macrolides has traditionally been considered very rare; however, a recent study showed a somewhat higher anaphylaxis rate of 4.5%.⁶⁷ Cross-reactivity can occur between different macrolides.^{67,68} A case of successful desensitization to clarithromycin in a pediatric patient has been reported.⁶⁹

AMINOGLYCOSIDES

Aminoglycoside use occurs more so in the newborn and cystic fibrosis populations than in healthy children. In general, anaphylaxis in the neonatal period is uncommon; however, a case report of anaphylaxis to amikacin in a premature newborn has been reported.⁷⁰ Neomycin is a recognized contact allergen, and patch tests with neomycin have been shown to be positive in 5% of children with contact dermatitis less than 3 years of age.⁷¹ Overall, however, aminoglycoside hypersensitivity is uncommon, but immediate reactions can be evaluated by skin testing. Cross-reactivity between different aminoglycoside antibiotics has been shown to occur.⁷² Desensitization, particularly in cystic fibrosis patients, has been performed successfully.⁷²⁻⁷⁴

FLUOROQUINOLONES

Historically, fluoroquinolone use in pediatrics has been avoided because of concern for adverse effects, although fluoroquinolone prescription rates have increased in recent years.⁷⁵ In adults, frequency of immediate reactions to quinolones appear to be increasing, possibly because of increased use of these antibiotics, and it is likely that the same trend will manifest in pediatrics.⁹ Use of fluoroquinolones is particularly relevant in the cystic fibrosis population; desensitization has been performed in children with and without cystic fibrosis.^{76,77} Patients with allergy to 1 fluoroquinolone antibiotic may be able to tolerate another, and there are no clear patterns of cross-reactivity.⁷⁸

CHEMOTHERAPEUTICS

Hypersensitivity reactions have been reported with almost all chemotherapeutic agents.⁷⁹⁻⁸¹ Diagnosing hypersensitivity to chemotherapeutics is challenging, because patients receiving these agents are frequently immunocompromised, are administered multiple medications simultaneously, and have symptom overlap with infusion reactions, chemotherapy toxicity, or graft-versus-host disease.⁸² In particular, cutaneous eruptions occur commonly in children receiving chemotherapy; for example, Lim and colleagues⁸³ recently reported a case of flagellate dermatitis in a child most likely from doxorubicin. Another phenomenon reported by Webber and colleagues⁸² was described as a distinct, self-limited intertriginous eruption, which was not associated with a particular malignancy or medication but was associated with high-dose chemotherapy regimens. Of note, corticosteroids, often used in the treatment of hypersensitivity reactions, must be used with caution in the oncology population. For instance, pediatric patients with acute myelogenous leukemia have an

increased risk of death associated with corticosteroid administration.⁷⁹ This discussion focuses on select chemotherapeutic agents, which more commonly cause hypersensitivity reactions in children and those for which desensitizations have been performed. The 3-solution, 12-step protocol published by Castells and colleagues⁸⁴ has been shown to be widely applicable to multiple medications, with similar protocols currently being used in pediatric patients.⁸⁵

PLATINUM-BASED DRUGS (CISPLATIN, CARBOPLATIN, OXALIPLATIN)

Carboplatin is used for multiple types of pediatric cancers. In general, carboplatin induces mild to moderate hypersensitivity reactions, although it is well recognized that anaphylaxis can occur. The incidence of severe carboplatin hypersensitivity in children has been reported to range from 4% to 8%.^{86,87} Most reactions are early onset and thought to be IgE mediated.^{81,88} However, delayed onset reactions occurring hours to days later have rarely been reported.^{80,81} As in adults, carboplatin-induced hypersensitivity typically manifests after multiple cycles, with most pediatric reactions occurring during the eighth cycle.^{89,90} Repeated exposure increases the risk of reaction. Genc and colleagues⁸⁹ identified weekly carboplatin infusions, younger age, and female gender as risk factors for reactions in pediatric patients with brain tumors. Management options include drug discontinuation, substitution with another platinum-based drug, and desensitization. Switching from carboplatin to cisplatin may not be feasible owing to cross-reactivity between the 2 compounds, although the incidence of carboplatin and cisplatin cross-reactivity has not been well defined.⁸⁰ Oxaliplatin reaction rates are lower but may be rising with increased use of the drug.⁸¹

Skin testing has been shown to be useful for carboplatin-induced hypersensitivity, and the recommended concentration for epicutaneous testing is 10 mg/mL and up to 5 mg/mL for intradermal testing.⁹¹ Multiple cases of successful carboplatin desensitizations have been reported in pediatric patients.^{92–94} Rodriguez Del Rio and colleagues⁹⁴ used a slightly modified version of the 12-step protocol published by Castells and colleagues⁸⁴ to desensitize 7 patients with low-grade gliomas.⁸⁴ In addition, a modified carboplatin desensitization protocol has been described by Lazzareschi and colleagues,⁸⁶ in which 6 children were successfully desensitized without use of premedications.⁸⁶ Sims-McCallum and colleagues⁹² also reported the case of a 10-year-old female patient with bilateral optic glioma who underwent successful inpatient carboplatin desensitization and was subsequently able to receive carboplatin desensitization and treatment in the outpatient infusion center, with appropriate monitoring.

L-ASPARAGINASE (NATIVE *ESCHERICHIA COLI* ASPARAGINASE, PEGYLATED-ASPARAGINASE, *ERWINIA* ASPARAGINASE)

L-Asparaginase is particularly important in the treatment of acute lymphoblastic leukemia, and hypersensitivity reactions are relatively common. The 3 preparations commercially available in the United States are derived from bacterial sources. Hypersensitivity reactions to pegylated (PEG)-asparaginase are least frequent and range from 3% to 24%. Risk of hypersensitivity to PEG-asparaginase increases with prior exposure to native *Escherichia coli* asparaginase, because of their shared bacterial source.⁹⁵ Most reactions are immediate and are thought to be either IgE induced or related to IgM- or IgG-induced complement activation.^{81,88} Hypersensitivity reactions have been reported after the first dose but are more common with repeated doses, especially with reintroduction or dosing intervals of a week or longer.^{79,88} Administration is almost never via the intravenous route owing to higher rates of hypersensitivity. Patients who display hypersensitivity to L-asparaginase should generally be switched

to an alternate preparation; those with native L-asparaginase hypersensitivity can often tolerate PEG-asparaginase, and those with *E coli*-derived asparaginase hypersensitivity can be switched to *Erwinia* asparaginase. It should be noted, however, that cross-reactivity between *E coli* and *Erwinia* derivatives has been reported.⁹⁶

Skin testing is not standardized and is of limited value because it may produce false negatives. The recommended amount is 0.1 mL intradermally of a 20-IU dilution of the drug. Test doses are of limited value because small doses rarely produce a reaction.⁸⁸ Desensitization is also an option and has been successfully performed.^{80,81,97}

METHOTREXATE

Methotrexate is widely used in pediatric blood cancers and osteosarcoma. Hypersensitivity reactions are rare, and severe reactions are reported in less than 1% of cases.⁸⁰ Most reactions are thought to be IgE mediated, although anaphylactoid reactions have been reported.⁹⁸ Reactions can range from mild to life threatening. Skin tests have not routinely been performed owing to the high frequency of negative results,^{80,85} and the few case reports detailing methotrexate desensitizations have used prolonged infusions.^{80,81,98,99} However, Dilley and colleagues¹⁰⁰ recently published a novel case series describing skin testing, graded challenge, and desensitization to methotrexate in 7 pediatric patients. Four patients who did not require urgent drug administration underwent skin prick testing to methotrexate, which was performed at a concentration of 10 mg/mL followed by intradermal testing with 0.1-mg/mL, 1-mg/mL, and 10-mg/mL concentrations. One patient with a history of mild reaction and negative skin test tolerated graded challenge. A total of 17 desensitizations were performed in the remaining 6 patients. Most patients successfully underwent 12-step desensitization protocol; 1 patient who did not was able to tolerate a 16-step protocol.

ANTHRACYCLINES (DAUNORUBICIN, DOXORUBICIN, AND EPIRUBICIN)

Anthracyclines are used with multiple types of pediatric cancers, but hypersensitivity reactions are rare. Skin testing is not typically performed due to cutaneous toxicity.⁸⁵ Premedication is often not useful, but slowing the infusion rate, especially with the PEG liposomal formulation, which can induce rapid-onset symptoms, can produce good results.⁸⁰

VINCA ALKALOIDS (VINCRIStINE, VINBLASTINE)

Vincristine is used widely in pediatric cancers, but hypersensitivity reactions are very rarely reported. Interestingly, Hill and colleagues¹⁰¹ recently reported 8 patients with reactions to vincristine, consistent with anecdotal reactions at other institutions. Mass spectrometry of medication lots was concerning for possible contaminant. Skin testing to vincristine is not performed due to irritant reactions. Case reports of desensitization have been published.⁹³

SUMMARY

BL antibiotics and NSAIDs remain the most common causes of pediatric drug hypersensitivity, although only a minority of reactions is generally confirmed as true drug allergy. Evaluation of penicillin allergy in children, especially those considered low risk, is trending away from skin testing and toward direct drug provocation challenge, although it is unclear whether this is also the best method for adolescents. The utility of prolonged challenges has also been addressed. Regarding NSAID hypersensitivity,

the need for a pediatric-specific classification of NSAID hypersensitivity reactions has been recognized. Diagnosis typically requires drug challenges because of the lack of standardized and widely available in vivo and in vitro testing. Non-BL antibiotics are less common but still noteworthy causes of pediatric hypersensitivity reactions. Nonirritating skin test concentrations have been published but for the most part have not yet been validated in children. In the realm of chemotherapeutics, hypersensitivity to platinum-based drugs and L-asparaginase occurs relatively frequently; skin testing to carboplatin has been shown to be useful, and desensitization is a feasible option. Overall, an understanding of pediatric drug allergies and confirmation through accepted diagnostic methods is crucial to prevent overdiagnosis.

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