

Management of Children with Hypersensitivity to Antibiotics and Monoclonal Antibodies



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KEYWORDS

- Pediatric drug allergy • Drug hypersensitivity • Allergy skin testing • Desensitization
- Antibiotic allergy • Monoclonal allergy • Drug provocation

KEY POINTS

- Testing in young children should not be avoided because of parental or physician fear of testing because it has been confirmed to be safe.
- Accurate diagnosis for both antibiotic allergy and monoclonal antibody allergy leads to better workup and management of these allergies.
- The range of hypersensitivity reactions that occur in monoclonal antibody allergy overlaps with antibiotic allergy but is also distinctly different.
- Graded challenges are the gold standard in diagnosis and have been proven to be safe in children.
- Desensitization should only be pursued if there are no alternatives and is contraindicated in drug reactions with severe skin disease.

INTRODUCTION

Proper management of drug allergy in children is based on accurate diagnosis. Unfortunately, there is a lack of understanding of drug allergy in this population as well as provider or parental fear of testing children, which can lead to incomplete workup and misdiagnosis. Overlabeling in antibiotic allergy is a huge health burden and leads to drug-resistant bacteria.¹ Overdiagnosis is rather common in children, likely because

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of the frequency of rashes that occur during an antibiotic course in a child and reluctance of testing to confirm allergy.^{2,3} However, proper management should be based on a thorough history, in vitro testing (if available), in vivo testing, and if negative, drug challenge for delabeling because accurate diagnosis and management of the antibiotic allergic child are key factors in preventing children from carrying drug allergy labels that persist until adulthood.

It may also be difficult to determine the precise timing that a reaction begins in an infant or young child, making it challenging to ascertain immediate reactions from non-immediate reactions. Distinguishing the type of reaction is important because the workup and management vary depending on the timing and associated symptoms of the reaction. In addition, providers often choose avoidance over testing in children, although intradermal testing and drug challenge have been proven to be safe and well tolerated in children.^{4,5}

Monoclonal antibodies are proteins, of human or murine origin, increasingly used in oncologic and autoimmune diseases in children. Their larger protein structure, as opposed to the small chemical structures of antibiotics, promotes immunogenicity and can elicit hypersensitivity reactions.^{6,7}

This article focuses on the workup, management, and treatment of pediatric antibiotic and monoclonal antibody allergy.

EPIDEMIOLOGY

It is difficult to obtain a true incidence of drug allergy in the pediatric population.⁸ Epidemiologic studies indicate that drug allergy affects more than 10% of children and adolescents, although community studies suggest that this number is grossly overestimated.² When these children undergo diagnostic studies, including skin testing or drug provocation testing (DPT), less than 10% are confirmed to be truly allergic to the suspected drug.^{4,9,10}

Penicillin allergy is the most commonly reported drug allergy, with a prevalence rate of 5% to 10% in adults and children.^{11–14} Amoxicillin has now replaced benzyl penicillin as the most frequently reported drug allergy in children.¹⁵ Non- β -lactam (BL) allergy is rare in children and estimated to affect 1% to 3% of this population. In regards to the most commonly reported reactions to non-BL drugs, sulfonamides are the most commonly reported, followed by macrolides.¹⁶

In contrast to antibiotic allergy, monoclonal antibody allergy is infrequently reported in children and is limited to case reports and case series.^{6,7,17–19}

GENERAL PRINCIPLES

The general principles of drug allergy are based on the classic mechanisms initially described by Gell and colleagues²⁰ in 1968 and updated by Pichler in 2003 to include subtypes IVa to IVd as demonstrated in [Table 1](#).^{20–23} However, as new approaches to drug allergy have emerged, an additional classification based on precision medicine has recently been proposed. This newer classification is based on phenotype, endotypes, and biomarkers in drug allergy.²⁴

Phenotypes are determined by specific clinical symptoms associated with timing from exposure to the culprit drug. Phenotypes are divided into the following 2 broad categories:

- Immediate-onset drug allergy: occurs within 1 to 6 hours of exposure to the drug and is associated with cutaneous, respiratory, gastrointestinal symptoms, or anaphylaxis.

Table 1
Gell and Coombs classification of reaction and management

Type of Reactions	Mechanism	Clinical Features	Timing	Testing	Management
Type I	Immediate or IgE-directed release of histamine and mediators via mast cells/basophils	Anaphylaxis, urticaria, angioedema, bronchospasm	Immediate: <1 h after ingestion of drug	Skin prick testing, serum-specific IgE, DPT	• Specific drug avoidance/cross-reacting drugs • Choose first-line alternative drugs if possible • Desensitization if alternative drugs cannot be used
Type II	Cytotoxic or antibody-dependent, hypersensitivity reactions	Drug-induced hemolytic anemia, thrombocytopenia, nephritis	1–2 wk after exposure ^a	Drug-specific antiplatelet antibodies	• Specific drug avoidance
Type III	Immune complex	Serum sickness, vasculitis	1–2 wk after exposure ^a	No testing	• Specific drug avoidance
Type IV: IVa IVb IVc IVd	Delayed or T-cell mediated	Benign delayed skin rashes: allergic contact dermatitis, maculopapular exanthema Severe cutaneous skin rashes: AGEP, FDE, EM, DRESS, and SJS/TEN	Nonimmediate: a few days to weeks after exposure	LTT, ELISpot; patch testing; delayed IDT, HLA screening	• Specific drug/class avoidance

Abbreviations: AGEP, Acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; EM, erythema multiforme; FDE, fixed drug eruption; HLA, human leukocyte antigen; IDT, Intradermal testing; LTT, lymphocyte transformation testing; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

^a May be sooner if there are preformed antibodies.

Data from Refs.^{20–23}

- Delayed-onset drug allergy: presents within days to weeks after drug exposure with a wide range of clinical symptoms from maculopapular rash, urticaria and fixed drug eruption, to severe cutaneous adverse reactions (SCARs). Symptoms are not always isolated to one organ and may also affect the hepatic, renal, pulmonary, or hematologic system.

Endotypes are phenotypic subclasses associated with specific mechanisms of underlying disease. Endotypes for drug allergy are divided into the following categories:

- Immunoglobulin E (IgE)-mediated reactions
- T-cell-mediated reactions
- Pharmacologic interactions
- Genetic predispositions

Biomarkers used to distinguish disease in drug allergy vary depending on the phenotype and endotype and include the following:

- Skin prick testing and serum-specific IgE (immediate hypersensitivity testing)
- Basophil activation testing and basophil histamine release assay (immediate hypersensitivity testing)
- Mediators (ie, tryptase)
- Cells (ie, lymphocyte transformation testing in T-cell-mediated disease, granulysin, and granzyme B in Stevens-Johnson syndrome [SJS])
- Patch testing (useful in maculopapular exanthems, fixed drug eruptions, acute generalized exanthematous pustulosis [AGEP], and potentially in drug reaction with eosinophilia and systemic symptoms [DRESS], and SJS in specific drugs)
- HLA markers (ie, HLA-B*57:01 in abacavir drug hypersensitivity)

RISK FACTORS

Risk factors for drug allergy include structures inherent within the drug itself as well as the host. Some drugs are better than others at inducing immunologic reactions.

Drug-related risk factors include the following:

- Ability to act as a hapten
- Ability to act as a pro-hapten
- Ability to bind covalently to immune receptors (p-i concept)^{23,25,26}

The hapten and pro-hapten concept explains how drugs and other small molecular weight proteins (<1000 D) like antibiotics can become immunogenic. Haptens are small chemically reactive compounds that bind to proteins or peptides, enabling them to stimulate an immune response. Pro-haptens are not immunogenic until they are modified chemically into haptens. Both haptens and pro-haptens can stimulate the immune system either innately or specifically.

The hapten theory does not explain how proteins such as monoclonal antibodies or carbohydrate substances can be immunogenic.²⁷ The p-i concept is a direct pharmacologic interaction of drugs with immune receptors. The p-i concept explains how a drug directly stimulates the immune system without modification or processing.

In addition to the drug structure, it is known that route, dose, duration, and repeated exposure are known risk factors. For example, a drug given parenterally is known to be more sensitizing compared with a dose administered orally.²⁸

Host risk factors in children include specific genetic polymorphisms and previous drug reactions to unrelated drugs or multiple drug allergy syndrome.^{28,29} It is really not known if sex, age, and atopy are risk factors for the development of drug allergy in children. In a

large retrospective study by Ponvert and colleagues,³⁰ in the 1865 children with suspected BL allergy that were evaluated, sex, age, and atopy were not risk factors.

Very few studies have evaluated risk factors for drug allergy in children. It is not known whether family history of drug allergy actually predisposes one to drug allergy. However, one study of Turkish children evaluated 97 subjects aged 8 months to 18 years with a history of immediate or nonimmediate drug allergy. Children with confirmed drug allergy by skin testing or patch testing in this study were 4.4% more likely to have a family history of drug allergy. In addition, children with index reactions that were supported by strong histories were 3.5 times more likely to have a confirmed drug allergy than those with vague histories of reaction.³¹

CLINICAL FEATURES

Clinical features of drug allergy vary depending on the immunologic mechanisms of the reaction. Immediate-onset reactions typically occur within 1 to 6 hours of exposure to the drug, whereas nonimmediate or delayed-onset reactions, depending on severity, can occur within hours to weeks after treatment with the drug.²⁷

Immediate-onset reactions (<6 hours) can be divided into IgE-mediated reactions and non-IgE-mediated reactions (anaphylactoid or pseudoallergic). Clinical features associated with immediate reactions include urticaria, angioedema, bronchospasm, gastrointestinal symptoms, or anaphylaxis.

Nonimmediate reactions to drugs can also vary in clinical features, timing, and severity depending on the immunologic mechanism.²⁷

Clinical reactions to monoclonal antibodies vary by drug and range from acute idiosyncratic infusion reactions, rash, anaphylaxis, to serum sickness.³² They are classified as immediate or nonimmediate, based on timing of reaction. Immediate reactions have recently been described by 3 mechanisms, as discussed below, although mixed reactions can occur.⁷

Cytokine Release Syndrome

Cytokine release syndrome typically occurs immediately upon first exposure to a monoclonal antibody and can be characterized by flushing, dyspnea, fever, hypotension/hypertension, chest/back pain, throat tightness, dizziness, and gastrointestinal symptoms.⁷ In some cases, death has even occurred.³³ These clinical symptoms are a result of complement or antibody-mediated cell destruction. Management includes slowing the infusion rate and using premedication, such as corticosteroids and acetaminophen.⁷

Immunoglobulin E-Mediated Reactions

IgE-mediated reactions typically require prior exposure, although some monoclonal antibodies such as cetuximab are known to elicit reactions on first exposure via preformed antibodies.⁷ Symptoms can range from typical IgE-mediated symptoms and anaphylaxis to atypical symptoms like fevers and chills. Serum tryptase levels may be elevated. Management includes skin testing with nonirritating concentrations. If testing is positive, desensitization should be considered.⁷ Because the predictive value of skin testing is not known, desensitization may be attempted in cases with negative skin testing depending on the clinical history.

IgG-Mediated Reactions

Immunoglobulin G or IgG-mediated reactions typically require prior exposure. Symptoms vary but clinically may appear like IgE-mediated reactions or may present as reduced efficacy through increased clearance or by blocking antibody binding sites.⁷

The most common nonimmediate symptoms reported with monoclonal antibodies are serum sickness-like reaction. These reactions typically require prior exposure, but have been reported to occur on first exposure as well. Some reactions that occur several hours after drug exposure may be IgE mediated, especially if they were administered subcutaneously.⁷

DIFFERENTIAL DIAGNOSIS AND CROSS-REACTIVITY

Differential diagnosis for drug reactions in children depends upon the immunologic basis of the reaction. However, drug reaction in children is often confused with symptoms that accompany a viral illness (Tables 2 and 3).^{5,34}

Knowledge of cross-reactivity is important in the management of a pediatric antibiotic allergy. Cross-reactivity is well studied within BL drugs but less understood with non-BL antibiotics. Patients with penicillin allergy rarely react to cephalosporins, typically 2%, unless the 2 antibiotics share a particular side chain that arises from the BL ring, called the R1 side chain. When a penicillin-allergic patient is administered a cephalosporin with identical R1 side chains, the risk for allergic reaction increases by 30%.³⁵ Therefore, when choosing an alternative drug for a penicillin-allergic child, a provider should choose a BL with a different side chain. Penicillin-allergic patients have a rare chance of reactivity to carbapenems and aztreonam, lower than 1%.^{36,37} Thus, these drugs can be used safely in a penicillin-allergic child. Macrolides and quinolones are known to have some cross-reactivity within their own groups; therefore, patients allergic to these drugs should choose another class of drugs for treatment.^{2,38}

DIAGNOSTIC TESTING

Studies indicate that clinical history alone is a poor indicator of allergic status. Skin testing or DPT are imperative for confirmation of drug allergy and should be considered, even in young children.⁹

Skin testing protocols for BL drugs, in particular penicillin, have been well established, but not for non-BL drugs. However, there are published data regarding nonirritating concentrations on several antibiotics.^{39,40} Testing for BL drugs should always include PRE-PEN (benzylpenicilloyl polylysine), minor determinants, and ampicillin/amoxicillin. When skin testing is negative, one must undergo DPT to delabel the drug allergy.³⁹

Table 2 Differential diagnosis of immediate reactions	
Non-IgE-mediated (pseudoallergic/anaphylactoid)	Anaphylaxis IgE-mediated reaction
IgE-mediated	Food allergy Venom allergy Idiopathic urticaria and angioedema Idiopathic anaphylaxis Non-IgE-mediated reaction

Data from Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children—our 10-year experience in allergy work-up. *Pediatr Allergy Immunol* 2016;27(5):533–8; and Caubet JC, Kaiser L, Lemaitre B, et al. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011;127(1):218–22.

Table 3
Differential diagnosis of delayed drug reactions

Delayed drug reaction	Viral exanthem IgE-mediated drug allergy Early DRESS or SJS/TEN
SJS/TENS	Erythema multiforme Bullous skin diseases Fixed drug eruption DRESS
DRESS	Delayed drug rash Early SJS/TEN Severe eczema or psoriasis
AGEP	Pustular psoriasis Bullous impetigo Subcorneal pustular dermatosis DRESS
Serum sickness–like reaction	Vasculitis Rheumatic fever

Data from Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children—our 10-year experience in allergy work-up. *Pediatr Allergy Immunol* 2016;27(5):533–8; and Caubet JC, Kaiser L, Lemaître B, et al. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011;127(1):218–22.

Monoclonal antibodies have much higher molecular weights; therefore, skin testing is more diagnostic compared with drugs that are small molecular weight or haptens.⁴¹ Although skin testing to monoclonal antibodies has not been standardized, nonirritating concentrations have been published. Skin prick testing strengths vary depending on the monoclonal antibody but are typically tested at full strength. Intradermal testing can be done at 1:100 dilution, and if negative, proceed to 1:10.^{7,32}

Selection of testing is based upon the type of reaction that occurred:

- Immediate drug allergy (based on timing and IgE-mediated symptoms):
 - Skin prick testing and intradermal testing to the drug, with nonirritating concentrations.
 - If testing is negative and there is a history of a mild reaction, then the allergist should consider DPT even in young children.
 - If testing is positive, clinical scenario does not allow testing because of time pressure, or history is suggestive of a more severe or potentially anaphylactic type reaction, the allergist should recommend avoidance of drug and any possible cross-reacting drug. Desensitization may be considered if no alternate treatment is available or the drug is first-line treatment.
- Nonimmediate or delayed drug allergy:
 - Consider delayed intradermal testing to a nonirritating concentration of the culprit drug.⁴²
 - If testing is negative or challenge is deemed low risk, the allergist should seek DPT and delabel.
 - If testing is positive, the allergist should recommend avoidance or could consider DPT, only if index reaction was not severe. Desensitization may be considered in some cases.

- SCARs, such as DRESS syndrome, SJS, and toxic epidermal necrolysis (TEN):
 - No widely used commercially available testing.
 - Lymphocyte transformation testing (LTT) and Elispot are novel testing, but not commercially available.
 - DPT and desensitization are contraindicated.

DRUG CHALLENGE AND DESENSITIZATION

The gold standard for diagnosis of drug allergy is drug challenge or DPT. DPT in the form of single-dose challenge or graded challenge has been demonstrated to be well tolerated in children and is a diagnostic measure/delabeling strategy as opposed to desensitization, which is a therapeutic measure for safe administration of a drug in children who are known to be allergic to that drug.^{4,30,43} Both DPT and desensitization should be done in an appropriate medical setting with continual monitoring and equipped with staff and medical equipment capable of treating anaphylaxis, should it occur.²⁸

The literature demonstrates that testing with BL drugs with skin testing followed by DPT in even large groups of children suspected of drug allergy yields small numbers of children who are proven allergic. Results from recent studies in children are summarized in **Table 4**.^{4,5,30,43–45}

When DPT exceeds 4 steps, downregulation of mast cells may occur, resulting in desensitization rather than challenge. A single- or multidose challenge with 2 to 3 steps alternatively can be used to confirm or deny allergy without the untoward consequence of desensitization.²⁸

There are published reports on desensitization in pediatrics to both BL and non-BL drugs.^{46,47} In general, drug desensitization protocols for children differ little from those in adults with the exception of the cumulative dose, because the drug goal is typically weight based.⁴⁸ **Table 5** is an example of the commonly used 12-step desensitization protocol.

Monoclonal antibodies are often life saving or disease modifying, leaving allergic patients little options for alternatives, other than desensitization. Desensitization to

Table 4 Confirmation of drug allergy to antibiotics via drug provocation testing				
Publication	Culprit Drugs	Age of Subjects	Timing of Drug Reaction	Confirmed Allergy (No. of Positive Skin Prick Testing ± DPT/%)
Atanaskovic-Markovic et al, ⁵ 2016	BL	1–18 y	Nonimmediate	7.4% of 1026 subjects
Mill et al, ⁴³ 2016	Amoxicillin	Median age 1.7 y	Immediate Nonimmediate	5.9% (48/818)
Moral et al, ⁴⁴ 2011	BL	Mean age 6.7 y	Nonimmediate	1/50
Ponvert et al, ³⁰ 2011	BL	4 mo–17 y	Immediate Nonimmediate	7.7% (111/1431)
Vezir et al, ⁴ 2014	BL	Median age of 4.3 y	Nonimmediate	4/119
Zambonino et al, ⁴⁵ 2014	BL	1–14 y	Immediate Nonimmediate	7.92% (62/783)

Data from Refs.^{4,5,30,43–45}

Table 5
Desensitization to antibiotics (example ampicillin)

Full dose	Ampicillin Target 1000 mg		IV Q6	Total mg to be injected in each bottle ^a
	1000.0	mg		
Solution 1	250	cc of	0.040 mg/mL	10.000
Solution 2	250	cc of	0.400 mg/mL	100.000
Solution 3	250	cc of	3.969 mg/mL	992.130

Step	Solution	Rate (cc/h)	Time (min)	Administered Dose (mg)	Cumulative Dose (mg)
1	1	2	15	0.0200	0.0200
2	1	5	15	0.0500	0.0700
3	1	10	15	0.1000	0.1700
4	1	20	15	0.2000	0.3700
5	2	5	15	0.5000	0.8700
6	2	10	15	1.0000	1.8700
7	2	20	15	2.0000	3.8700
8	2	40	15	4.0000	7.8700
9	3	10	15	9.9213	17.7913
10	3	20	15	19.8426	37.6339
11	3	40	15	39.6852	77.3191
12	3	75	186	922.6809	1000.0000
Total time =			351	minutes	

^a Note to pharmacy: The total milligrams injected is more than the final dose because solutions 1 and 2 are not completely infused.

Data from Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;124(6):1259–66.

monoclonal antibodies has been reported mostly for adults, but there are successful desensitizations in children as well.^{6,7,49} The desensitization protocols to monoclonal antibodies use the 12-bags protocol, similar to antibiotic protocol in [Table 5](#), and have been described by Brennan and colleagues.³² This same procedure can be used in children but may need to be modified based on weight and reaction, as described by Dilley and colleagues⁶ for rituximab allergy ([Table 6](#)).³²

Desensitization should only be pursued in a child if there are no alternative drugs available for the care of the child. Desensitization is time consuming and costly, but safe in children. Desensitization and graded challenge should never be performed in children with a history of severe T-cell-mediated drug reaction such as TEN/SJS or DRESS.²⁸

FUTURE CONSIDERATIONS

Management of drug allergy in children depends on accurate diagnosis of drug allergy that can lead to appropriate testing depending on the type of reaction that occurred. New classifications based on phenotypes and endotypes may lead to more individualized treatments for drug allergy in the future. Testing young children should not be avoided because of parental or physician fear of testing because it has been confirmed to be safe in the pediatric populations and would help to address overlabeling. Monoclonal antibody allergy is likely to increase as more of these products

Table 6							
Protocol for desensitization to monoclonal antibodies in children (example rituximab)							
Name of medication:		Rituximab					
Target Dose (mg)						225.0	
Standard volume per bag (mL)						250	
Final rate of infusion (mL/hr)						30	
Calculated final concentration (mg/mL)						0.9	
Standard time of infusion (minutes)						187.5	
							Total mg per bag
Solution 1	250	mL of	0.009	mg/mL	2.250		
Solution 2	250	mL of	0.090	mg/mL	22.500		
Solution 3	250	mL of	0.896	mg/mL	224.115		
*** PLEASE NOTE ***							
The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are <i>not completely infused</i>							
Step	Solution	Rate (mL/hr)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)	
1	1	1.0	15	0.25	0.0023	0.0023	
2	1	2.5	15	0.63	0.0056	0.0079	
3	1	5.0	15	1.25	0.0113	0.0191	
4	1	10.0	15	2.50	0.0225	0.0416	
5	2	2.5	15	0.63	0.0563	0.0979	
6	2	5.0	15	1.25	0.1125	0.2104	
7	2	10.0	15	2.50	0.2250	0.4354	
8	2	20.0	15	5.00	0.4500	0.8854	
9	3	5.0	15	1.25	1.1206	2.0059	
10	3	10.0	15	2.50	2.2411	4.2471	
11	3	20.0	15	5.00	4.4823	8.7294	
12	3	30.0	482.5	241.25	216.2706	225.0000	
Total time (minutes) =			647.5	= 10.79 h			

Data from Dille MA, Lee JP, Platt CD, et al. Rituximab desensitization in pediatric patients: results of a case series. *Pediatr Allergy Immunol Pulmonol* 2016;29(2):91–4; and Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;124(6):1259–66.

become available on the market with pediatric indications. Accurate diagnosis for both antibiotic allergy and monoclonal antibody allergy leads to better workup and management of these allergies.

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