Antibiotic Allergy in Pediatrics

Allison Eaddy Norton, MD,[a] Katherine Konvinse, MS,[b] Elizabeth J. Phillips, MD,[a,b,c,d,e] Ana Dioun Broyles, MD[f]

The overlabeling of pediatric antibiotic allergy represents a huge burden in society. Given that up to 10% of the US population is labeled as penicillin allergic, it can be estimated that at least 5 million children in this country are labeled with penicillin allergy. We now understand that most of the cutaneous symptoms that are interpreted as drug allergy are likely viral induced or due to a drug–virus interaction, and they usually do not represent a long-lasting, drug-specific, adaptive immune response to the antibiotic that a child received. Because most antibiotic allergy labels acquired in childhood are carried into adulthood, the overlabeling of antibiotic allergy is a liability that leads to unnecessary long-term health care risks, costs, and antibiotic resistance. Fortunately, awareness of this growing burden is increasing and leading to more emphasis on antibiotic allergy delabeling strategies in the adult population. There is growing literature that is used to support the safe and efficacious use of tools such as skin testing and drug challenge to evaluate and manage children with antibiotic allergy labels. In addition, there is an increasing understanding of antibiotic reactivity within classes and side-chain reactions. In summary, a better overall understanding of the current tools available for the diagnosis and management of adverse drug reactions is likely to change how pediatric primary care providers evaluate and treat patients with such diagnoses and prevent the unnecessary avoidance of antibiotics, particularly penicillins.

Antibiotic allergy labeling leads to significant individual and public health consequences. Unlike vaccination, there is no systematic approach to address antibiotic allergy during routine office visits, and allergy labels persist into adulthood. Antibiotic allergy usually comes to light when treatment is imminent, and physicians often find themselves choosing more expensive and time-intensive procedures, such as desensitization, or using higher-cost alternative antibiotics with potentially more side effects. These measures may satisfy the immediate need for treatment but do not address the primary problem.

Antibiotic allergy labels are often acquired because of rashes reported by parents, and most children never undergo an allergy evaluation to address the diagnosis. In a recent study, 75% of children diagnosed with penicillin allergy were labeled before their third birthday.[1] The prevalent carriage of these childhood allergy labels into adulthood perpetuates the use of alternative antibiotics, which are often more expensive, less effective, and contribute to an increase in antibiotic-resistant bacteria.[2–4] However, studies reveal that when children are tested and/or undergo drug challenging, >90% are able to tolerate the antibiotic.[5–7] Unfortunately, even when the diagnosis of drug allergy is excluded by such procedures, not only parents but many providers are still resistant to drug allergy delabeling.[8,9]

Prescription costs are 30% to 40% higher in patients with suspected penicillin allergy.[10] If just half of the children who visit a physician for acute otitis media annually were to receive amoxicillin instead of cefdinir (a common alternative prescribed for treating patients with

abstract

[a]Division of Allergy, Immunology and Pulmonology, Monroe Carell Jr. Children's Hospital at Vanderbilt, and [c]John A. Oates Institute for Experimental Therapeutics and Department of Pharmacology, School of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; Departments of [d]Division of Infectious Disease, Medicine and [b]Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee; [e]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Australia; and [f]Division of Allergy and Immunology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

Dr Norton conceptualized and outlined the article, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Konvinse aided in the conception and outline of the article, drafted sections of the article, and reviewed and revised the manuscript; Drs Phillips and Broyles aided in conceptualizing and outlining the article, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Allison Eaddy Norton, MD, Division of Pediatric Allergy, Immunology, and Pulmonology, Vanderbilt Children's Hospital, Vanderbilt University, 2200 Children's Way, 11215 DOT, Nashville, TN 37232. E-mail: allison.norton@vanderbilt.edu

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a history of penicillin allergy), the estimated annual savings would exceed $34 million.[11] Researchers in a recent cohort study were able to match 51 582 subjects with and without penicillin allergy at hospital admission. It confirmed that patients who require alternative drugs, such as fluoroquinolones, clindamycin, and vancomycin, because of a penicillin allergy have 23.4% more *Clostridium difficile*, 14.1% more methicillin-resistant *Staphylococcus aureus*, and 30.1% more vancomycin-resistant enterococci infections compared with controls.[4] The accumulation of adverse drug labels is more limiting in populations that are susceptible to frequent infections, such as cystic fibrosis, particularly when drug resistance develops.[12–14]

In this state-of-the-art review, we aim to provide clinicians with an evidence-based toolbox for the diagnostic workup of children with antibiotic allergy. The ultimate goal is to improve patient and provider education to address and reconcile allergy labels early to prevent children from carrying these potentially false antibiotic allergy labels into adulthood.

EPIDEMIOLOGY OF ANTIBIOTIC ALLERGY

Epidemiologic studies in children with antibiotic allergy are scarce and fraught with inconsistencies. It is challenging to accurately assess the incidence of true allergy in the United States, particularly because the term "allergic" has been used frequently without definition, which allows one to conclude that nonallergic reactions were included in many epidemiologic studies.[15] Antibiotics are responsible for up to one-third of reported adverse drug reactions (ADRs), and ~35% of ADRs seen in the emergency department are reported as allergic.[16–18] In addition, as many as 10% of parents report that their children are allergic to 1 or more medications.[19–23]

Researchers in 1 large study in the United States evaluating 411 543 adult and pediatric medical records found that the overall incidence of self-reported antibiotic allergy was as high as 15.3%.[24] Despite the high number of reported cases, <10% of cases are confirmed to be allergic after testing and/or challenge,[25–31] indicating that true allergy to antibiotics is rare and overdiagnosed.[32,33]

The drug allergy box is the major place in most medical records where ADRs are documented, often without reference to the immunologic basis of the reaction. This label does not typically discriminate between pharmacological effects, side effects, temporally associated observations, or true drug allergies, making the drug allergy box subject to overestimation of true allergy risk.[34]

This overestimation has been demonstrated in multiple studies in which the initial drug allergy label was based on questionnaires and/or the opinions of experienced physicians, but subsequent drug challenges were used to disprove the majority of them.[35–37] In a large study of consecutive patients with or without a history of penicillin allergy, the rate of positive skin testing results in those who were labeled as penicillin allergic with vague histories was 1.7%, which is the same as in those without a history of penicillin allergy.[23]

In 1 study, Erkoçoğlu et al[33] found that of the 10 096 questionnaires returned, in 792 (7.87%), parents reported a history of drug allergy, but only 117 (1.1%) of these were consistent with an immunoglobulin E (IgE)–mediated reaction by history. There were 101 children for whom further workup was done, and only 7 (0.11%) of those with suggestive histories had positive testing results.

Penicillin allergy, which is the most common reported drug allergy, has a prevalence rate of 5% to 10% in community populations of adults and children and is as high as 20% in those linked to ongoing medical care.[18,38–41] An allergy to amoxicillin is the most common drug allergy in children.[32] Although the epidemiology in the United States is currently unknown, hypersensitivity to clavulanic acid appears prevalent in southern Europe and has been described in children.[26,42,43]

Of ADRs in pediatric patients, 23% are reported to be caused by non–β-lactam antibiotics. Although rarely confirmed in pediatric studies, macrolides are reported to cause drug allergy, mostly benign cutaneous reactions.[44] Among macrolides, the 15-membered ring azalide (azithromycin) may be more allergenic than clarithromycin and without consistent cross-reactivity with clarithromycin, erythromycin, and other 14-membered ring traditional macrolides.[45,46] Sulfonamide antimicrobial agents infrequently cause IgE-mediated symptoms in children but are known to cause a wide array of T-cell–mediated symptoms, most commonly mild cutaneous exanthems, but more severe reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, fixed drug eruption, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced liver disease, and cytopenia have been reported as well, especially in patients with HIV.[12,47–50] Allergic reactions to quinolones, vancomycin, aminoglycosides, and tetracyclines are rare except in certain patient populations with chronic diseases, such as cystic fibrosis, likely because of repeated exposure to antibiotics.[44,51]

CLASSIFICATION OF ADRS

ADRs are clinically classified as type A and type B reactions. Type A (on-target) reactions are dose dependent and pharmacologically predictable on the basis of the accentuation of the drug's on-target

TABLE 1 Classification, Clinical Features, and Management of Classic Hypersensitivity Reactions to Antibiotics

Gell and Coombs Classification	Immune Mechanism	Clinical Features	Timing
Type I: immediate-type hypersensitivity	Mast cell and/or basophil mediator release directed by drug interaction and/or cross-linking of drug-specific IgE bound to these cells	Anaphylaxis, urticaria, angioedema, gastrointestinal, respiratory, cardiovascular, and neurologic symptoms	Immediate: <1 h after drug exposure
Type II: cytotoxic or antibody dependent, hypersensitivity	Natural killer cells and macrophages kill IgG- or IgM-coated cells that are directed against the drug or drug metabolite on the patient's cells	Drug-induced hemolytic anemia, thrombocytopenia	1–2 wk after exposure[a]
Type III: immune complex–mediated hypersensitivity	Antibody (IgG>IgM) binds to soluble antigen (often a drug or drug metabolite), forming a circulating immune complex	Serum sickness, vasculitis	1–2 wk after exposure[a]
Type IV: delayed-type hypersensitivities	An antigen-presenting cell expressing HLA bound to a peptide interacts with a T-cell receptor in the presence of a drug or drug metabolite[b,61]	Benign, delayed skin rashes	Nonimmediate: differs according to the specific phenotype (Table 3) but generally 24 h to 1 wk after first exposure and can be quicker (h) on rechallenge exposure
Type IVa		Allergic contact dermatitis, maculopapular exanthema, FDE, EM (typically infection, not drug)	
Type IVb		More severe cutaneous skin rashes	
Type IVc		Acute generalized exanthematous pustulosis, DRESS syndrome, SJS and/or TEN, generalized-bullous FDE	
Type IVd			

EM, erythema multiforme; FDE, fixed drug eruption; HLA, human leukocyte antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

[a] May be sooner if preformed antibodies.

[b] Multiple models have been proposed including hapten/prohapten model, pharmacological interaction (p-i) model and altered peptide repertoire model. In the hapten/prohapten model, a drug/drug metabolite covalently bound to larger protein undergoes intracellular processing to generate modified peptides that are incorporated onto HLA proteins for presentation to T cells.[61]

therapeutic effect. They comprise >80% of ADRs, including drug–drug interactions, and may be subject to genetic variation.[52,53] Common examples include bleeding with warfarin or tremor associated with albuterol. Antibiotic-associated type A reactions in pediatric practice include antibiotic-associated diarrhea because of an on-target effect dependent on dose and duration secondary to the alteration of the bacterial microbiome or dose-dependent adrenal suppression associated with azole antifungal agents.[47,54]

Type B (off-target) reactions are not predictable on the basis of the known target of therapeutic effect but are often dose dependent and subject to host genetic variation. A minority are dose independent, including antibody- and IgE-mediated reactions.[52,53,55,56] The off-target mechanism of non–IgE-mediated mast cell activation for many drugs (such as opiates, neuromuscular blocking agents, fluoroquinolones, and potentially vancomycin) entails the dose-dependent activation of a specific mas-related G protein–coupled receptor on mast cells.[57,58] Red man syndrome because of non–IgE-mediated mast cell activation secondary to vancomycin administration is a clinical example of a type B reaction in children.

Drug allergies comprise <15% of all ADRs; however, patients and physicians often erroneously refer to all ADRs as allergic.[19,51,56] The Gell and Coombs mechanism–based system (Table 1) classifies ADRs into 4 types (I, II, III, and IV) and, more recently, subtypes IVa, IVb, IVc, and IVd on the basis of their immune mediators.[57,59–63]

Other proposed classification systems are used to establish biomarkers depending on the patient phenotype and endotype. Phenotype is determined on the basis of timing (immediate or delayed onset) and associated symptoms. Endotypes include IgE-mediated

reactions, T-cell–mediated reactions, pharmacologic interactions, and genetic predisposition. Biomarkers include in vivo, in vitro and/or ex vivo testing, mediators, and genetic markers (such as human leukocyte antigen typing).[64]

CROSS-REACTIVITY

Cross-reactivity is a clinically relevant topic because clinicians are often faced with alternative antibiotic choices when a patient develops a rash during an antibiotic course. Most studies have been focused on β-lactam cross-reactivity; however, other antibiotics, such as macrolides and quinolones, are also known to cross-react within their group.[46,65–68]

β-lactams (penicillins, cephalosporins, carbapenems, monobactams, oxacephems, and β-lactamase inhibitors) are a group of drugs that share a 4-membered β-lactam ring. The β-lactam ring opens spontaneously in vivo into benzylpenicillin without active metabolism, resulting in the formation of the major determinant, benzylpenicilloyl. Additionally, benzylpenicillin (the native penicillin drug) and the minor determinants (penicilloate and penilloate) can be immunogenic. There is a side chain that arises from the β-lactam ring (R1). Cephalosporins additionally have a 6-membered ring and another side chain (R2).[47,69]

The β-lactam ring was initially believed to be the predominant cause of cross-reactivity between cephalosporins and penicillins.[69] However, the R1 side chain and, less frequently, the R2 side chain have been demonstrated to contribute significantly to cross-reactivity within the penicillin class itself and also between penicillins and cephalosporins in vitro, in vivo through skin testing and challenge, and clinically through selective tolerance or reactivity (Figs 1–5).[63,69–72] Approximately 2% of patients with penicillin allergy would be expected

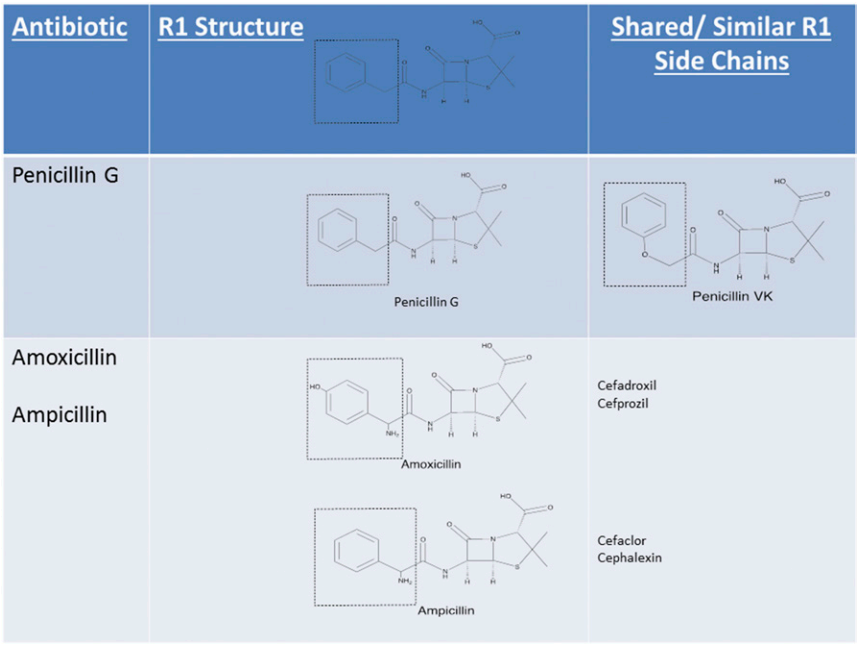


FIGURE 1
Penicillin-cephalosporin cross-reactivity based on side-chain similarity. Penicillin G, benzylpenicillin; penicillin VK, phenoxymethylpenicillin potassium. Approximately 2% of penicillin allergic patients would be expected to react to a cephalosporin, however this number may exceed 30% when administered cephalosporins with identical R1 side chains. Cefditoren and cefpodoxime are oral cephalosporins with the same side chain.

to react to a cephalosporin; however, this number may exceed 30% when administered cephalosporins have identical R1 side chains.[47,71–73] The 2% figure is based on the statistic that only 10% of individuals with a history of penicillin allergy are expected to test positive to penicillins, and of those, ~2% will develop a reaction to cephalosporins. The mechanism behind this is unknown but may be secondary to coexisting allergy. In the Practice Parameter on drug allergy, the Joint Task Force recommends skin testing individuals with penicillin allergy to penicillin and its major and minor determinants (although the percentage is low) before administering a cephalosporin because fatal anaphylaxis has been reported.[47] When skin testing is not available, there is clinical evidence to support choosing a cephalosporin with a different R1 side chain to reduce reaction risk.[69–76]

Cefazolin, which is a common cause of perioperative anaphylaxis, does not share R1 or R2 groups with other cephalosporins, and accumulating evidence supports that patients with IgE-mediated reactions to cefazolin may tolerate other cephalosporins and penicillins.[77–80] Researchers in some studies have reported on subjects who are allergic >1 β-lactam drug, although their sensitivity cannot be explained by side-chain similarity.[70,75] Ideally, testing to cephalosporins should be pursued along with penicillin reagents in children with a strong history of penicillin allergy or positive penicillin skin testing results.[47,70] The rate of cross-reactivity between penicillins and both carbapenems and aztreonam in children has been determined to be <1%, so it is safe for a patient with penicillin allergy to receive these drugs.[75,81–84] The tolerability of carbapenems in individuals with penicillin allergy has also recently been demonstrated in delayed-type drug allergy.[83]

CLINICAL PHENOTYPING

An accurate and detailed history helps identify the nature of the

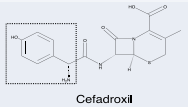
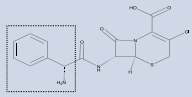
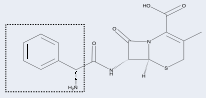
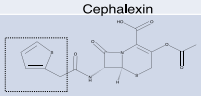
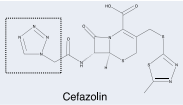
Antibiotic	R1 Structure	Shared and/or Similar R1 Side Chains
Cefadroxil	 Cefadroxil	Amoxicillin Ampicillin Cefaclor Cefprozil Cephalexin
Cefaclor	 Cefaclor	Amoxicillin Ampicillin Cefadroxil Cefprozil Cephalexin
Cephalexin	 Cephalexin	Amoxicillin Ampicillin Cefadroxil Cefaclor Cefprozil
Cephalothin	 Cephalothin	Cefoxitin
Cefazolin	 Cefazolin	None

FIGURE 2

First-generation cephalosporin cross-reactivity. Approximately 2% of penicillin allergic patients would be expected to react to a cephalosporin, however this number may exceed 30% when administered cephalosporins with identical R1 side chains. Cefditoren and cefpodoxime are oral cephalosporins with the same side chain.

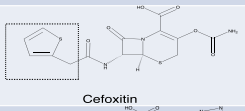
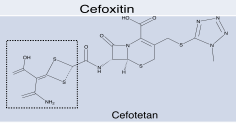
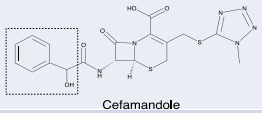
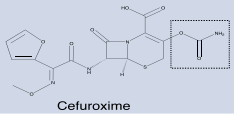
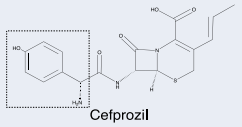
Antibiotic	R1 Structure	Shared and/or Similar R1 Side Chains
Cefoxitin	 Cefoxitin	Cephalothin
Cefotetan	 Cefotetan	None
Cefamandole	 Cefamandole	None
Cefuroxime	 Cefuroxime	None (***cefoxitin, R2 side chain***)
Cefprozil	 Cefprozil	Amoxicillin Ampicillin Cefaclor Cefadroxil Cephalexin

FIGURE 3

Second-generation cephalosporin cross-reactivity. Approximately 2% of penicillin allergic patients would be expected to react to a cephalosporin, however this number may exceed 30% when administered cephalosporins with identical R1 side chains. Cefditoren and cefpodoxime are oral cephalosporins with the same side chain.

adverse reaction and the most appropriate management.[85] Urticaria is the most common clinical symptom of a drug reaction, drug–viral interaction, as well as non–IgE-mediated mast cell activation.[15,32,86] When it occurs within an hour of exposure to a drug, particularly if it's reproducible on drug challenge, it can represent an immediate reaction potentially associated with anaphylaxis.[6,33,87] Pseudoallergic reactions, also known as "anaphylactoid" reactions or non–IgE-mediated mast cell activation, can resemble type I hypersensitivity reactions (Table 2).[47,57,88,89] Delayed or nonimmediate reactions range from benign to severe and can be classified by timing and clinical features (Table 3).[47,88,89] Delayed urticaria that occurs several hours to days after drug exposure is often non-IgE mediated. The underlying cause of cutaneous drug reactions during viral infections may involve a viral-induced polyclonal activation of lymphocytes, an enhancement of cellular immunity, or changes in drug metabolism.[90]

In children, rashes during antibiotic treatment can be difficult to assess because they often result from a variety of triggers that are common in the pediatric population. Maculopapular rashes have been observed in 3% to 7% of children who are on ampicillin.[92] In fact, researchers in recent studies have attempted to reveal the underlying viral causes of rashes by performing viral diagnostic studies with simultaneous allergy workup.[31,35] In a 2011 study by Caubet et al,[31] of 88 children with a history of nonimmediate drug allergy, only 6 had positive challenge results, and 5 of these were confirmed to have an underlying infection known to cause rash. Delayed-onset urticarial or maculopapular rashes are also frequently observed in children who are treated with β-lactam, with an estimated frequency of 1% to 5% experiencing rashes per prescription.[39]

AVAILABLE GUIDELINES AND CONSENSUS STATEMENTS

Most information on pediatric drug allergy is tailored for specialists and extrapolated from guidelines for adults. Specialists refer to both American and European guidelines and consensus statements.[44,47,89,93–98]

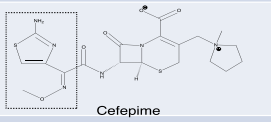
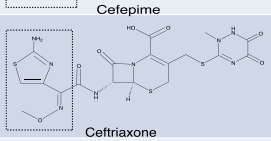
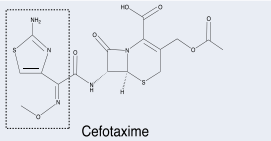
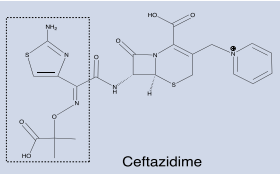
Antibiotic	R1 Structure	Shared and/or Similar R1 Side Chains
Cefepime	 Cefepime	Ceftriaxone Cefotaxime
Ceftriaxone	 Ceftriaxone	Cefepime Cefotaxime
Cefotaxime	 Cefotaxime	Ceftriaxone Cefepime
Ceftazidime	 Ceftazidime	Aztreonam

FIGURE 4
Third-, fourth-, and fifth-generation cephalosporin cross-reactivity. Approximately 2% of penicillin allergic patients would be expected to react to a cephalosporin, however this number may exceed 30% when administered cephalosporins with identical R1 side chains. Cefditoren and cefpodoxime are oral cephalosporins with the same side chain.

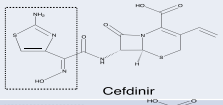
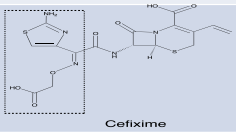
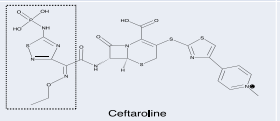
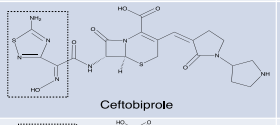
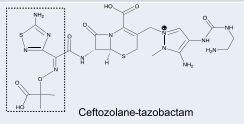
Antibiotic	R1 Structure	Shared and/or Similar R1 Side Chains
Cefdinir	 Cefdinir	Cefixime
Cefixime	 Cefixime	Cefdinir
Ceftaroline	 Ceftaroline	Ceftobiprole Ceftozolane-tazobactam
Ceftobiprole	 Ceftobiprole	Ceftaroline Ceftozolane-tazobactam
Ceftozolane-tazobactam	 Ceftozolane-tazobactam	Ceftaroline Ceftobiprole

FIGURE 5
Third-, fourth-, and fifth-generation cephalosporin cross-reactivity (continued). Approximately 2% of penicillin allergic patients would be expected to react to a cephalosporin, however this number may exceed 30% when administered cephalosporins with identical R1 side chains. Cefditoren and cefpodoxime are oral cephalosporins with the same side chain.

DIAGNOSIS AND TREATMENT OF ANTIBIOTIC ALLERGY IN CHILDREN

An accurate history that combines all subjective and objective information available is key in the diagnostic evaluation of children with antibiotic allergy.[38,44,55,56,89,99–101]

The accurate documentation of medications taken at the time of the reaction is crucial because the presence of cofactors or coprescribed drugs may change the onset or progression of a reaction[47,89] and could also be causal. The mechanism could be a true allergic reaction associated with immunologic memory or an off-target effect, such as non–IgE-mediated mast cell activation exacerbated by multiple inciting drugs administered concurrently (eg, opiates and vancomycin).[52] Previous exposure to the same antibiotic or structurally similar antibiotics is important in determining the immunologic mechanism. The physician should gather particular signs and symptoms as precisely as possible and consider, on the basis of these symptoms, whether the reaction should be considered severe, benign, immediate, or nonimmediate. The provider should determine if treatment was required for the reaction as well as the response to treatment.[32,55,102,103]

If a provider is suspicious that an IgE-mediated allergic reaction occurred (Table 1), workup should be considered (Fig 6). Immediate reactions that typically occur within 1 hour of exposure to oral drugs or within 15 to 20 minutes for parenteral drugs should prompt referral to an allergist for further workup. In reality, the immunologic mechanisms of the reactions may be accelerated in nature (1–72 hours after dosing), and these overlap considerably in time or may not be clearly differentiated by the medical history, which is why if there is any suspicion of drug allergy, referral should be considered.[80]

IN VIVO TESTING: IMMEDIATE REACTIONS

When performed by trained professionals, skin prick and intradermal skin testing are safe and efficacious procedures to aid in the

TABLE 2 Immediate Reactions: Clinical Features and Management

Type of Reaction	Timing of Reaction	Symptoms of Reaction	Possible Laboratories in Acute Setting	Differential Diagnosis	Commonly Involved Antibiotics	Testing	Management
Non–IgE-mediated reaction, mast cell activation (anaphylactoid, pseudoallergic)	Immediate or during infusion Can occur on first course of drug	Urticaria Flushing Angioedema (occasionally) Hypotension Mild fever Muscle pain in severe instances	Elevated mast cell tryptase	IgE-mediated reaction Anaphylaxis	Quinolones Vancomycin (Red man syndrome)	Serum total tryptase level[a] Serum histamine[b]	Pretreatment Slow infusion speed (with Red man syndrome) Antihistamines Desensitize in some cases
IgE-mediated, anaphylactic-producing, immediate reaction	1–6 h after administration of the drug	Angioedema Urticaria Rhinitis Conjunctivitis Hypotension Laryngeal edema Gastrointestinal symptoms Bronchospasm Cardiovascular shock and hypotension	Elevated mast cell tryptase	Non–IgE-mediated mast cell activation Food allergy Venom allergy Idiopathic urticaria and anaphylaxis	β-lactams (ie, aminopenicillins) Rarely non-β-lactams (macrolides)	Acute testing as above Allergy referral testing and possible tests Skin prick testing Serum-specific IgE Drug provocation testing	Avoid drugs and/or cross-reacting drugs Desensitization

[a] Obtain serum total tryptase 15 minutes to 3 hours after reaction.
[b] Obtain 2-15 minutes after reaction.

diagnosis of immediate reactions to antibiotics, particularly in β-lactams.[26,102,104,105]

If possible, skin testing should be delayed for 2 to 3 weeks after an inciting reaction because of the potential depletion of mediators, which may temporarily lead to false-negative results.[55] Most guidelines suggest waiting 4 to 6 weeks after the complete resolution of all clinical symptoms and signs of a suspected delayed hypersensitivity reaction before testing.[44,47,89,106]

Standardized antibiotic skin testing protocols exist for penicillin, although the only labeled skin testing reagent currently available in the United States is penicillin major determinant (Pre-Pen). There are also published data regarding nonirritating concentrations and test specificity to other antibiotics that allergists may choose to use before challenging.[107,108]

IN VIVO TESTING: NONIMMEDIATE REACTIONS

Some researchers suggest delayed intradermal testing reads at 24 to 48 hours or patch testing with reads at 48 hours, 72 hours, 96 hours, and 1 week for nonimmediate reactions. However, sensitivity has been reported to be <50% in many studies and is likely to be dependent on the specific antibiotic and the pretest clinical probability.[35,98]

FEASIBILITY OF SKIN TESTING IN CHILDREN

Skin prick testing is performed easily in children of any age, even in infancy.[109] Although intradermal skin testing is less well tolerated because of the discomfort from injections, when indicated, it is possible to perform this test in young children with adequate preparation. In routine clinical practice, the risk of resensitization to a drug after a negative testing result is extremely uncommon.[27,110]

TABLE 3 Nonimmediate Reactions: Clinical Features and Management

Type of Reaction	Timing	Cutaneous Symptoms	Systemic Symptoms	Possible Laboratories in Acute Setting	Differential Diagnosis	Commonly Involved Antibiotics	Testing	Management
Delayed drug reaction	7–14 d	Maculopapular exanthema	Low-grade fever	Eosinophilia (mild)	Viral exanthem	Aminopenicillins	Delayed intradermal testing	Avoidance drugs and/or cross-reactive drugs
		Urticaria	Pruritus		IgE-mediated drug allergy Early DRESS syndrome or SJS and/or TEN	Sulfonamides Clindamycin		Drug provocation testing
SJS and/or TEN	4–28 d	Painful erythematous macules with purpuric or dusky centers	Prodrome	Anemia	EM	Sulfonamides	LTT and/or ELISPOT	Avoidance drug and/or drug class
		Superficial sloughing	High fever	Lymphopenia	Bullous pemphigoid	Minocycline (used for acne)	HLA screening	
		Mucositis in ≥2 surfaces	Malaise		Staphylococcal scalded skin syndrome	β-lactams		
			Pneumonitis (occasionally)		FDE DRESS syndrome			
DRESS syndrome	2–8 wk	Morbilliform eruption >50% BSA	Fever	Eosinophilia	Viral or drug exanthem	Vancomycin	Patch testing	Avoidance of drugs and/or cross-reacting drugs
		Nonerosive mucositis	Lymphadenopathy	Atypical lymphocytes	Early SJS and/or TEN	β-lactams	LTT and/or ELISPOT	
		≥2 facial edema, infiltrated lesions, scaling, and purpura		Hepatitis Renal impairment	Severe eczema or psoriasis	Tetracyclines Rifampin Antituberculosis drugs Sulfonamides and/or sulfones[a,91]	HLA screening	
FDE	1–14 d[b]	1 or more well-demarcated, round, dusky-to-violaceous macules or plaques	None	None	EM	Sulfonamides	Patch testing	Drug provocation testing[c]
		Blistering may occur Mucosal predilection but limited mucositis			Bullous pemphigoid SJS and/or TEN	Tetracyclines β lactams		Avoidance of drug and/or cross-reactive drug
		Postinflammatory hyperpigmentation				Quinolones Fluconazole		
Acute generalized exanthematous pustulosis	24–48 h	Dozens to hundreds of pustules on erythematous background	High fever	Neutrophilia	Pustular psoriasis	Aminopenicillins	Patch testing	Avoidance of drugs and/or cross-reactive drugs
		Flexural accentuation	Edema	Eosinophilia	Bullous impetigo Subcorneal pustular dermatosis DRESS syndrome	Clindamycin Sulfonamides Quinolones		

TABLE 3 Continued

Type of Reaction	Timing	Cutaneous Symptoms	Systemic Symptoms	Possible Laboratories in Acute Setting	Differential Diagnosis	Commonly Involved Antibiotics	Testing	Management
Serum-sickness–like reaction	1–2 wk	Pruritic urticarial or serpiginous plaques (usually at injection site)	High fever Malaise Polyarthralgia or polyarthritis	Neutropenia Mild eosinophilia Mild proteinuria	Vasculitis Rheumatic fever Other drug reactions	β lactams (especially cefaclor) Macrolides Sulfonamides	None	Avoidance of specific drug[d]

BSA, Body Surface Area; EM, erythema multiforme; FDE, fixed drug eruption; HLA, human leukocyte antigen.

[a] Sulfonamides include trimethoprim-sulfamethazole and sulfones include dapsone. There is no cross reactivity between sulfa antimicrobials and non-antibiotic sulfonamides (such as acetazolamide, bumetanide, celecoxib, chlorothiazide, diazoxide, dorzolamide, furosemide, glyburide, hydrochlorothiazide, indapamide, metolazone, sumatriptan, torsemide and zonisamide).

[b] Rapid recurrence on drug re-exposure.

[c] Contraindicated in generalized FDE.

[d] Controversial. Some sources recommend avoiding drug and drug class while others (ie cefaclor) just recommend avoiding culprit drug.

IN VITRO AND/OR EX VIVO TESTING

Serum-mature tryptase (β tryptase), a mast cell mediator, can be used as an adjunct for suspected IgE-mediated reactions during which peak levels will be reached within 30 minutes to 2 hours of the onset of symptoms and typically return to normal within 24 hours. Non–IgE-mediated mast cell activation can produce a positive mast cell tryptase in ∼10% of cases.[111] Although a normal tryptase level does not rule out anaphylaxis and/or IgE-mediated drug allergy, an elevated level compared with baseline can be helpful in the diagnosis of such reactions.[47]

DRUG-SPECIFIC TESTS

There are currently no validated in vitro or ex vivo tests that have adequate sensitivity and/or specificity to be widely applied in clinical practice. The in vitro–specific IgE testing that is commercially available for penicillin has a low sensitivity, ranging from 0% to 25%, and in some studies, false-positive testing results have been found.[112,113] Researchers in multiple studies have reported false-negatives when testing was done close to the acute reaction and when testing is delayed beyond 6 months despite a lack of tolerance.[114–116]

There are other ex vivo and in vitro assays that are potentially clinically useful but are currently only used in research settings. The basophil activation test is an in vitro test for antibiotics using flow cytometry to detect basophil surface (CD63 and/or CD203c) and intracellular (phospho-p38 mitogen-activated protein kinases) markers.[85,112,117–120] Lymphocyte transformation testing (LTT) is used to measure T-cell proliferation to a drug in vitro and is possibly useful for the diagnosis of drug-induced type IV (delayed) hypersensitivities, although both false-negative and false-positive testing results have been reported.[95,121–123]

Enzyme-linked immunospot (ELISPOT) assays are used to analyze low-frequency, antigen-specific, cytokine-producing cells in the peripheral blood of patients with a type IV hypersensitivity reaction after stimulation with pharmacological drug concentrations. ELISPOT can be used to measure cytokine responses, including interleukin (IL)-13, interferon γ, IL-10, IL-5, granzyme B, granulysin, and tumor necrosis factor α. ELISPOT has been reported to have better sensitivity than LTT in detecting drug-specific T-cell responses and a specificity ranging from 95% to 100%.[112,124–131] Intracellular cytokine staining is used to measure the production of targeted cytokines by T cells in response to drug stimulation.[122]

Tests such as the ELISPOT assay and intracellular cytokine staining potentially could be of great utility, particularly because many children are on multiple antibiotics at the time they develop a severe reaction such as DRESS syndrome or SJS and/or TEN, when delayed intradermal skin testing or patch testing may be riskier or lack sensitivity. The extent to which these tests remain positive over time is not known, and differences may exist between drugs and classes of drugs.[132]

DRUG CHALLENGE

The drug challenge, also referred to as a graded challenge or drug provocation test, is considered to be a gold standard for drug allergy diagnosis. It can be administered as a single dose or in multiple doses. Drug challenge strategies to reduce the risk of severe reaction, when the pretest probability of an IgE-mediated reaction is high and the negative predictive value of skin testing is low, include a 2-step graded challenge in which 10% of

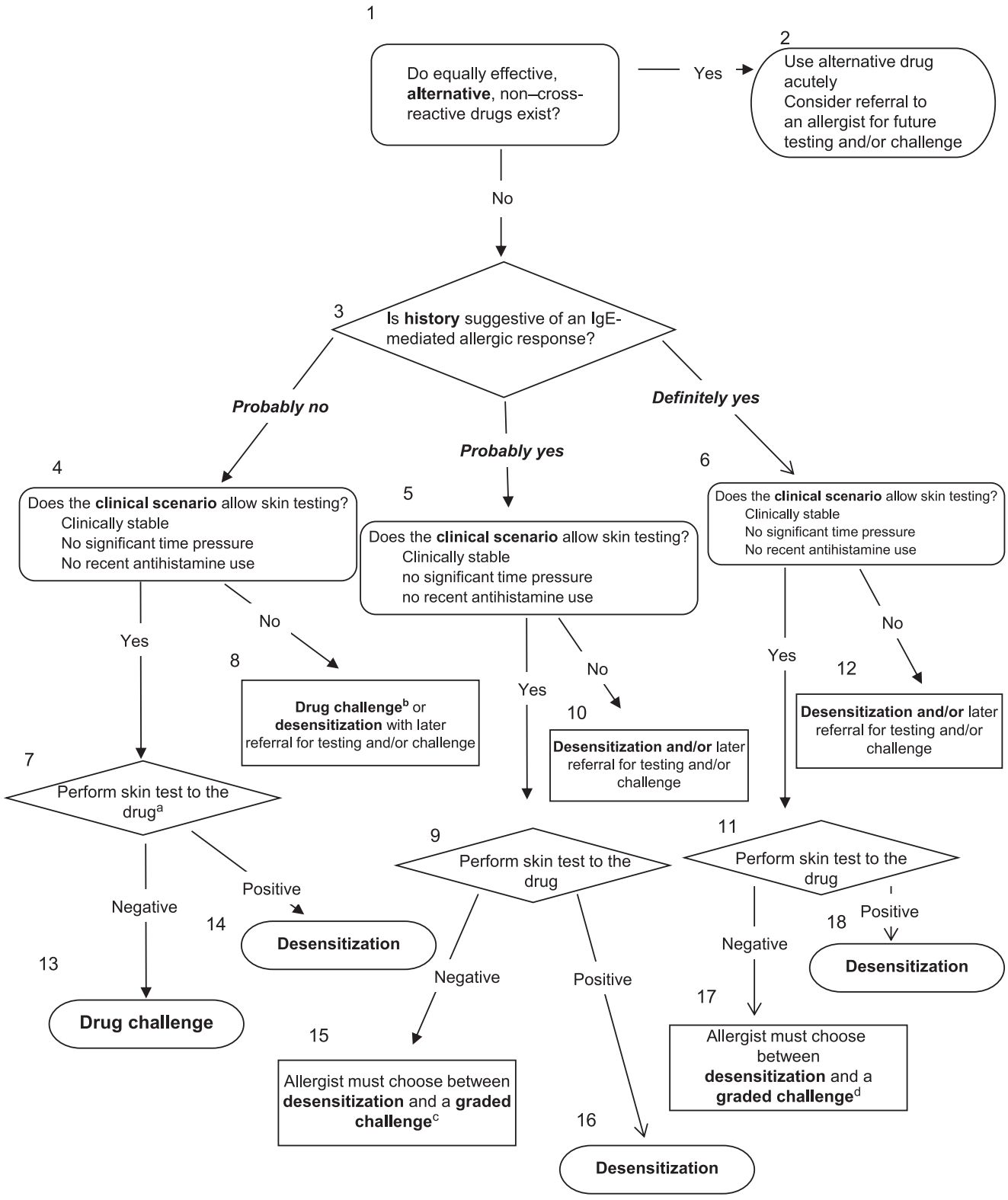


FIGURE 6

Stepwise approach to the evaluation and treatment of patients with type I IgE-mediated drug allergy (see Table 1). This approach cannot be used in the case of severe reactions, including SJS, TEN, DRESS syndrome, nephritis, hepatitis, and hemolysis. Adapted from Turvey SE, Cronin B, Arnold AD, Dioun AF. Antibiotic desensitization for the allergic patient: 5 years of experience and practice. *Ann Allergy Asthma Immunol.* 2004;92(4): p. 430 and Dioun AF. Management of multiple drug allergies in children. *Curr Allergy Asthma Rep.* 2012;12(1): p. 81.See Figs 1–5 for cross reactivity. [a]Pursuing skin testing is dependent on negative predictive value of testing and reagent dependent. Consider going straight to challenge if reaction was mild and inconsistent with

a weight-based dose is given and then the remaining 90% is given after a specified observation time of 30 to 60 minutes with an additional observation time of 60 minutes. For instance, if a penicillin testing result is negative, then it is reasonable to proceed with a single-dose challenge because the negative predictive value of penicillin testing has been well established at 97% to 99%. For all other antibiotics, the predictive values have not been determined in large population studies; therefore, if a testing result is negative, a graded challenge is the safest way to proceed.[23,31,47] If >3 doses are administered, a graded challenge can be used to downregulate mast cells and runs the risk of desensitizing patients.[47]

The majority of studies in which researchers evaluate drug challenges reveal that they are safe and well tolerated in the pediatric population. Researchers in several studies report that if reactions were to occur as a result of drug challenge, they are similar or less severe than the original reaction.* Researchers support the use of allergy testing and challenge in special populations, such as oncologic and immune-compromised patients, and have comparable positive and negative predictive values to the general population.[133,134]

DRUG DESENSITIZATION

Drug desensitization is described as a temporary induction of drug tolerance by the administration of incremental doses of the drug.[47] It is important to realize that drug desensitization is a therapeutic measure for the safe administration of a drug to a patient who has either a proven or is highly likely to have a drug allergy as opposed to drug challenge, which is a diagnostic procedure performed in cases of low probability of drug allergy.[23,47] In addition, drug challenge and desensitization should be done in a monitored setting and are contraindicated in patients with severe non–IgE-mediated reactions, such as SJS, TEN, DRESS syndrome, interstitial nephritis, hepatitis, or hemolytic anemia.[47]

Drug desensitization procedures vary depending on several factors, such as the drug itself, the route of administration, and the patient's reaction and its severity. The starting dose is typically in fractions of a milligram, doubling every 15 to 30 minutes until a cumulative therapeutic dose has been achieved. The goal of desensitization is to render the individual nonreactive to the drug as long as he or she is receiving treatment with the drug. Once the drug is no longer present in the serum, the individual loses the tolerance to the drug, and repeat desensitization is usually indicated if there is a delay of >2 half-lives.[47,55]

There are few studies on antibiotic desensitization in children, so most of our knowledge of this procedure is extrapolated from adult studies.[135,136] A high efficacy and safety rate has been reported in both β-lactam and non–β-lactam drugs.[47,50,137–140] Case reports of successful desensitization in children to other β-lactam drugs (including meropenem, cefotaxime, ceftriaxone, and ceftazidime) as well as non–β-lactam drugs (such as macrolides or sulfa antimicrobial agents) have been reported.[50,138–140]

Desensitization is most effective in IgE-mediated reactions; however, there is evidence for its use in some non–IgE-mediated reactions, particularly with sulfa antimicrobial agents.[141–144] Desensitization is also frequently employed and effective in the setting of suspected non–IgE-mediated reactions in children with cystic fibrosis.[14,135,145]

ANTIBIOTIC STEWARDSHIP PROGRAMS

Patients requiring frequent medical care or hospitalization are at high risk to be labeled as allergic to multiple antibiotics.[3,146] In addition, labels frequently stick despite negative testing results and challenge.[9] In fact, it is estimated that 36% to 49% of patients with negative penicillin testing results may have a persistence or redocumentation of their allergy despite proven negative testing results.[147–149]

Current evidence reveals that an interactive and electronically accessible drug allergy box in a medical record that is regularly reconciled improves the management of patients labeled with drug allergies. In 1 study, the electronic medical record was used proactively to identify patients for testing, which was then performed in the inpatient unit by a trained pharmacist. Researchers in this study reduced the use of second-line antibiotics during hospitalization and discharge.[150] Researchers in another small pilot study prevented redocumentation with several interventions, including an electronic alert notifying providers when a penicillin allergy is added back for a patient with documented negative testing results.[148]

Targeting prospective antibiotic allergy management in adults has led to a positive impact on antibiotic use and appropriateness.[151] Blumenthal et al[152] used a quasi-experimental design to measure the impact of different strategies over discreet time

* Refs 25,26,28,31,35–37,43,154,155.

FIGURE 6 Continued

IgE mediated drug allergy. [b] Consider graded challenge for milder reactions or desensitization for more severe reactions. [c]Consider graded challenge for milder reactions. [d]Consider desensitization regardless of skin test, particularly if index reaction was severe.

periods among an internal medicine service and showed that inpatient skin testing to β-lactam drugs directed by an allergist and the use of previously adopted, computerized guidelines resulted in an increase in penicillin and cephalosporin use.[153] Trubiano et al[146] measured the impact of an integrated and responsive outpatient antibiotic allergy testing and antimicrobial stewardship program at 2 Australian centers and determined that after testing, appropriate antibiotics were more likely to be prescribed. To date studies using antibiotic allergy management as an antimicrobial stewardship tool have focused on adults. Programs in which researchers prioritize pediatric populations, in which the majority of antibiotic allergy labels are first realized, are warranted.

FUTURE DIRECTIONS

Educating the public and health care providers about the differences in ADRs and drug allergies could reduce overdiagnosis and promote appropriate referrals and procedures, such as skin testing and drug challenging, that will prevent the overlabeling of drug allergy. Education directed at community providers to make a more accurate diagnosis of drug allergy could potentially improve global health. An interactive electronic medical record that is regularly reconciled could help improve the management of patients with drug allergy. In the future, accessibility to preventive genetic testing and more sensitive diagnostic tests for both immediate and delayed antibiotic allergy could be invaluable. These tests would ideally aid in preventing reactions, unraveling the diagnostic complexity of multiple antibiotic allergies, or determining the underlying cause of a reaction and whether it is the drug, a virus, or a drug–virus interaction. If sufficiently sensitive and/or specific and widely available, such testing would also greatly reduce the risks in drug challenges, decrease the use of the more time-intensive and costly procedure of desensitization, and increase the use of first-line antibiotics.

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ABBREVIATIONS

ADR: adverse drug reaction
DRESS: drug reaction with eosinophilia and systemic symptoms
ELISPOT: enzyme-linked immunospot
IgE: immunoglobulin E
IL: interleukin
LTT: lymphocyte transformation testing
R1: side chain that arises from the β-lactam ring
R2: side chain that arises from the dihydrothiazine ring on cephalosporins
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

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