Current Allergy and Asthma Reports (2019) 19: 11
https://doi.org/10.1007/s11882-019-0841-y

ANAPHYLAXIS AND DRUG ALLERGY (DAVID A. KHAN & MARIANA CASTELLS, SECTION EDITORS)

Pediatric Drug Hypersensitivity

Christine R. F. Rukasin[1] · Allison E. Norton[2] · Ana Dioun Broyles[3]

Published online: 22 February 2019

Abstract

Purpose of Review Pediatric drug hypersensitivity is a rapidly evolving field. The purpose of this paper is to review the current state of pediatric drug hypersensitivity and highlight new developments in diagnosis and management.

Recent Findings This paper will discuss the safety and use of risk stratification to proceed directly to oral challenge without prior skin testing for β-lactam reactions. We review unique aspects of pediatric drug challenges and desensitizations.

Summary It is important to accurately diagnose pediatric drug hypersensitivity reactions through a detailed history, physical examination, and available diagnostic testing. Understanding of the underlying mechanism leads to appropriate classification which is necessary to direct management. The decision to perform drug challenge, desensitization, or recommend avoidance of a medication can have a significant impact on a patient's treatment. Utilization of weight-based dose and infusion rate adjustments for current drug challenge and desensitization protocols optimize success.

Keywords Pediatric · Drug hypersensitivity · Drug allergy · Medication allergy · Desensitization · Drug challenge

Introduction

Drug reactions in children can be distressing to the child, parent, and medical providers. It is estimated that 2–11% of children have a reported drug allergy [1, 2••]. The presence of a drug allergy label in children can be problematic as these could persist for a lifetime without proper evaluation leading to the use of potentially less effective alternative therapies, broad-spectrum antibiotics, higher healthcare costs, and development of antibiotic-resistant bacteria [3–5, 6••, 7••, 8]. There has been continued effort to formalize evaluation for pediatric drug hypersensitivity reactions (DHRs) so children can receive the best available therapy and reduce unnecessary avoidances. This review aims to present the current approach to the diagnosis and management of DHRs in children.

Epidemiology

Adverse drug reactions (ADRs) are defined by the World Health Organization as any noxious and unintended response to a drug that occurs at standard doses used for diagnosis (example, radio contrast media), prevention (example, antibiotic prophylaxis), or treatment (example, chemotherapeutic agents) [9]. It is estimated that 2% of ADRs require hospitalization. In addition, ADRs impact approximately 1.5% of non-hospitalized children and 9.5% of hospitalized children [10, 11]. Drugs are the suspected trigger for 1.6–7% of all anaphylactic reactions in Canadian children [12]. Deaths due to drug-induced anaphylaxis has been estimated to be 0.04 per million, making drugs the most common cause of fatal anaphylaxis in children in the United States (US) [13]. Deaths due to severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), erythema multiforme major, acute generalized erythematous pustulosis (AGEP), and exfoliative dermatitis, occur at higher rates, approximately 2.9% in children [14•]. Hypersensitivity reactions can be seen with all drugs. In

This article is part of the Topical Collection on *Anaphylaxis and Drug Allergy*

✉ Ana Dioun Broyles
ana.broyles@childrens.harvard.edu

[1] Division of Allergy, Pulmonary and Critical Care, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA

[2] Division of Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN 37232, USA

[3] Division of Allergy and Immunology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave., Boston, MA 02115, USA

children, the common culprit drugs are antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) as well as antiepileptic drugs (AEDs) and the most frequent finding of a drug reaction is rash [15••, 16].

Classification

ADRs are largely divided into predictable (type A) and unpredictable (type B) reactions. Predictable reactions can occur in any person that takes the medication. They are due to on-target or off-target pharmacological effects of the drug. These account for approximately 80% of ADRs. Unpredictable reactions, or DHRs, include drug intolerance, drug allergy, and non-IgE-mediated mast cell degranulation and generally occur in susceptible persons only [17]. DHRs are heterogeneous and encompass complex mechanisms, many of which are still unknown, demonstrating the intricate interaction between a drug and the immune system [18•]. Drug allergy is a specific term for a reaction that has evidence of an immunologic-mediated response [6••, 7••]. Immunologic-mediated responses have been classified using Gell-Coombs classifications: Type I immediate IgE-mediated hypersensitivity, type II cytotoxic or antibody-dependent hypersensitivity, type III immune complex–mediated hypersensitivity, type IV delayed T cell–mediated hypersensitivity. However, this mechanism-based classification system does not account for all clinical reactions [19].

Additional ways to group reactions include timing of the reaction, major organ involvement, class of medication, proposed mechanism, or a newer approach based on precision medicine categorizing the reactions by phenotype, endotype, and biomarkers [6••, 19–22]. The broadest group is based on the timing of symptoms. Immediate DHRs occur within minutes to 6 h of exposure to a drug and generally present with symptoms due to mast cell degranulation [7••, 22]. Nonimmediate DHRs occur within hours to days after exposure to a drug with symptoms ranging from single organ involvement (example, nephritis), isolated symptoms (example, maculopapular eruption), or severe reaction with or without systemic organ involvement (example, SJS/TEN) [22–25].

There are available guidelines for drug hypersensitivity based mainly on adult data [6••, 7••, 16, 26, 27], a single pediatric-focused guideline [15••], and vaccines [28••, 29••].

History and Physical Examination

An organized, detailed history with review of available medical records and objective data obtained during the acute reaction is critical in guiding the diagnostic evaluation of DHRs [6••, 9, 30]. The following questions should be considered in obtaining the history:

- *What is the exact name of the medication of concern?* For example, amoxicillin, penicillin, amoxicillin-clavulanate, or in the case of cephalosporins, the specific cephalosporin the patient has a history of reaction to.
- *Were there any medications given concurrently?* Co-administered medications may alter the presentation or may be the culprit medication. For example, patients on opiates may develop pruritus which may be interpreted as a reaction to a concomitantly administered medication. If multiple medications were given, a clear timeline utilizing a medication administration record, if available, is beneficial to determine the culprit drug. It is also important to ask about supplements, herbs, and/or over-the-counter medications that were taken during the same time period or concurrently. For children, medications may also be co-administered with food, drink, or other substances to improve palatability and may confound identification of the culprit allergen.
- *Has this medication been taken before?* For most IgE-mediated reactions and other reactions with an immunologic basis, prior sensitization must occur. In infants and young children, the possibility of exposure to medications while in utero or breastfeeding should be considered.
- *What was the reason for taking the medication?* Infections, especially viruses, are a common cause of rash which may be mistaken for a drug reaction. In many situations, symptoms are rarely reproducible and allergy is seldom confirmed [31]. This demonstrates the complex interaction of childhood infections, the immune system, and drug exposure that may predispose them to nonimmediate reactions, such as maculopapular eruptions with infectious mononucleosis and amoxicillin which is known to not be a true drug allergy [31–33].
- *What were the presenting symptoms and signs of the reaction? Are medical records available for review of vital signs or physical exam findings at the time of a reaction?* If a rash was present, it is important to obtain specific details about the appearance and distribution of the rash. As technology has advanced, it has become easier for patients, caregivers, and healthcare providers to photograph cutaneous findings for future reference which can aid in evaluation. Also, it is crucial to know about any findings suggesting a severe reaction, such as mucosal involvement, fever, airway compromise, abnormal laboratory studies suggestive organ involvement, or hypotension.
- *When did the symptoms develop in relation to starting or stopping the medication? How long did the symptoms last?* A clear timeline can help in determining the underlying mechanism, SCAR diagnosis, or if symptoms were potentially unrelated to the medication.

- *What was the timing of the symptoms in relation to the actual administration of a specific dose of the medication?* Urticaria that develops within 1 h after administration of a medication would be more concerning for an immediate-type drug allergy versus urticaria that occurs hours after ingestion of the medication. The underlying mechanism determines the timing of the reaction and this will guide additional diagnostic steps.
- *Was the medication stopped after developing symptoms? If so, did the symptoms improve? If not stopped, did the symptoms progress or recur with any subsequent doses?*
- *What treatment, medications, or interventions were used for symptoms?* Was the reaction severe enough to require overnight hospitalization or intensive care? This information may provide clues to the underlying mechanism and/or severity of the reaction.
- *What diagnostic testing, if any, was done during the acute reaction? If anaphylaxis occurred, was a serum tryptase obtained? Were laboratory studies done to assess organ involvement? Was a skin biopsy completed?*
- *Have any similar or related medications been taken since the reaction? If so, did the child develop any symptoms?* Amoxicillin/penicillin allergy could be delabeled if the child subsequently tolerated amoxicillin-clavulanate after a previous reaction to amoxicillin.
- *Does the child have any other medical conditions or similar symptoms in the absence of taking medications?* Symptoms and signs associated with conditions such as asthma, chronic idiopathic urticaria, and eczema can be mistaken for drug reactions. In addition, cystic fibrosis, human immunodeficiency (HIV), asthma, and chronic idiopathic urticaria increase the likelihood of drug reactions [6••, 33–36].

A thorough physical examination during the reaction is vital with particular attention to cutaneous findings. Important aspects include a clear description of the type of eruption/lesion, distribution, body surface area involved, mucosal involvement, lymphadenopathy, hepatomegaly, splenomegaly, respiratory involvement, joint effusions/swelling, or angioedema. Synthesizing the clinical information to classify the reaction can direct diagnostic testing and management [2••, 6, 15••, 16].

Diagnostic Evaluation

General Tests

Diagnostic evaluation to determine the presence and classification of a DHR performed during the reaction can range depending on the clinical picture. Measurement of serum tryptase, ideally within 4 h of anaphylaxis, can be a useful diagnostic tool. For nonimmediate reactions, the following laboratory studies can be helpful to assess organ involvement and/or evaluate other causes of symptoms: complete blood count with differential (eosinophilia), renal function, transaminases, complement components, urinalysis, urine eosinophils, erythrocyte sedimentation rate, C-reactive protein, and nuclear and cytoplasmic autoantibodies. Skin or tissue biopsy can provide valuable diagnostic information [6••].

Drug Hypersensitivity-Specific Tests

Skin Testing: Immediate Reactions

Skin prick and intradermal tests are useful and safe diagnostic tools for suspected IgE-mediated reactions in children and are ideally completed at least 4–6 weeks after the suspected reaction, to reduce the chance of false-negative results [6••, 7••, 15••, 30, 37]. Penicillin skin testing is the only validated drug skin testing available and is performed with the following reagents: major determinant (PREPEN), penicillin G, and depending on the history, ampicillin. Minor determinants and intravenous amoxicillin are commercially available in Europe for testing but not in the US [6••, 38].

Non-irritating concentrations have been reported for other medications including other antibiotics, chemotherapeutics, corticosteroids, local anesthetics, monoclonal antibodies, and neuromuscular blocking agents [6••, 39, 40, 41•, 42, 43]. In these cases, a negative skin test does not effectively exclude the possibility of an IgE-mediated reaction, but in conjunction with the history, aids in decision-making for graded challenge versus desensitization [6••]. If there is concern for vaccine hypersensitivity, skin testing with the vaccine itself as well as potential allergenic components is recommended [28••, 29••, 44]. Awareness of the limitations of skin testing is important in interpretation of results [15••].

Skin Testing: Delayed Reactions

Skin testing has variable sensitivity and predictive values with more variability when utilized for nonimmediate DHRs [45]. Delayed reading of intradermal skin testing, interpreted after 48–72 h, has been reported as potentially useful and safe in evaluation of T cell–mediated reactions in children [6••]. They can aid in the diagnosis of mild nonimmediate reactions and are also being used in selected cases of SCARs, though the potential benefits versus potential risks of such testing should be carefully considered [16, 32, 41•].

Patch testing with drug allergens is also used in diagnosis of nonimmediate reactions, in particular, contact dermatitis or SCARs [15••, 46]. However, these tests are limited by poor sensitivity and lack of positive control and variable predictive values in addition to limited experience in the pediatric population [45, 47]. If patch testing is positive, a biopsy of the site

may provide additional diagnostic information if the specific SCAR cannot be determined by history alone [6••, 48].

In Vitro Studies: Immediate Reactions

In the US, detection of drug-specific IgE by immunoassay is available for penicillins only [6••]. However, sensitivity is much lower than skin testing and a negative test result should always be followed by skin testing if feasible and/or not contraindicated [48]. Drug-specific IgE levels can decrease with time; therefore, testing should ideally be performed within 3 years of a reaction [48].

Basophil activation test (BAT) detects the presence of CD63 and CD203c on basophils that have been activated by an allergen. Sensitivity and specificity ranges for various drugs. These tests have not been standardized and are not commercially available in the US but could be helpful in the future in determining risk for immediate reaction [6••, 48].

In Vitro Studies: Delayed Reactions

Lymphocyte transformation test (LTT), a research test, has the potential to be a supplementary diagnostic tool for nonimmediate reactions. However, it has not yet been optimized and there are few studies in children [45, 49–51]. This flow cytometry test measures the amount of T cell stimulation due to suspect drugs.

Enzyme-linked immunosorbent spot (ELISpot) assays which quantify cytokines, B or T cell products may be helpful in diagnosis of nonimmediate reactions, specifically identifying culprit drugs in SCARs [45, 50]. Cell markers and cytokine release can be measured using flow cytometry or enzyme-linked immunosorbent assay (ELISA). A small study in children with maculopapular eruptions (MPE), SJS, or DRESS showed promise in identification of culprit drugs in the acute phase [50]. Currently, these tests are reserved for research.

Genetic testing, specifically HLA genotyping, is currently recommended for evaluating the risk of abacavir, allopurinol, and carbamazepine hypersensitivity prior to starting the medications [7••, 20, 52•]. Other genetic variants are being explored to evaluate risk for DHRs or to explain mechanisms of DHRs [22, 53].

Re-Exposure to Medications

The decision to re-expose a child to a suspected medication is dependent on the clinical history, diagnostic testing (if applicable), and availability of alternative medications. Drug challenge is generally used for diagnostic purposes. Drug desensitization is used for therapeutic re-administration allowing a patient to receive a necessary medication. Re-administration with a slowed rate and pre-medication is an additional option for monoclonal antibodies and other medications depending on the underlying mechanism (example, vancomycin-induced non-IgE mediated mast cell degranulation producing red man syndrome) [42, 54, 55]. Re-exposure to a medication is contraindicated with a history consistent with severe, life-threatening immunocytotoxic reactions such as vasculitic syndromes, hepatitis, nephritis, hemolytic anemia and SCARS such as SJS/TEN, erythema multiforme major, AGEP, and exfoliative dermatitis [6••].

Drug Challenge

Drug challenge is the gold standard for diagnosis of drug hypersensitivity. It may be used for children whose history suggests a mild non-IgE-mediated reaction that is unlikely to be related to the drug, and it is often performed after negative skin testing. Drug challenges are administered in a monitored clinical setting with cautious introduction of a medication in order to reduce the risk of reaction. It does not modify the patient's immunologic response to a drug [6••]. Challenges can be done with all forms of medications: oral, subcutaneous (example, local anesthetics), or intramuscular (example, vaccines) [6••]. There are a variety of protocols including single, graded, or multiple day challenges to assess for DHR and predict tolerance. There are no standardized drug challenge protocols and the duration is debatable [15••, 56•, 57•, 58•]. Generally, the starting dose is 10% of the total age/weight appropriate treatment dose followed by 30–60 min of observation, then the remaining 90% followed by 60–120 min of observation. Alternatively, the initial dose is 1/100th of the total age appropriate dose and slowly increased, usually in tenfold increments and in fewer than 5 steps [59]. Protocols are longer for NSAIDs [60•] and local anesthetics [6••]. If a drug challenge is tolerated, the patient is cleared to take that medication in the future without any subsequent challenges or desensitization.

Skin testing is usually done prior to drug challenge but this can be limited by lack of standardization, knowledge of non-irritating concentrations, or poor predictive values, with the exception of penicillins. Recently, several studies have used risk stratification and omitted skin testing prior to drug challenge in children, specifically for β-lactams (Table 1) [15••, 56•, 61–63, 64••, 65, 66•]. This is an appealing option as parents/caregivers may perceive skin testing as uncomfortable and defer evaluation. European pediatric guidelines suggest oral challenge without prior testing for mild nonimmediate eruptions [16]. Vyles et al. explored the utility of a pediatric allergy questionnaire in a pediatric emergency room to determine risk for hypersensitivity upon re-administration of penicillin [67•]. If a child was deemed low risk, he/she underwent three step evaluation (skin prick, intradermal testing, and drug challenge) with all children tolerating the drug challenge

Table 1 Recent publications with β-lactam antibiotic drug challenges without utilization of skin test results to guide decision for re-exposure

Publication	Number of patients	Age of subjects	Drug challenge	Summary of results
Mill et al. [56•]	818	1–10 years	2 step graded challenge with amoxicillin	Subjects with immediate and nonimmediate cutaneous findings, except Stevens-Johnson syndrome or toxic epidermolysis, were included in this study. In the initial oral challenge, 770 (94.1%) tolerated, 17 (2.1%) developed mild immediate hives, and 31 (3.8%) developed nonimmediate symptoms Subjects who developed immediate symptoms during the oral challenge underwent skin testing 2–3 months later. Only 1/17 (8.5%) had a positive skin test This study reported amoxicillin-graded challenge had a specificity of 100%, negative predictive value of 89.1%, and positive predictive value of 100% for immediate and nonimmediate cutaneous reactions
Vezir et al. [63]	119	2–7.5 years	5 dose graded followed by 5-day prolonged challenge with penicillin, aminopenicillin, or cephalosporin	All subjects had mild nonimmediate reactions to β-lactam antibiotics at least 1 month prior to study. The majority, 115 (96.6%), tolerated the oral challenge. Only 4 subjects developed symptoms: 1 (0.08%) had immediate urticaria and 3 (2.5%) had nonimmediate urticaria with only 1 occurring after the 1st day This study demonstrated a confirmation rate of 3.4% based on oral challenge alone for mild nonimmediate reactions
Iammatteo et al. [64••]	155	7 years and older included, mean age 51 years	Placebo followed by 2 dose graded challenge with amoxicillin	Subjects with non-life-threatening reactions to amoxicillin underwent initial oral challenge, 120 (77.4%) tolerated, 5 (2.6%) had a mild reaction, 16 (10%) developed non-allergic symptoms to placebo, and 15 (9.6%) developed non-allergic symptoms to amoxicillin Allergy determined by oral challenge was 2.6% which was lower than allergy diagnosis by positive skin testing 14/170 (8.2%) in a prior study at the same institution (adults) This study concluded that oral challenge without prior skin testing is safe and results in a lower confirmation of allergy
Confino-Cohen et al. [65]	642 (435 children)	0.1–83 years, mean 19.9 years	2 dose graded challenge followed by 4-day prolonged challenge with penicillin or amoxicillin	Subjects with a history of nonimmediate reaction to β-lactam antibiotics underwent skin testing but were invited to participate regardless of skin testing results A total of 617 subjects underwent oral challenge, of which, 30 (4.9%) had positive skin testing and 197 (31.9%) had equivocal skin testing results. In the 9 patients who had immediate reactions during oral challenge, 1 had a positive skin test and 1 had an equivocal skin test. Of the 54 who developed delayed reactions, 1 had a positive skin test and 20 had equivocal skin tests This study demonstrates low predictive value and correlation with skin test results in nonimmediate reactions and recommends proceeding directly to oral challenge in non-life-threatening nonimmediate reactions

Table 1 (continued)

Publication	Number of patients	Age of subjects	Drug challenge	Summary of results
Ibáñez et al. [66]	732	Mean age 5.5 years ± 3.8 years (SD)	3 dose graded challenge with culprit drug. If index reaction was nonimmediate, subjects completed prolonged challenge matching the number of days that triggered the reaction	Subjects with a history of non-severe reaction to β-lactam antibiotics were included and underwent skin testing but completed oral challenge regardless of skin test results. Allergy was confirmed in 35 (4.8%) subjects, of those, 6 (0.8%) developed immediate mild cutaneous or gastrointestinal symptoms and 29 (3.9%) developed nonimmediate symptoms. Of the subjects with positive oral challenges, only 3 (8.6%) had positive skin tests. Of the subjects with negative oral challenges, 10 (14%) had positive skin tests This study concludes that skin testing is of low value and the safety profile of an oral challenge is acceptable for patients with non-severe reactions

[68•]. Iammatteo et al. had a lower percentage of children retaining an allergy label when they compared drug challenge results with skin testing results, suggesting that skin testing contributes to overdiagnosis [64••]. It is recommended that evaluation be completed by an allergy specialist due to the complexity of evaluation and management of drug hypersensitivity in children.

Drug Desensitization/Temporary Induction of Tolerance

Desensitization or temporary induction of tolerance can allow a patient with a confirmed or highly suspected DHR to safely receive the medication by incremental increases in the amount of medication, usually over several hours until the goal dosage is reached. It is typically used and most effective for IgE-mediated DHRs. It can also be utilized when no validated skin test is available; skin testing cannot be performed due to urgent need for the medication or there is a high suspicion for an immediate clinical reaction based on history. Desensitization alters a patient's response to a medication by inducing temporary tolerance which allows them to receive the medication safely [69]. The mechanism is not fully understood but may be due to changes in calcium flux and altered internalization of antigen/IgE/FcεR1 complexes on mast cell and basophils [21, 70]. Patients can safely receive subsequent doses during the treatment course, but tolerance will generally be lost if they have not been exposed to the medication for more than 2 half-lives in which case repeat desensitization is required [6••, 30]. This procedure should be performed in a monitored clinical setting with staff trained in performing drug desensitization that understand the importance of timely, accurate dosing and close monitoring for development of any symptoms suggestive of a DHR.

Protocols vary based on medication, goal dose, and indication for desensitization. Usually, the starting dose is 1/10,000 of the final goal dose with doubling of incremental doses every 15 min until reaching the cumulative target dose [21, 71, 72]. However, some protocols may last for days or dosages increase after hours [59, 73]. Many adult protocols have been adapted for pediatrics adjusting for smaller dosages, volumes, and infusion rates with weight-based dosing [74•, 75].

Desensitization may also be utilized in benign non-IgE-mediated DHRs like fixed drug eruption (FDE), though protocols may differ from desensitizations designed for IgE-mediated DHRs and are not standardized [21, 25]. A proposed mechanism for temporary induction of tolerance in FDE is a shift from CD8+ T cells to CD25+ CD4+ T cells which have regulatory and immune-suppressive functions in the epidermis of the FDE [76]. Desensitization is contraindicated for type II, type III, and severe type IV SCARs such as DRESS, SJS/TEN, AGEP, and exfoliative dermatitis [6••, 21, 59].

There are many reports of successful desensitizations in pediatric patients including β-lactam antibiotics [77, 78], non-β-lactam antibiotics [73, 78], monoclonal antibodies [42, 55, 74•, 79], chemotherapeutics [77], methotrexate [80], rifampin [81], von Willebrand factor [82], antiepileptics [83–85], factor IX in hemophilia B [69], and enzymes used in lysosomal storage diseases [86, 87]. Pediatric desensitization protocols for NSAIDs have not been described and, if necessary, would require appropriate modification to adult protocols using weight-based dosing [60•].

Specific Drugs

Antibiotics

Antibiotics are the most common drug allergy label with β-lactams being the most widely studied in children [67•]. Other frequent culprit antibiotics are macrolides, sulfonamides, glycopeptides, and quinolones, but there are reports of DHRs to all antibiotics [15••, 88, 89]. The most common finding is rash, often maculopapular exanthema or delayed urticaria. Nonimmediate reactions are more challenging to diagnose and rash could be the result of the underlying infectious disease rather than the drug [27, 32, 90]. β-Lactam antibiotics are a group of drugs that share a β-lactam ring and understanding of cross-reactivity can prevent avoidance of whole classes of medications. Both penicillins and cephalosporins have a side chain, R1, arising from the β-lactam ring. In addition, cephalosporins can have another side chain, R2. β-Lactam cross-reactivity is primarily due to R1 and less frequently the R2 side chains rather than the β-lactam ring (Fig. 1). Avoidance of medications with shared R1 and R2 side chains should be recommended for drug hypersensitivity reactions. It is also important to evaluate medications with similar R1 and R2 side chains in order to confirm safety of these medications. This allows for patients to safely receive β-lactams that have different side chains [17, 91, 92•]. Cross-reactivity within other classes of antibiotics is not known [45, 93, 94]. Diagnostic evaluation is described previously. Accurate evaluation of antibiotic DHR is an essential part of antibiotic stewardship efforts as delabeling a patient with drug allergy can reduce unnecessary avoidances. This is especially pertinent in children as antibiotic allergy labels can remain lifelong with potential negative consequences [3–8].

Nonsteroidal Anti-inflammatory Drugs

Many NSAIDs are readily available over the counter and frequently used in children of all ages. They rank second in reported allergies with prevalence in children of approximately 0.3% but more frequent in asthmatics and patients with chronic urticaria [35, 36]. Other risk factors include family history of atopy, clinical reactions to multiple NSAIDs, and reaction within the first hour [95]. Confirmation rate of NSAID hypersensitivity is greater than β-lactams, ranging from 21 to 68% [95]. There is a spectrum of presentations, but primary symptoms are typically cutaneous or respiratory (Fig. 2) [35, 36, 60•, 95, 96]. Proper phenotyping and classification is important to guide evaluation and management. Patients may be select responders with DHR to a single NSAID or cross-intolerant with DHRs to multiple NSAIDs, which ranges from 25 to 83% in children [35, 60•, 95]. Cross-intolerance is determined by an initial drug challenge to acetyl salicylic acid, if not the culprit drug, which has been reported as a safe procedure in children [97•, 98].

Antiepileptic Drugs

Antiepileptic drugs are the third most common cause of DHRs in children. This is significant as AEDs are often implicated in benign cutaneous eruptions and SCARs, but immediate hypersensitivity can occur as well [84]. There can be cross-reactivity among the aromatics. Risk factors include history of taking multiple anticonvulsants, aromatic AEDs, and older age [46]. In patients with concern for AED hypersensitivity, a thorough history is of utmost importance since diagnostic testing is limited and re-exposure can have deleterious effects.

Monoclonal Antibodies

Monoclonal antibodies are prone to provoking hypersensitivity through various mechanisms: IgE-mediated, cytokine release syndrome, IgG antibody-mediated cytotoxicity, and IgG antibody inhibition of action [42, 79, 99]. Determination of the mechanism through history and skin testing, in addition to consideration of severity, will guide the decision for re-exposure with slowed rate, graded challenge, desensitization, or avoidance [42, 55]. It is important to note that based on a case series of pediatric patients, higher rates of infusion that are typically tolerated in the adults undergoing desensitization to monoclonal antibodies may not be tolerated in the pediatric population and it is optimal to consider a maximum rate based on the weight of the child [74•].

Vaccines

Vaccination is a vital part of preventative medicine in childhood. True DHRs to vaccines are rare, with the reported rate of 1 in 50,000 to 1 in 1,000,000 [29••] and the rate of anaphylaxis of 1.31 in 1,000,000 [100]. Hypersensitivity is rarely due to the microbial element but rather a component of the vaccine. Familiarity with components can guide evaluation and potential avoidance of other vaccines [28••, 29••, 100, 101]. Two unique populations include children with egg allergy and alpha-gal allergy. The recommendations from the Center for

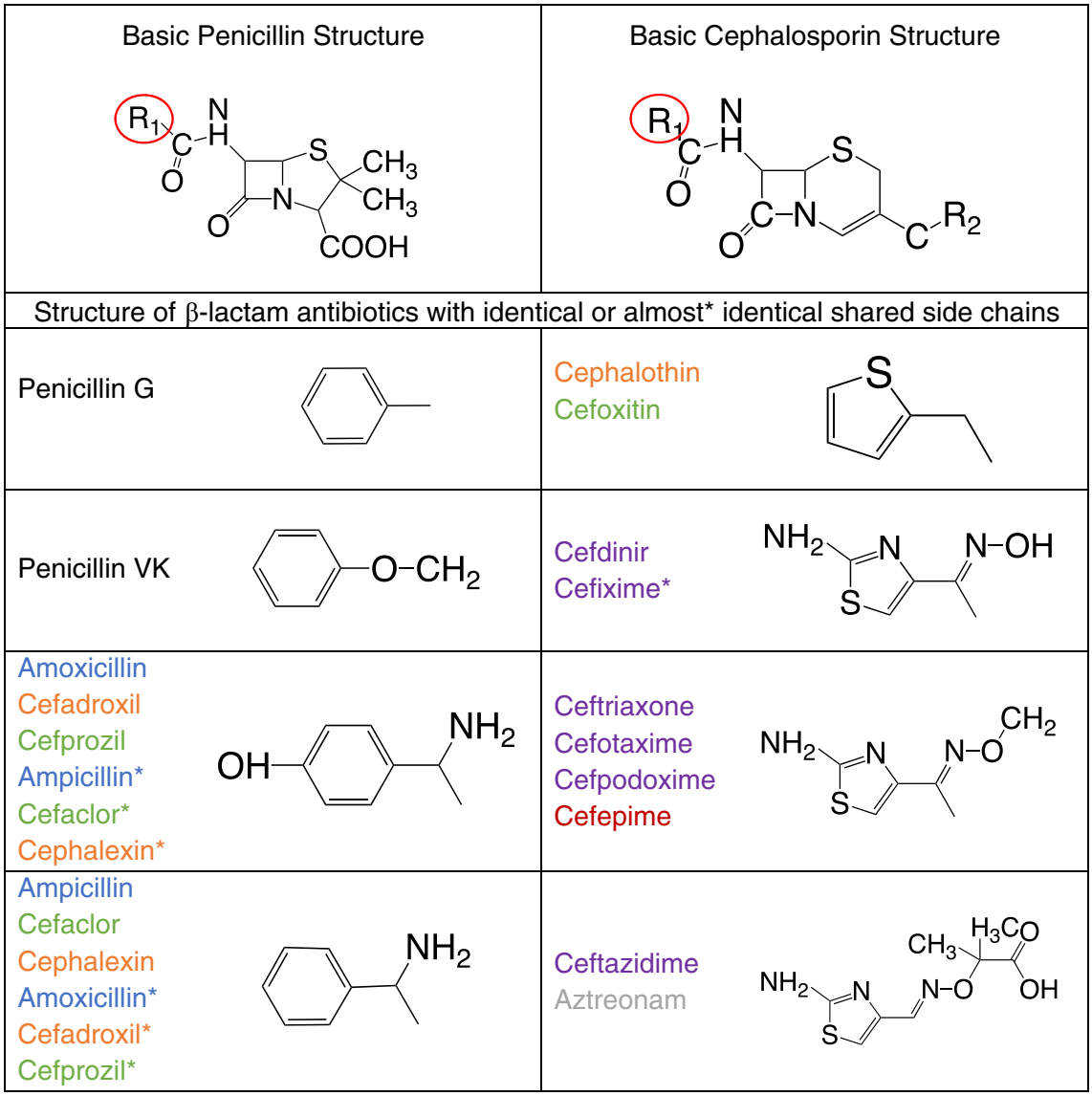

Fig. 1 Penicillin and cephalosporin basic structures and R1 side chains. Legend of β-lactam antibiotics: Penicillins: penicillin G, penicillin VK; (blue) aminopenicillins: ampicillin, amoxicillin; (orange) 1st-generation cephalosporins: cefadroxil, cephalexin, cephalothin; (green) 2nd-generation cephalosporins: cefprozil, cefaclor, cefoxitin; (purple) 3rd-generation cephalosporins: cefdinir, cefixime, ceftriaxone, cefotaxime, cefpodoxime, ceftazidime; (red) 4th-generation cephalosporins: cefepime; (yellow) 5th-generation cephalosporins: none in table; (gray) monobactam: aztreonam

Disease Control (CDC) state that it is safe for egg-allergic persons to receive any influenza vaccine [100, 102]. There is a subset of patients with alpha-gal allergy that will react to the porcine or bovine gelatin contained in measles, mumps and rubella (MMR), and varicella zoster vaccines [100, 103]. Additional aspects of diagnostic evaluation may include measurement of protective titers and gelatin-specific IgE [28••, 29••, 54, 101]. Desensitization has been used for successful vaccination with MMR, yellow fever, diphtheria, tetanus, and pertussis for children with positive skin tests [104–106]. All reactions to vaccines should be reported through the Vaccine Adverse Event Reporting System (VEARS).

Special Populations

Patients with cystic fibrosis, malignancy, or immunocompromising conditions are at elevated risk for developing DHRs. This is likely related to increased exposure to medications as well as alterations in the immune system and its response to drugs. In cystic fibrosis, colonization with pseudomonas appears to be an additional risk factor suggesting immune modification by microbes [34]. Hypersensitivity to all chemotherapy medications have been reported with various mechanisms [6••]. Much of the data surrounding HIV and DHRs is in adults, but it can be postulated that this is similar in pediatric patients [6••, 107, 108]. Given the increased

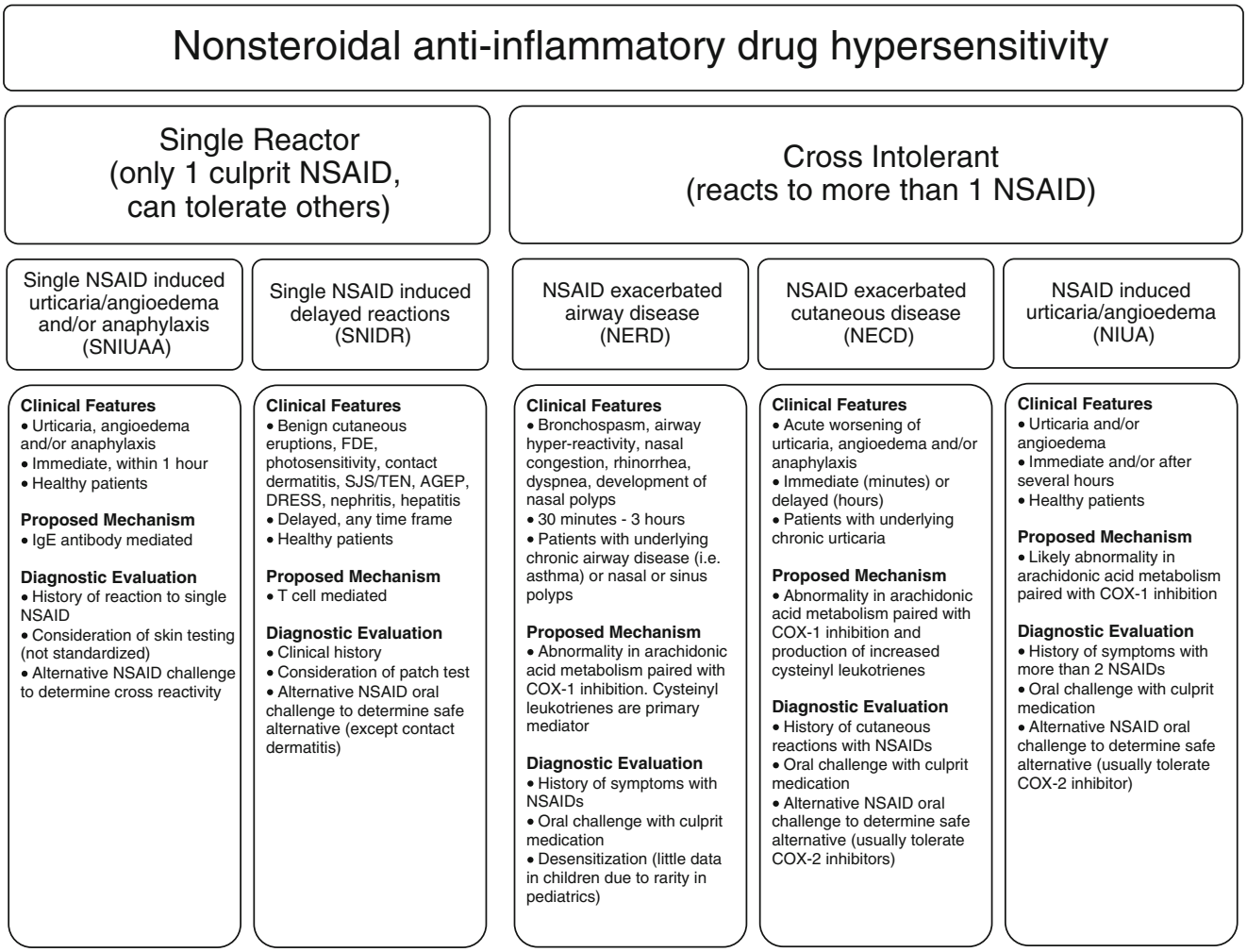

Fig. 2 Classification, clinical features, and diagnostic evaluation of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. NSAID, non-steroidal anti-inflammatory drug; SNIUAA, single nonsteroidal anti-inflammatory drug-induced urticaria/angioedema, and/or anaphylaxis; SNIDR, single nonsteroidal anti-inflammatory drug-induced delayed reactions; FDE, fixed drug eruption; SJS/TEN, Stevens-Johnson Syndrome/toxic epidermal necrolysis; AGEP, acute generalized erythematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; NERD, nonsteroidal anti-inflammatory drug exacerbated airway disease; COX-1, cyclooxygenase 1; NECD, nonsteroidal anti-inflammatory drug exacerbated cutaneous disease; COX-2, cyclooxygenase 2; NIUA nonsteroidal anti-inflammatory drug-induced urticaria/angioedema

likelihood of requiring medications, an accurate diagnosis of DHR is paramount in these populations.

Conclusions

Drug hypersensitivity is a growing problem in pediatrics and requires accurate diagnosis through history, physical examination, skin testing, and possible laboratory evaluation. Such thorough diagnostic evaluation is crucial in the management of DHRs and decision-making for re-exposure by drug challenge or desensitization, if indicated. It is possible that in the future, questionnaires and algorithms will serve as decision support tools to guide clinicians with determining the risk of re-exposure to a β-lactam antibiotic by performing direct drug challenge. Additional studies specific to the pediatric population would aid in optimizing the diagnostic evaluation and management of children with DHRs.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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