

Drug Allergy in Pediatric Patients

CME EDUCATIONAL OBJECTIVES

1. Identify features that delineate common pathologic types of drug allergies.
2. Discuss the epidemiology of drug allergy in children.
3. Define the diagnostic evaluation necessary to confirm the diagnosis of drug allergy in children.

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Drug and device allergies present with a spectrum of deleterious signs and symptoms with varied pathologies that are associated with either the therapeutic dose of a medication or the appropriate use of a particular medical device.¹⁻³ Discerning the features that are worrisome for serious pathology related to a drug allergy represents an essential skill required for pediatric health care professionals, given the high frequency of drug reactions occurring in office and hospital settings.

In children, drug allergy has been reported with a relatively high frequency, occurring in up to 8.7% of pediatric patients in varied hospital settings⁴⁻⁶ and between 1% to 8% of visits in the outpatient pediatric offices.^{6,7} The evaluation of a drug reaction requires an in-depth, time-oriented history, appropriate skin testing and challenges, and sometimes laboratory testing to support the diagnosis and to guide treatment of the immediate event while aiding in the selection of future drugs or devices.

COMMON TYPES OF ALLERGY Immediate Hypersensitivity

The best known and understood of the drug/device reactions is the acute type I hypersensitivity reaction, which is IgE-mediated. These reactions are expected to occur within 1 hour of drug administration or during an infusion.

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The symptoms often include urticaria with or without angioedema; upper and lower airway involvement with rhinitis, shortness of breath, and wheezing; gastrointestinal symptoms, such as nausea, vomiting, or diarrhea; and sometimes cardiovascular collapse. The most common IgE-mediated reactions result from treatment with penicillin-related drugs and other antibiotics.

As part of the history, the context in which the allergic reaction is occurring is also important. For example, a rash occurring while being treated with amoxicillin during infectious mononucleosis may not represent an IgE sensitization to the beta-lactam but rather a reaction to viral proteins. With appropriate evaluation, amoxicillin can usually be re-administered in the future without complication.⁸

After a detailed history evaluating the onset of the drug reaction, skin

prick, and/or serum specific IgE testing may be performed to determine the likelihood of a future reaction to the beta-lactam or other antibiotics in question.⁹ Ultimately, the diagnosis of drug allergy can only be made formally with re-exposure to the offending drug under controlled conditions and is typically only performed when a great deal of therapeutic value has been assigned to use of the drug of interest.

Further, if the drug remains critical for patient care, it may still be administered using drug desensitization methodologies and close monitoring while hospitalized. Alternatively, if a different drug provides adequate therapy, it can be used in place of the original drug associated with the adverse drug reaction (see Table, page 202).

Latex is the primary clinical material associated with IgE-mediated allergies. Similar to antibiotic drug allergy, latex

can often be evaluated with specialized testing for evidence of serum-specific IgE antibodies.^{10,11} Fortunately, pediatric care facilities have made efforts to eliminate latex from their facilities. These efforts have been successful in reducing problems with latex allergies in patients with spina bifida.

Immediate hypersensitivity reactions can also be non-IgE-mediated, representing a direct action of the drug on mast cells, resulting in acute histamine release. Perhaps the best known example is red-man syndrome, which is often noted in pediatric hospital settings and can be due to the rate of infusion of vancomycin.

Red-man syndrome can be treated by prolonging the duration of the infusion and dividing the dose of the drug and the use of histamine blockade,^{12,13} because most of the reactions are dose and/or rate dependent. Similar acute

TABLE.

Alternatives to Drugs Associated with Adverse Reactions

Drug Associated with Adverse Reaction	Alternatives
Beta-lactams (penicillin, amoxicillin, etc.)	Trimethoprim and sulfamethoxazole (TMP/SMX); clarithromycin; azithromycin
ACE inhibitors (lisinopril, enalapril, etc.)	Losartan; valsartan; hydrochlorothiazide; metoprolol
Salmeterol/fluticasone diskus (lactose-containing, potentially containing milk protein)	Nebulized budesonide and evaluation by allergist (non-lactose containing medications)

Source: Abonia JP.

reactions can be seen for opioids and radiocontrast media in which an IgE mechanism cannot be identified. Pre-treatment with histamine blockade and steroids has been shown to be very effective at blocking these reactions.^{3,14}

Delayed Hypersensitivity

Beyond the immediate reactions occurring within 1 hour of exposure, there are delayed-type reactions that can occur several hours after exposure and appear to be primarily T-cell mediated. The dermal reactions seen in these cases can be non-life-threatening, such as erythema multiforme minor and maculopapular and urticarial reactions, or can be quite devastating within the spectrum of blistering disorders of the skin, such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). These more severe and potentially fatal syndromes are associated with fever and injury to the mucosal surfaces.

Further, TEN is associated with generalized and often painful erythema and diffuse epidermal detachment.¹⁵⁻¹⁷ For moderate and severe reactions, removal of the drug in question remains the primary therapy. For the more severe drug reactions, treatment with either high-dose intravenous immune globulin and/or steroids can be considered, although their use remains controversial for SJS and TEN.³ Once a patient has presented with these severe reactions, drug avoidance is mandatory (if identified) and no desensitization is recommended.

Drug Reaction/Rash with Eosinophilia and Systemic Syndrome

Drug reaction/rash with eosinophilia and systemic syndrome (DRESS) represents a syndrome noted in response to medication often given for a prolonged duration that is associated with fever, rash, peripheral eosinophilia, internal organ injury, and the presence of atypical lymphocytes.¹⁸

DRESS was originally described as occurring with anti-convulsant medications.¹⁹ Lymphadenopathy is typically present, and there is often hepatic involvement with evidence of elevated liver transaminases and other organ injury.^{19,20} This drug reaction often occurs late (about 3 weeks after drug is first administered). The course can be prolonged, even after the discontinuation of the drug.²¹ Of concern for this syndrome is the significant mortality that has been reported in up to 10% in one case series.²¹

Unusual Drug Reactions

Recently, there has been a switch to dry powder inhalers that contain lactose for the treatment of asthma. To date, there has been only a single report describing a young child with a history of severe milk allergy who was being treated with salmeterol/fluticasone diskus. After tolerating its use for several months, he received a new lot of his

inhaler and began to have clearly documented bronchospasm associated with the use of the new inhaler.²² As a single-reported anecdote, if a patient with milk allergy has sudden onset of worsening asthma associated with an inhaler, consideration should be given to milk proteins in the inhaler as a cause.

There are also non-immune mediated drug reactions associated with specific drugs. For example, angiotensin converting enzyme (ACE) inhibitors have been clearly associated with coughing in up to 20% of adult patients and angioedema in up to 1% of adults patients being treated for hypertension.³ As there are now a large number of children being treated for hypertension or diabetes with ACE inhibitors, drug-related symptoms should be considered in the differential in a child with new onset cough, although this problem was not common (less than 1%) in a small pediatric population treated with an ACE inhibitor.^{23,24}

Alternative drugs for the affected population would include an angiotensin receptor blocker that is less associated with drug-related cough (see Table). A similar difference in the frequency of drug sensitivity to aspirin exists, which is well described in adults, but not commonly found in children. This further reminds us that findings in adults cannot be applied to the pediatric population.

Allergy Testing/Drug Desensitization

Drug/device allergy testing is driven by the history obtained and is typically used to support the suspected diagnosis and to provide guidance regarding the future use of the drug or device in question. Of the available tests, the most useful clinically to make a diagnosis of IgE-mediated hypersensitivity is skin testing for penicillin and other beta-lactams. A negative skin test for penicillin carries with it a high-negative predictive value, suggesting that the patient will be able to tolerate penicillin,²⁵ although a controlled challenge is mandatory after a negative skin test.

Similar information is not as readily available for other beta-lactams; however, skin testing remains a useful tool to provide clinical guidance for these and other drugs. In certain cases, blood may be drawn to measure the serum specific IgE-antibodies for penicillin if skin testing is not readily available or cannot be performed.^{26,27}

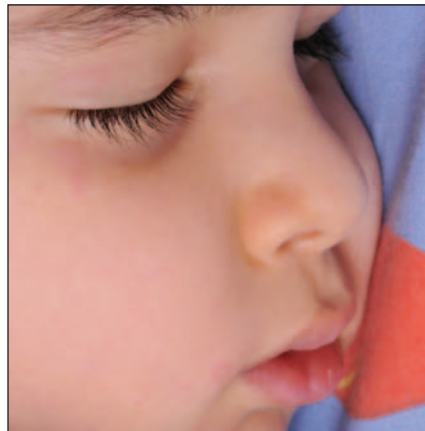
After an acute anaphylactic episode, tryptase levels obtained within 30 minutes to 2 hours of the event can demonstrate clear evidence of systemic mast cell degranulation, which is associated with more severe reactions. Other testing can include the use of CBC with differential for evidence of eosinophilia and other hematologic findings, as well as the use of skin biopsies for non-characteristic rashes.

In the event of a life-threatening infection or other severe clinical condition that requires the use of a medication responsible for a type I IgE and non-IgE hypersensitivity reaction, drug desensitization may be considered under the supervision of a clinical allergist while the patient is hospitalized or in an outpatient allergy clinic.²⁸ Although desensitization can be achieved for most drugs in this manner, those drugs that result in non-anaphylactic drug reactions associated with severe dermal le-

sions (ie, SJS, TEN) or systemic organ involvement (ie, DRESS) cannot undergo a desensitization process.

Reporting a Drug Allergy

A common clinical scenario is that of a toddler who is prescribed a penicillin to treat a febrile illness such as an ear infection. A few days into treatment, the parent of the child calls the office to



The pediatrician needs to be aware of common adverse reactions to commonly used antibiotics.

report a pruritic rash. The physician or nurse by phone recommends discontinuation of the penicillin, administering diphenhydramine, and changing to a new antibiotic. The child's medical record is flagged as "allergic to penicillin." The child's rash improves within 1 or 2 days and diphenhydramine is discontinued. A day or two later the parent calls the office again because the rash has persisted, and the second antibiotic is discontinued; the same management is repeated, and the child's medical record is flagged with a second antibiotic allergy.

There are several alternate approaches to this management. An examination of the child while the rash is present may provide valuable diag-

nostic information. A picture of the rash taken with a cell phone or digital camera is a powerful diagnostic tool to differentiate hives from non-urticarial rashes. The rash most commonly described by the parents as "hives" or "welts," on exam may be more of a maculopapular rash more consistent with a viral syndrome.

The reason for prescribing the antibiotic may have resolved (eg, the otitis media or the febrile illness was viral and required no further antibiotics). Once a drug rash is diagnosed, a more prudent management is to discontinue the antibiotic, treat the rash symptoms and not to start another antibiotic if at all possible. If still indicated, a second antibiotic can be started after complete resolution of the first rash.

Alternatively, the exam may reveal additional signs that the parents may not have identified (eg, joint swelling or mucus membrane involvement that could be signs of a more serious drug allergy reaction, Kawasaki disease, or another problem).

The pediatrician needs to be aware of common adverse reactions to commonly used antibiotics. For example, penicillin is commonly associated with a maculopapular rash, while cefaclor and cefdinir are more commonly associated with a serum sickness-like reaction with blotchy red rash, arthralgias, or arthritis. Although serum sickness-like reactions are traditionally thought of as occurring 2 weeks after the drug is administered, our clinical experience shows that they occur commonly during the administration of the drug if the drug is given for a prolonged course (more than 7 to 10 days).

The pediatrician's clinical acumen and vigilance in examining children with reported drug reactions and documenting the clinical exam is the most important factor that later aids the allergist in the work up of a patient with a past history of an antibiotic allergy.

CONCLUSION

Drug and device allergy represent a range of unexpected reactions to clinical therapy. The primary evaluation and therapy includes a detailed history and exam followed by discontinuation of the suspected agent. The more serious reactions may require emergent treatment for anaphylaxis or hospitalization with treatment with either immunosuppressive or immunomodulatory agents.

If a drug is critically required for a patient's therapy, then consideration can be given for the use of desensitization procedures. However, if an alternative drug can be used in place of the drug associated with the adverse drug reaction, it should be strongly considered. Only a first-line drug should be considered for desensitization, which will induce temporary tolerance of the required drug.

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