Cutaneous Drug Reactions in Children

P
ediatric patients are exposed to a variety of medications during their childhood. From over-the-counter (OTC) medications, the latest oral antibiotic or antiepileptic, to vitamins and supplements, medications are a significant part of pediatric care. Ad-

Brandon D. Newell, MD; and Kimberly A. Horii, MD

EDUCATIONAL OBJECTIVES

1. Describe some of the most common types of cutaneous drug reactions encountered in children.
2. Review the more severe adverse drug eruptions.
3. Discuss the most appropriate therapy for common drug eruptions.

Brandon Newell, MD, is Assistant Professor; and Kimberly A. Horii, MD, is Associate Professor, University of Missouri-Kansas City, Children’s Mercy Hospitals and Clinics.

Address correspondence to: Brandon D. Newell, MD, of Missouri-Kansas City, Children’s Mercy Hospitals and Clinics, 2401 Gilham Road, Kansas City, MO 64108; fax: 816-983-6710; or e-mail: bnewell@cmh.edu.

Dr. Newell and Dr. Horii have disclosed no relevant financial relationships.

doi: 10.3928/00904481-20100922-10
Additionally, some medications labeled for one diagnosis now have wider indications. For example, anticonvulsants are prescribed not just for seizure disorders but also for behavioral modification in certain patients. Identifying reactions to medications can sometimes be simple, but can also be elusive. Reactions range from a morbilliform eruption to Stevens-Johnson syndrome/toxic epidermal necrolysis or even a drug hypersensitivity reaction (DHS).

There are a number of ways to classify or approach reactions to medications. To simplify the array of reaction patterns, we begin by addressing some of the most common types of cutaneous drug reactions, then review the more severe adverse drug eruptions. Stevens-Johnson syndrome and toxic epidermal necrolysis are covered separately in this issue. Each type of drug eruption is covered in detail, grouped by the type of drug eruption itself. The included tables offer a brief overview of the characteristics (from symptoms to diagnosis) of each drug eruption (see Table 1), as well as the responsible medications and potential treatment options (see Table 2, page 620).

### EXANTHEMATOUS OR MORBILLIFORM DRUG ERUPTIONS

Drug-induced exanthematous or morbilliform eruptions (see Figure 1, page 621) typically occur about 1 to 2 weeks...
after the introduction of the offending medication. This particular type of cutaneous eruption represents one of the most common reactions that children experience to a medication and is characterized by diffuse, small, pink-to-red macules and papules that may coalesce into patches and plaques over the entire body. Lesions can be quite numerous and progressive. Morbilliform drug eruptions may be confused with a scarlatiniform rash but can be differentiated by history and a rapid strep test/throat bacterial culture. Morbilliform drug reactions are most commonly seen in patients receiving ampicillin (or another penicillin). Additionally, this reaction is often exacerbated by concomitant viral infections, the most notable of which are the exanthematous reactions that develop when ampicillin is given during an Epstein-Barr virus infection. Morbilliform drug eruptions can also be mistaken for a viral exanthem, allergic contact dermatitis, or even an irritant contact dermatitis. Lesions are typically symmetric in nature, which helps distinguish this from other conditions, such as asymmetric periflexural exanthem of childhood (also known as unilateral laterothoracic exanthem, which is a benign transient eruption of probable viral etiology).

Treatment of exanthematous or morbilliform drug eruptions is primarily supportive and requires prompt recognition and removal of the offending medication. Oral antihistamines, such as diphenhydramine or hydroxyzine, may help decrease any associated pruritus. Liberal application of bland emollients, such as white petrolatum or a moisturizing lotion, may provide some comfort. Low-potency topical steroids can be useful in providing symptomatic relief. Systemic steroids are usually not indicated for this type of reaction. Resolution of the cutaneous eruption can take several days or more after discontinuation of the offending drug and may leave temporary postinflammatory hyperpigmentation and/or hypopigmentation, depending on the patient’s skin type.

**URTICARIAL DRUG ERUPTIONS**

Urticarial drug eruptions (see Figure 2, page 621) may present initially with solitary or multiple lesions, which can range in size from a few millimeters to several centimeters. Urticarial lesions can vary from small, pink macules and papules to large, red edematous wheals. Urticarial drug eruptions can also be annular, pseudoannular (partial rings), or polycyclic (resembling a group of conjoined rings). The varied appearance of the skin lesions is classic for an urticarial presentation. They are typically symmetric in nature, which helps distinguish this from other conditions, such as asymmetric periflexural exanthem of childhood (also known as unilateral laterothoracic exanthem, which is a benign transient eruption of probable viral etiology).

**TABLE 2. Overview of Common Medication Reactions in Children**

<table>
<thead>
<tr>
<th>Type of Drug Reaction</th>
<th>Implicated Medications/Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exanthematous or morbilliform drug eruptions</td>
<td>Penicillins</td>
<td>Discontinue offending drug; supportive care</td>
</tr>
<tr>
<td>Urticarial reactions</td>
<td>Nonsteroidal anti-inflammatory medications, sulfonamides, phenytoin, morphine, codeine, penicillins, and cephalosporins</td>
<td>Discontinue offending drug; supportive care; oral antihistamines</td>
</tr>
<tr>
<td>Serum sickness-like reactions (SSLR)</td>
<td>Cefaclor, griseofulvin, cefuroxime, bupropion, and minocycline</td>
<td>Discontinue offending drug; supportive care; oral antihistamines; systemic steroids only in severe cases</td>
</tr>
<tr>
<td>Fixed drug eruption (FDE)</td>
<td>Sulfonamides, acetaminophen, ibuprofen, loratadine, pseudoprophedrine, phenolphthalein, barbiturates, penicillin, tetracycline, erythromycin, quinine, metronidazole, potassium iodide, and tartarazine</td>
<td>Discontinue offending drug; supportive care; reintroduction causes recurrence of the eruption (in the same site(s))</td>
</tr>
<tr>
<td>Acute generalized exanthematous pustulosis (AGEP)</td>
<td>Beta-lactam antibiotics, vaccinations, or viral illness</td>
<td>Discontinue offending drug; supportive care; oral antihistamines</td>
</tr>
<tr>
<td>Drug hypersensitivity reactions (DHS); Stevens-Johnson syndrome; toxic epidermal necrolysis (TEN)</td>
<td>Sulfonamides, phenytoin, carbamazepine, phenobarbital, primidone, lamotrigine, minocycline, tetracycline, doxycycline, dapsone, and allopurinol.</td>
<td>Discontinue offending drug; avoid reintroduction of drug or cross-reacting drug; supportive care; oral antihistamines; laboratory investigation; (CBC, liver profile, metabolic profile, etc.); systemic steroids may be needed; thyroid evaluation 2-3 months after initial reaction</td>
</tr>
</tbody>
</table>
drug eruption (differentiating it from the monomorphic appearance of target lesions seen with erythema multiforme). Urticarial lesions are blanchable and lack the central, dusky zone of the target lesions of erythema multiforme. Lesions are generally pruritic in nature, although some children who are unable to complain verbally of itching may be irritable or complain of discomfort. Chronologically, urticarial lesions are dynamic with the lesions developing, fading, and reforming in different areas over the course of 24 hours. Parents can circle or trace several lesions with a ballpoint pen and have the lesions re-examined after 24 hours to prove their transitory nature. Children may also experience transient edema of their hands and feet in association with an urticarial eruption without true arthritis. Facial or periorbital swelling may also occur concomitantly.

Nonsteroidal anti-inflammatory medications, sulfonamides, phenytoin, morphine, codeine, penicillins, and cephalosporins are among the most common causes of urticarial drug eruptions. Supportive care and discontinuation of the possible offending medication are necessary if an urticarial drug eruption is suspected. Oral antihistamines are usually helpful in reducing the associated pruritus and appearance of lesions.

SERUM SICKNESS-LIKE REACTIONS

True serum sickness reactions are allergic reactions that occur in response to certain medications (historically, horse or rabbit antiserum were the classic two offending agents). They occur as a result of the formation of circulating immune complexes that trigger complement activation leading to immune complex deposition and widespread inflammation. In contrast, serum sickness-like reactions (SSLR) occur in children, although they occur infrequently. Although cefaclor is a well-known culprit for causing SSLR, many other medications have been reported to cause SSLR, including griseofulvin, cefuroxime, bupropion, and minocycline. SSLR typically occur 7 to 21 days after exposure to the offending medication.

SSLR are characterized by urticarial-like annular patches and plaques, often with dull purple or dusky centers. Patients can have fever, lymphadenopathy, arthritis, and even joint swelling. Unlike true serum sickness reactions, renal involvement is not seen in SSLR. Once the offending agent is removed, patients readily improve. Oral antihistamines are commonly used for associated pruritus. In severe reactions, particularly those with significant arthralgias, treatment with systemic corticosteroids may be helpful.

FIXED DRUG ERUPTIONS

Fixed drug eruptions (FDE) are cutaneous reactions that occur and recur in the same specific area(s). FDE initially take 7 to 14 days to develop, can last for several days to weeks, and often resolve, leaving postinflammatory hypopigmentation or hyperpigmentation, which can last for months. Once the initial FDE resolves, reintroduction of the offending medication causes the reaction in the same location within a few days. Lesions are typically round to oval, erythematous patches or plaques with a central violaceous/dusky hue (see Figure 3).
Lesions vary in size from a few millimeters to several centimeters. FDEs occur anywhere on the body but tend to localize to the face, genital/buttock region, and upper trunk. Lesions are commonly mistaken for urticaria, erythema multiforme, or even cellulitis. Common medications known to cause FDEs include sulfa-containing medications, acetaminophen, ibuprofen, loratadine, pseudoephedrine (found in common cold medications), phenolphthalein (previously found in older OTC laxatives), barbiturates, penicillin, tetracycline, erythromycin, quinine, metronidazole, potassium iodide, and tartrazine, a synthetic yellow food coloring (yellow no. 5).

Treatment of a FDE involves removal and future avoidance of the offending medication.

**ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS**

Acute generalized exanthematous pustulosis (AGEP) is a distinct drug eruption that typically presents with sudden onset erythroderma (full body erythema), fever, and tiny 1- to 2-mm sterile pustules (see Figure 4). Not to be confused with folliculitis, these pustules are sterile and not follicular-based. Pruritus is common. AGEP can be mistaken for a toxin-mediated reaction to an underlying infection, allergic contact dermatitis, or miliaria. Although AGEP is more commonly seen in adults, it can occur in children. Causes of AGEP include a variety of drugs, including beta-lactam antibiotics, vaccinations, or a viral illness. Treatment includes recognition of and removal of the offending agent. AGEP usually resolves spontaneously within a few days to 2 weeks after removal of the drug. Supportive treatment is recommended, including antihistamines and bland emollients.

**DRUG HYPERSENSITIVITY REACTIONS**

Drug hypersensitivity reactions (DHS) are a distinct form of adverse drug reaction, which presents with fever, rash, lymphadenopathy, and potentially severe underlying organ system involvement. The risk of a DHS ranges from 1/10,000 to 1/1,000. DHS have been referred to in the literature as drug reaction with eosinophilia and systemic symptoms (DRESS), anticonvulsant hypersensitivity syndrome (AChS), and pseudolymphoma syndrome. DHS occurs 2 to 8 weeks after the introduction of the offending drug, even after medication discontinuation due to the formation of reactive metabolites. Fever and fatigue are among the first symptoms, followed by cervical lymphadenopathy (see Figure 5) and/or pharyngitis.

Recognition of DHS can be challenging. DHS can be confused for an upper respiratory tract infection, staphylococcal scalded skin syndrome, measles, SSLR, drug-induced lupus, Kawasaki disease, viral exanthem, streptococcal pharyngitis, or even mononucleosis. If the patient is receiving multiple medications, it may be difficult to delineate the exact causative medication. Also, be-
cause hypersensitivity reactions can occur weeks after the introduction of the medication, DHS may not be considered as a possible etiology for the patient’s symptoms.

The cutaneous eruption associated with a DHS is typically symmetric and often begins cranially and progresses caudally. Facial edema and extremity edema are characteristic features. Skin lesions vary and can be an exanthematous or morbilliform eruption (see Figure 6), target-shaped lesions sometimes with dusky centers (see Figure 7, and Figure 8, page 624), diffuse erythroderma, and even diffuse vesicles and bullae with skin sloughing. Late in the clinical course, fine desquamation of the affected areas can occur.16,17

Additional clinical findings may include conjunctivitis, ranging from mild (this represents the majority) to severe involvement. Oral mucosal involvement can range from mild erythema to erosions and bullae. Genital and anal mucosa may even be affected.16,17

There are a number of medications known to cause DHS, the most common being sulfonamides and anticonvulsant medications. Aromatic anticonvulsants such as phenytoin, phenobarbital, and carbamazepine are of particular concern because they are all metabolized by the cytochrome P450 isoenzymes and can cross-react. If a patient develops DHS to one of these medications, then the others should be avoided.18

Primidone, which is metabolized to phenobarbital, can also cause DHS. Although not an aromatic anticonvulsant, lamotrigine has been reported to cause DHS.19 Additional medications known to cause DHS include minocycline, tetracycline, doxycycline, dapsone, and allopurinol.16,17,20 Many reports exist suggesting that reactivation of human herpes virus 6 may have a role in the development of DHS.16,20

Once the hypersensitivity reaction begins, reactive lymphocytes can affect organ systems, most commonly the hematologic, hepatic, and renal systems. Affected patients commonly experience an atypical lymphocytosis, peripheral eosinophilia, leukocytosis, leukopenia, anemia, and thrombocytosis.15-17,21

Hepatic alterations are among the most commonly found abnormalities due to associated hepatitis and have been associated with a high mortality. Patients can experience elevated transaminases, prolongation of their prothrombin time and/or partial thromboplastin time, hypoaalbuminemia, or hyperbilirubinemia.16,17,22 Nephritis can occur, causing elevations of the BUN and creatinine levels, and hematuria and proteinuria may be noted on urinalysis.
Pneumonitis and pleural effusions/edema can occur in the setting of DHS and may be worsened by hypoalbuminemia. Pancreatitis results in elevated lipase and amylase levels. Rarely, myositis occurs, leading to an elevated CPK (creatinine phosphokinase). Not all organ systems are affected immediately after the DHS reaction occurs. Autoimmune thyroiditis has been noted to occur 2 to 3 months after development of DHS.

Patients who are suspected of having DHS, even with few systemic symptoms, warrant a complete laboratory evaluation to assess for visceral organ system involvement and may require hospitalization. Screening laboratory studies should include a CBC, metabolic profile, which includes BUN and creatinine, liver function testing (including transaminases), PT, PTT, total protein and albumin, and urinalysis. If the patient shows any signs of respiratory symptoms, a chest X-ray may be warranted. Other laboratory monitoring, based on symptoms and index of suspicion, may include a lipase, amylase, and CPK. Repeat testing and close monitoring is recommended, as severity of involvement can change even if the cutaneous symptoms improve. Thyroid function testing and thyroid auto-antibodies should be obtained 2 to 3 months after DHS, particularly if the causative agent was a sulfonamide or anticonvulsant medication.

Treatment of DHS involves removal and future avoidance of the offending medication, including avoidance of potentially cross-reacting medications. Patients should be counseled on the various names of similar medications and instructed to always ask their pharmacist to aid them if necessary. Medication alert bracelets (see Figure 9) are of particular help, especially in younger children who may inadvertently be re-exposed to a high risk or cross-reacting medication.

Symptomatic treatment of associated pruritus can be helped with oral antihistamines and low to midpotency topical steroids. If any ocular signs or symptoms are suspected, an ophthalmology evaluation is recommended. Patients experiencing visceral involvement, most notably hepatic involvement, may require systemic corticosteroids (at doses of 1 to 2 mg/kg/day) that can be tapered slowly over several weeks to months. Premature termination of systemic steroids can result in flare of the visceral and even cutaneous involvement. In cases of DHS to anticonvulsant medications, benzodiazepines can be used acutely for seizure management. Alternative anticonvulsant medications that have been used include gabapentin, valproic acid, and topiramate.

CONCLUSION

Adverse drug reactions in pediatric patients can vary from mild, transient cutaneous eruptions to severe drug hypersensitivity reactions with multi-organ system involvement that can have potentially devastating consequences. An adverse drug reaction should be suspected in any child who develops a new cutaneous eruption after introduction of a medication. Proper education of parent and patient and avoidance of future exposure are critical in preventing recurrences.

REFERENCES


