

# Cutaneous Reactions to Drugs in Children

Alissa R. Segal, PharmD, PhC<sup>a</sup>, Kevin M. Doherty, PharmD<sup>b</sup>, John Leggott, MD<sup>c</sup>, Barrett Zlotoff, MD<sup>d</sup>

<sup>a</sup>Department of Pharmacy Practice, Massachusetts College of Pharmacy & Health Sciences, Boston, Massachusetts; <sup>b</sup>Texoma Medical Center, Denison, Texas;

<sup>c</sup>Department of Family and Community Medicine, School-Based Health Centers, and <sup>d</sup>Department of Dermatology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

Cutaneous eruptions are a commonly reported adverse drug reaction. Cutaneous adverse drug reactions in the pediatric population have a significant impact on patients' current and future care options. A patient's recollection of having a "rash" when they took a medication as a child is a frequent reason for not prescribing a particular treatment. The quick detection and treatment of cutaneous adverse drug reactions, plus identification of the causative agent, are essential for preventing the progression of the reaction, preventing additional exposures, and ensuring the appropriate use of medications for both the current condition and others as the patient ages. The purpose of this review is to discuss a reasonable approach to recognition and initial management of cutaneous adverse drug reactions in children.

[www.pediatrics.org/cgi/doi/10.1542/peds.2005-2321](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-2321)

doi:10.1542/peds.2005-2321

### Key Words

adverse drug reactions, children, dermatology, cutaneous reactions

### Abbreviations

CADR—cutaneous adverse drug reaction  
ADR—adverse drug reaction  
FDA—Food and Drug Administration  
ECE—exanthematous cutaneous eruption  
EM—erythema multiforme  
FDE—fixed drug eruption  
NSAID—nonsteroidal antiinflammatory drug  
SSLR—serum sickness–like reaction  
DHS—drug hypersensitivity syndrome  
SJS—Stevens-Johnson syndrome  
TEN—toxic epidermal necrolysis

Accepted for publication Mar 3, 2007

Address correspondence to Alissa R. Segal, PharmD, PhC, Massachusetts College of Pharmacy & Health Sciences, Department of Pharmacy Practice, 179 Longwood Ave, Boston, MA 02115-5896. E-mail: [alissa.segal@mcphs.edu](mailto:alissa.segal@mcphs.edu)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics

CUTANEOUS ADVERSE DRUG reactions (CADRs) are a commonly reported type of adverse drug reaction (ADR).<sup>1</sup> A large study of hospitalized adults found that ADRs occurred at a rate of 5.5% per drug exposure, of which 2.2% were CADRs.<sup>2,3</sup> Likewise, CADRs account for the majority of ADRs in hospitalized children.<sup>4</sup> Outpatient studies of CADRs estimate that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CADR.<sup>5-8</sup> Because viral exanthems are very common in children, clinicians are often faced with a diagnostic dilemma when children who are taking medications present with a rash. This review is designed to provide clinical pearls of wisdom regarding common skin reactions in children to enable providers to distinguish between reactions and infections.

Although CADRs account for a substantial proportion of reported ADRs, they are rarely considered serious.<sup>4-7</sup> Nevertheless, CADRs are conspicuous and concerning to patients and their families and account for a substantial proportion of clinic visits.<sup>9</sup> Providers who are confronted with mild eruptions often have limited time to conduct an exhaustive investigation into the cause. Furthermore, the pressing concerns of a child's family may motivate the clinician to label the child as "allergic" to a drug and discontinue its use.<sup>10</sup>

This approach has potential implications for a child's future care. A retrospective review in 1 hospital and clinic found that 80% of drug allergies attributed to  $\beta$ -lactam and sulfa antibiotics and only 30% of the cases that were related to opioid analgesics were found to be allergic in nature on the basis of the clinical description of the event.<sup>11</sup> In children, misattribution of a cutaneous reaction to a drug might be even more common. A study of pediatric patients who were referred to an allergy clinic found that antibiotic-associated CADRs were reproducible with a drug rechallenge in only 8 of 62 patients.<sup>12</sup> Another study confirmed true drug allergies in only 4% of the patients referred to their clinic.<sup>13</sup> Because a known "allergy" is a contraindication for prescribing an associated drug, and possibly all drugs in the same class, a hasty diagnosis can unnecessarily limit therapeutic options, which can increase the risk of using medications that are more toxic, less effective, and more costly.<sup>14</sup> In addition, an allergy label will remain with a child over a large proportion of his or her life. As adults, many patients will have difficulty recalling the details of an early cutaneous reaction, which leaves one to assume that the allergy was serious and the patient cannot use that particular drug. Therefore, good management of a CADR requires an efficient method of estimating the probability of a drug association, determining the likelihood of a relapse with drug rechallenge, and communicating this assessment to patients and their families.

The goal of this article is to outline and discuss a reasonable approach to recognize and initially manage

CADRs in children. Topics include historical information that is useful in assessing the probability of a CADR, terminology associated with cutaneous reactions, mechanisms of CADRs, common CADR patterns in children, and drugs that are commonly associated with those patterns. Serious CADRs will be discussed with an emphasis on early recognition. Finally, strategies for managing the majority of acute CADRs will be presented.

### ESTABLISHING ETIOLOGY

Causality assessments based on history have proven to be a worthy method of estimating the probability of drug culpability of an ADR.<sup>15-20</sup> Causality assessments often use questions that weigh the biological plausibility of a drug causing a reaction.<sup>1</sup> Gathering such information is akin to taking a history of the behavior of a particular drug in the population treated with it. The Naranjo et al<sup>18</sup> assessment classifies a reaction to a drug as "definite" when (1) there is a reasonable temporal sequence after a drug level had been established in body fluids, (2) followed by a recognized response to the suspected drug, (3) confirmed by improvement after drug withdrawal, and (4) the reaction reappeared on reexposure. A "probable" reaction, in contrast, follows conditions 1 and 3 and cannot be explained by the patient's condition but was not confirmed by a rechallenge of the drug. A "possible" reaction follows condition 1 but involves an unpredictable reaction that could be explained by the patient's condition. Unless a rechallenge is performed, the vast majority of CADRs in children can only, at best, be considered as possibly associated to a drug.

Clinicians will often consult tertiary drug references or product labeling to associate drugs and adverse effects. There are some limitations to these information sources, particularly for children. Information for product labeling is drawn initially from preclinical trials. Children do not participate in these trials; therefore, potential differences in their physiology that could contribute to adverse drug effects are not measured. Many CADRs in children occur in conjunction with viral or autoimmune disorders.<sup>21</sup> Subjects in preclinical trials are usually in good health or have a single disease condition for which a medicine is being tested. With regard to cutaneous reaction patterns, various reaction patterns are associated with different drugs, and yet all are reported in product-labeling monographs as 1 category: "rashes."

### DESCRIPTION OF THE CUTANEOUS REACTION

Whether submitting an ADR report to the Food and Drug Administration (FDA) or documenting the reaction in a medical chart, the best approach is to describe the morphology, configuration, and course of the reaction with detailed and apt terminology.<sup>17</sup> The mere use of the term "rash" is nonspecific and inadequate.<sup>16,22</sup> For example, exanthems are skin eruptions that often accompany viral and streptococcal bacterial

diseases.<sup>22</sup> Types of exanthems include morbilliform eruptions that resemble measles and scarlatiniform eruptions that resemble eruptions that accompany scarlet fever.<sup>23</sup>

A CADR not accompanied by a viral or bacterial illness can be referred to as either a macular-papular eruption or, if it resembles measles, morbilliform.<sup>10</sup> Drugs can produce many variants of macular-papular eruptions.<sup>22</sup> Adequate descriptions of such reactions would include distribution, morphology, configuration, and progression. Exanthems or macular-papular eruptions are commonly erythematous macules and papules from 1 to 5 mm in diameter that may coalesce into patches and plaques, respectively. Eruptions begin on the face, neck, or upper torso and progress bilaterally and symmetrically toward the limbs. Exanthems are often accompanied by pruritis and mild fever. As the eruption resolves, the skin usually desquamates and occasionally leaves areas of hyperpigmentation or hypopigmentation.<sup>24</sup> A good description of a cutaneous reaction will include as many of these details as possible. Table 1 includes definitions for terminology that is suitable for a descriptive report of a cutaneous reaction.

#### CLASSIFICATION OF CADRS

In general, ADRs are divided into 2 categories.<sup>27-29</sup> Type A reactions that are related to the known pharmacologic effects of a drug are dose dependant, predictable, mild to moderate in severity, and account for the majority of ADRs. Type A reactions can usually be recognized as common adverse effects reported on drug labeling (Table 2). Conversely, type B reactions are not related to the known pharmacologic effects of a drug and are dose independent (even occurring at miniscule doses), unpredictable, idiosyncratic, often serious, and account for a smaller proportion of ADRs.<sup>27,29</sup> Such reactions have been categorized as immunologic (true-allergy) hypersensitivity reactions, pseudoallergic, and idiosyncratic drug reactions (Table 2).<sup>10,27</sup> CADRs in children are often type B ADRs and can be unpredictable, mechanistically complex, and difficult to identify.

#### FIVE COMMON CADR PATTERNS IN CHILDREN

At least 29 drug-related cutaneous reaction patterns have been identified.<sup>22</sup> The 5 reactions described below are common in the pediatric population.<sup>21,30</sup>

##### Exanthematous Drug Eruptions

Exanthematous cutaneous eruptions (ECEs) are the most common kind of CADR in children<sup>21,22</sup> (Fig 1). The eruption usually occurs abruptly during the first 5 to 14 days of treatment.<sup>22</sup> Five percent to 10% of patients treated with ampicillin develop an ECE. This frequency increases substantially during a viral infection; as many as 95% of patients who are infected with the Epstein-

Barr virus and treated with ampicillin develop an ECE<sup>22</sup> (Tables 3 and 4 and Fig 2).

Management of an exanthematous cutaneous reaction includes discontinuation of the likely culprit and supportive care. Initially, oral antihistamines or corticosteroids can be helpful in alleviating more-severe symptoms.<sup>21</sup> Second-generation H<sub>1</sub> blockers are associated with fewer sedative effects when compared with first-generation H<sub>1</sub> blockers.<sup>32-34</sup> Cetirizine, a second-generation agent, comes in a liquid formulation and can be used in children as young as 6 months.<sup>35</sup>

As the eruption resolves, desquamation often occurs. If pruritis is bothersome, low- to midpotency topical steroids (hydrocortisone, triamcinolone) and liberal bland, nonsensitizing emollients (petroleum jelly) can provide some relief. Topical diphenhydramine and lidocaine-containing products have often been associated with contact dermatitis and, therefore, are not recommended.<sup>21</sup> In children with medium to darker skin tones, a postinflammatory hypopigmentation or hyperpigmentation can occur. This effect resolves over a period of months to years, and sun avoidance or protection should be recommended.

##### Urticaria

It is estimated that 15% to 25% of all persons experience urticaria during their lifetime.<sup>36,37</sup> Because acute urticaria in children is usually mild, self-limiting, and short lived, it is difficult to estimate the prevalence in the general pediatric population<sup>38</sup> (Table 5). Studies have demonstrated that acute urticaria, unlike chronic urticaria, results from immunoglobulin E-mediated or drug-induced mast cell degranulation.<sup>39</sup> These eruptions occur in a generalized fashion but tend to occur more frequently in areas covered by clothing. The plaques, also known as wheals, hives, or welts, result from localized edema of the dermis. They appear as white, edematous zones that vary in size between a few millimeters to centimeters, are surrounded by erythema, and are often accompanied by pruritus<sup>40</sup> (Figs 3 and 4). This is in contrast to erythema multiforme (EM), which includes a third central dusky blue-hued zone. Angioedema involves subcutaneous or submucosal tissues and can be an early symptom of impending anaphylaxis. Urticaria is usually transient, although between 9% and 32% of cases presenting to clinics or hospitals are chronic (lasting >6 weeks).<sup>41-44</sup> Our discussion here will be restricted to acute urticaria.

Two recent prospective investigations found that infections were associated with the majority of episodes of acute urticaria. Sackesen et al<sup>44</sup> found that 58% of patients (aged 1-19 years) with an acute, single urticarial episode had an infection; 25% of these patients had positive urine-culture results (all *Escherichia coli*), 13% were positive for *Chlamydia pneumoniae*, 8% had positive *Streptococcus* throat cultures, and 4% had positive *Mycobacterium*

**TABLE 1** Definitions of Select Terms Used to Describe Cutaneous Eruptions

Term	Definition
Acneiform lesions	The primary lesions of acne or acneiform eruptions include comedones (whiteheads or blackheads) along with erythematous papules and pustules.
Alopecia	"Absence or loss of hair, esp. of the head."
Anaphylaxis	"Anaphylactic reaction is an acute Type I hypersensitivity/allergic reaction of the immediate type, associated with mast cell degranulation with histamine release and characterized by 1 or more of the following symptoms: Skin: itching, erythema, urticaria, angioedema. Respiratory system: laryngeal edema or spasm, bronchospasm. Cardiovascular system: hypotension. In addition, the following symptoms may occur: Gastrointestinal system: abdominal cramps, diarrhea Neuropsychological: anxiety, agitation, loss of consciousness"
Angioedema	"Angioedema is an eruption similar in mechanism to urticaria but with larger, edematous peri-oral and facial plaques involving dermal, subcutaneous or submucosal tissues. Discrete wheals or "hives" are not a feature of angioedema. It is sometimes associated with severe respiratory distress due to edema of the upper airways."
Aphthous stomatitis	"An erosion (loss of epidermis) or ulceration (loss of epidermis and part of epidermis) of the skin or mucous membranes (eg, of the oral mucosa, conjunctiva, or genitalia). It is usually less than 0.5 cm in diameter. If it persists for longer than 2 weeks, it should be biopsied to rule out cancer. SYN: aphthous stomatitis; canker sore."
Bullous eruptions Dermatitis (eczema)	A bullae is similar in morphology to a vesicle but, by definition, is >5 mm in surface area. "Preamble The terms dermatitis and eczema are synonyms although the term eczema is more often used to describe the dermatitis observed in atopic dermatitis. The term contact dermatitis is used to describe dermatitis produced by direct contact with a causative agent, which may be an irritant or an allergen. Definition Dermatitis or eczema is a superficial skin inflammation. In the acute phase it is characterized by vesicles, redness, edema, oozing and crusting. In the chronic phase there is marked scaling and thickening of the epidermis. There is usually itching."
Enanthema Erythroderma (exfoliative dermatitis)	"eruption occurring on a mucosal secreting surface, such as on the mouth or vagina." "Preamble The terms erythroderma and exfoliative dermatitis are used synonymously. Preference should be given to exfoliative dermatitis in an acute setting and erythroderma in a chronic setting. Definition Exfoliative dermatitis is a potentially life-threatening inflammation of the entire skin, characterized by redness of the skin and scaling, with acute onset."
Lichenoid (lichen-planus-like) eruptions	"Lichenoid drug eruption is a subacute violaceous papular/plaque eruption. Wickham's striae and polygonal configuration, characteristic of lichen planus, are not present, and the eruption does not always involve the sites most likely to be affected by lichen planus (ie, the flexures of the wrists and ankles, and the oral mucosa)."
Exanthems	"Exanthems, commonly resembling viral rashes . . . Describes as macular-papular or morbilliform eruptions, these flat, barely raised erythematous patches, from one to several millimeters in diameter, are usually bilateral and symmetrical."
Macules	"A flat spot on the skin less than 0.5 cm in diameter whose color may be lighter or darker than the surrounding skin. Some common examples are freckles, petechiae, and vitiligo."
Papules Patch Petechia	"A small bump less than 0.5 cm in diameter that rises above the surface of the neighboring skin." Similar to a macule but >0.5 cm. "A small round flat dark-red spot caused by bleeding into the skin or beneath a mucous membrane." Petechiae, in contrast to telangectasia or other vascular lesions, do not blanch when pressed on, because the hemoglobin is not contained within the vessel.
Plaque	Raised, palpable lesion on the skin that is >0.5 cm in diameter.
Pruritus	"[A] tingling or faintly burning skin sensation that prompts a person to rub or scratch."
Pustule	"Pustular eruption is a sudden, symmetrical and widespread eruption consisting of numerous small sterile pustules arising on edematous painful erythema. Lesions usually predominate in intertriginous areas. Fever, leukocytosis and eosinophilia are usual."
Urticaria	"Urticaria is a skin eruption consisting of multiple transient wheals, usually with itching."
Vesicle	Blister filled with clear fluid <0.5 cm in diameter.
Wheal	A papule or plaque of dermal edema.

Source: refs 16 and 23–26. Quotations are from ref 23.

*plasma pneumoniae* or *Helicobacter pylori* serologies. Seven patients with positive urine-culture results had not been treated with antibiotics, and the urticarial symptoms resolved with treatment. Of the remaining reactions, 5% were associated with drugs (aspirin) and 3% with foods.

Mortureux et al<sup>41</sup> found somewhat similar results in younger children (average age: 20 months). Thirty-one percent ( $n = 18$ ) of the children tested positive for viral infections, of which 12 were being treated with drugs (including amoxicillin and erythromycin). In 3 cases,

**TABLE 2 General Types of CADR**

Type A: common and predictable reactions
Undesirable effect at a site other than the drug target
Doxycycline and phototoxic reactions
Toxic effect from a supratherapeutic or high cumulative dose
Skin necrosis occurring with an infiltration of doxorubicin
Blue-gray skin pigmentation that occurs with prolonged and/or high-dose exposure to amiodarone
Type B: uncommon and unpredictable reactions
Hypersensitivity reactions (allergic)
Anaphylactic reaction to penicillin
Pseudoallergic reactions
Anaphylactic like reactions to iron dextran and ciprofloxacin
III. Idiosyncratic drug reactions
Warfarin-induced skin necrosis

Adapted from refs 10, 22, 27, and 28.



**FIGURE 1**  
Maculopapular exanthem.

urticarial eruptions returned with amoxicillin treatment. Other studies have generally confirmed the prominent role of infections in acute urticaria; however, some have implicated drugs in a higher proportion of cases.<sup>42,43,45-47</sup>

As described for exanthematous reactions, in the absence of other systemic symptoms (severe urticaria, respiratory distress, etc), the strongest association of a drug is obtained by means of a drug rechallenge at a later date when the child is well.<sup>21,45</sup> If a drug is implicated, it should be discontinued. Providers are often concerned with cross-sensitivity between penicillins and cephalosporins. Recently, Apter et al<sup>48</sup> found that 70% of patients experienced urticaria after receiving penicillins and cephalosporins. Genetic predisposition rather than cross-sensitivity is presumed to explain this phenomenon because of similar subsequent reactions to cephalosporins in patients with documented urticaria with sulfonamide antibiotics.

Antihistamine therapy remains the mainstay of management of acute urticarial reactions.<sup>48</sup> Again, second-generation agents such as loratadine and cetirizine are recommended.<sup>49,50</sup> With severe discomfort from pruritis, the sedative effects from hydroxyzine might be desirable,

**TABLE 3 Exanthematous Drug Eruptions**

Appearance	Begin as macules, can develop into papules.
Morbilloform	Generalized eruption of erythematous macules and papules progressing centripetally
Scarlatiniform	Erythematous patches develop sandpaper-like texture then desquamate; often with mucous membrane involvement
Differential diagnosis	Viral exanthems
Time from drug administration to onset	Sudden onset during the first 2 wk of drug therapy; semisynthetic penicillins after the first 2 wk
Commonly implicated drugs	Recurs on rechallenge Phenytoin  Carbamazepine Penicillin family of drugs (aminopenicillins) NSAIDs Sulfonamides Antituberculous drugs Phenobarbital
Pathogenesis	Poorly understood
Risk factors	Viral infections, Epstein-Barr virus
Treatment	Discontinue drug Oral antihistamines and systemic corticosteroids could be helpful Use emollients during resolution Avoid sunlight to hasten normalization of skin color
Resolution	As erythema fades, superficial desquamation is common Transient hyperpigmentation resolves over months to years Similar resolution for viral or bacterial exanthems

Adapted from refs 21, 22, 24, and 30.

as well.<sup>47</sup> Some success has been reported with low-dose doxepin (10 mg 3 times daily), an antidepressant medication that blocks both H<sub>1</sub> and H<sub>2</sub> receptors.<sup>51</sup> Although the evidence is not conclusive, oral prednisolone added to antihistamine therapy can result in decreased itch and more-rapid rash resolution of acute urticaria.<sup>52,53</sup> Of note, specialists have been found to use oral steroids less frequently than general practitioners.<sup>54</sup>

### Fixed Drug Eruptions

Fixed drug eruptions (FDEs) occur almost anywhere on the skin and, curiously, reappear in the exact same location when an offending drug is readministered<sup>22,55</sup> (Table 6). FDEs begin as soon as 30 minutes and as long as 2 months after drug ingestion.<sup>21,22,54</sup> They initially appear as well-demarcated, solitary or multiple edematous papules or plaques. Their color varies from dusky red to violet (Fig 5). The lesions can be intensely pruritic.<sup>22</sup> As the inflammation fades, the lesions become more round, and their color becomes grayish brown. The pigmented lesions can persist for years. Depending on the severity of the reactions, crusting and desquamation can occur in the postinflammatory phase. On rechallenge, the FDE will occur in the exact same location.<sup>55</sup>

**TABLE 4** Estimated Etiological Prevalence of Exanthema Patterns in Adults and Children

Pattern	Etiology, %				
	Drug	Virus	Bacteria	Parasite	Undiagnosed
Macular	9.8	5.4	3.6	0.9	8.9
Macular-papular	5.3	8.9	6.2	0.9	16.1
Papular	3.6	0	0	0	3.6
Macular-papular with petechiae	0	2.7	2.7	0	0.9
Erythematovesicular	0	9.8	0	0	9.8
Erythematopustular	3.6	0	0	0	4.5
Urticarial	0	1.8	1.8	0.9	1.8

Adapted from ref 31.

**FIGURE 2**  
Morbilliform reaction to amoxicillin.

As the diagnostic criteria for various cutaneous eruptions become more stringent, the relative prevalence of FDEs seems to increase. In a prospective and methodical study of pediatric outpatients (aged 1–18 years) in India who presented with a CADR, 26% were diagnosed with macular-papular eruptions, 22% with FDEs, and 6% with urticaria.<sup>30</sup> In contrast, Ibia et al<sup>3</sup> found a higher proportion of urticarial eruptions. The authors of this study surveyed parents by mail and did not distinguish EM or miscellaneous eruptions from FDEs. Mild drug eruptions (especially in relation to sulfamethoxazole and trimethoprim) are often misdiagnosed as macular-papular eruptions.<sup>56</sup> FDEs are probably underdiagnosed by most primary care providers.<sup>56</sup> Rechallenge remains the

**TABLE 5** Urticarial Drug Eruptions

Appearance	Edematous papules and plaques (wheals) are markedly pruritic Transient and effervescent, the individual lesions do not last >24 h in 1 location on the skin
Differential diagnosis	Childhood hives (acute urticaria) Allergies to foods, additives, excipients Viral infections
Time from drug administration to onset	Develops within hours to days of drug administration The generalized urticarial reaction pattern can last for weeks from a single dose of medication or resolve within hours
Commonly implicated drugs	NSAIDs Penicillin family of drugs (aminopenicillins, penicillin, cephalosporins) Sulfonamides Antituberculous drug Phenytoin Carbamazepine Others: histamine-releasing drugs (morphine, quinine, intravenous radiocontrast dye, etc)
Pathogenesis	Early type I hypersensitivity reaction or drug stimulation of mast cells
Risk factors	Atopic diathesis (allergies, asthma), viral infection with commonly associated drug
Treatment	Discontinue drug Oral antihistamines and systemic corticosteroids are helpful Use emollients during resolution
Resolution	Rechallenge on the basis of the severity of the reaction Avoid in anaphylaxis Desensitization procedures are available

Adapted from refs 21, 22, 24, and 30.

gold standard for diagnosis of FDEs and is usually safe to perform at a later date, depending on the severity of the initial reaction.<sup>21</sup>

Many drugs have been associated with FDEs, although some, such as sulfamethoxazole and trimethoprim, are implicated frequently. Reactions can occur in a generalized fashion or only on the torso, torso and limbs, lips, or genitalia; the majority of reactions occur in multiple sites.<sup>57–62</sup> Generalized eruptions have been significantly associated with phenytoin, whereas



FIGURE 3  
Urticaria with dermatographism.



FIGURE 4  
Urticaria.

eruptions specific to tetracycline tend to involve the genitalia.<sup>59,60</sup> Recently, ciprofloxacin has been associated with a substantial proportion of FDEs in India.<sup>63</sup> FDEs are often missed when they are secondary to episodic use of nonsteroidal antiinflammatory drugs (NSAIDs) or laxatives that contain phenolphthalein.<sup>55,56</sup> In addition, cross-reactivity has been reported between tetracycline derivatives, sulfonamides, and even unrelated anticonvulsant agents.<sup>64–66</sup>

When an FDE is suspected, the offending agent should be stopped, because continued administration can intensify the inflammation.<sup>22</sup> Management is supportive, as described earlier. Treatment with topical steroids may hasten resolution of an FDE. If a rechallenge is performed at a later date, the initial challenge dose should be smaller than the normal therapeutic dose, but it can be cautiously increased until the reaction is elicited.

TABLE 6 Fixed Drug Eruptions

Appearance	Solitary or multiple round, erythematous to violaceous, edematous, and distinct lesions 2–10 cm in diameter that often fade to gray or light-brown patches over time
Differential diagnosis	Bruises Insect bites EM Viral infections Child abuse
Time from drug administration to onset	30 min to 8 h
Commonly implicated drugs	Sulfonamides NSAIDs Ciprofloxacin Metronidazole Penicillins (ampicillin) Antituberculous drugs Phenytoin Phenolphthalein containing laxatives Pseudoephedrine (can cause a nonpigmented FDE) Acetaminophen
Pathogenesis	Unknown
Treatment	Discontinue drug Rechallenge is okay
Resolution	Inflammation fades, lesions become gray-brown pigmented patches May be recurrent at the same location for months or years Some develop a crust and desquamate

Adapted from refs 21, 22, 30, 56, and 63.



FIGURE 5  
Fixed drug eruption.

ed.<sup>67</sup> In some cases, 2 to 3 times the original dose may be required to elicit a repeat reaction.<sup>67</sup>

### Photosensitivity Reactions

Up to 8% of cutaneous drug eruptions are photosensitivity reactions, including phototoxic and photoallergic

reactions.<sup>22,68-70</sup> Drug-induced phototoxicity occurs when photoradiation interacts with a chemical within the skin to generate free radicals, which induces host cytotoxic effects. The site of the eruption coincides with sun-exposed areas of the skin, including the face, pre-sternal area, and the dorsum of the hands.<sup>70</sup>

Phototoxic reactions are nonimmunologic and dose dependant and often occur soon after initial ingestion of the drug. There are 3 general variations of phototoxic reactions.<sup>70</sup> The first is an intense and delayed erythema and edema that occurs 8 to 24 hours after exposure to sunlight. This reaction can involve hyperpigmentation and be a darker red than sunburn. Hydrochlorothiazide is an example of a trigger for this first type of phototoxic reaction. A second, more-immediate variation can occur within 30 minutes after light exposure and can last for a day or two (Fig 6). In this variant, erythema occurs without edema and is accompanied by local burning and pruritis. This more-immediate variation is often associated with doxycycline and the coal-tar derivatives such as anthracene and acridine. The third variant is associated with porphyrins and manifests as a rapid, transient, urticarial-like eruption that can be activated by room-lighting. Because the skin beneath the fingernails lacks melanin, phototoxic reactions that involve tetracyclines have been associated with onycholysis. By contrast, photoallergic reactions occur after a period of sensitization and can reoccur with small doses of the offending agent. Such reactions may appear with papulovesicular eruption, pruritis, and eczematous dermatitis 1 to 14 days after exposure to sunlight. Clinicians should include lupus and photoallergic reactions in their differential diagnosis when they evaluate a photograph-distributed eruption<sup>70-74</sup> (Table 7).

Management of phototoxic reactions parallels that of minor burn care.<sup>21,70</sup> Soothing creams and emollients can help with the discomfort. In more-severe cases, vesicles



FIGURE 6  
Phototoxic reaction.

TABLE 7 Photosensitivity Reactions

Appearance	Appears in sun-exposed areas of the skin: face, forehead, cheeks, nose, and along the rims of the ears
Phototoxic	Dose dependent; resembles sunburn; pruritis possible
Photoallergic	Ecematous, pruritic; requires sensitization
Differential diagnosis	Childhood hives (acute urticaria) Allergies to foods, additives, excipients Viral infections
Time from drug administration to onset	
Phototoxic	Immediate with drug administration and exposure to the sun
Photoallergic	Requires sensitization
Commonly implicated drugs	
Phototoxic	Tetracyclines: doxycycline > tetracycline > minocycline Fluoroquinolones Amiodarone Psoralens (in coal-tar preparations) Griseofulvin Diuretics (furosemide and thiazides) NSAIDs (ibuprofen, naproxen) Antipsychotic agents (chlorpromazine, prochlorperazine) St John's wort Topical (furocoumarins from lime, lemon, celery, parsley, and figs)
Photoallergic	Sunscreens, fragrances, antibacterial agents, latex Thiazide diuretics Griseofulvin Quinidine Sulfonamides Sulfonureas Pyridoxine (vitamin B <sub>6</sub> ) NSAIDs (naproxen)
Pseudoporphyria	
Pathogenesis	
Phototoxic	UV radiation interacts with chemicals in the skin to form free radicals, which lead to local host cytotoxic effects
Photoallergic	Type IV variant reaction; light enables the drug to conjugate with a carrier protein
Risk factors	Atopic diathesis (allergies, asthma)
Treatment	Discontinue drug Oral antihistamines and systemic corticosteroids are helpful with pruritis Use emollients during resolution
Resolution	Hyperpigmentation resolves over months to years

Adapted from refs 21, 22, 24, and 70-74.

form and rupture, and topical antibiotic creams can be considered. For photoallergic reactions, oral antihistamines and topical corticosteroids can provide symptomatic relief.<sup>21,70</sup> Although it is preferable to discontinue the offending agent, minimizing or eliminating light exposure is an option when few or no alternate agents are available. Avoidance of sunlight and application of sunscreens that block UV-A and UV-B may be recom-

mended with the awareness, however, that sunscreens are the most common cause of photoallergic reactions.<sup>75</sup>

### Serum Sickness–Like Reactions

A true serum sickness reaction, a type III hypersensitivity reaction, occurs when antibody–antigen complexes deposit in the microvasculature of the skin and joints and activate a complement cascade that leads to an inflammatory response and tissue damage.<sup>76</sup> In contrast to a true immunologic reaction, serum sickness–like reactions (SSLRs) do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.<sup>22</sup> SSLRs are characterized by fever, pruritis, urticaria, and arthralgias that usually begin 1 to 3 weeks after drug exposure and resolve soon after drug discontinuation.<sup>21</sup> The urticarial skin eruption becomes more erythematous as the reaction progresses and can evolve into dusky centers with round plaques. SSLRs have been most commonly associated with cefaclor, with which SSLRs are estimated to occur in 0.024% of exposures in controlled clinical trials and 0.5% in published reports.<sup>77–82</sup> Investigation of the mechanism of SSLRs that occur as a result of cefaclor use suggests a variant metabolic pathway.<sup>83</sup> No cross-reactivity with other cephalosporins has been demonstrated.

The development of bacterial resistance to cefaclor has limited its utility in the treatment of pediatric infections.<sup>84</sup> For this reason, SSLRs might be less common now than in the recent past. Case reports have implicated a number of other anti-infective agents in SSLRs, including penicillin, amoxicillin, cefprozil, sulfonamides, macrolides, ciprofloxacin, tetracyclines, rifampin, griseofulvin, and itraconazole.<sup>78–81,85–92</sup> Bupropion and fluoxetine have also been implicated<sup>91–93</sup> (Table 8).

Management is usually guided by symptomatology (as described previously); however, more-severe symptoms such as arthralgias could benefit from a short course of systemic corticosteroids.<sup>21,91</sup>

### RECOGNITION OF SEVERE CADRs

The risk of a severe CADr ranges between 1 in 1000 and 1 in 10 000, depending on the kind of reaction and the culprit drug.<sup>17,21,96,97</sup> Early recognition and prompt discontinuation of the offending agent can reduce mortality.<sup>98</sup> The most serious CADRs include anaphylaxis, drug hypersensitivity syndrome (DHS, also referred to as drug reaction with eosinophilia and systemic symptoms),<sup>24</sup> Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Our discussion here will be restricted to DHS, SJS, and TEN. In all cases, the likely culprit drugs should be discontinued immediately. Table 9 compares these eruptions.

DHS can occur 1 to 6 weeks after the initiation of drug therapy.<sup>97,99,100</sup> The initial presentation of DHS can resemble SSLR (fever, exanthematous eruption, lymphadenopathy, and eosinophilia); however, arthralgias are

**TABLE 8 Serum Sickness–Like Reactions**

Appearance	Fever, pruritis, urticarial eruptions, arthralgias
Differential diagnosis	Serum sickness (an SSLR lacks hypocomplementemia, vasculitis, and renal lesions) EM (an SSLR usually does not have target-like lesions with multiple centers) Viral infections
Time from drug administration to onset	1 to 3 wk after drug exposure
Commonly implicated drugs	Recurs on rechallenge Cefaclor (not known to be cross-reactive with other cephalosporins) Ciprofloxacin Macrolides Penicillins Sulfonamides Tetracyclines (scattered case reports) Rifampin (scattered case reports) Bupropion (scattered case reports) Fluoxetine (scattered case reports)
Pathogenesis	Mechanism is not well understood
Treatment	Discontinue drug Use oral antihistamines, systemic corticosteroids, and intravenous immunoglobulin

Adapted from refs 21, 22, 24, 30, 79–83, and 85–95.

rarely present with DHS.<sup>97</sup> The cutaneous eruption in DHS often progresses from a macular erythema, which starts on the face, upper trunk, and upper extremities, to a dusky reddish and confluent papular rash that is pruritic and can often desquamate.<sup>21,96,97</sup> Edema is a hallmark of DHS, particularly in a facial distribution.<sup>24</sup> The confluence seen in DHS occurs in contrast to the more-distinct and local areas of eruption seen in SSLRs. Visceral involvement in DHS can include the kidneys, liver, heart, lung, thyroid, and brain. Hepatitis is found in up to half of all cases.<sup>99</sup> In contrast to SJS and TEN, involvement of the mucous membranes is rare. DHS is associated most commonly with aromatic anticonvulsant agents, including phenytoin, carbamazepine, and phenobarbital (which are cross-reactive), and antibiotics such as minocycline and sulfamethoxazole.<sup>21,95–97,99,100</sup>

Controversy exists over the relationship between EM, SJS, and TEN.<sup>16,101–106</sup> In this review we followed definitions of these conditions that were provided by the World Health Organization and distinguish EM from SJS and TEN.<sup>16,104</sup>

It is unclear whether EM is associated with medications, but it deserves mention because it is often confused with urticaria and FDE. EM occurs over a period of 12 to 24 hours and is usually self-limiting and

**TABLE 9** Serious Drug Eruptions

Diagnosis	Mucosal Lesions	Typical Skin Lesions	Prodromal/Signs and Symptoms	Drug Associated, %	Drugs Most Often Implicated	Typical Time to Onset, wk	Alternative Causes Not Related to Drugs
DHS	Infrequent	Severe exanthematous rash (could become edematous, pustular, purpuric), exfoliative dermatitis	30–50% involve fever, lymphadenopathy, hepatitis, nephritis, carditis, eosinophilia, atypical lymphocytes	≥90	Phenytoin, carbamazepine, phenobarbital, sulfonamides, allopurinol, minocycline, nitrofurantoin, and terbinafine	1–6	Cutaneous lymphoma
SJS	Erosions at ≥2 sites	Crops of lesions on skin, conjunctivae, mouth, and genitalia; detachment of ≤10% of body surface area	High fever, sore throat, rhinorrhea, cough	48–64	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, and NSAIDs	1–3	
TEN	Erosions at ≥3 sites	Lesions similar to those with SJS; confluent epidermis separates readily with lateral pressure; detachment of ≥30% of body surface area	Fever, headache, sore throat; nearly all cases involve fever, “acute skin failure,” leukopenia, lesions of the respiratory and/or gastrointestinal tracts	43–65	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, and NSAIDs	1–3	Exanthematous stage of Kawasaki disease; staphylococcal scalded-skin syndrome

Adapted from refs 21–24 and 101–105.



**FIGURE 7**  
Erythema multiforme.

benign.<sup>16,21,22,101,103,105,107</sup> In about half of the cases the eruption is preceded by a relatively mild prodromal phase that resembles an upper respiratory infection. The papular lesions occur symmetrically on the extremities and are target-shaped, with 3 different-colored zones and a blister in the center clearly demarcated from the surrounding skin (Fig 7). Mucosal involvement is usually limited to the oral mucosa. EM has been associated most often with herpes simplex, followed by *M pneumoniae*; less commonly, orf and histoplasmosis are involved.<sup>21,24,108–111</sup> The literature reports vary from 0% to 10% association with medications.<sup>110,112</sup>

SJS manifests as 2 mucosal sites of involvement in conjunction with widespread skin lesions that may either be target-shaped or consist of erythematous macules.<sup>16,21,22,96,97,101–106,113,114</sup> The prodromal phase of the eruption is more intense than that seen with EM and includes fever, arthralgia, malaise, headache, vomiting, diarrhea, and myalgia. Lesions almost always involve the eyes, usually the mouth, and occasionally the upper airway, gastrointestinal tract, myocardium, and/or kidneys (Fig 8). Drugs are associated with ~50% of the eruptions diagnosed as SJS in children; anticonvulsant agents, penicillin, and sulfonamides have been blamed for 90% of these cases.<sup>103,107,113</sup> One study examined the result of discontinuing all potentially causative drugs at the first sign of a blister or erosion (typical of SJS or TEN) that was not explained by another cause.<sup>98</sup> The difference in mortality was 11% for early recognition and drug withdrawal versus 27% for late withdrawal (when the drugs had short elimination half-lives).<sup>98</sup>

With TEN, a morbilliform eruption occurs soon after drug administration and is accompanied by large erythematous and tender areas of the skin.<sup>21,22,101–105,107,113,115–117</sup> This symptom rapidly progresses to blistering and exfoliation of the epidermis that is characterized by widespread erythematous areas with epithelial necrosis and epidermal detachment, which leaves bare dermis (Fig 9). TEN is defined by >30% cutaneous surface involve-



FIGURE 8  
SJS with mucocutaneous involvement.

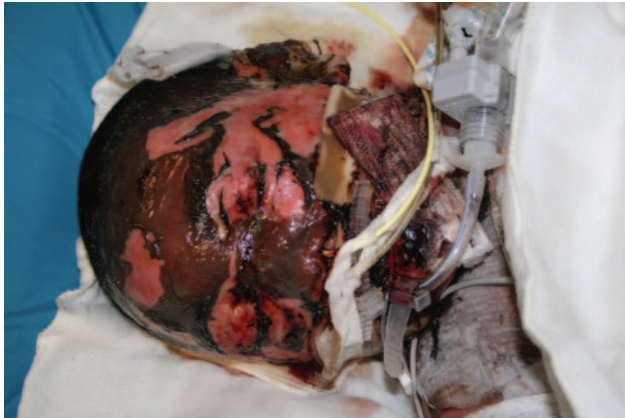


FIGURE 9  
Toxic epidermal necrolysis.

ment. A positive Nikolsky sign (detachment of epidermis with lateral pressure from a finger) is indicative of TEN.<sup>118</sup> SJS with >10% cutaneous involvement is often classified as SJS/TEN overlap.<sup>104</sup> Extensive mucosal erosion is frequent. Prodromal symptoms are often severe and include nausea, vomiting, angina, high fever, malaise, and painful skin. Morbidity and mortality is high (25%–50%), usually from fluid and electrolyte imbalances and secondary bacterial infections. Up to 90% of TEN cases in adults have been associated with drugs.<sup>113</sup> Although a majority of TEN cases in children are touted to be drug related, up to half the cases in 1 study could not be associated with a specific cause.<sup>117</sup>

### RISK FACTORS FOR CADRs IN CHILDREN

Risk factors for cutaneous eruptions in children can be divided into drug and patient factors. Drugs have been associated with cutaneous reactions roughly in propor-

tion to their use. All of the epidemiologic studies cited in this review detected CADRs and accounted for the proportions of culprit drugs associated with those CADRs.<sup>28,30,119</sup> Both antibiotics and infections are frequently associated with CADRs. In addition, anticonvulsant agents (phenytoin, phenobarbital) appear frequently as implicated medicines in pediatric reactions. Drugs that are associated with predictable type A reactions, such as phototoxic reactions, are used with the understanding that a CADR may occur.

Patient risk factors include infection and the possibility of a genetic variation leading to altered metabolism of a drug, with a partially or fully immunologic consequence. Although little is known about the specific mechanisms, children with parents who have a true drug allergy are at a 15-fold relative risk for allergic reactions to the same drugs.<sup>28</sup> Studies have found some links between genetic variation in drug metabolism and CADRs.<sup>12,13,120,121</sup>

### INITIAL MANAGEMENT OF A CADR

Early pattern recognition and severity assessment of a CADR are the cornerstones of initial management and prevention of reaction progression. Always attempt to obtain a careful and thorough history of the reaction and a good description of the eruption. Refer to Table 10 for helpful questions to determine the history and cause of a CADR. If the type of reaction is easily recognizable, refer to the treatment section of the specific reaction type in Tables 3 through 8. Determination of the causative agent is more difficult when patients are taking multiple medications. Assessment of culprit drugs should be based on published associations. If clarification is needed on the assessment, particularly with severe, persistent, or recurrent CADRs, providers should contact an allergist for additional testing and confirmation. After this assessment, providers with definite associations to specific medications should report the CADR to the FDA by completing the MedWatch 3500 form online ([www.fda.gov/medwatch](http://www.fda.gov/medwatch)) or by calling 1-800-FDA-1088 (1-800-332-1088). Reporting of CADRs to the FDA or in the publication of case reports is essential for the continued evaluation of medications by providers for their patients who experience these events. The management of CADRs for these patients differs on the basis of the severity of the reaction. Table 11 provides suggestions

TABLE 10 Useful Questions for Assessing CADR History

What was the patient taking when the reaction occurred?
How long had the patient been taking the medication(s)?
Has the patient ever taken the medicine(s); if so what happened?
Has the patient ever taken similar medicine(s); if so, what happened?
Why was the patient taking the medicine(s)?
How and where did the reaction appear when it was first noticed, and how has it changed in appearance?

Adapted from refs 11 and 122.

**TABLE 11 Approach to the Patient With a Cutaneous Reaction Who Is Receiving Multiple Drugs**

Mild reaction
Discontinue the drug that is most likely causing the reaction
In patients with a viral infection, especially AIDS, consider "treating through" or continuing therapy
Substitute a chemically unrelated chemical compound for the indication
If needed for pruritis, use antihistamines or topical steroids
Observe for prompt resolution
If no resolution, select the next most likely drug, and repeat the cycle
Document the reaction and notify the patient and/or patient's family
Severe reaction
Discontinue the drugs that are most likely causing the reaction
Substitute chemically unrelated chemical compounds for each indication
Observe for prompt resolution
If no resolution, select the next most likely drug, and repeat the cycle
Document the reaction and notify the patient and/or patient's family

Adapted from refs 21, 27, and 48.

for the management of mild and severe reactions. Diagnosis of CADR in any patient should be considered provisional unless a rechallenge is performed.

### CONCLUSIONS

CADRs account for the majority of ADRs. Up to 10% of young children who are taking antibiotics could develop a cutaneous drug eruption. The majority of the reactions are not true drug allergies and will not occur at a later date when the child is rechallenged with the drug. In cases of serious CADR, prompt recognition and drug cessation can mitigate the severity of the reaction. Establishing firm associations between drugs and CADR is a relatively complex and subtle art. Previous familiarity with history taking, typical reaction patterns, and the present state of epidemiologic knowledge are necessary for timely assessments and recommendations (Table 12).

As an antidote to the complexity of diagnosis, we recommend Litt's *Drug Eruption Reference Manual*<sup>22</sup> and *The Pocketbook of Drug Eruptions and Interactions*.<sup>25</sup> These handy references list case reports that associate many specific cutaneous reactions with various drugs.

**TABLE 12 Summary of Steps for Evaluating the Possibility of a Drug-Induced Reaction**

Obtain an adequate history of the reaction
Obtain an accurate description of the reaction
Develop a comprehensive drug history
Know the immunologic and nonimmunologic mechanisms involved in cutaneous drug reactions
Match clinical manifestations of a particular cutaneous reaction to known drug-induced syndromes and patterns
Note factors that favor the development of allergic reactions to drugs
Assess the likely culprit drug(s)
Develop a plan that includes
The feasibility of discontinuing the culprit medication(s)
Monitoring the expected course of symptom resolution
The feasibility of strengthening the case against a suspect drug by rechallenge

Adapted from ref 123.

### REFERENCES

1. Cutaneous drug reaction case reports: from the world literature. *Am J Clin Dermatol.* 2003;4:511–521
2. Miller RR. Drug surveillance utilizing epidemiological methods: a report from the Boston Collaborative Drug Surveillance Program. *Am J Hosp Pharm.* 1973;30:585–592
3. Bigby M, Jick S, Jick H, Arndt K, et al. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA.* 1986;256:3358–3363
4. Kushwaha KP, Verma RB, Singh YD, Rathi AK. Surveillance of drug induced diseases in children. *Indian J Pediatr.* 1994; 61:357–365
5. Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children: survey in a private practice setting. *Arch Dermatol.* 2000;136:849–854
6. van der Linden PD, van der Lei J, Vlug AE, Stricker BH. Skin reactions to antibacterial agents in general practice. *J Clin Epidemiol.* 1998;51:703–708
7. Cirko-Begović A, Vrhovac B, Bakran I. Intensive monitoring of adverse drug reactions in infants and preschool children. *Eur J Clin Pharmacol.* 1989;36:63–65
8. Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, Leduc DG. Adverse drug reactions in general pediatric outpatients. *J Pediatr.* 1985;106:305–310
9. Johnson ML, Johnson KG, Engel A. Prevalence, morbidity, and cost of dermatologic diseases. *J Am Acad Dermatol.* 1984; 11:930–936
10. Gruchalla R. Understanding drug allergies. *J Allergy Clin Immunol.* 2000;105:S637–S644
11. Pilzer JD, Burke TG, Mutnick AH. Drug allergy assessment at a university hospital and clinic. *Am J Health Syst Pharm.* 1996; 53:2970–2975
12. Huang SW, Borum PR. Study of skin rashes after antibiotic use in young children. *Clin Pediatr (Phila).* 1998;37:601–607
13. Martin-Munoz F, Moreno-Ancillo A, Dominguez-Noche C, et al. Evaluation of drug-related hypersensitivity reactions in children. *J Investig Allergol Clin Immunol.* 1999;9:172–177
14. Preston SL, Briceland LL, Lesai TS. Accuracy of penicillin allergy reporting. *Am J Health Syst Pharm.* 1994;51:79–84
15. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther.* 1977;21:247–254
16. Council for International Organization of Medical Sciences. Harmonizing use of adverse drug reaction terms: definitions of terms and minimum requirements for their use—respiratory disorders and skin disorders [published correction appears in *Pharmacoepidemiol Drug Saf.* 1997;6:293]. *Pharmacoepidemiol Drug Saf.* 1997;6:115–127
17. Roujeau JC, Stern R. Medical progress: severe cutaneous reactions to drugs. *N Engl J Med.* 1994;331:1272–1285
18. Naranjo CA, Busto U, Sellers EM, et al. A method of estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239–244
19. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions: I. Background, description, and instructions for use. *JAMA.* 1979;242:623–632
20. Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions: II. Demonstration of reproducibility and validity. *JAMA.* 1979;242:633–638
21. Shin HT, Chang MW. Drug eruptions in children. *Curr Probl Pediatr.* 2001;31:207–234
22. Litt J. *Drug Eruption Reference Manual.* New York, NY: Parthenon; 2000
23. *Taber's Cyclopedic Medical Dictionary.* Philadelphia, PA: F. A.

- Davis Co; 2003. Available at: [www.rxlist.com](http://www.rxlist.com). Accessed January 3, 2003.
24. Lookingbill DP, Marks JG Jr. *Principles of Dermatology*. Philadelphia, PA: WB Saunders; 2000
  25. Litt J. *The Pocketbook of Drug Eruptions and Interactions*. 2nd ed. New York, NY: Parthenon; 2001
  26. Rawlins MD. Clinical pharmacology: adverse reactions to drugs. *Br Med J (Clin Res Ed)*. 1981;282:974–976
  27. Assem EK. Drug allergy and tests for its detection. In: Davies DM, Ferner RE, de Glanville H, eds. *Davies's Textbook of Adverse Drug Reactions*. 5th ed. London, United Kingdom: Chapman & Hall Medical; 1998:791–815
  28. DeShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA*. 1997;278:1895–1906
  29. Coombs R, Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Coombs R, Gell PGH, Lachman PJ, eds. *Clinical Aspects of Immunology*. Oxford, United Kingdom: Blackwell Scientific; 1975:761–781
  30. Sharma VK, Dhar S. Clinical pattern of cutaneous drug eruption among children and adolescents in north India. *Pediatr Dermatol*. 1995;12:178–183
  31. Drago F, Rampini E, Rebora A. Atypical exanthems: morphology and laboratory investigations may lead to an aetiological diagnosis in about 70% of cases. *Br J Dermatol*. 2002;147:255–260
  32. Horowitz R, Reynolds S. New oral antihistamines in pediatrics. *Pediatr Emerg Care*. 2004;20:143–146
  33. Simons FE. H<sub>1</sub>-antihistamines in children. *Clin Allergy Immunol*. 2002;17:437–464
  34. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. *Drug Saf*. 2001;24:119–147
  35. Simons FE, Silas P, Portnoy JM, et al. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 2003;111:1244–1248
  36. Tamayo-Sanchez L, Ruiz-Maldonado R, Laterza A. Acute annular urticaria in infants and children. *Pediatr Dermatol*. 1997;14:231–234
  37. Kanwar AJ, Greaves MW. Approach to the patient with chronic urticaria. *Hosp Pract*. 1996;31:175–179, 183–184, 187–189
  38. Kubly J. Immunology. In: Allen D, Julet MR, Maass DC, eds. *Hypersensitive Reactions*. 3rd ed. New York, NY: WH Freeman; 1997:413–438
  39. Solley GO, Gleich GJ, Jordon RE, Schroeter AL. The late phase of the immediate wheal and flare skin reaction: its dependence upon IgE antibodies. *J Clin Invest*. 1976;58:408–420
  40. Carder KR. Hypersensitivity reactions in neonates and infants. *Dermatol Ther*. 2005;18:160–175
  41. Mortureux P, Léauté-Labrèze C, Legrain-Lifermann V, Lamiereau T, Sarlangue J, Taïeb A. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol*. 1998;134:319–323
  42. Legrain V, Taïeb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol*. 1990;7:101–107
  43. Balaban J. Medicaments as the possible cause of urticaria in children. *Acta Dermatovenereol Croat*. 2002;10:155–159
  44. Sackesen C, Sekerel BE, Orhan F, et al. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol*. 2004;21:102–108
  45. Schuller DE. Acute urticaria in children: causes and an aggressive diagnostic approach. *Postgrad Med*. 1982;72:179–185
  46. Sakurai M, Oba M, Matsumoto K, Tokura Y, Furukawa F, Takigawa M. Acute infectious urticaria: clinical and laboratory analysis in nineteen patients. *J Dermatol*. 2000;27:87–93
  47. Bilbao A, Garcia JM, Pocheville I, et al. Round table: urticaria in relation to infections [in Spanish]. *Allergol Immunopathol (Madr)*. 1999;27:73–85
  48. Apter AJ, Kinman JL, Bilker WB, et al. Is there cross-reactivity between penicillins and cephalosporins? *Am J Med*. 2006;119:354.e11–354.e19
  49. Twarog FJ. Urticaria in childhood: pathogenesis and management. *Pediatr Clin North Am*. 1983;30:887–898
  50. Kennard CD, Ellis CN. Pharmacologic therapy for urticaria. *J Am Acad Dermatol*. 1991;25:176–187
  51. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. *Ann Pharmacother*. 1997;31:633–635
  52. Poon M, Reid C. Do steroids help children with acute urticaria? *Arch Dis Child*. 2004;89:85–86
  53. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venereol*. 1996;76:295–297
  54. Henderson RL Jr, Fleischer AB Jr, Feldman SR. Allergists and dermatologists have far more expertise in caring for patients with urticaria than other specialists. *J Am Acad Dermatol*. 2000;43:1084–1091
  55. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol*. 1998;37:833–838
  56. Morelli JG, Tay YK, Rogers M, Halbert A, Krafchik B, Weston WL. Fixed drug eruptions in children. *J Pediatr*. 1999;134:365–367
  57. Lee AY. Topical provocation in 31 cases of fixed drug eruption: change of causative drugs in 10 years. *Contact Dermatit*. 1998;38:258–260
  58. Ozkaya-Bayazit E. Specific site involvement in fixed drug eruption. *J Am Acad Dermatol*. 2003;49:1003–1007
  59. Sharma VK, Dhar S, Gill AN. Drug related involvement of specific sites in fixed eruptions: a statistical evaluation. *J Dermatol*. 1996;23:530–534
  60. Thankappan TP, Zachariah J. Drug-specific clinical pattern in fixed drug eruptions. *Int J Dermatol*. 1991;30:867–870
  61. Nussinovitch M, Prais D, Ben-Amitai D, Amir J, Volovitz B. Fixed drug eruption in the genital area in 15 boys. *Pediatr Dermatol*. 2002;19:216–219
  62. Brown SG. Fixed drug eruptions in deeply pigmented subjects: clinical observations on 350 patients. *Br Med J*. 1964;2(5416):1041–1044
  63. Dhar S, Sharma VK. Fixed drug eruption due to ciprofloxacin. *Br J Dermatol*. 1996;134:156–158
  64. Tham SN, Kwok YK, Chan HL. Cross-reactivity in fixed drug eruptions to tetracyclines. *Arch Dermatol*. 1996;132:1134–1135
  65. Chan HL, Tan KC. Fixed drug eruption to three anticonvulsant drugs: an unusual case of polysensitivity. *J Am Acad Dermatol*. 1997;36:259
  66. Tornero P, De Barrio M, Baeza ML, Herrero T. Cross-reactivity among p-amino group compounds in sulfonamide fixed drug eruption: diagnostic value of patch testing. *Contact Dermatit*. 2004;51:57–62
  67. Kanwar AJ, Bharija SC, Singh M, Belhaj MS. Ninety-eight fixed drug eruptions with provocation tests. *Dermatologica*. 1988;177:274–279
  68. Selvaag E. Clinical drug photosensitivity: a retrospective analysis of reports to the Norwegian Adverse Drug Reactions Committee from the years 1970–1994. *Photodermatol Photoimmunol Photomed*. 1997;13:21–23
  69. Bligard CA, Storer JS. Photosensitivity in infants and children. *Dermatol Clin*. 1986;4:311–319
  70. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Saf*. 2002;25:345–372

71. Drugs that cause photosensitivity. *Med Lett Drugs Ther.* 1995; 37:35–36
72. Ernst E, Rand JI, Barnes J, Stevinson C. Adverse effects profile of the herbal antidepressant St. John's wort (*Hypericum perforatum* L.). *Eur J Clin Pharmacol.* 1998;54:589–594
73. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Saf.* 1996;14: 252–259
74. Vassileva SG, Mateev G, Parish LC. Antimicrobial photosensitive reactions. *Arch Intern Med.* 1998;158:1993–2000
75. Fotiades J, Soter NA, Lim HW. Results of evaluation of 203 patients for photosensitivity in a 7.3-year period. *J Am Acad Dermatol.* 1995;33:597–602
76. Lawley TJ, Bielory L, Gascon P, Yancey KB, Young NS, Frank MM. A prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med.* 1984;311: 1407–1413
77. Sanklecha MU. Cefaclor induced serum sickness like reaction. *Indian J Pediatr.* 2002;69:921
78. Martin J, Abbott G. Serum sickness like illness and antimicrobials in children. *N Z Med J.* 1995;108:123–124
79. Hebert AA, Sigman ES, Levy ML. Serum sickness-like reactions from cefaclor in children. *J Am Acad Dermatol.* 1991;25: 805–808
80. Levine LR. Quantitative comparison of adverse reactions to cefaclor vs. amoxicillin in a surveillance study. *Pediatr Infect Dis.* 1985;4:358–361
81. Platt R, Dreis MW, Kennedy DL, Kuritsky JN. Serum sickness-like reactions to amoxicillin, cefaclor, cephalixin, and trimethoprim-sulfamethoxazole. *J Infect Dis.* 1988;158:474–477
82. Heckbert SR, Stryker WS, Coltin KL, Manson JE, Platt R. Serum sickness in children after antibiotic exposure: estimates of occurrence and morbidity in a health maintenance organization population. *Am J Epidemiol.* 1990;132:336–342
83. Kearns GL, Wheeler JG, Childress SH, Letzig LG. Serum sickness-like reactions to cefaclor: role of hepatic metabolism and individual sensitivity. *J Pediatr.* 1994;125:805–811
84. Rosenfeld RM, Culpepper L, Doyle KJ, et al. Clinical practice guideline: otitis media with effusion. *Otolaryngol Head Neck Surg.* 2004;130(5 suppl):S95–S118
85. Parshuram CS, Phillips RJ. Retrospective review of antibiotic-associated serum sickness in children presenting to a paediatric emergency department. *Med J Aust.* 1998;169:116
86. Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. *Arch Dermatol.* 1997;133:1224–1230
87. Harel L, Amir J, Livni E, Straussberg R, Varsano I. Serum-sickness-like reaction associated with minocycline therapy in adolescents. *Ann Pharmacother.* 1996;30:481–483
88. Slama TG. Serum sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother.* 1990;34:904–905
89. Parra FM, Pérez Elias MJ, Cuevas M, Ferreira A. Serum sickness-like illness associated with rifampicin. *Ann Allergy.* 1994; 73:123–125
90. Colton RL, Amir J, Mimouni M, Zeharia A. Serum sickness-like reaction associated with griseofulvin. *Ann Pharmacother.* 2004;38:609–611
91. McCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. *Ann Pharmacother.* 2000;34: 471–473
92. Peloso PM, Baillie C. Serum sickness-like reaction with bupropion. *JAMA.* 1999;282:1817
93. Waibel KH, Katial RK. Serum sickness-like reaction and bupropion. *J Am Acad Child Adolesc Psychiatry.* 2004;43:509
94. Park H, Knowles S, Shear NH. Serum sickness-like reaction to itraconazole. *Ann Pharmacother.* 1998;32:1249
95. Shapiro LE, Knowles SR, Shear NH. Fluoxetine-induced serum sickness-like reaction. *Ann Pharmacother.* 1997;31:927
96. Revuz J. New advances in severe adverse drug reactions. *Dermatol Clin.* 2001;19:697–709
97. Knowles S, Shapiro L, Shear NH. Serious dermatologic reactions in children. *Curr Opin Pediatr.* 1997;9:388–395
98. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol.* 2000;136:323–327
99. Kaur S, Sarkar R, Thami GP, Kanwar AJ. Anticonvulsant hypersensitivity syndrome. *Pediatr Dermatol.* 2002;19:142–145
100. Carroll MC, Yueng-Yue KA, Esterly NB, Drolet BA. Drug-induced hypersensitivity syndrome in pediatric patients. *Pediatrics.* 2001;108:485–492
101. Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol.* 1996;135:6–11
102. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Severe cutaneous adverse reactions: correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis—results of an international prospective study. *Arch Dermatol.* 2002; 138:1019–1024
103. Léauté-Labrèze C, Lamireau T, Chawki D, Maleville J, Taïeb A. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child.* 2000;83:347–352
104. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129:92–96
105. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol.* 1990;126:43–47
106. Hurwitz S. Erythema multiforme: a review of its characteristics, diagnostic criteria, and management. *Pediatr Rev.* 1990; 11:217–222
107. Villiger RM, von Vigier RO, Ramelli GP, Hassink RI, Bianchetti MG. Precipitants in 42 cases of erythema multiforme. *Eur J Pediatr.* 1999;158:929–932
108. Tay YK, Huff JC, Weston WL. *Mycoplasma pneumoniae* infection is associated with Stevens-Johnson syndrome not erythema multiforme (von Hebra). *J Am Acad Dermatol.* 1996;35: 757–760
109. Weston WL. What is erythema multiforme? *Pediatr Ann.* 1996;25:106–109
110. Carrozzo M, Togliatto M, Gandolfo S. Erythema multiforme: a heterogeneous pathologic phenotype [in Italian]. *Minerva Stomatol.* 1999;48:217–226
111. Schallock PC, Dinulos JGH, Pace N, Schwarzenberger K, Wegner JK. Erythema multiforme due to *Mycoplasma pneumoniae* infection in two children. *Pediatr Dermatol.* 2006;23:546–555
112. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol.* 1995;131:539–543
113. Schöpf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol.* 1991;127:839–842
114. Ginsburg CM. Stevens-Johnson syndrome in children. *Pediatr Infect Dis.* 1982;1:155–158
115. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal

- necrolysis: clinical findings and prognosis factors in 87 patients. *Arch Dermatol*. 1987;123:1160–1165
116. Guillaume JC, Roujeau JC, Revuz J, Penso D, Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol*. 1987;123:1166–1170
117. Prendiville JS, Hebert AA, Greenwald MJ, Esterly NB. Management of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Pediatr*. 1989;115:881–887
118. Fritsch PO, Sidoroff A. Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *Am J Clin Dermatol*. 2000;1:349–360
119. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents—a 6 year series from Chandigarh, India. *J Postgrad Med*. 2001; 47:95–99
120. Rademaker M, Oakley A, Duffil MB. Cutaneous adverse reactions to drugs in the hospital setting. *N Z Med J*. 1995;108: 165–166
121. Ponvert C, Le Clainche L, de Blic J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. *Pediatrics*. 1999;104(4). Available at: [www.pediatrics.org/cgi/content/full/104/4/e45](http://www.pediatrics.org/cgi/content/full/104/4/e45)
122. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination: is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA*. 2001;285:2498–2505
123. Elias SS, Patel NM, Cheigh NH. Drug induced skin reactions. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 5th ed. Norwalk, CT: Appleton and Lange; 2002:1705–1716