

Cutaneous Drug Reactions in the Pediatric Population

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KEYWORDS

- Drug allergy • Hypersensitivity • Exanthems • Urticaria • DRESS syndrome
- Stevens-Johnson syndrome • Toxic epidermal necrolysis

KEY POINTS

- Adverse drug reactions (ADRs) frequently manifest on the skin. Cutaneous ADRs (CADRs) in children are a diagnostic challenge because CADRs can mimic many other childhood eruptions.
- Urticaria is an immediate hypersensitivity reaction, usually immunoglobulin E-mediated, predominantly manifesting as wheals.
- Maculopapular morbilliform exanthems are the most frequent form of hypersensitivity reactions in children.

OVERVIEW

Any unintended harmful reaction to a medicine or drug is known as an adverse drug reaction (ADR) according to the definition by the World Health Organization.^{1,2} ADRs are classified as type A (augmented) or type B (bizarre) according to whether it is a predictable side effect related to the pharmacologic action of a drug or if it is an idiosyncratic reaction, respectively (**Fig. 1**).^{3–5} There are several examples of each type of reaction, many of which manifest on the skin. Therefore, the dermatologist plays an important role in the team management of these patients. This article discusses the clinical manifestations of cutaneous ADRs (CADRs) and their pathophysiology.

In children, ADRs represent a diagnostic challenge. On the one hand, children are more susceptible than adults to drug-dosage errors because of their smaller body size¹; on the other hand, ADRs can mimic other skin diseases of children, especially viral exanthems, frequently appearing as a maculopapular or morbilliform rash sometimes indistinguishable from a CADR.⁶

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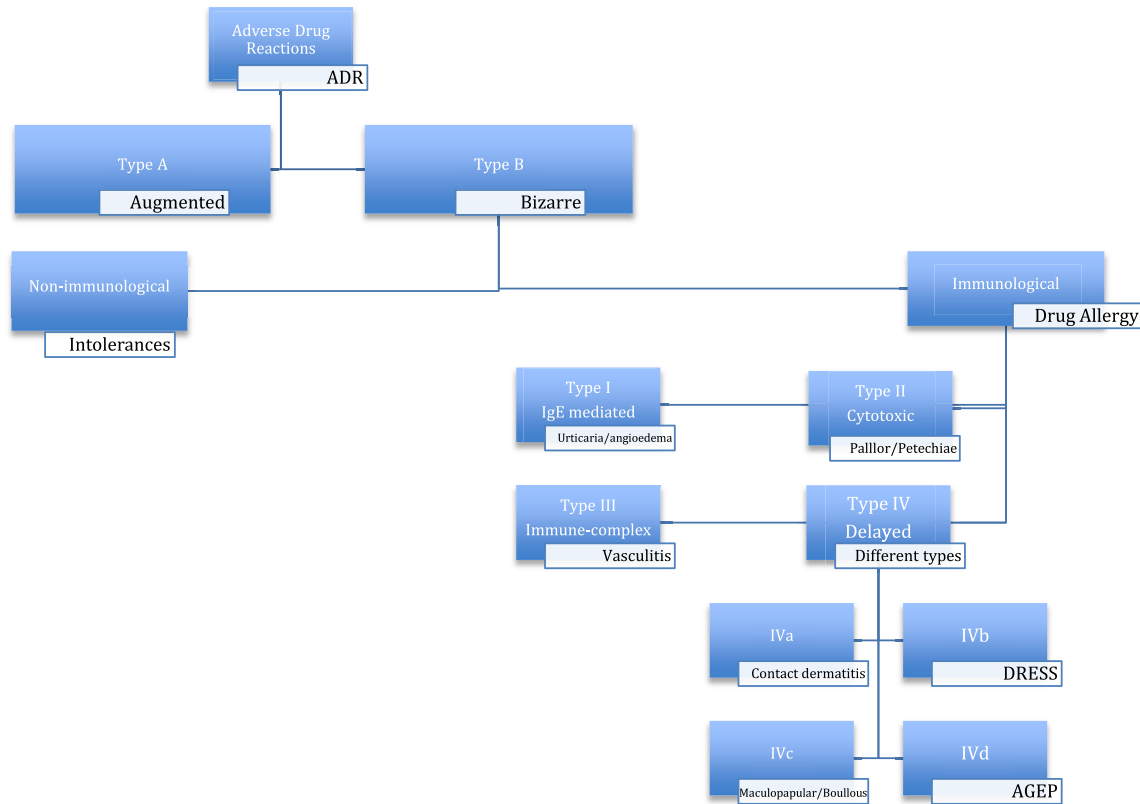


Fig. 1. Summary of adverse drug reactions according to the new concepts. DRESS, drug reactions with eosinophilia and systemic symptoms; AGEP, acute generalized exanthematic pustulosis.

PATHOPHYSIOLOGY

In ADRs of type A, a predictable side effect is related to the pharmacologic action of the drug, hence this type of reaction is considered nonimmunologic. It can be produced by overdose, cumulative or delayed toxicity, drug interactions, abnormalities in patient metabolism, or exacerbation of a preexisting disease ([Table 1](#)).

Alternatively, drugs can bind covalently to proteins and then induce an immune response. These reactions are different in nature and severity depending on the patient's specific metabolic pathways. An example of such variations and how they are influenced genetically is the increased incidence of induced systemic lupus

Table 1
Adverse drug reactions produced by nonimmunologic mechanisms

Nonimmunologic Factor	Mechanism	Drug Example	Manifestation on Skin
Overdose	Exaggeration of drug's pharmacologic actions		
Side effect	Undesirable or toxic effects that cannot be separated from the desired pharmacologic actions	Chemotherapeutic agents	Chemotherapeutic agents producing alopecia, mucositis
Cumulative toxicity	Prolonged exposure to a medication may lead to cumulative toxicity	Minocycline, amiodarone	Discoloration of skin
Delayed toxicity (nonimmunologic)	Dose-dependent effect that occurs months to years after the discontinuation of a medication	Arsenic	Squamous cell carcinomas and palmoplantar keratoses
Drug interactions	Interactions between 2 or more drugs administered simultaneously	Tetracycline and calcium, methotrexate and sulfonamides, cyclosporine and azoles, and methotrexate and probenecid	
Alteration in metabolism	Drugs may induce cutaneous changes by their effects on the nutritional or metabolic status of the patient	Bexarotene, isoniazid	Bexarotene may induce severe hypertriglyceridemia and eruptive xanthomas, whereas isoniazid may be associated with pellagra-like changes
Exacerbation of disease	Exacerbation of preexisting dermatologic disease	Androgen, lithium, interferon	Acne vulgaris (androgens), psoriasis (lithium and interferon)

syndrome by sulfonamide/procainamide in slow acetylators in comparison with rapid acetylators. In addition, certain human leukocyte antigen (HLA) alleles increase the risk of ADRs (see later discussion). Immunologically mediated reactions are considered drug hypersensitivity reactions, and are included as 4 types in the basic immune classification by Coombs and Gell⁷ (see **Fig. 1**):

1. Type I: Cross-linked reactions with high-affinity immunoglobulin (Ig)E receptor, whereby mast cells and basophils release mediators responsible for anaphylaxis; for example, urticarial reactions.
2. Type II: IgG-mediated cytotoxic mechanisms against an antigenic component of the cell surface; for example, hemolytic anemia, thrombocytopenia.
3. Type III: Circulating immune complexes lead to endothelial damage and complement activation, and usually manifest as vasculitis, which can be seen on the skin.
4. Type IV: All delayed hypersensitivity reactions are included in this category, sub-classified as⁸:
 - a. IVa: Mediators such as interferon (IFN)- γ and tumor necrosis factor α (from T-helper 1 cells) produce macrophage activation and immune response; for example, contact dermatitis, tuberculin reactions.
 - b. IVb: Certain cytokines (interleukin [IL]-5, IL-4, IL-13) interact with eosinophils, which become the main cells involved; clinical manifestations include maculopapular exanthems with eosinophilia (drug reactions with eosinophilia and systemic symptoms [DRESS syndrome]).
 - c. IVc: Perforins, granzyme-B, and Fas ligand are incriminated, activating cytotoxic T cells, natural killer (NK)/T cells, and NK cells clinically manifesting as contact dermatitis, maculopapular rash, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN) exanthems.⁹ In bullous exanthems there is a higher percentage of perforin-positive CD8⁺ killer T cells in the epidermis and dermis.¹⁰
 - d. IVd: CxCL8 and granulocyte macrophage colony-stimulating factor induce neutrophil activation, and can manifest on the skin as acute generalized exanthematic pustulosis (AGEP).

According to several studies, the most frequent cause of ADRs is antibiotics, including β -lactams and macrolides, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) and barbiturates/antiepileptic drugs.¹¹ A genetic predisposition has been demonstrated to exist in many of these reactions; for example, abacavir hypersensitivity is linked to HLA-B*5701. The pharmacogenetics of these reactions is currently being investigated, with promising results in the screening of patients before the administration of medications with high risk for severe ADRs (**Box 1**).¹²

EPIDEMIOLOGY

CADRs represent a major pediatric health problem frequently encountered in clinical practice.³ However, few epidemiologic studies have addressed the incidence of common, non-life-threatening CADRs, including reactions of both delayed and immediate hypersensitivity, such as maculopapular exanthem, fixed drug eruption, or urticaria.¹³ CADRs represent 35% to 36% of any ADRs in children, only being surpassed by gastrointestinal symptoms (39%). In 2000, Menniti-Ippolito and colleagues¹⁴ performed an active monitoring system of ADRs in children through a network of family pediatricians; more than 24,000 patients were recruited, and the reported incidence of ADRs was 15.1 per 1000 children.^{6,14}

Box 1**Drugs frequently related to cutaneous adverse drug reactions**

Antibiotics

- Penicillins
- Cephalosporins
- Carbapenems
- Fluoroquinolones
- Macrolides
- Sulfonamides
- β -Lactam inhibitors
- Glycopeptides

Nonsteroidal anti-inflammatories

- Metamizole sodium
- Diclofenac
- Acetylsalicylic acid
- Ibuprofen

Anticonvulsants

- Carbamazepine
- Lamotrigine
- Phenobarbital

Antifungals

- Clotrimazole
- Terbinafine

Data from Heinzerling LM, Tomsitz D, Anliker MD. Is drug allergy less prevalent than previously assumed? A 5-year analysis. *Br J Dermatol* 2012;166(1):107–14.

It is of great importance that parents often report drug hypersensitivity events in their children that are not confirmed by diagnostic tests. In a study by Rebelo Gomes and colleagues,¹⁵ 94% of patients diagnosed with hypersensitivity reactions were actually able to tolerate the initially suspected drug. The authors believe that it is important to confirm and document any self-reported drug reaction. Identification of the harmful drug can limit potentially life-threatening reexposure and will also prevent avoidance of innocent drugs that can be life-saving.

PROGNOSIS

The spectrum of drugs causing CADRs differs substantially when the various clinical conditions are considered.¹³ Most ADRs with cutaneous involvement are mild, and resolve on withdrawal of the causative drug. The most common forms of CADRs are maculopapular exanthems and urticarial reactions, both of which have excellent outcomes. Less frequent, but more severe reactions may have a risk of mortality, estimated at 10% for DRESS syndrome, 1% to 5% for SJS, 25% to 35% for TEN,¹⁶ and less than 5% for acute generalized exanthematic pustulosis.¹⁷

CLINICAL FEATURES

Urticaria

Urticaria is a common disorder in children and adults, usually caused by IgE-mediated or direct degranulation of mast cells in response to antigens, drugs, chemical compounds, or proteases.¹⁸ In children the main cause of urticaria is infection, although when antibiotics or other drugs have been administered, it is difficult to determine whether drugs play a role because of the time line. Drug-induced urticaria can appear within the first 2 weeks after starting a drug. β -Lactam antimicrobials, sulfonamides, and NSAIDs are the most common reported causes.¹⁹ NSAIDs can produce urticarial reactions resulting from both immunologic and nonimmunologic intolerance, the latter attributable to enhanced synthesis of leukotrienes.²⁰ Characteristically, nonimmunologic urticarial reactions are usually retarded, starting 24 hours after drug intake, unlike type I immunologic reactions that are usually immediate.

Acute urticaria is manifested by wheals or hives (**Fig. 2**) that appear as pruritic erythematous or pale-pink edematous patches, which coalesce into plaques of varying size. Individual lesions last less than 24 to 36 hours but reappear in subsequent attacks with asymmetric distribution. The condition is self-limiting and can last up to 6 weeks, resolving without residual signs. There are some particularities of urticaria in children; pruritus is an inconstant symptom and angioedema is relatively frequent. Annular or polycyclic giant lesions are not uncommon in infants.²¹ The wheals can evolve into purpuric macules because of capillary fragility (**Fig. 3**). Usually children with urticaria have a good general status.²² Angioedema describes large subcutaneous swellings of the eyelids, hands and feet, genitalia, or even mucous membranes; it can co-occur with urticaria or appear isolated.²³

These types of reactions are mild and, in general, non-life-threatening, but cause discomfort and parent anxiety.²⁴ Anaphylaxis, also a type I hypersensitivity reaction, is a life-threatening condition that may follow a course with urticarial lesions plus systemic symptoms including weakness, dyspnea, hypotension, abdominal pain, diarrhea, vomiting, and circulatory collapse.²³ It often occurs after ingestion of food, but



Fig. 2. Typical wheals appear as pruritic, erythematous or pale pink, edematous patches, which coalesce into plaques of varying size.



Fig. 3. Wheals or hives can look like annular or polycyclic lesions in infants.

can also be drug related. Although incidence varies according to different reports, approximately 9% of the cases of drug-induced anaphylaxis occur in children younger than 18 years.²⁵ There have been reports of anaphylaxis following immunizations, although this remains a rare adverse event. No cases were related to vaccines given as part of the routine infant and preschool immunization program, despite more than 5.5 million vaccines being delivered per year.²⁶

Treatment consists of withdrawal of the causative drug and antihistamines to control pruritus. A short course of oral steroids can be used to control symptoms in refractory cases. Anaphylaxis treatment goes beyond the aims of this article, and consists of rapid administration of epinephrine and life-support therapy.

Serum Sickness–Like Reactions

Serum sickness–like reaction (SSLR) is considered a drug reaction characterized by the triad of rash, arthralgia, and fever, without evidence of cutaneous or systemic vasculitis. It may occur within the first 3 weeks after a drug is started. Its pathophysiology is not well known and is not thought to be a type III hypersensitivity reaction.²⁷ Historically cefaclor was frequently associated with SSLR, with an estimated frequency of 1% to 2% of all children who received cefaclor. Despite a decline in the use of cefaclor, SSLR continues to occur in the pediatric population in association with a variety of antibiotic agents such as penicillins, tetracyclines, cefprozil, sulfonamides, macrolides, griseofulvin, and itraconazole.^{23,28}

SSLR produces a rash that can be urticarial, or may take the form of polycyclic hives with central clearing that may appear ecchymotic or morbilliform. In contrast to true urticaria, lesions are fixed and do not fade within 24 to 36 hours.²⁹ Accompanying symptoms are frequent, including malaise, fever, lymphadenopathy, splenomegaly, proteinuria, and arthralgia.²³ Differential diagnosis with these symptoms must be made with DRESS syndrome, which usually manifests also with facial edema and eosinophilia. The biopsy of SSLR shows edema on the dermis, with superficial peri-vascular urticarial lymphocytic infiltrate and no evidence of vasculitis.²⁷

The rash usually resolves between 1 and 6 weeks after the causative drug is withdrawn, and the treatment is symptomatic, with antihistamines to control pruritus and NSAIDs to relieve pain and fever.

Maculopapular Exanthems

Maculopapular exanthems are the most common type of drug-induced eruption, usually beginning 7 to 14 days after initiation of medication in nonsensitized patients. If

a patient has been previously sensitized, the first signs of this CADR on the skin can appear as soon as 6 to 12 hours after drug intake.^{6,30} Drugs frequently associated with this condition include penicillins, sulfonamides, cephalosporins, and antiepileptic medications. This type of reaction is more frequent in the presence of viral infections, especially acute Epstein-Barr virus (EBV) infections, although its incidence in well-designed studies may be no higher than 33%,³¹ much lower than the previously reported 90% to 100%.²³ Clinically the eruption starts on the trunk and progresses to the face and extremities, producing diffuse erythroderma in some cases. The maculopapular exanthem is usually morbilliform (Fig. 4). Signs of alarm such, as mucous membrane involvement or the Nikolsky sign, do not occur. Palms and soles may be mildly affected, and other symptoms may include low-grade fever and pruritus. The evolution to resolution usually takes about 2 weeks, with the exanthem turning brownish-red and resolving with desquamation.

The pathophysiology is thought to be a T-cell-mediated hypersensitivity reaction, type IVc according to the modified Coombs and Gell classification (see earlier discussion).³

Differential diagnoses include viral infections, mostly indistinguishable from CADRs and very frequent in children (EBV, human herpesvirus 6, adenovirus), bacterial infections (*Streptococcus pyogenes*), systemic juvenile arthritis (Still disease), Kawasaki syndrome, graft-versus-host disease in hematopoietic stem cell transplant recipients, and erythema multiforme.³²

Most of these skin reactions are not severe or life-threatening,³⁰ and thus need only symptomatic treatment. If the rash is mild and the drug cannot be discontinued, it can be kept under strict monitoring. It is important to remark here that maculopapular exanthems do not progress to severe CADR, but sometimes these severe reactions may resemble at onset an innocent exanthem or a morbilliform maculopapular eruption. Assessing the likelihood of a severe CADR can be very challenging at the beginning, and the caring physician should be alert for alarm signs, such as mucous membrane lesions, bullae, Nikolsky sign, facial edema, or fever.



Fig. 4. Macules and erythematous papules of morbilliform appearance.

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

DRESS syndrome is a potentially life-threatening severe ADR, with a potential 10% mortality rate.³³ Its exact mechanism of production remains unknown. A type IVb hypersensitivity reaction⁸ has been proposed, but reactivation of viral infections, particularly herpesvirus 6, has also been shown to play a role.³⁴ It is also well determined that individuals with specific HLA haplotypes are predisposed to develop DRESS syndrome when exposed to certain medications.³⁵

The European Registry of Severe Cutaneous Adverse Reaction study group (RegiSCAR), a multinational registry of severe CADR, found that antiepileptic drugs, especially carbamazepine but also lamotrigine, phenobarbital, phenytoin, valproic acid, and zonisamide, were involved in 35% of the cases, allopurinol in 18%, antimicrobial sulfonamides and dapsone in 12%, and other antibiotics in 11%. The median time interval after drug intake was 22 days for all drugs with very probable causality, with differences existing between drugs.³⁶

DRESS usually starts with unspecific prodromal symptoms such as asthenia, pruritus, and fever. Unexplained fever of 38° to 40°C can precede by several weeks the cutaneous rash, which usually appears as a widespread, unspecific maculopapular morbilliform exanthem. The rash is present in 95% of patients,³⁶ starting on the face and upper trunk, then expanding quickly downward and developing a violaceous hue. Intense facial edema is seen in 25% of patients (Fig. 5).³³

Systemic involvement includes lymph node enlargement, hematologic abnormalities with eosinophilia or atypical lymphocytes, and multiple internal organ dysfunction.³⁷ The liver is the most frequently affected organ, but renal failure, pulmonary impaired function, pneumonitis, heart failure secondary to myocarditis, neurologic symptoms manifesting as meningitis or encephalitis, gastroenteritis, and thyroid or pancreatic dysfunction can also occur.^{33,38}

Skin histopathology shows a perivascular lymphocytic infiltrate in the papillary dermis, with eosinophils, atypical lymphocytes, and spongiosis.

Diagnosis is based on proposed diagnostic criteria by RegiSCAR or the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) (Boxes 2 and 3).³⁹

Vesiculobullous Eruptions (SJS and TEN)

TEN and SJS are severe adverse mucocutaneous drug reactions producing epidermal and mucosal detachment. These reactions are considered a continuum of the same disease. There are approximately 1 or 2 cases of SJS/TEN per 1,000,000 individuals annually, and it is considered a medical emergency as it is potentially fatal.



Fig. 5. Generalized, violaceous maculopapular exanthem in a patient with DRESS syndrome.

Box 2

Diagnostic criteria for DRESS established by the J-SCAR group

1. Maculopapular rash developing >3 weeks after starting with a limited number of drugs

2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug

3. Fever (>38°C)

4. Liver abnormalities^a (alanine aminotransferase >100 U/L)

5. Leukocyte abnormalities (at least 1 present)

a. Leukocytosis (>11 × 10⁹/L)

b. Atypical lymphocytosis (>5%)

c. Eosinophilia (>1.5 × 10⁹/L)

6. Lymphadenopathy

7. Human herpesvirus-6 reactivation

For correct “typical” diagnosis, all 7 criteria must be met; for atypical hypersensitivity syndrome the presence of criteria 1 to 5 is necessary.

^a This can be replaced by other organ involvement such as renal involvement.

The main causes of SJS/TEN are drugs, but some infections such as *Mycoplasma pneumoniae* and herpes simplex virus are well documented.⁹ In children, the most common causative drugs are antibiotics (sulfonamides, penicillins, cephalosporins, and macrolides), followed by antiepileptics (phenobarbital, valproic acid, lamotrigine, carbamazepine), benzodiazepines, NSAIDs (salicylates, acetaminophen, and others), and more rarely corticosteroids, antihistamines H1, mucolytic agents, vitamins, or even vaccines.⁴⁰

There is a strong genetic association between HLA and a specific drug-induced SJS/TEN.⁴¹ There have been some studies suggesting that HLA testing before starting therapy would be effective to identify individuals at risk of hypersensitivity (Fig. 6, Table 2).⁴²

Box 3

Diagnostic criteria for DRESS proposed by the RegiSCAR

1. Acute rash

2. Reaction suspected drug related

3. Hospitalization

4. Fever (>38°C)

5. Laboratory abnormalities (at least 1 present)

a. Lymphocytes above or below normal

b. Low platelets

c. Eosinophilia

6. Involvement of >1 internal organ

7. Enlarged lymph nodes >2 sites

The first 3 criteria are necessary for diagnosis, and the presence of 3 out of the other 4.



Fig. 6. Epidermal detachment presenting as blisters and areas of denuded skin. The extension of skin detachment determines the diagnosis of Stevens-Johnson syndrome or toxic epidermal necrosis.

Clinical manifestations at the beginning can be unspecific. Patients can manifest fever, discomfort, stinging in the eyes, and difficulty swallowing. A few days later, erythema and purpuric annular macules may appear on the trunk and face, followed by mucocutaneous tenderness with hemorrhagic erosions and epidermal detachment presenting as blisters and areas of denuded skin. The extension of skin detachment determines the diagnosis; if skin detachment affects less than 10% of the body surface area (BSA), a diagnosis of SJS is made; if more than 30% BSA, TEN is diagnosed; and if between 10% and 30% BSA is involved, SJS/TEN overlap is considered.

Diagnosis is mainly clinical. The epidermal detachment can be revealed by exerting a tangential mechanical pressure on the erythematous zones (Nikolsky sign), although it should be noted that this sign is positive in other bullous disorders.¹⁶ The histologic analysis of a skin biopsy shows full-thickness epidermal necrosis and detachment caused by extensive keratinocyte apoptosis.

Management of patients with SJS/TEN requires rapid diagnosis and evaluation of the prognosis using the scoring system (SCORTEN) based on independent clinical

Table 2 Genetic associations between human leukocyte antigens (HLA) and a specific drug-induced Stevens-Johnson syndrome/toxic epidermal necrosis		
Population	HLA	Drug/Medication
Asian	HLA-B*1511	Carbamazepine
	HLA-B*1518	
European	HLA-B*73	Oxicam
	HLA-B*12	
	HLA-A*2	
	HLA-B*12	Sulfamethoxazole
	HLA-A*29	
Asian and European	HLA DR7	Allopurinol Carbamazepine/lamotrigine/ oxcarbazepine/phenytoin Carbamazepine
	HLA-B*5801	
	HLA-B*1502	
	HLA-B*3101	

and laboratory variables within 24 hours of admission and at day 3; these variables include age, malignancy, BSA detached, tachycardia, and serum glucose, bicarbonate, and urea.⁴³ Treatment implies the identification and interruption of the suspected causative drug. Patients with suspicion of SJS/TEN should be referred to a burns unit or pediatric intensive care unit with expertise in caring for such patients within 7 days of diagnosis. It is important to bear in mind that the different countries and centers may have different protocols for management, with which physicians should be familiar. This knowledge has been shown to dramatically decrease the mortality rate. Prophylactic antibiotics are not routinely advised.⁴⁴ Wound care is important, but no specific approach has been shown to significantly modify survival rates or reepithelialization of the skin. Surgical debridement with nonadherent silver-impregnated gauze⁴⁵ and biosynthetic skin substitutes such as Biobrane have been used with success.⁴⁶ An eminently feasible way of managing the skin in these patients is antishear wound care, which consists of puncturing bullae with a sterile needle and leaving the skin on top to act as a biological dressing; this provides an effective alternative approach to wound care with equivalent success.⁴⁷ Intravenous Ig (IVIg), cyclosporin, corticosteroids, and even biological therapies have been used, with varying rates of success. More than 50% of patients surviving TEN suffer from long-term sequelae of the disease,¹⁶ mostly ocular complications including dry eyes, trichiasis, symblepharon, distichiasis, visual loss, and corneal ulceration. It should be noted that the diagnosis of TEN does not imply a more severe ocular involvement than SJS, and an appropriate intervention during acute ocular disease is key to preventing late complications (see Fig. 6).⁴⁸

Acute Generalized Exanthematous Pustulosis

AGEP is a serious cutaneous reaction, considered to be a type IVd hypersensitivity reaction.⁴ Its incidence is about 1 to 5 cases per million inhabitants per year. It has been rarely described in children and is usually related to infections, both viral (parvovirus B19, Coxsackie, cytomegalovirus) and bacterial (*Chlamydia pneumoniae*, *M pneumoniae*), or even vaccinations.⁶ When drugs are involved, penicillins, cefixime, clindamycin, vancomycin, and macrolides are the most common agents.⁴⁹

AGEP presents as an acute onset of asymptomatic or mildly pruritic erythema with hundreds of superimposed sterile, nonfollicular pustules, smaller than 5 mm in diameter. Fever and asthenia are often associated. In very rare cases, children may present with overlapping features of other ADRs such as DRESS (with facial edema) or SJS/TEN (some epidermal detachment) (Fig. 7).⁶



Fig. 7. Mildly pruritic erythema with hundreds of superimposed sterile, nonfollicular pustules, smaller than 5 mm, in a patient with AGEP.

Typical histologic findings include subcorneal pustules with neutrophils, along with marked dermal edema, and perivascular infiltrates with occasional neutrophils. Eosinophils in the superficial dermis and focal necrosis of keratinocytes can also be seen.⁵⁰

Differential diagnosis must be made with pustular psoriasis, DRESS syndrome with pustules, and subcorneal pustular dermatosis (Sneddon-Wilkinson disease).

Withdrawal of the offending factor is the main therapy, with expected spontaneous resolution in 1 to 2 weeks, with a pattern of punctate scaling. Scarring is absent or limited. Antihistamines can be used for pruritus, and a short course of oral corticosteroids may be helpful.⁵¹

Miscellaneous

Fixed drug eruption

Fixed drug eruption is a drug reaction presenting clinically as a localized, circumscribed, round to oval erythematous or violaceous patch, sometimes with vesicles and blisters.⁵² Its main characteristic is that it recurs in the same site each time a particular drug is administered.⁵³ It may be very difficult to determine the causative drug because most parents often think that trivial over-the-counter medications are harmless,¹ and do not relate the medication with the episode. The pathogenesis is not clear, but cytotoxic memory CD8 cells in the epidermis may play a major role by releasing proinflammatory cytokines on stimulation by drug intake.⁵⁴ The most common drugs implicated in fixed drug eruption are antibiotics, especially trimethoprim-sulfamethoxazole, NSAIDs, and paracetamol.^{55,56}

The clinical presentation is a single patch or multiple ones with erythema and edema accompanied by pruritus or pain on the lesion. The patch usually turns dusky or violaceous, and resolves after the discontinuation of the medication involved, leaving residual hyperpigmentation. Some lesions may contain vesicles or large bullae. The diagnostic hallmark is the recurrence at previously affected sites.⁵³ Lesions first occur within 2 weeks of original ingestion of the medication, but subsequent intakes lead to much more rapid reappearance (**Fig. 8**).⁵⁷

Acneiform eruptions

These eruptions are types of pustular reactions in acne-prone areas. The key medications producing this type of reaction are the corticosteroids, with a risk directly proportional to the dose and duration of therapy. It can also be elicited after intake of androgens, lithium, iodides, phenytoin, and isoniazid.⁵⁷ New drugs used for the treatment of solid tumors, such as the inhibitors of epidermal growth factor receptor (EGFR/HER1) cetuximab, erlotinib, and panitumumab, are therapeutic agents with a high incidence of acneiform eruptions.⁵⁸

Typical lesions are follicular papules and sterile pustules in acne-prone sites with no mucosal changes. In contrast to acne vulgaris, the acneiform reactions can also appear in atypical areas for acne, such as the arms and legs. The lesions are characteristically monomorphic and heal without scarring.⁵¹

Benzoyl peroxide preparations with topical or oral antibiotics, as well as topical tretinoin cream can be helpful, but in such cases it will be necessary to withdraw the medication.

Others

Other less frequent or milder drug reactions that may involve the skin of children include drug-induced lupus, lichenoid drug reactions, psoriasiform reactions, vasculitis, bullous pemphigoid, linear IgA bullous dermatosis (LABD), pseudoporphyria, dyschromatosis, nail abnormalities, gingival enlargement, phototoxic and photoallergic reactions, cutaneous lymphoid hyperplasia (pseudolymphoma), warfarin-induced



Fig. 8. Fixed drug eruption can be seen as an erythematous round or oval patch that usually turns dusky or violaceous.

necrosis (WIN), and heparin-induced necrosis (HIN), among others.^{58,59} WIN or HIN are easily recognized because of necrosis in acral or fat-rich areas such as the abdomen in patients receiving these medications; erythema occurs, followed by purpura and necrosis. WIN is due to protein C deficiency, and patients affected by HIN have heparin antibodies with or without thrombocytopenia.^{60,61}

LABD deserves special mention because of the singularity of its clinical presentation. It has been reported that almost two-thirds of LABD cases may be drug induced, but this is rare in children, in whom LABD behaves as an idiopathic autoimmune blistering disease. Commonly implicated medications include antibiotics (frequently vancomycin), NSAIDs, and diuretics.⁶² The clinical picture consists in the acute development of vesicles and bullae often on sites of noninflamed skin. Frequently new blisters form at the periphery of the resolving lesions forming rosette-like plaques, widely distributed on the face, trunk, and extremities, especially around the genitals and perioral areas.⁶³ The prognosis is excellent, with rapid resolution following cessation of the offending drug; there have been some reports of high morbidity because of pruritus.⁶²

Children with malignancy are very much exposed to drugs and are at risk of skin reactions. Such reactions can include mild and well-known reactions such as anagen effluvium, mucositis, and skin pigmentation changes,⁶⁴ or be truly life-threatening, such as severe and generalized acneiform reactions (**Fig. 9**), DRESS, SJS/TEN, or AGEP.

DIFFERENTIAL DIAGNOSIS

Assigning a cutaneous reaction to a particular drug can be very difficult, because many patients with skin conditions such as viral exanthems or Kawasaki disease may have received oral medications before their rash has appeared.⁶⁵ When examining a child with a suspected CADR, personal history (allergies or previous diseases), and history of recent medications and their doses should be recorded. Assessment of



Fig. 9. Generalized acne-like reaction in an adolescent with malignant recurrent glioma receiving adjuvant chemotherapy with bevacizumab and steroids.

the general status is also very important. The chronology of onset and evolution of the skin lesions allows an estimation of the type of hypersensitivity reaction and the causative drug.³⁰

The authors suggest an approach based on the type of skin lesions: wheals, macules and papules, pustules, and vesicles and bullae. Wheals indicate an urticarial rash, and thus common urticarial reactions and SSLRs are likely. The presence of fever, arthralgia, and asthenia suggest an SSLR. Mucous involvement with angioedema and anaphylaxis are the most harmful complications in this group.

If the rash is maculopapular, an incipient vesiculobullous disease and mucosal involvement must be ruled out. Mucosal involvement or minimal epidermal detachment might indicate severe CADR such as SJS/TEN. If a true maculopapular reaction is observed, a common morbilliform rash must be differentiated from DRESS syndrome. The presence of fever, lymphadenopathy, and liver or spleen enlargement suggest the latter.

If the Nikolsky sign is positive or there are vesicles or bullae or mucous membrane involvement, a bullous exanthem is considered, and SJS/TEN is strongly suggested. The presence of pustules over a diffuse erythema should lead one to consider AGEF (Fig. 10).

DIAGNOSTIC RECOMMENDATIONS

Laboratory Studies

Because many ADRs are systemic hypersensitivity reactions involving not only the skin, a thorough investigation is mandatory to rule out internal organ involvement (Fig. 11).³⁰ This evaluation can be done in the emergency room fairly quickly, with a complete blood count panel, basic serum chemistry for renal and liver function, and urinalysis. Radiology tests are not usually necessary unless a severe ADR is suspected. For example, if DRESS syndrome is suspected, a chest radiograph or computed tomography scan is mandatory to search for interstitial pneumonitis or pleural effusion.⁶⁶

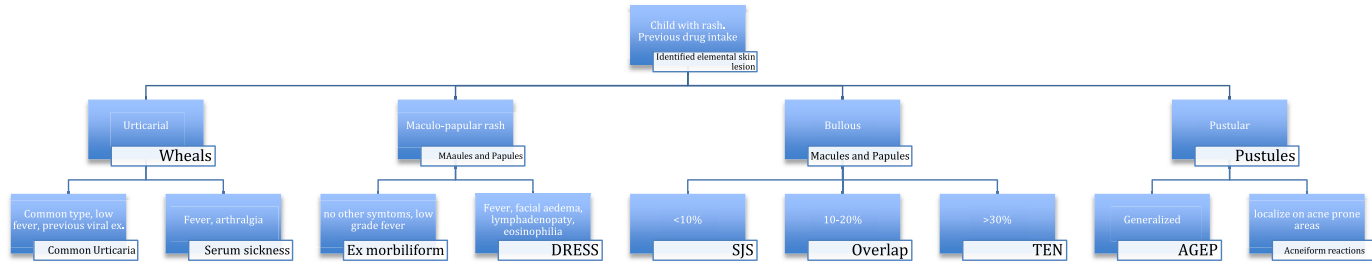


Fig. 10. Initial approach with simplified differential diagnosis. SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

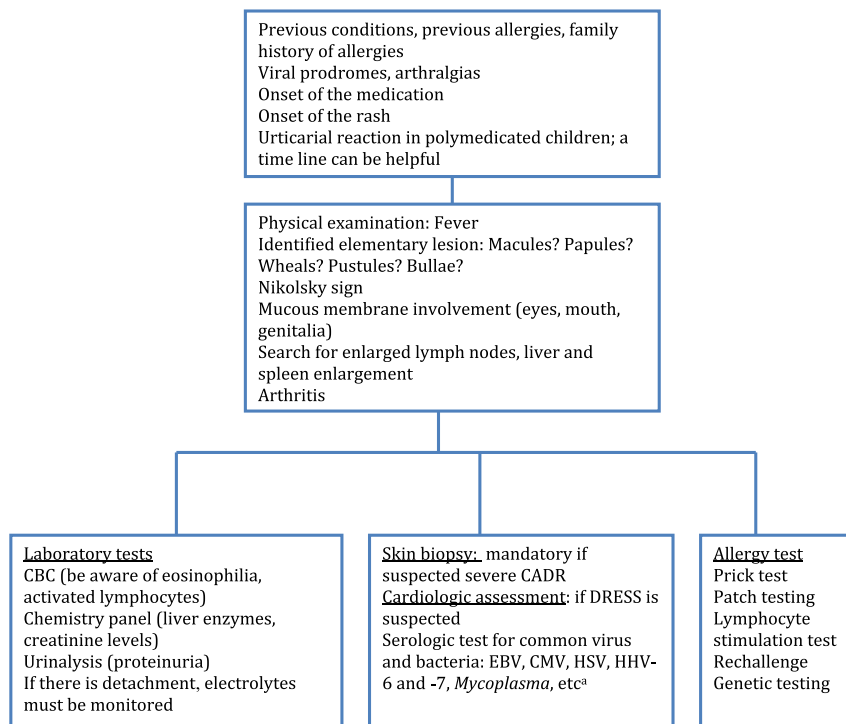


Fig. 11. Approach to the patient with suspected drug reaction. ^a It is important that a positive serologic test does not exclude the diagnosis of a CADR, because some of these reactions may occur in the context of a viral infection or reactivation (eg, DRESS with HHV-6 or maculopapular exanthema with EBV, and antibiotics). CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus.

Skin biopsy can be helpful, but is not indicated in all cases. In urticarial reactions and maculopapular exanthems biopsies are often unspecific and unhelpful, and are not routinely recommended. If DRESS syndrome, SJS/TEN, or AGEP is suspected, a skin biopsy must be performed immediately.

Identifying the suspected causative drug is important in avoiding reexposure. After complete recovery and within an interval of 6 weeks to 6 months, diagnostic procedures can be undertaken. Allergy evaluation with skin prick and intracutaneous testing is indicated for immediate reactions. Patch testing for delayed reactions and, in special cases, the lymphocytic transformation test (LTT), usually performed by an immunologist or allergist, can help identify causes of severe reactions. The LTT attempts to quantify T-cell activation in response to a drug. Unfortunately this test cannot be routinely recommended because it is not yet standardized,⁶⁷ although it has been shown to be a reliable test when performed at the appropriate time depending on the type of drug reaction. A lymphocyte transformation test should be performed within 1 week after the onset of rashes in patients with maculopapular exanthems and SJS/TEN, and after 5 to 8 weeks in patients with DRESS.⁶⁸ Finally, challenging with drug reexposure should be carefully considered and conducted by an allergist. It is important that this is not indicated in cases of DRESS or SJS/TEN because of the greater severity of the recurring reaction.⁶⁵

Although all the data found in recent studies about HLA testing and specific drug reactions need further investigation and clinical correlation before general genetic testing can be recommended, it is thought that this approach will lead to improved prevention of severe ADRs and a more personalized medicine. The Food and Drug Administration recently approved the recommendation of genetic testing before starting abacavir (HLA B*5701) and carbamazepine (HLA B*1502 in patients with Asian ancestry) before starting therapy.⁶⁹

THERAPEUTIC RECOMMENDATIONS

Nonpharmacologic Treatment

The main goal of treatment is to discontinue the suspected drug, although this is not always possible. If a patient is on several medications, it may be difficult to identify exactly which is the causative drug. In such cases one might opt for sequential withdrawal considering the type of reaction, the temporal relation, and the frequency with which the drug has been associated with the patient's cutaneous reaction, always keeping in mind that the patient should be monitored closely.

Pharmacologic Treatment

Treatment varies according to the type of reaction and its severity. Urticarial reactions and mild cases of maculopapular morbilliform exanthems can be managed only symptomatically with antihistamines, but if the rash is very symptomatic, topical corticosteroids can help to reduce skin inflammation and pruritus. When the reaction is moderate to severe, systemic corticosteroids can be helpful, usually 1 mg/kg/d until resolution with careful tapering.²² For severe CADR, because they are rare and there are no available randomized controlled trials, the management is based on cohort series and case reports. AGEF can also be managed empirically with corticosteroids.³

For DRESS syndrome the treatment of choice depends on the severity and response to the withdrawal of the suspected drug. Oral steroids at 1 mg/kg/d, intravenous methylprednisolone bolus at 30 mg/kg/d, and corticosteroid-sparing agents such as IVIg, plasmapheresis, cyclophosphamide, and cyclosporine have all been used, with variable results.^{70–72}

No clear therapeutic guidelines regarding the use of medications for the treatment of SJS/TEN in children exist.⁷³ Undoubtedly, appropriate skin and mucosal care along with life support are essential. Patients should be transferred to the pediatric intensive care unit. Systemic corticosteroids, plasmapheresis, IVIg, and immunosuppressive agents have been reported to be effective, with no evidence favoring any of them in particular.⁷⁴ The use of cyclosporin based on the capability of calcineurin inhibitors to rapidly block the functions of cytotoxic T cells has been advocated.⁷⁵

CADRs in children on chemotherapy for cancer may pose important problems, because suspected drugs may be life-saving and cannot be withdrawn. The goal in these cases is to keep the patient comfortable and treat the CADR while maintaining the medication, unless a severe or even fatal reaction occurs. For example, acneiform drug reactions attributable to EGFR inhibitors can be treated with oral corticosteroids and topical and oral retinoids, or can be prevented with oral doxycycline or minocycline before and during treatment.⁵⁸

SUMMARY

- ADRs frequently manifest on the skin. CADR in children are a diagnostic challenge because these reactions can mimic many other childhood eruptions.

- Urticaria is an immediate hypersensitivity reaction, usually IgE mediated, predominantly manifesting as wheals.
- Maculopapular morbilliform exanthems are the most frequent form of hypersensitivity reactions in children.
- DRESS syndrome is a systemic and potentially fatal CADR manifesting as fever, rash, lymph node enlargement, eosinophilia, and multiorgan dysfunction.
- SJS and TEN are severe CADRs characterized mainly by mucous and cutaneous necrosis with epidermal detachment.
- Fixed drug eruption is a curious drug reaction presenting clinically as a circumscribed, erythematoviolaceous, round to oval plaque, recurring in the same place after drug reexposure.
- AGEP is a severe CADR characterized by erythroderma and numerous small, sterile, nonfollicular pustules.
- New and old chemotherapeutic agents continue to have a high incidence in CADRs.
- Diagnostic testing after resolution should be aimed at identifying the causative drug so as to prevent morbidity and mortality associated with reexposure.
- A high index of suspicion should be maintained to make a rapid diagnosis and in managing children with severe CADRs.

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