Chapter 16: Dermatologic Drug Reactions and Common Skin Conditions

INTRODUCTION

- *Drug-induced skin reactions* can be irritant or allergic in origin. Allergic drug reactions are classified into exanthematous, urticarial, blistering, and pustular eruptions.
- Severe cutaneous adverse reactions to drugs (SCARs) include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).
- Skin disorders discussed in this chapter include contact dermatitis, diaper dermatitis, and atopic dermatitis.

PATHOPHYSIOLOGY

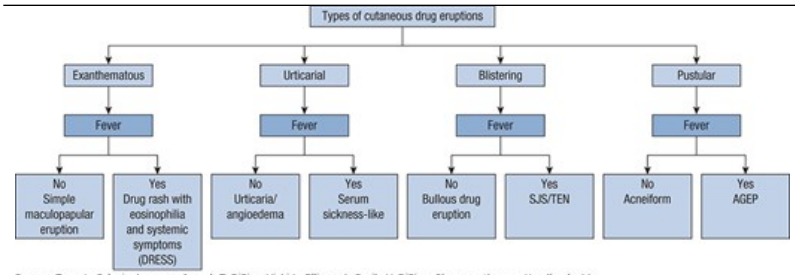
- *Exanthematous* drug reactions include maculopapular rashes and drug hypersensitivity syndrome. *Urticarial* reactions include urticaria, angioedema, and serum sickness-like reactions. *Blistering* reactions include fixed drug eruptions, Stevens–Johnson syndrome, and toxic epidermal necrolysis. *Pustular* eruptions include acneiform drug reactions and acute generalized exanthematous pustulosis (AGEP) (**Fig. 16-1**).
- Drug-induced *hyperpigmentation* may be related to increased melanin (eg, hydantoins), direct deposition (eg, silver, mercury, tetracyclines, and antimalarials), or other mechanisms (eg, fluorouracil).
- Drug-induced photosensitivity reactions may be *phototoxic* (a nonimmunologic reaction) or *photoallergic* (an immunologic reaction). Medications associated with phototoxicity include amiodarone, tetracyclines, sulfonamides, psoralens, and coal tar. Common causes of photoallergic reactions include sulfonamides, sulfonylureas, thiazides, nonsteroidal anti-inflammatory drugs (NSAIDs), chloroquine, and carbamazepine.
- *Contact dermatitis* is skin inflammation caused by irritants or allergic sensitizers. In *allergic contact dermatitis* (ACD), an antigenic substance triggers an immunologic response, sometimes several days later. *Irritant contact dermatitis* (ICD) is caused by an organic substance that usually results in a reaction within a few hours of exposure.
- *Diaper dermatitis* (diaper rash) is an acute, inflammatory dermatitis of the buttocks, genitalia, and perineal regions that are covered by the diaper. It is a type of contact dermatitis resulting from direct fecal and moisture contact with the skin in an occlusive environment.
- *Atopic dermatitis* (eczema) is an inflammatory condition with genetic, environmental, and immunologic mechanisms. Neuropeptides, irritation, or pruritus-induced scratching may cause release of proinflammatory cytokines from keratinocytes.

FIGURE 16-1

Types of cutaneous drug eruptions.

(AGEP, acute generalized exanthematous pustulosis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.)

(*Adapted from Knowles, S. Drug-Induced Skin Reactions, Table 3, Description of Drug Eruptions. In: Compendium of Therapeutic Choices for Minor Ailments. 2nd ed. Ottawa, ON: Canadian Pharmacists Association; © 2016.*)



CLINICAL PRESENTATION

- *Maculopapular skin reaction* presents with erythematous macules and papules that may be pruritic. Lesions usually begin within 7–10 days after starting the offending medication and generally resolve within 7–14 days after drug discontinuation. Because of the delayed reaction, the offending agent could be discontinued (eg, a 7-day antibiotic treatment course) before the lesions appear. Lesions may spread and become confluent. Common culprits include penicillins, cephalosporins, sulfonamides, and some anticonvulsants.

- *Drug hypersensitivity syndrome* (also known as drug reaction with eosinophilia and systemic symptoms or DRESS) is an exanthematous eruption accompanied by fever, lymphadenopathy, and multiorgan involvement (kidneys, liver, lung, bone marrow, heart, and brain). Signs and symptoms begin 1–4 weeks after starting the offending drug, and the reaction may be fatal if not promptly treated. Drugs implicated include allopurinol, sulfonamides, some anticonvulsants (barbiturates, phenytoin, carbamazepine, and lamotrigine), and dapsone.

- *Urticaria* and *angioedema* are simple eruptions that are caused by drugs in 5%–10% of cases. Other causes are foods (most common) and physical factors such as cold or pressure, infections, and latex exposure. Urticaria may be the first sign of an emerging anaphylactic reaction characterized by hives, extremely pruritic red raised wheals, angioedema, and mucous membrane swelling that typically occurs within minutes to hours. Offending drugs include penicillins and related antibiotics, aspirin, sulfonamides, radiograph contrast media, and opioids.

- *Serum sickness-like reactions* are complex urticarial eruptions presenting with fever, rash (usually urticarial), and arthralgias usually within 1–3 weeks after starting the offending drug.

- *Fixed drug eruptions* present as pruritic, red, raised lesions that may blister. Symptoms can include burning or stinging. Lesions may evolve into plaques. These so-called fixed eruptions recur in the same area each time the offending drug is given. Lesions appear and disappear within minutes to days, leaving hyperpigmented skin for months. Usual offenders include tetracyclines, barbiturates, sulfonamides, codeine, phenolphthalein, and NSAIDs.

- *Stevens–Johnson syndrome* (SJS) and *toxic epidermal necrolysis* (TEN) are blistering eruptions that are rare but severe and life-threatening. They are considered variants of the same disorder and are often discussed together as SJS/TEN. Onset occurs within 7–14 days after drug exposure. Patients present with generalized tender/painful bullous formation with fever, headache, and respiratory symptoms leading to rapid clinical deterioration. Lesions show rapid confluence and spread, resulting in extensive epidermal detachment and sloughing. This may result in marked fluid loss, hypotension, electrolyte imbalances, and secondary infections. Usual offending drugs include sulfonamides, penicillins, some anticonvulsants (hydantoins, carbamazepine, barbiturates, and lamotrigine), NSAIDs, and allopurinol.

- *Acneiform drug reactions* are pustular eruptions that induce acne. Onset is within 1–3 weeks. Common culprits include corticosteroids, androgenic hormones, some anticonvulsants, isoniazid, and lithium.

- *Acute generalized exanthematous pustulosis* (AGEP) has an acute onset (within days after starting the offending drug), fever, diffuse erythema, and many pustules. Generalized desquamation occurs 2 weeks later. Common offending drugs include β-lactam antibiotics, macrolides, and calcium channel blockers.

- *Sun-induced skin reactions* appear similar to a sunburn and present with erythema, papules, edema, and sometimes vesicles. They appear in areas exposed to sunlight (eg, ears, nose, cheeks, forearms, and hands).

- *Diaper dermatitis* results in an erythematous rash, and severe cases may have vesicles and oozing erosions. The rash may be infected by *Candida*

species and present with confluent red plaques, papules, and pustules.

- *Atopic dermatitis* presents differently depending on age. In infancy, an erythematous, patchy, pruritic, papular skin rash may first appear on the cheeks and chin and progress to red, scaling, oozing lesions. The rash affects the malar region of the cheeks, forehead, scalp, chin, and behind the ears while sparing the nose and paranasal creases. Over several weeks, lesions may spread to extensor surfaces of the lower legs (due to the infant's crawling), and eventually the entire body may be involved except for the diaper area and nose. In childhood, the skin is often dry, flaky, rough, and cracked. Pruritus is a quintessential feature, and a diagnosis cannot be made if there is no history of itching. Scratching and rubbing itchy skin may result in bleeding and lichenification. In adulthood, lesions are more diffuse with underlying erythema. The face is commonly involved and may be dry and scaly. Lichenification may be seen.

DIAGNOSIS

- A comprehensive patient history is important to obtain the following information:
  - ✔ Signs and symptoms (onset, progression, timeframe, lesion location and description, presenting symptoms, and previous occurrence)
  - ✔ Urgency (severity, area, and extent of skin involvement; signs of a systemic/generalized reaction or disease condition)
  - ✔ Medication history (temporal correlation, previous exposure, and nonprescribed products)
  - ✔ Differential diagnosis
- Lesion assessment includes identifying macules, papules, nodules, blisters, plaques, and lichenification. Some skin conditions cause more than one type of lesions.
- Inspect lesions for color, texture, size, and temperature. Areas that are oozing, erythematous, and warm to the touch may be infected.

TREATMENT

- Goals of Treatment: Relieve bothersome symptoms, remove precipitating factors, prevent recurrences, avoid adverse treatment effects, and improve quality of life.

Drug-Induced Skin Reactions

- If a drug-induced skin reaction is suspected, the most important treatment is discontinuing the suspected drug as quickly as possible and avoiding use of potential cross-sensitizers.
- The next step is to control symptoms (eg, pruritus). Signs or symptoms of a systemic or generalized reaction may require additional supportive therapy. For high fevers, acetaminophen is more appropriate than aspirin or another NSAID, which may exacerbate some skin lesions.
- Most maculopapular reactions disappear within a few days after discontinuing the agent, so symptomatic control of the affected area is the primary intervention. Topical corticosteroids and oral antihistamines can relieve pruritus. In severe cases, a short course of systemic corticosteroids may be warranted.
- Treatment of fixed drug reactions involves removal of the offending agent. Other therapeutic measures include topical corticosteroids, oral antihistamines to relieve itching, and perhaps cool water compresses on the affected area.
- Photosensitivity reactions typically resolve with drug discontinuation. Some patients benefit from topical corticosteroids and oral antihistamines, but these are relatively ineffective. Systemic corticosteroids (eg, oral prednisone 1 mg/kg/day tapered over 3 weeks) are more effective.
- For life-threatening SJS/TEN, supportive measures such as maintenance of adequate blood pressure, fluid and electrolyte balance, broad-spectrum antibiotics and vancomycin for secondary infections, and IV immunoglobulin (IVIG) may be appropriate. Corticosteroid use is controversial; if used, employ relatively high doses initially, followed by rapid tapering as soon as disease progression stops.

- Inform patients about the suspected drug, potential drugs to avoid in the future, and which drugs may be used instead. Give patients with photosensitivity reactions information about preventive measures, such as use of sunscreens and sun avoidance.

Contact Dermatitis

- The first intervention involves identification, withdrawal, and avoidance of the offending agent.
- The second treatment is symptomatic relief while decreasing skin lesions. Cold compresses help soothe and cleanse the skin; they are applied to wet or oozing lesions, removed, remoistened, and reapplied every few minutes for a 20- to 30-minute period. If affected areas are already dry or hardened, wet dressings applied as soaks (without removal for up to 20–30 minutes) will soften and hydrate the skin; soaks should not be used on acute exudating lesions. **Calamine lotion** or **Burow solution (aluminum acetate)** may also be soothing.
- **Topical corticosteroids** help resolve the inflammatory process and are the mainstay of treatment. ACD responds better to topical corticosteroids than does ICD. Generally, use higher potency corticosteroids initially, switching to medium or lower potency corticosteroids as the condition improves (see Chapter 17, Table 17–1, for topical corticosteroid potencies).
- **Oatmeal baths** or oral **first-generation antihistamines** may provide relief for excessive itching.
- **Moisturizers** may be used to prevent dryness and skin fissuring.

Diaper Dermatitis

- Management involves frequent diaper changes, air drying (removing the diaper for as long as practical), gentle cleansing (preferably with nonsoap cleansers and lukewarm water), and use of barrier products. **Zinc oxide** has astringent and absorbent properties and provides an effective barrier. **Petrolatum** also provides a water-impermeable barrier but has no absorbent ability and may trap moisture.
- Candidal (yeast) diaper rash should be treated with a topical antifungal agent and then covered by a barrier product. **Imidazoles** are the treatment of choice. The antifungal agents should be stopped once the rash subsides and the barrier product continued to prevent recurrence.
- In severe inflammatory diaper rashes, a very low potency topical corticosteroid **(hydrocortisone 0.5%–1%)** may be used for short periods (1–2 weeks).
- Medical referral is indicated if the rash does not respond after a week of treatment, if pain or inflammation increases during therapy, if ulcerations develop, or if systemic signs or symptoms are present (eg, fever, diarrhea, skin lesions elsewhere).

Atopic Dermatitis

- Nonpharmacologic measures for infants and children include the following:

  ✔ Apply moisturizers frequently throughout the day

  ✔ Give lukewarm baths

  ✔ Apply lubricants/moisturizers immediately after bathing

  ✔ Use nonsoap cleansers (which are neutral to low pH, hypoallergenic, fragrance free)

  ✔ Use wet-wrap therapy (with or without topical corticosteroid) during flare-ups for patients with moderate-to-severe disease. Wet-wrap involves applying damp tubular elasticized bandages and occlusive dressing to the limbs to promote skin hydration and absorption of emollients and topical corticosteroids.

  ✔ Keep fingernails filed short

  ✔ Select clothing made of soft cotton fabrics

✔ Consider sedating oral antihistamines to reduce scratching at night

✔ Keep the child cool; avoid situations that cause overheating

✔ Learn to recognize skin infections and seek treatment promptly

✔ Identify and remove irritants and allergens

- Topical corticosteroids are the drug treatment of choice. Low-potency agents (eg, **hydrocortisone 1%**) are suitable for the face, and medium-potency products (eg, **betamethasone valerate 0.1%**) may be used for the body. For longer-duration maintenance therapy, low-potency corticosteroids are recommended. Use mid-strength and high-potency corticosteroids for short-term management of exacerbations. Reserve ultra-high and high-potency agents (eg, **betamethasone dipropionate 0.05%** and **clobetasone propionate 0.05%**) for short-term treatment (1–2 weeks) of lichenified lesions in adults. After lesions have improved significantly, use a lower-potency corticosteroid for maintenance when necessary. Avoid potent fluorinated corticosteroids on the face, genitalia, and intertriginous areas and in infants.

- The topical immunomodulators **tacrolimus** (Protopic) and **pimecrolimus** (Elidel) inhibit calcineurin, which normally initiates T-cell activation. Both agents are approved for atopic dermatitis in adults and children older than age 2. Tacrolimus ointment 0.03% (for moderate-to-severe atopic dermatitis in patients ages 2 and older) and 0.1% (for ages 16 and older) is applied twice daily. Pimecrolimus cream 1% is applied twice daily for mild-to-moderate atopic dermatitis in patients older than age 2. The most common adverse effect is transient burning at the site of application. Both drugs are recommended as second-line treatments due to concerns about a possible risk of cancer. For this reason, sun protection factor (SPF) 30 or higher is recommended on all exposed skin areas.

- **Coal tar preparations** (**crude coal tar**, **liquor carbonis detergens**) have been widely used, but few controlled trials support their efficacy. These products are also staining and malodorous, although newer products may be more cosmetically acceptable. They are not recommended on acutely inflamed skin, since this may result in additional skin irritation.

- **Crisaborole** (Eucrisa) 2% ointment is a phosphodiesterase (PDE) 4 inhibitor approved for treatment of mild-to-moderate AD in adults and children 2 years of age or older. A thin layer of ointment is applied twice daily to affected areas. Burning or stinging may occur at the site of application.

- Phototherapy may be recommended when the disease is not controlled by topical corticosteroids and calcineurin inhibitors. It may also be steroid sparing, allowing for use of lower-potency corticosteroids, or even eliminating the need for corticosteroids in some cases.

- **Dupilumab** (dupixent) subcutaneous (SC) injection is an interleukin-4 receptor alpha antagonist FDA approved for treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used but should be reserved for problem areas such as the face, neck, intertriginous, and genital areas. The recommended adult dose is 600 mg initially (given as two 300-mg SC injections), followed by 300-mg SC every other week. The dose for patients 12–17 years of age is based on body weight: <60 kg, 400 mg (two 200-mg injections) then 200 mg every other week; >60 kg, 600 mg (two 300-mg injections) then 300 mg every other week. The most common adverse reactions (≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

- Other systemic therapies that have been used (but not FDA approved) for atopic dermatitis include other biologic agents, corticosteroids, cyclosporine, interferon-γ, azathioprine, methotrexate, mycophenolate mofetil, and IVIG.

EVALUATION OF THERAPEUTIC OUTCOMES

- Provide patients with information regarding causative factors, avoidance of substances that trigger skin reactions, and potential benefits and limitations of nondrug and drug therapy.

- Evaluate patients with chronic skin conditions periodically to assess disease control, the efficacy of current therapy, and the presence of possible adverse effects.

See Chapter e16, Skin Care and Minor Dermatologic Conditions, by Rebecca M. Law and Howard I. Maibach; Chapter 115, Atopic Dermatitis, by Rebecca M. Law, Wayne P. Gulliver, and Po Gin Kwa; and Chapter 117, Dermatologic Drug Reactions, Contact Dermatitis, and Common Skin Conditions, by Rebecca M. Law, David T.S. Law, and Howard I. Maibach, for more detailed discussions of these topics.