Chapter e121: Dermatologic Drug Reactions, Contact Dermatitis, and Common Skin Conditions

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UPDATE SUMMARY

Update Summary

May 1, 2023

The following section was updated:

- Added self-assessment questions and answers

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 16, Dermatologic Drug Reactions and Common Skin Conditions.

KEY CONCEPTS

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1. Patients presenting with a skin condition should be interviewed thoroughly regarding signs and symptoms, urgency, other subjective complaints, and medication history. The skin eruption should be carefully assessed to help distinguish between a disease condition and a drug-induced skin reaction.

2. Drug-induced skin reactions may be caused by systemic or topical medications and can be irritant (if topical route) or allergic (topical or systemic route) in nature.

3. Allergic drug reactions can be classified into exanthematous, urticarial, blistering, and pustular eruptions. Exanthematous 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 (SJS/TEN). Pustular eruptions include acneiform drug reactions and acute generalized exanthematous pustulosis. Other drug-induced skin reactions include hyperpigmentation and photosensitivity. Genotyping may help identify patients at higher risk of a severe reaction.

4. Not all skin reactions are drug induced. In clinical practice, a diagnosis of drug-induced skin reaction is often a diagnosis of exclusion (ie, the diagnosis is reached after other possible diagnoses have been ruled out).

5. Contact dermatitis is a common skin disorder caused either by an irritant contactant or an allergic/sensitizing contactant, resulting in irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD).

6. An ICD is confined to the area of chemical contact, whereas an ACD may extend beyond the areas of contact. However, it may sometimes be difficult to differentiate an ICD from an ACD.

7. Patch testing is a criterion standard for the diagnosis of ACD—the crucial investigative and diagnostic method used together with a detailed clinical history and physical examination/workup.

8. The first goals of therapy in the management of contact dermatitis involve identification, withdrawal, and avoidance of the offending agent. A thorough history, including occupational history, must be carefully reviewed for potential contactants.

9. Other goals of therapy for contact dermatitis include providing symptomatic relief, implementing preventive measures, and providing coping strategies and other information for patients and caregivers.

10. Photoaging is premature skin aging most commonly due to sun exposure.

11. Skin cancers include squamous cell carcinoma, basal cell carcinoma, and malignant melanoma.

12. Skin manifestations of COVID-19 infection go beyond the chilblains-like lesions commonly called “COVID-toes,” and may also present as morbilliform/maculopapular, papulosquamous, vesicular, urticarial, or erythema multiform-like lesions. In addition, purpuric pressure ulcers or vascular lesions (petechiae, purpura, and livedo) may present in patients with COVID-19.

PATIENT CARE PROCESS

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Two patient cases are given later in this chapter to enhance learning, as follows:

1. Patient case 1 – Dermatologic drug reaction
2. Patient case 2 – Contact dermatitis

BEYOND THE BOOK

BEYOND THE BOOK

Review Chapter e17 "Skin Care and Minor Dermatologic Conditions" in this textbook for background on skin structure and function, transdermal drug absorption, and definitions of macules, papules, nodules, and nevi. In particular, the section on "Sun Damage—Issues and Prevention" is a precursor to the sections on "Photoaging" and "Skin Cancers and Precancerous Conditions" in this chapter.

INTRODUCTION

As the fictional character, Lois Lane said, "… the light always returns to show us things familiar … and things entirely new, or long overlooked. It shows us new possibilities, and challenges us to pursue them … you can see it. All you have to do is look …" (Justice League movie, 2017).[1]

This chapter builds on concepts from Chapter e17, Skin Care and Minor Dermatologic Conditions, the first concept in dermatology is learning how to look at the skin. The reader is strongly encouraged to review that chapter prior to reading this one.

As emphasized in that chapter, changes on the skin that are slow or subtle such as slowly enlarging and evolving dysplastic nevi or cancerous skin lesions often get overlooked. As healthcare professionals, we must learn to pay attention. At a minimum, we should be able to distinguish between common self-treatable skin lesions and equally common skin lesions that must be seen and treated professionally (medical/surgical)—such as melanoma, basal cell, and squamous cell carcinomas. This chapter builds on the Lesion Assessment section in Chapter e17 to discuss Patient Assessment—what questions to ask the patient and what signs and symptoms to look for. Skin cancers are briefly discussed here with the focus on recognition rather than treatment. The majority of this chapter deals with drug-induced skin conditions and contact dermatitis (irritant and allergic). Besides Chapter e17 and this chapter, Acne Vulgaris, Psoriasis, and Atopic Dermatitis are the other chapters in the dermatology section. Skin infections and infestations are discussed in the infectious diseases sections.

Specific food allergies can cause skin reactions (eg, rashes, hives). Patients with atopic dermatitis often have multiple food sensitivities and allergies, resulting in hives and skin rashes and/or systemic manifestations.

PATIENT ASSESSMENT

When patients present with dermatologic disorders, including a suspected cutaneous adverse drug reaction (ADR), a standard approach to assessment should be used.[2,3] Skin disorders range from inconsequential to life-threatening and it is essential that the clinician be able to distinguish between them. A standard approach to assess the patient is especially important for pharmacists who must decide whether to recommend nonprescription therapies or refer patients to physicians, nurse practitioners, or physician assistants, to further evaluate symptoms and/or prescribe prescription medication and/or decide whether a supervising physician or dermatologist should be involved.

Patient History: Questions to Ask

1 Patients presenting with any skin condition, including a possible ADR, should be interviewed thoroughly regarding signs and symptoms, urgency, other subjective complaints, and medication history. The skin eruption should be carefully assessed to help distinguish between a disease condition

and a drug-induced skin reaction.

Activities include questioning and physically assessing the patient to obtain the following information:

1. Signs and Symptoms

   a. *Onset.* When did the lesions first appear? It is important to distinguish between an *acute* versus a *chronic* condition.

   b. *Progression.* Are the lesions improving or worsening? Resolving or spreading? If lesions are worsening, how quickly are the lesions becoming more severe or widespread? Are the lesions changing and if so, how? Enlargement or increasing density of lesions (often to the point where multiple lesions coalesce) would be indications of worsening. Also, in most cases, the more quickly the evolution, the more urgent the situation.

   c. *Time frame.* Did the occurrence of skin lesions correlate temporally with the use of any medications? This may help to distinguish between drug-induced condition and disease-related condition. This is also useful in identifying contact allergens and irritants.

   d. *Location(s) and description of the lesions.* Specific details about where the lesions occur and what they look like will help to identify the type of skin condition. *Refer to the Lesion Assessment section in Chapter e17 for further information.* Some dermatologic conditions are diagnosed based on this—for example, plaque psoriasis is usually diagnosed in this manner and not through laboratory means. However, for conditions such as skin cancers,[4] a skin biopsy is usually needed to establish a definitive histopathologic diagnosis.

   e. *Presenting symptoms.* Is there pruritus (itch)? Are the lesions painful? Is there a fever? Pruritus is a common symptom for various skin conditions (eg, atopic dermatitis, allergic and irritant contact dermatitis (ICD), psoriasis, bullous pemphigoid, lichen planus, pityriasis rosea) as well as systemic conditions (eg, chronic renal failure, hepatobiliary diseases, malignancy, parasitosis) and drug reactions,[5] that is, it is a nonspecific symptom. However, keep in mind that a sudden onset of pruritus (particularly in the paraoral region, palms, plantae, or on the scalp) is one of the most important prodromal symptoms in anaphylaxis.[6] Fever is another nonspecific symptom which is of great importance in assessing skin conditions and reactions, as its presence heralds systemic involvement (ie, not just confined to the skin). Many severe dermatological drug reactions are preceded or accompanied by fever.[7] Thus, fever should be regarded as a warning sign of a potentially serious condition. In fact, fever and neutrophilia are the diagnostic criteria for acute generalized exanthematous pustulosis (AGEP).[7] Furthermore, drug fever may be the only manifestation of a drug hypersensitivity reaction.

   f. *Previous occurrence.* Has the patient presented with similar lesions before? If so, that may be extremely helpful in establishing a diagnosis and deciding on a course of treatment.

2. Urgency

   a. *Severity, area, and extent of skin involvement.* If a large area of the body is involved or if signs of severe disease such as skin sloughing or hives (and in some cases, if the face is involved) are present, more urgent treatment may be required, and an immediate referral to a physician would be appropriate if the patient was first seen by another health professional such as a pharmacist. In some cases, a dermatology consult or an emergency hospital admission would be needed.

   b. *Signs of a systemic or generalized reaction or disease condition.* If there is any indication that the patient has a systemic disease condition, whether drug-induced or disease-related, and particularly if the patient is febrile (as discussed above), this generally indicates a more urgent situation requiring immediate medical attention. For example, erythrodermic psoriasis is distinguishable from plaque psoriasis and would require immediate medical care (see Chapter 118 for details about psoriasis).

3. Medication History

   a. *Temporal correlation.* Is the patient using any medication that could potentially cause the observed skin condition? Temporal correlation with medication use is important in evaluating for a potential dermatologic drug reaction. Although possible, dermatologic drug reactions do not generally begin after the offending agent has already been discontinued. On the other hand, for some medications, it is possible for the patient to have been using the offending drug for months to years before a skin reaction occurs.

   b. *Previous exposure.* If the patient had presented with similar skin lesions previously, was the patient taking the same or similar medication(s) at

that time? If so, did the skin lesions improve after drug discontinuation? Note that for some allergic skin reactions, sensitization occurs; so the previous reaction might have been less severe or even localized rather than generalized, if there was one.

c. *Nonprescribed drugs and other products.* Ensure that the medication history is complete and comprehensive. In particular, use of any over-the-counter (OTC) medications or natural health products (NHP) or supplements or herbal teas should be specifically asked about, as they may be the culprit in a cutaneous ADR; and the patient may not have thought to voluntarily disclose when asked generally about medication use. For example, OTCs such as nonsteroidal anti-inflammatory drugs (NSAIDs) are common offenders.[2]

4. Differential Diagnosis

a. Is this a disease-related problem, a drug-induced problem, a chemical-induced problem, or a food allergy? What other possible diseases or conditions might present in this manner? It is not possible to provide a thorough discussion about differential diagnoses of skin lesions in this chapter. The reader should be aware that there are differential diagnoses for each type of skin lesion. For example, besides drugs (eg, antimalarials, cyclophosphamide, clofazimine, busulfan, 5-fluorouracil), other causes of hyperpigmentation include Wilson's disease, malabsorption syndromes, lymphomas, porphyria cutanea tarda, neurofibromatosis, Albright's syndrome, physical trauma, and others.[8] Besides drugs (eg, aspirin, NSAIDs, penicillins, sulfonamides, opiates), other causes of urticaria include infection (viral, bacterial, fungal, parasitic), insect stings, foods and food additives, cold, pressure, dermatographism, cholinergic stimulation (exercise, hot shower, emotional stress), hereditary C1 inhibitor deficiency, and others.[9]

Lesion Assessment—See Chapter e17. Please review if not already done. Lesion assessment knowledge is needed for other sections in this chapter and for other dermatology chapters.

DERMATOLOGIC DRUG REACTIONS

The skin is among the most common organs of manifestation for adverse drug reactions (ADR) and accounts for at least 15%[2] to 20%[6] of all ADRs. About 636,000 cutaneous ADR-related healthcare visits occur in the United States annually.[10] Some patients may be more prone to developing hypersensitivity ADRs, and risk factors include the following[6]: a prior drug reaction (inducing drug-specific antibodies, etc.), multiple drug therapy or intermittent/repeated use of the same drug (vs continuous therapy), some concurrent illnesses (eg, HIV, Epstein-Barr virus, CMV), dosage/serum drug level increases (eg, too rapid an IV vancomycin administration rate), topical route of administration (most immunogenic, ie, topical > subcutaneous > intramuscular > oral > IV with respect to immunogenicity), certain genetic factors (eg, certain human leukocyte antigen [HLA]-B alleles predispose for drug allergies), and certain comorbidities (eg, asthma).

Types of Dermatologic Drug Reactions

2 Drug-induced skin reactions may be caused by systemic or topical medications and can be irritant (if topical route) or allergic (topical or systemic route) in nature.

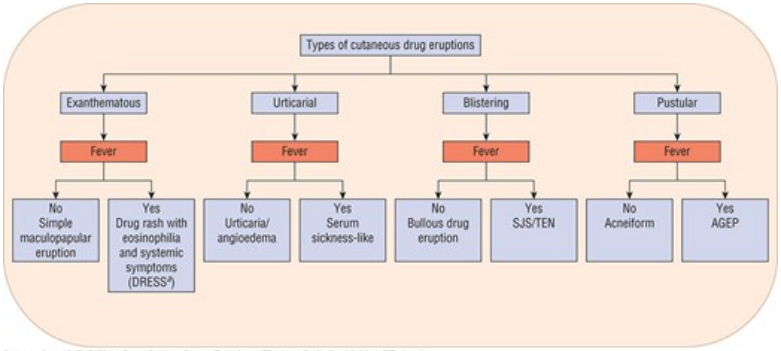
Irritant reactions are localized (ICD). Examples include chemical vaginitis, such as those resulting from vaginal douches, spermicides, and imidazoles; and vesication (blistering), produced by drug extravasation, as with chemotherapy agents like anthracyclines.

Allergic reactions depend on inducing an immune response from the host; thus, the reaction may be systemic rather than limited to skin manifestations. Furthermore, even if the first reaction is a skin manifestation, on the subsequent exposures, the reaction may become systemic.

3 Allergic drug reactions can be classified as exanthematous, urticarial, blistering, or pustular eruptions (Fig. e121-1).[11] Skin reactions accompanied by fever are generally more serious systemic disorders. These may be life threatening in some cases, although afebrile skin reactions are not always minor or innocuous (eg, urticaria, angioedema). Severe cutaneous adverse reactions to drugs (SCARs) include Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which are further discussed below. (Additional information about SJS/TEN is provided in Appendix A, and the case in the casebook [*Pharmacotherapy Casebook: A Patient-Focused Approach,* available on the AccessPharmacy Website] is about SJS/TEN.) Genetic associations between specific HLA alleles and SCARs have been discovered and this is an area of ongoing research.[12]

FIGURE e121-1

Types of cutaneous drug eruptions. (SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; AGEP, acute generalized exanthematous pustulosis.) *(Adapted from Knowles S. Drug-induced skin reactions. CTMA: Compendium of Therapeutics for Minor Ailments. Ontario, Canada: Canadian Pharmacists Association; 2014;634–643.)*



Maculopapular skin reaction is an afebrile exanthematous eruption that is the most commonly encountered allergic skin reaction. Signs and symptoms of a maculopapular skin rash include erythematous macules and papules that may be pruritic. However, fever, blisters, or pustules are not present. The lesions usually begin within 7 to 10 days after starting the offending medication and generally resolve within 7 to 14 days after drug discontinuation. Because this is often a delayed hypersensitivity reaction, it is possible that the offending agent is already discontinued (eg, a 7-day antibiotic treatment course) prior to the skin manifestation (eg, on day 11).[7] However, in a previously sensitized patient, the onset may be earlier (within 2-3 days). The lesions may spread and become confluent. Common drug culprits include penicillins, cephalosporins, sulfonamides, and some anticonvulsant medications.

Drug hypersensitivity syndrome (DHS)—more commonly known as drug reaction with eosinophilia and systemic symptoms (DRESS)—is a serious exanthematous eruption accompanied by fever, lymphadenopathy, and multiorgan involvement (including the kidneys, liver, lung, bone marrow, heart, and brain). Signs and symptoms usually begin 1 to 4 weeks after starting the offending drug, and the reaction may be fatal if not promptly treated.

Common drug culprits include allopurinol, sulfonamides, some anticonvulsants (barbiturates, phenytoin, carbamazepine, lamotrigine), and dapsone. For patients taking allopurinol, several factors increase the risk of serious skin reactions: renal impairment, hypertension, and use of thiazide diuretics or excessive allopurinol doses (ie, not dose adjusted for renal impairment).[13,14]

Urticaria and angioedema are simple eruptions that are caused by drugs in about 5% to 10% of cases. Other causes include foods (likely the most significant offenders) and physical factors such as cold or pressure, infections, and exposure to latex.[15] The condition may also be idiopathic.

Urticaria has been called the cutaneous manifestation of anaphylaxis. It is an IgE-related (type 1) allergic reaction that may be the first symptom of an emerging anaphylactic reaction. Table e121-1 provides brief descriptions of the four types of immunologic (hypersensitivity) reactions (for further information, see Chapter e108, "Drug Allergies"). A prodrome of pruritus that suddenly occurs (especially on the scalp, around the mouth, on palms, and soles) may precede the appearance of visible lesions; and this is a sign of imminent anaphylaxis.[6] Urticaria is characterized by hives, extremely pruritic red raised wheals, angioedema, and mucous membrane swelling. Early symptoms of angioedema of the tongue and larynx include the urge to clear the throat, hoarseness, and throat "tightness." Urticarial symptoms typically occur within minutes (anaphylactic) to hours (anaphylactoid) (Fig. e121-2). Individual lesions typically last less than 24 hours, but new lesions may continually develop. Offending drugs include penicillins and related antibiotics, AS.A, sulfonamides, x-ray contrast media, opiates, and others.

FIGURE e121-2

(*A*) Wheals are rounded or flat-topped papules or plaques that are characteristically evanescent, disappearing within hours. An eruption consisting of wheals is termed *urticaria* and usually itches. (*B*) Wheals may be tiny papules 3 to 4 mm in diameter, as in cholinergic urticaria. (*C*) Alternatively, wheals may present as large, coalescing plaques, as in allergic reactions to penicillin or other drugs or alimentary allergens. *(Reprinted, with permission, from*

Stewart MI, Bernhard JD, Cropley TG, Fitzpatrick TB. The structure of skin lesions and fundamentals of diagnosis. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:18.)

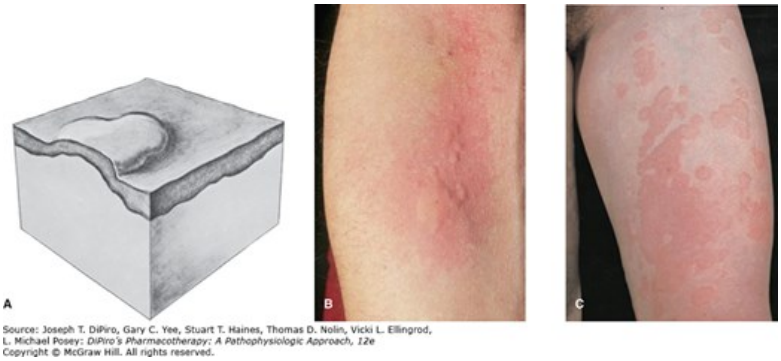


TABLE e121-1

Types of Immunological (Hypersensitivity) Reactions

Type	Description	Examples
Type I	IgE-mediated. Activation of mast cells and basophils results in release of chemical mediators (histamine, leukotrienes, etc.)	Urticaria, angio-edema, anaphylaxis
Type II	Cytotoxic reactions. IgG or IgM mediated. Antibody binding to cells with subsequent binding of complement and cell rupture.	Blood cell dyscrasias (eg, hemolytic anemia, autoimmune thrombocytopenia)
Type III	Immune complex formation. Antigen-antibody immune complexes usually with IgG or IgM. Deposition of immune complexes in skin, kidneys, joints, GI tract, etc.	Serum sickness, vasculitis
Type IV	Delayed cell-mediated hypersensitivity reactions. T-cell mediated. Can be further divided into subtypes based on T-lymphocyte subset and cytokine expression profiles.	Allergic contact dermatitis, SJS/TEN

Latex allergy (an immunologic contact urticaria) is linked to the natural rubber latex (NRL) proteins, which bind with human IgE and result in contact urticaria, asthma, and anaphylaxis.[15] Latex allergy is common in healthcare workers.[16] Aside from latex gloves and medical products, other sources of NRL proteins include rubber insoles of shoes, balloons, inflatable mattresses, and poinsettia plants.

Serum sickness–like reactions are complex urticarial eruptions presenting with fever, rash (usually urticarial), and arthralgias, usually within 1 to 3 weeks after starting the offending drug. This is not a true serum sickness, and the patient does not have immune complex formation, vasculitis, or renal lesions.[10,17] This reaction is most commonly seen in young children (<6 years old), typically after a second or subsequent course of antibiotics such as cefaclor.[17] Other common drug culprits include penicillins, other antibiotics, and NSAIDs.

Fixed drug eruptions are simple eruptions presenting as pruritic, red, raised lesions that may blister. Symptoms can include burning or stinging. Lesions may evolve into plaques.[10] These so-called "fixed" drug eruptions recur in the same area each time the offending drug is given. Lesions appear within minutes to days and disappear within days, leaving hyperpigmented skin for months. Usual drug culprits include tetracyclines, barbiturates, sulfonamides, codeine, phenolphthalein, acetaminophen, and NSAIDs.[7]

Stevens-Johnson syndrome (SJS) and *toxic epidermal necrolysis* (TEN) are complex blistering eruptions that, together with erythema multiforme (EM), are known as *acute bullous disorders.* They are histologically similar and have been considered part of an "EM spectrum of diseases."[18] EM may be considered a dermatologic disorder not associated with a drug reaction, whereas SJS and TEN are immune complex or cell-mediated allergic responses to offending agents, including drugs.[18,19] Because of their histologic similarity, in the past SJS and TEN have been considered either distinct disorders or progressions of the same disorder based on the percentage of skin area involved. They are now considered variants of the same disorder

but distinct from EM, and these two entities are often discussed together as SJS/TEN.[18] Genetic associations between some drug causes of SJS/TEN and HLA alleles have been identified. For example, carbamazepine-induced SJS/TEN is associated with HLA-B*15:02, with this allele being specific for the carbamazepine-induced activation of cytotoxic T cells that release granulysin, a mediator responsible for the epidermal sloughing in SJS/TEN.[12]

SJS/TEN are rare, severe, and life-threatening conditions with an acute onset (within 7-14 days of drug exposure). Patients present with generalized tender or painful bullous formation with accompanying systemic signs and symptoms, including fever, headache, and respiratory symptoms, that rapidly deteriorate. Lesions show rapid confluence and spread, resulting in extensive epidermal detachment and sloughing.[18] This may result in marked loss of fluids; drop in blood pressure; electrolyte imbalances; and secondary infections, including *Staphylococcus epidermidis* and methicillin-resistant *Staphylococcus aureus (MRSA)*. Immediate hospitalization in an intensive care setting—preferably in reverse isolation—is warranted (see Management section and Appendix A for further treatment details). Usual drug culprits include sulfonamides, penicillins, some anticonvulsants (hydantoins, carbamazepine, barbiturates, lamotrigine), NSAIDs, and allopurinol. In children, a pooled analysis using data from two multicenter international case-control studies confirmed the following drug risk factors for SJS/TEN: anti-infectives, sulfonamides, phenobarbital, carbamazepine, and lamotrigine.[19] In addition, acetaminophen use is suspected to increase the risk.[19] However, cases in children only represented 10% of the population in both studies because the incidence of SJS/TEN increases with age.[19] See Appendix A for further discussion about SJS/TEN.

Acneiform drug reactions are simple pustular eruptions caused by medications that induce acne (whiteheads or blackheads). The onset is usually between 1 and 3 weeks. Common drug culprits include corticosteroids, androgenic hormones, some anticonvulsants, isoniazid, and lithium. Topical acne treatments can be used to manage symptoms if the offending drug cannot be discontinued or replaced.

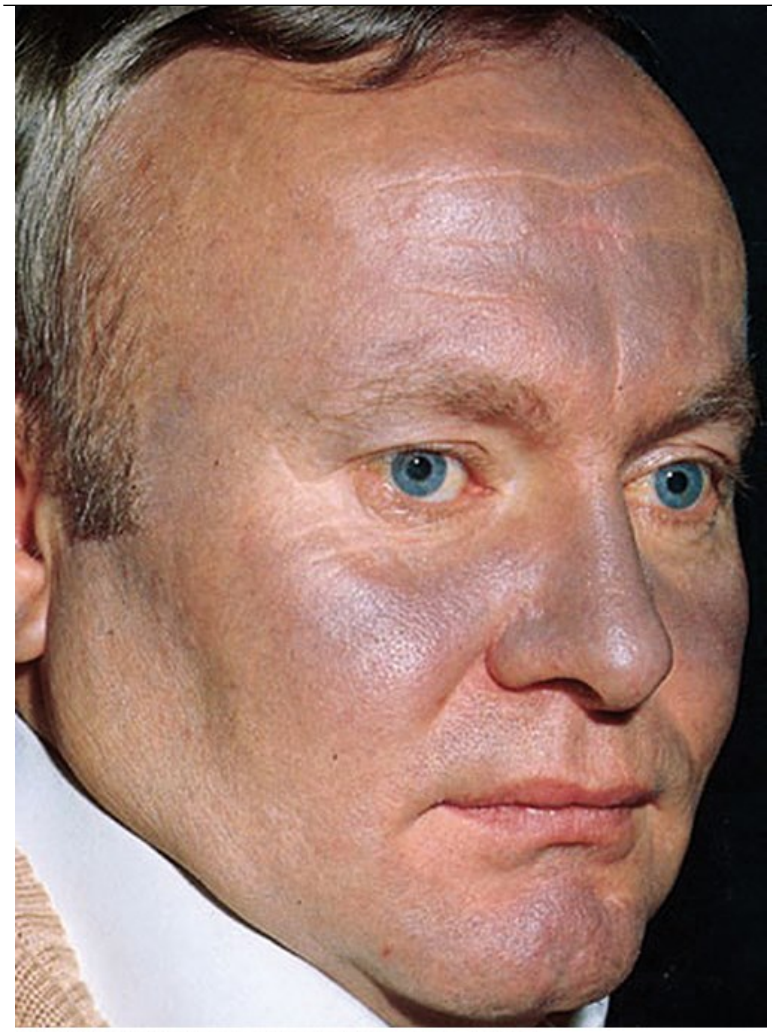
Acute generalized exanthematous pustulosis (AGEP) is a complex pustular eruption characterized by acute onset (usually within days after starting the offending drug), fever, diffuse erythema, and many pustules. About 50% of patients have other cutaneous lesions, and 25% may have mucosal erosions. Generalized desquamation occurs 2 weeks later.[10] Common drug culprits include β-lactam antibiotics, macrolides, and calcium channel blockers.

Other Drug-Induced Skin Reactions

Hyperpigmentation of the skin (Fig. e121-3) may be related to increased melanin (eg, hydantoins), direct deposition (eg, silver, mercury, tetracyclines, antimalarials), or other mechanisms (some cytotoxic drugs, such as 5-fluorouracil, may cause banding on nails or tracking along veins).

FIGURE e121-3

Hyperpigmentation. This patient exhibits a striking amiodarone-induced, slate-gray pigmentation of the face. The blue color (ceruloderma) is caused by deposition of a brown pigment in the dermis contained in macrophages and endothelial cells. *(Reprinted, with permission, from Ortonne J-P, Bahadoran P, Fitzpatrick TB, et al. Hypomelanoses and hypermelanoses. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:876.)*

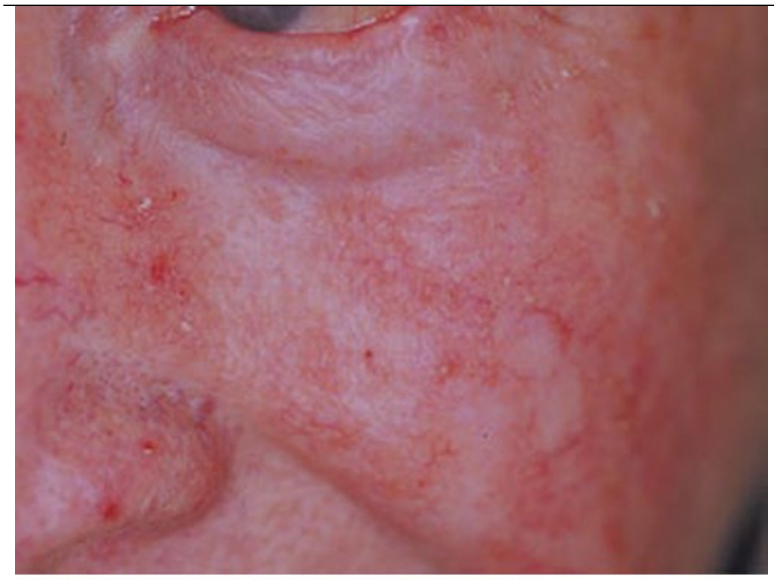


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Photosensitivity reactions (Fig. e121-4) may be phototoxic or photoallergic. Drugs that induce phototoxic reactions absorb UVA light, resulting in skin damage. Severity tends to be proportional to the drug dose. Usual drug culprits include amiodarone, tetracyclines, sulfonamides, psoralens, and coal tar. Drug-induced photoallergic reactions result from UVA transformation of medications into allergens. In this syndrome, skin damage may occasionally spread beyond sun-exposed skin. These reactions require sensitization to the offending drug (ie, reaction may be delayed or appear on a second or subsequent use), and are not dose related. Common drug culprits include sulfonamides, sulfonylureas, thiazides, NSAIDs, chloroquine, and carbamazepine.

FIGURE e121-4

Photosensitivity. Severe solar damage to the face revealing both telangiectasias and actinic keratoses at different stages in development, including flat, pink macules, and hyperkeratotic papules. *(Reprinted, with permission, from Duncan KO, Leffell DJ. Epithelial precancerous lesions. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:722.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Management and Prevention of a Dermatologic Drug Reaction

4 The first rule of thumb in managing skin reactions is to remember that not all reactions are drug induced. In clinical practice, a diagnosis of drug-induced skin reaction is often a diagnosis of exclusion (ie, the diagnosis is reached after other possible diagnoses have been ruled out). Potential foods and other causes have to be thoroughly investigated, and a detailed patient interview is important, as discussed earlier.

Consistent with the assessment for any ADR, the likelihood of a drug-induced skin reaction should be categorized as probable, possible, or not probable (unlikely). It may not be possible to categorize a drug-induced skin reaction as definite because this requires rechallenge with the potentially offending agent, and this should not be done with most reactions. Reactions are often unpredictable adverse drug reactions unrelated to the normal pharmacologic effects of the drug. Fortunately, unpredictable adverse drug reactions (eg, allergic, idiosyncratic, carcinogenic) usually affect only a small percentage of patients.

If a drug-induced skin reaction is suspected, the most important treatment (first step) in nearly all cases is discontinuing the suspected drug as quickly as possible and avoiding the use of potential cross-sensitizers. In most instances, that is the only specific treatment required. In severe cutaneous cases, a short course of systemic corticosteroids may be needed. In a few instances, it may be possible to continue the offending drug and "treat through" the reaction[10] (eg, ampicillin-associated maculopapular skin rash). When discontinuing the offending drug, remember to consider whether it needs to be replaced by an alternate non-cross-sensitizing drug (eg, a different antibiotic or a different class of antihypertensive agent).

The next step is to control symptoms associated with the drug reaction (eg, pruritus). Furthermore, any signs or symptoms of a systemic or generalized reaction may require additional supportive therapies specific to the severity and type of signs and symptoms seen. For high fevers, an antipyretic such as acetaminophen is more appropriate than ASA or an NSAID, because these may exacerbate skin lesions for some reactions. Depending on the type of skin reaction, the affected skin condition may take days to weeks or months to resolve.

For patients with life-threatening SJS/TEN, supportive measures such as maintenance of adequate blood pressure and fluid and electrolyte balance, use of broad-spectrum antibiotics and vancomycin for secondary infections, and IV immunoglobulin (IVIG) may all be appropriate.[18-20] IVIG has been shown to halt disease progression, decrease mortality, and enhance recovery in patients with SJS or TEN.[18-20] The use of corticosteroids for SJS/TEN is controversial: although they may curb disease progression, they may also increase the risk of infection and thus contribute to increased mortality.[18] If used, relatively high-initial doses followed by rapid tapering as soon as disease progression halts are indicated.[18] Refer to Appendix A and the Dermatologic Drug Reactions case in the *Pharmacotherapy Casebook* to further explore management.

Patient education should be provided. Advice to the patient should include information about the suspected drug and potential drugs to avoid in the

future, and which drugs may be used. Potential cross-sensitizers should be identified. For patients with photosensitivity reactions, information should be provided about preventive measures such as the use of sunscreens and sun avoidance. For patients with severe reactions (eg, anaphylaxis), information about MedicAlert programs may be appropriate. Genetic predisposition has not been established for most drug-induced reactions, but for SCARs such as SJS/TEN or DRESS, the risk may be higher in first-degree relatives of affected patients. There is ongoing research in this area.

HLA Genotypes and Drug-Induced Skin Reactions

The risk of drug hypersensitivity is increased when certain specific HLA alleles are present. This is particularly true for SCARs. Specific HLA alleles are linked to specific drugs. Since these are genetic predispositions, certain patient populations may become high-risk groups for developing SCARs. With this in mind, there is increasing guidance that at-risk populations should be screened. Targeted drugs include allopurinol, phenytoin, and carbamazepine, all with the potential of causing SCARs. Of note, genetic prescreening is also being used to target patients who may respond to specific treatments, such as for cancers and psychiatric conditions.

Carriers of the *HLA-B*58:01* genotype are at higher risk of developing allopurinol-induced SCARs including SJS/TEN and DRESS. This allele is more commonly found in East Asian populations. Genetic screening before prescribing allopurinol is being performed but is likely underused.[21,22]

Carriers of the *HLA-B*15:02* genotype are at higher risk of carbamazepine-induced hypersensitivity reactions, including SCARs.[23] This genotype is strongly associated with carbamazepine-induced SJS/TEN; and FDA-approved drug labeling for carbamazepine states that before initiating carbamazepine therapy, testing for *HLA-B*15:02* should be performed for all patients with ancestry in populations with increased frequency of *HLA-B*15:02* (Southeast Asian). The FDA drug monograph provides detailed prevalence rates. However, FDA cautions that there is wide variability in *HLA-B*15:02* rates even within ethnic groups, and there may be difficulty in ascertaining ethnic ancestry, and some people are of mixed ancestry.[23] If testing indicates that the patient is positive for *HLA-B*15:02*, the product labeling states that carbamazepine should not be used unless the benefits clearly outweigh the risks.[23]

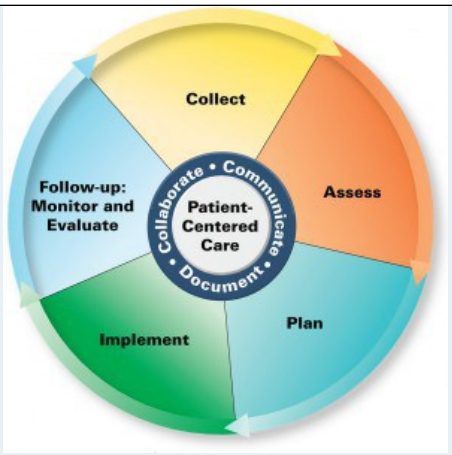
Phenytoin has a narrow therapeutic index, and its toxicities are well known and well documented.[24] Its metabolism follows Michaelis–Menten kinetics, with CYP2C9 being one of its main metabolizing enzymes. Variant *CYP2C9* alleles are known to influence serum phenytoin concentrations.[25] In addition, carriers of the variant *HLA-B*15:02* allele are also at higher risk of developing phenytoin-induced SJS/TEN. Thus, patients found to have the *HLA-B*15:02* while testing before carbamazepine use should also avoid phenytoin use.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) in the United States has recommended avoidance of carbamazepine and phenytoin (or its prodrug fosphenytoin) for any *HLA-B*15:02* carrier regardless of CYP2C9 genotype, patient ancestry, or age.[25] CPIC further recommends a 25% reduction in starting maintenance dose for patients who are *HLA-B*15:02* negative but are CYP2C9 intermediate metabolizers, and at least a 50% dose reduction for CYP2C9 poor metabolizers who are *HLA-B*15:02 negative*.[25] Due to the high degree of individual patient variability in phenytoin metabolism, CPIC recommends adjusting subsequent maintenance doses based on therapeutic drug monitoring and response, as is usually done clinically.[25]

Refer to Appendix A for further discussion of genotypes relating specifically to SJS/TEN, including other drugs whose metabolism may be affected by genomic variations.

PATIENT CARE PROCESS

Patient Care Process for Drug-Induced Skin Reaction



Collect

- Patient characteristics (eg, age, sex, pregnancy)
- Patient medical history (personal and family)
- Patient medication history (including when doses of medications were last taken and prior exposure, if any)
- Size and shape of skin lesions of concern
- Time frame of lesion occurrence—and time correlations with medication use, if any
- Recent changes in the appearance of lesions. If present, how quickly the lesions are changing

Assess

- Appearance of lesions (concerning features include rapidity of changes, extensive/generalized lesions)
- Urgency (concerning features include fever or other systemic signs or symptoms)
- Relevant patient lab work, if needed (eg, for SJS/TEN would need electrolytes, and serum creatinine)

Plan*

- Discontinue suspect drug
- Provide needed treatments as warranted by the type of reaction, if needed (eg, acetaminophen for fever, life support measures for SJS/TEN)
- Consider whether the discontinued drug needs to be replaced by a non-cross-sensitizing drug, to continue treating the original condition

Implement*

- Discontinue suspected medication
- If needed, begin treatment with a replacement medication for the original condition the medication was being used to treat (eg, if reaction was to an antibiotic, would need to consider treatment of the original infection with an alternate agent with no cross-sensitivity to the suspect drug)
- Provide treatments for the drug reaction, as needed

Follow-up: Monitor and Evaluate*

- Patient and caregiver education as needed (eg, provide a list of cross-sensitizers if appropriate)

- Set up follow-up appointments as appropriate for the reaction

Collaborate with patient, caregivers, and other healthcare professionals as needed.

CONTACT DERMATITIS

5 Contact dermatitis has been defined as an inflammation of the skin caused by irritants or allergic sensitizers.[26] It describes and includes all skin reactions resulting from direct contact of the skin or mucous membranes with an exogenous agent, which may be a "foreign" molecule such as a drug or chemical, UV light, or temperature.[26] Unlike drug-induced cutaneous reactions, the irritant (ICD) or allergen (allergic contact dermatitis—ACD) has to come from the outside—externally causing a disruption of the skin's permeability barrier, penetrating into the living epidermis or eventually the dermis,[27] and inducing a biologic response which manifests as a cutaneous inflammation. It is known that once an irritant or an allergen has disturbed the skin barrier, the resulting ICD or ACD will facilitate its own penetration.[27] Skin barrier repair is likely the last step of the healing phase, which may require several days to weeks after clinical healing of the contact reaction.[27]

6 Although skin or mucous membrane reacts nonimmunologically or immunologically to an exogenous agent to cause either an irritant or allergic skin reaction, the distinction between an ACD and ICD has become increasingly blurred; and the two types may, and often do, coexist.[26,28] An ICD is confined to the area of chemical contact, whereas an ACD may extend beyond the areas of contact. However, it may sometimes be difficult to differentiate an ICD from an ACD. Distinguishing between the two may be difficult to do clinically, even for a dermatologist.[28] The most reliable method for diagnosing ACD is the patch test.[26,28] ICD is often a diagnosis of exclusion, as in cases when patch test results for ACD are negative.[26] A diagnostic approach to ACD and ICD has been delineated[28]; this is discussed more fully in a later section.

Because ACD is immunologically mediated, the patient may have tolerated exposure to the offending agent for some time, making it more difficult to pinpoint the culprit. Furthermore, the reaction may continue to develop for some time after the offending agent is removed.

Additionally, an exogenous dermatitis can be superimposed on an endogenous skin eruption such as acne.[26] Irritant effects may be considerably enhanced by occlusion. Contact dermatitis must also be distinguished from atopic dermatitis and other dermatologic conditions such as dyshidrotic dermatitis, lichen simplex dermatitis, acne rosacea, and other conditions (see Chapter 119 for a discussion on atopic dermatitis).

Pathophysiology

ICD is a multifactorial response involving contact with a substance that chemically abrades, irritates, or otherwise damages the skin.[26,28] Depending on which type of substance is contacted, a broad range of disruptive effects on the epithelium can be seen—the three primary pathophysiological changes being skin barrier disruption, cellular epidermal change, and mediator release.[28] ICD is the clinical result of direct inflammation from proinflammatory cytokines principally released from damaged conified skin cells and from viable, activated keratinocytes.[28] Cellular damage in ICD occurs via T cells (activated by irritant or innate mechanisms) releasing proinflammatory cytokines.[26] Skin irritants can activate the skin's innate immune mechanisms independent of the antigen presentation pathway, that is, proinflammatory mediators can be induced to recruit and activate T lymphocytes without inducing antigen-specific memory T cells.[28] In fact, cytokines/factors and cell adhesion molecules associated with ACD (eg, ICAM-1, lymphocyte function-associated antigen [LFA]-1, IL-1 alpha, IL-1 beta, TNL-alpha, granulocyte macrophage-colony-stimulating factor [GM-CSF], and IFN-gamma) have been found in the epidermis and dermis in irritant reactions.[28]

ACD is a type IV (delayed hypersensitivity) reaction,[29] the clinical manifestation of contact hypersensitivity elicited by allergens.[28,29] Skin allergens tend to be low-molecular-weight (LMW) molecules (haptens) that become immunogenic after conjugation with skin proteins, resulting in a complex series of interactions that involve antigen-presenting Langerhans or other dendritic cells or CD4+ and CD8+ T cells,[26] including interleukin-17–producing TH17 cells[29]; that is, this inflammatory response is orchestrated by clonally expanded allergen-primed memory T cells.[28]

In greater detail, ACD has a two-phase hypersensitivity mechanism with an initial sensitization phase followed by an elicitation phase.[28] During the sensitization phase, LMW chemicals—which are small in size, thus able to penetrate through the skin barrier—act as haptens to recruit and activate

leukocytes and dendritic cells. The haptens or conjugated hapten-peptide complexes are pinocytosed or endocytosed and processed by dendritic cells to upregulate major histocompatibility (MHC) molecules and costimulatory factors (eg, IL-1, TNF-alpha).[28] Innate immunity is activated through keratinocyte release of IL-1 alpha, IL-1 beta, TNF-alpha, GM-CSF, IL-8, and IL-18.[29] Concomitantly, Langerhans and dendritic cells migrate to regional lymph nodes to present the haptenated peptides together with MHC class I and II molecules to specific MHC class I-restricted CD8+ and MHC class II-restricted CD4+ T cells.[28] Antigen-specific T cells are activated (ie, T_H1, T_H2, T_H17, and regulatory T cells), then proliferate, leave the lymph nodes and enter the circulation, secondary lymphatic organs and tissues, and skin site of exposure.[28,29] Skin-homing factors are expressed (eg, cutaneous lymphocyte-associated antigen or CCR4), so these activated T-cells can preferentially recirculate into the skin.[28] During the elicitation phase, when re-exposed to the same LMW chemical, antigen-specific effector T cells already present on the skin are activated to orchestrate and promote an inflammatory response—this is acquired immunity.[28,29] Thus, ACD differs from ICD in that the inflammatory lesion results from both an innate and an acquired immune response.

Prevalence

Contact dermatitis is a common skin problem for which 5.7 million physician visits are made per year.[27] Almost any of the more than 85,000 chemicals in the world environment may be a skin irritant, and more than 3,700 substances have been identified as contact allergens.[26] Although all age groups may be affected, ACD is rare in the first few years of life (<10 years), but the rate of occurrence in older children may exceed that in adults.[26]

The prevalences of ACD to individual allergens are similar in children and adults; common allergens include nickel, fragrances, *Toxicodendron* (formerly known as *Rhus*), and rubber chemicals.[26] There may be a slight female preponderance, presumably caused by exposure to specific contactants in jewelry and cosmetics.[26]

Allergen Identification

Patch Testing

Patch testing is a criterion standard for the diagnosis of ACD—the crucial investigative and diagnostic method used together with a detailed clinical history and physical examination/workup.[30] As mentioned earlier, the diagnosis of ICD is usually based on exclusion of ACD, plus detailed clinical history. However, false-positive and false-negative results can occur—a positive patch test may mean concomitant ACD and ICD, and a false negative may mean that the causative agent was not used—or even if used has led to a false-negative result.[28]

Standardized patch testing began when the Scandinavian Committee for Standardization of Routine Patch Testing was created in 1962.[31] Prior to this, different clinicians/researchers would use different concentrations, vehicles, etc. to detect a given allergy often without validation; and it became apparent that standardization was needed. There are standard panels of allergens used for testing which have been compiled and updated as needed by the North American Contact Dermatitis (Research) Group (NACDG) and the International Contact Dermatitis Research Group (ICDRG). The ICDRG was established in 1967[31] and consists primarily of members from European Union (EU) countries such as the Netherlands, although Dr. Howard I. Maibach (the United States) became a member in 1968.[32] The NACDG was founded by Dr. Maibach in 1970[32]—at that time the youngest member of the ICDRG—and consists of members from the United States and Canada. It was recognized that the most common contact allergens in North America may differ from those in the EU due to product differences/availability and frequencies of use, thus the need for a separate committee. Dr. Maibach would organize half-day meetings called “Short Reports” in association with the American Academy of Dermatology’s annual meeting, for the group to share and collate information. NACDG regularly publishes collated patch test results—for example, the 2013 to 2014 and 2011 to 2012 results were published in 2017[33] and 2015,[34] respectively.

In 1995, the Food and Drug Administration (FDA) in the United States approved the thin-layer rapid use epicutaneous test (TRUE Test) for patch testing—standardizing the patchtesting process with a panel of antigens in specific concentrations. By 2014, the North American standard panel included 35 allergens or mixes plus a negative control,[35] with a screening series (extended series) of 70 allergens.[33] In Table e121-2, frequencies (positive reaction rates) of the allergens in the screening series are listed in descending order.[33]

TABLE e121-2

Positive Reaction Rates of the 70 Allergens in the 2013 to 2014 North American Contact Dermatitis Group Screening Series in Descending Order of Prevalence

Allergen, formulation	Prevalence %	Allergen, formulation	Prevalence %
Nickel sulfate, 2.5% pet	20.1	Fragrance mix I, 8% pet	11.9
Methylisothiazolinone (MI), 0.02% aq	10.9	Neomycin, 20% pet	8.4
Bacitracin, 20% pet	7.4	Cobalt chloride, 1% pet	7.4
Myroxylon pereirae (Balsam of Peru), 25% pet	7.2	*p*-Phenylenediamine, 1% pet	7.0
Formaldehyde, 2% aq	7.0	MCI/MI, 0.02% aq	6.4
Fragrance mix II, 14% pet	5.7	Formaldehyde, 1% aq	5.6
Lanolin alcohol (Amerchol L 101), 50% pet	5.4	Carba mix, 3% pet	4.8
Quaternium-15, 2% pet	4.8	Iodopropynyl butylcarbamate, 0.5% pet	4.7
Cinnamic aldehyde, 1% pet	4.2	Diphenylguanidine, 1% pet	3.8
Methyldibromo glutaronitrile/phenoxyethanol, 2% pet	3.7	OPDMA, 0.1% aq	3.5
Thiuram mix, 1% pet	3.1	Propylene glycol, 100% aq	2.8
Hydroxyethylmethacrylate (HEMA), 2% pet	2.6	Potassium dichromate, 0.25% pet	2.2
Propylene glycol, 30% aq	2.2	2-Bromo-2-nitro-1,3-propanediol, 0.5% pet	2.1
Benzophenone-4, 10% pet	2.1	Tixocortol-21-pivalate, 1% pet	2.1
Colophony, 20% pet	1.9	Bisphenol A epoxy resin, 1% pet	1.8
Dimethylaminopropylamine, 1% aq	1.8	Composite mix, 6% pet	1.7
Decyl glucoside, 5% pet	1.7	Propolis, 10% pet	1.7
Benzocaine, 5% pet	1.6	Cocamidopropyl betaine, 1% aq	1.6
Diazolidinyl urea, 1% pet	1.6	Imidazolidinyl urea, 2% pet	1.6
Methyl methacrylate, 2% pet	1.3	*Canaga odorata* oil (ylang ylang), 2% pet	1.2
Ethylenediamine dihydrochloride, 1% pet	1.2	Amidoamine (stearamidopropyl dimethylamine), 0.1% aq	1.2
Ethyl acry late, 0.1% pet	1.1	Mixed dialkyl thioureas, 1.0% pet	1.0
Black rubber mix, 0.6%	1.0	1-,3-Dimethylol-5,5-dimethyl (DMDM) hydantoin, 1% pet	1.0

Lidocaine, 15% pet	1.0	*p-tert*-Butylphenol formaldehyde resin, 1% pet	1.0
Disperse blue mix 106/124, 1% pet	1.0	Tea tree oil, oxidized, 5% pet	0.9
Sesquiterpene lactone mix, 0.1% pet	0.9	Tosylamide formaldehyde resin, 10% pet	0.9
Budesonide, 0.1% pet	0.9	Cocamide DEA, 0.5% pet	0.9
Parthenolide, 0.1% pet	0.8	Glutaral, 1% pet	0.8
Carvone, 5% pet	0.7	2-Hydroxy-4-methoxy-benzophenone (benzophenone-3), 10% pet	0.6
Paraben mix, 12% pet	0.6	Tocopherol (DL-alpha-tocopherol), 100%	0.6
Peppermint oil (*Mentha piperita* oil), 2% pet	0.6	Mercaptobenzothiazole, 1% pet	0.5
Jasminium officinale oil (jasminium grandiflourium), 2% pet	0.5	4-Chloro-3,5-xylenol (PCMX, chloroxylenol), 1% pet	0.5
Ethyl-2-cyanoacrylate, 10% pet	0.4	Lavender oil (*Lavandula angustifolia*) oil, 2% pet	0.3
Ethylhexylglycerin, 5% pet	0.2	Desoximetasone, 1% pet	0.1
Clobetasol-17-propionate, 1% pet	0.1	Hydrocortisone-17-butyrate, 1% pet	0.1

MCI/MI, methylchlorisothiazolidinone/methylisothiazolinone.

Data from Reference 33.

The ICDRG had created the international standard series in 1997 with 20 allergens; and in 2011, the group used an evidence-based approach followed by members voting to expand their minimal baseline series to 32 allergens (Table e121-3).[36] Thus, the two minimal standard (baseline) allergen lists are similar but not identical.

TABLE e121-3

Selected Allergens and Concentrations Associated with Contact Dermatitis

2-Mercaptobenzothiazole[a] 2%
p-Phenylenediamine (4-phenylenediamine) 1%[b]
4-*t*-Butylphenol formaldehyde resin 1%[b]
Budesonide 0.01%[b]
Carba mix 3%
MCI/MI (Kathon CG[c]) 0.02%[b]
Cobalt chloride 1%

Colophony 20%[b]
Compositae mix 5%
Diazolidinylurea 2%
Epoxy resin 1%[b]
Formaldehyde (formalin)[a] 2%
Fragrance mix I 8%[b]
Fragrance mix II 14%[b]
Hydrocortisone-17-butyrate 1%
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral[d]) 5%
Imidazolidinylurea (imid urea) 2%[b]
Lanolin alcohol 30%[b]
Mercapto mix 2%[b]
Methyldibromoglutaronitrile 0.3%
Methylisothiazolinone 0.01%
Myroxilon pereirae resin (Balsam of Peru) 25%[b]
N-Isopropyl-*N*-phenyl-4-phenylenediamine 0.1%
Neomycin sulfate 20%[b]
Nickel sulfate 2.5%[b]
Paraben mix 16%
Potassium dichromate 0.5%[b]
Quaternium-15 2%[b]
Sesquiterpene lactone mix 0.1%
Thiuram mix 1%[b]
Tixocortol-21-pivalate 0.1%[b]
Tosylamide/formaldehyde resin 10%

MCI/MI, methylchlorisothiazolidinone/methylisothiazolinone.

[a]An allergen with a new concentration in the updated 2011 Minimal Baseline Series of the International Contact Dermatitis Research Group.[36]

[b]An allergen that was included in both the 2007 and 2011 lists of the Minimal Baseline Series of the International Contact Dermatitis Research Group.[36]

[c]Rohm and Haas Company, Philadelphia, PA.

[d]Dormer Laboratories, Rexdale, Ontario, Canada.

Data from Reference 36.

The reason for the extended/screening series: there is a concern that the limited numbers of allergens in the standard lists may result in missed relevant antigens.[35] For example, a 2013 study found that exclusive reliance on the TRUE test of 36 chambers versus an extended panel of 70 antigens or more can miss detection of sensitization to almost 30% of antigens.[37] Thus, extended panels are frequently used in practice. There are also standard panels used for children and extended panels which include dental products, and others. Most dermatologists combine the minimal baseline series with additional allergens, testing from 50 to 170 allergens at one time. Furthermore, patch testing to personal and occupational products may be useful—especially for face, eyelid, lip, and hand dermatitis.[35]

In addition, as new allergens emerge or frequencies of use change, more chemicals are considered for addition to the lists and voted on by members. One specific example is the volatile preservative methylisothiazolinone (MI), which is currently being considered for addition to the EU's baseline list—it is now widely used in paints and cosmetics for its preservative properties but its airborne, allergenic nature is causing havoc.[38-40] Its sister chemical, methylchloroisothiazolinone (MCI), is already part of the standard panel of allergens in both lists, as is MCI/MI; other isothiazolinones are also allergenic.[40,41]

Patch testing is indicated when a contact allergy is suspected. However, it has been shown that patch testing is significant in *both* confirming contact sensitivities suspected from the clinical history and in unveiling unsuspected sensitivities.[28] Clinical history alone is generally insufficient and unreliable in identifying causative allergens in a particular patient.

It is important to remember that for patch testing to be most useful, the patient must be involved in the patch-testing process. How? First and foremost, patient education: Information about the procedure, including patch testing basics, should be provided to the patient even before patch testing begins, as many patients may be misinformed and believe that patch testing and skin scratch/intradermal testing are identical.[42] Patients should be educated that patch testing is a delayed-type hypersensitivity reaction that differs from skin prick testing, which tests for an immediate hypersensitivity reaction. Second, grouping allergens may make it easier for patients to understand what they are, where they are found, and how they could potentially have contacted them.[42]

Other Tests

Patients can have a positive patch test result to a specific chemical without displaying a clinically problematic dermatitis—that is, an ACD may not be present.[29] A positive patch test could also indicate past relevance. Other diagnostic tests that may be useful include (a) Repeat Open Application Tests (ROAT)—to confirm that a positive patch test result will lead to dermatitis at usual allergen concentrations; (b) Lymphocyte Transformation Tests (LTT)—for use as an alternate to patch testing when that is not possible, for example, if the dermatitis is so generalized that there is not enough unaffected skin left for patch testing; (c) Atopy Patch Tests—for use in instances where the patient may have an underlying atopic dermatitis.[29]

Patch Testing remains the gold standard.

Clinical Presentation

The clinical presentation of contact dermatitis is that of an eczematous inflammation with erythema, vesicles, papules, crusting, fissuring, or scaling (Figs. e121-5 and e121-6). The area may itch, burn, or sting and may be extremely pruritic. The severity may range from a mild, short-lived condition to a

severe and persistent condition but is rarely life-threatening.[26] The gross and histologic appearances of ICD and ACD are often similar and may be difficult to distinguish—this needs to be kept in mind as discussed.[26] However, the rash or lesion for ICD is frequently localized, but for ACD, it may extend beyond the borders of the exposed area of contact, and the reaction may rarely become systemic (eg, latex allergy).

FIGURE e121-5

Acute dermatitis caused by poison ivy. Note the linear arrangement of lesions typical of phytodermatitis acquired by inadvertent contact with the plant. The severe vesiculobullous reaction is typical for urushiol, an oily poisonous irritant found in *Toxicodendron* spp. *(Reprinted, with permission, from Belsito DV. Allergic contact dermatitis. In: Freedberg IM, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:1167.)*

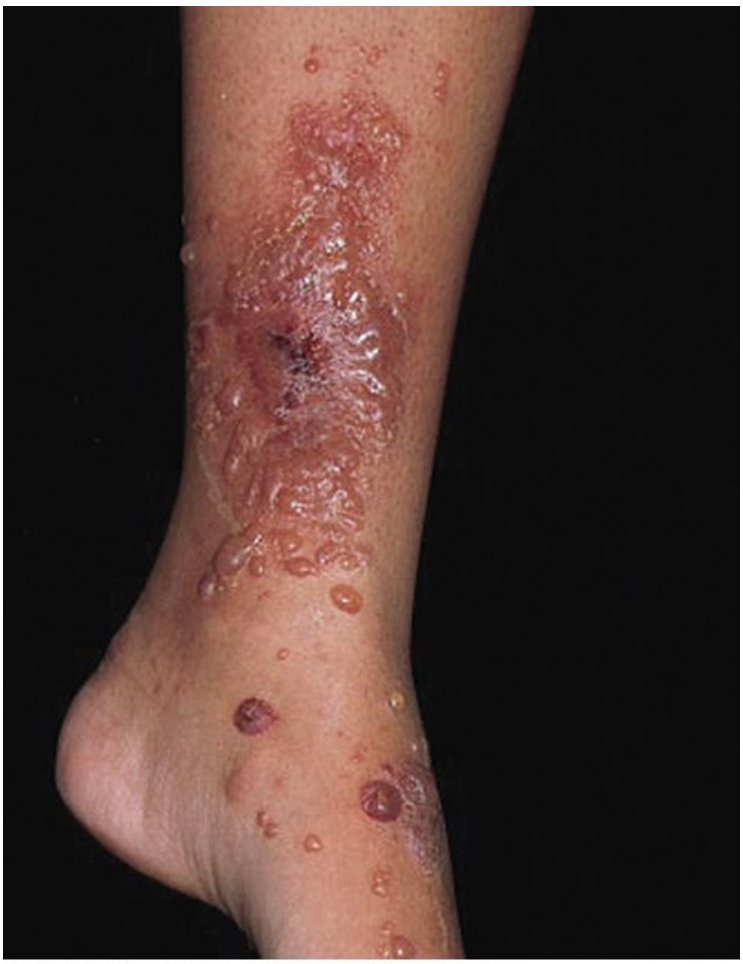
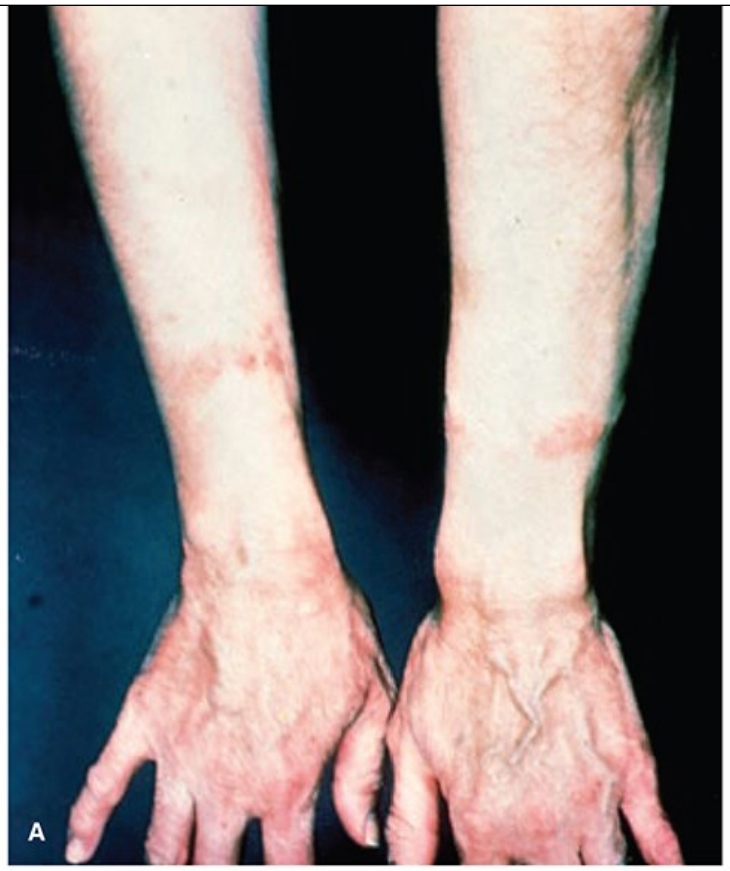
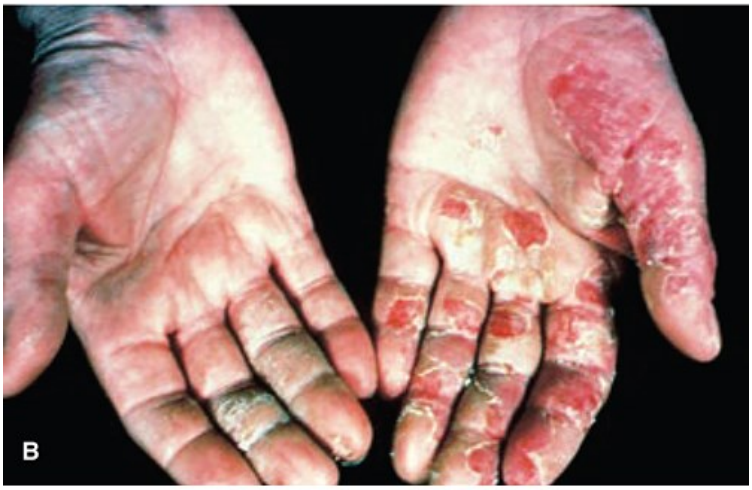


FIGURE e121-6

(*A*) This patient has allergic chronic dermatitis involving the dorsal aspects of the hands and the distal forearms but with minimal involvement of the palms. In this case, contact dermatitis is secondary to the use of thiuram present in rubber gloves prescribed for treatment of an irritant hand dermatitis. (*B*) This patient, a florist, has allergic contact dermatitis as a consequence of exposure to tuliposide A, the allergen in Peruvian lilies (*Alstroemeria* spp.). Note the more prominent involvement of the palms of the dominant hand. *(Reprinted, with permission, from Belsito DV. Allergic contact dermatitis. In: Freedberg IM, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:1167.)*





Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Management/Treatment Approach for Contact Dermatitis

8 The first goal of therapy in the management of contact dermatitis involves identifying, withdrawal, and avoidance of the offending agent. The key to "treatment" is avoidance.[43] An algorithmic diagnostic and management approach has been developed.[28] A thorough history, including work history, must be carefully reviewed for potential contactants. Nonwork activities such as hobbies (eg, painting, gardening, camping, fishing) may be additional potential sources of exposure. Patch testing is the gold standard for identifying a contact allergen,[26,28] but it is impractical to test an unlimited number of allergens.

As discussed earlier, standard panels of allergens have been designed and validated by collaborative research dermatologic societies; however, these may account for only 25% to 30% of the most relevant contact allergens.[26] Many patients need additional testing. Customized patch tests may be invaluable, depending on the patient's exposure history.[26] Additional tests (eg, ROAT, provocative use test) may sometimes be needed to confirm a causal relationship.[28]

Common causes of occupational contact dermatitis are chromium (leather exposure); rubber and rubber additives (gloves); nickel (work tools and metal working); food ingredients, including intact proteins (for food processing workers); fertilizers and pesticides (for farmers); and handwashing (disinfectants, irritants in soaps).[26] Some of the more common occupations with high rates of contact dermatitis include cosmetologists, metalworkers, healthcare workers, hairdressers, construction workers, agriculture workers, food workers, chefs, and waiters.[42,44] The most common site for occupational contact dermatitis is the hands.[42,44,45] "Wet work" is the most commonly implicated exogenous factor in occupational contact dermatitis.[44] Allergic contact dermatitis caused by nickel and chromates have been associated with particularly bad prognoses.[45]

The most common cause of plant dermatitis is *Toxicodendron (Rhus)* dermatitis. This genus includes poison ivy, poison oak, and poison sumac. These plants contain the offender urushiol oil, one of the several oleoresins that are sensitizers and irritants. Urushiol oil is also found in mango skin, cashew nut oil, ginkgo (female) leaves, Japanese lacquer, and Indian marking ink.[26] Other plant irritants include *Cruciferae* (black mustard), *Urticaceae* (nettles), *Solanaceae* (capsaicin, pepper), *Opuntia* (prickly pear), *Euphorbiaceae* (spurges, crotons, poinsettias, machineel tree), and *Racunculaeae* (buttercup).[44]

Cosmetics and personal hygiene products, such as hair conditioners and shampoos, nail polishes and hardeners, mascara, foundations, antiperspirants and deodorants, and toothpastes, may all contain potential causes of contact dermatitis. The most important classes are fragrances, preservatives (including those used in the cosmetic industry such as methylisothiazolinone or MI), formulation excipients, glues, and sunblocks,[26,44] with fragrances being among the most common causes of contact dermatitis in the United States.[26] Table e121-2 presented earlier provides specific reaction rates for the most common contact allergens in North America.

The second goal of therapy in contact dermatitis is to provide symptomatic relief while decreasing skin lesions. The affected skin may require supportive treatment such as the use of cold compresses to sooth and cleanse the skin or topical corticosteroids to help resolve the inflammatory process. Compresses are dressings that are applied to wet or oozing lesions, *removed*, remoistened, and reapplied *every few minutes* for a 20- to 30-minute period, in order to "remove the ooze." Calamine lotion or Burow solution (aluminum acetate) may be soothing as well.

Topical corticosteroids are considered the mainstay of treatment,[43] and patients with ACD respond better than those with ICD. Generally, higher potency corticosteroids are used initially, switching to medium- or lower-potency corticosteroids as the condition improves.[26] Refer to the Topical Corticosteroid Potency Chart in Chapter 118, "Psoriasis" (Table 118-2) for specific examples.

Other treatments may be effective. Tacrolimus ointment is effective for nickel-induced ACD in a small randomized placebo-controlled clinical trial.[46] Oatmeal baths and oral first-generation antihistamines may provide relief for excessive itching. If the affected areas are already dry or hardened (eg, lichenification), wet dressings applied as soaks (without removal for up to 20-30 minutes) will soften and hydrate the skin (these should not be used for acute exudating lesions because the skin area may become macerated, further damaging its barrier function).

The third goal of contact dermatitis therapy is to implement preventive measures. Prevention involves both primary and secondary measures.

Primary prevention may be done in the workplace by initiating surveillance programs and educating workers about proper skin care and chemical exposure.

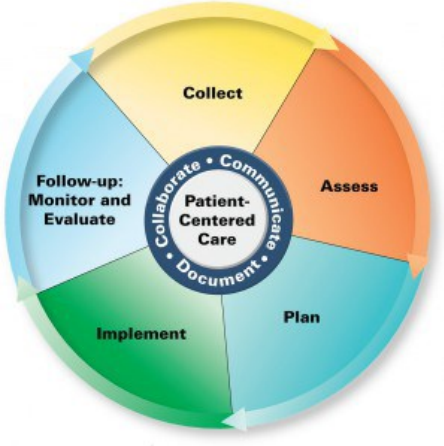
Secondary prevention involves the use of moisturizers to prevent dryness and fissuring of the skin.[43] The efficacy of barrier creams is controversial.[26,43,45] Inappropriate barrier cream application may exacerbate, rather than ameliorate, the problem[43]; and in practice are usually recommended for skin protection only from low-grade irritants (water, detergents, organic solvents, etc.) and to protect the face and neck from chemical dusts and vapors.[43] The damaged skin may need to be protected against secondary infections, at least until the acute stage subsides. Debris, produced by oozing, scaling, or crusting, should not be allowed to accumulate. Rarely, some workers may have persistent dermatitis despite removal

of offenders, and a small number of workers change jobs because of severe recalcitrant occupational contact dermatitis.[26,45]

9 A final goal of therapy is to provide patient and caregiver information and support, helping them to develop coping strategies for contact dermatitis, as required. Education about the process of patch testing has been discussed earlier.

PATIENT CARE PROCESS

Patient Care Process for Contact Dermatitis



Collect

- Patient characteristics (eg, age, sex, pregnancy)
- Patient medical history (personal and family)
- Patient occupational history (including what chemicals were contacted and prior exposure)
- Size and shape of skin lesions of concern
- Time frame of lesion occurrence—and time correlations with chemicals, if any
- Recent changes in the appearance of lesions. If present, how quickly are lesions changing

Assess

- Appearance of lesions (concerning features include rapidity of changes, extensive/generalized lesions)
- Urgency (concerning features include fever or other systemic signs or symptoms)
- Patch testing to assess for contact allergens (standard panels and extended series as appropriate. Patient-specific chemicals if available)
- Relevant patient lab work, if needed

Plan*

- Identify offending agent and avoid, if possible
- Provide needed treatments as warranted by the type of reaction and symptoms, if needed at all

Implement

- Withdrawal from contact and avoid future contact of offending agents, that is, contact allergens
- Provide symptomatic relief while skin lesions are healing (eg, compresses or topical corticosteroids, calamine lotion, oatmeal baths, tacrolimus ointment, etc.)
- Implement preventative measures (eg, primary prevention: surveillance programs in workplace, worker education; secondary prevention: moisturizers to prevent skin fissuring, protection for secondary infections, debridement of dead tissue/debris)

Follow-up: Monitor and Evaluate

- Collaborate with patient, caregivers, and other health professionals as needed (eg, develop coping strategies for contact dermatitis)
- Patient and caregiver education as needed (eg, provide a list of cross-sensitizers if appropriate)

**Collaborate with patient, caregivers, and other healthcare professionals.*

PHOTOAGING

10 Photoaging is premature skin aging which reflects long-term skin damage from the effects of sun exposure. Sun exposure is the primary environmental cause of skin damage, although there are also other external factors such as prolonged exposure to cold and wind which can also cause skin damage.[47]

Photoaging differs from the natural skin aging process over time, that is, chronological aging, which presents differently compared to photoaging.[47]

Characteristics of photoaging include the following[47]:

- Premature formation of wrinkles and loss of skin firmness—due to intensified destruction/degeneration of elastin fibers upon prolonged sun exposure; versus gradual degeneration in normal skin aging. When elastin fibers degenerate, the skin acquires fine wrinkles.
- Thickening of epidermis (more cells) in an irregular pattern; versus thinning of epidermis in non-sun–exposed areas due to normal aging
- Uneven skin pigmentation
- Solar lentigines (ie, “age spots”)
- Telangiectases (ie, dilated “spider” blood vessels in the skin)
- Possible development of skin tumors (both benign and malignant) related to photoaging (discussed later)

Management/Treatment Approach to Photoaging

Treatment goals would be to reduce visible effects of sun-induced skin damage and to protect the skin from further damage, if possible. The general treatment approach includes nonpharmacologic measures such as daily sun protection (sun avoidance, sunscreen use with SPF 30 or higher, wide-brimmed hats), appropriate skin care/cleansing, and hydration/moisturizer use, leading a physically and emotionally healthy lifestyle (regular physical activity, regular and sufficient sleeping hours, balanced diet and adequate hydration, healthy mental and emotional state, ie, maintaining a happy disposition).[47]

Generally, to minimize facial wrinkles, the following are some suggestions:

Sleep supine (on back). “It has been suggested that sleeping on one side causes stretching of the face in certain directions due to gravity, so diagonal wrinkles are formed on the cheeks and forehead. Therefore, sleeping in a supine position may be recommended.”[47]

Avoid “excessively exaggerated facial expressions … to prevent the formation of unnecessary expressive lines over time.”[47] There is some proof

that facial expressions can cause wrinkles: people with unilateral paralysis may, over time, appear younger on the paralyzed side of the face.[47]

Avoid unnecessary stretching of the skin.

In particular, avoid abrupt changes in weight: weight gain increases the amount of subcutaneous fat which stretches the skin above it, then subsequent weight loss will leave slack, excess skin that becomes wrinkles.[47]

Avoid smoking since smoking affects skin health, causing yellowing of the skin and development of deep lines radially from upper and lower lips and laterally from the eyes. Skin between these wrinkles may be somewhat thicker than in nonsmokers.[47]

Pharmacologic measures include topical retinoids, keratolytics, antioxidants (for fine facial wrinkles and dry skin), and hydroquinone or monobenzone (for pigmentation changes). Table e121-4 provides a brief summary of these agents in the treatment of photoaging.

TABLE e121-4

Pharmacologic Treatments for Photoaging

Topical Retinoids	OTC—retinol, retinyl palmitate (Pro-Retinol®, Neo-Retinol ®)	Must be converted to retinoic acid by the skin—this limits efficacy
	Rx—retinoic acid (isotretinoin)/all-trans retinoic acid (tretinoin) (Retisol-A®, Stieva-A®), tazarotene	Can reduce wrinkles, improve skin color, texture, and repair collagen (over 6-12 months)
Keratolytics	Alpha-hydroxy acids (AHAs—lactic acid, glycolic acid), beta-hydroxy acids (BHAs—salicylic acid), polyhydroxy acids	May cause skin irritation. Begin application gradually, starting every other night × 1 week and increase frequency as tolerated to a maximum of twice daily
Vitamins (antioxidants)/supplements	Vitamin E, C, Coenzyme Q10 (ubiquinone)	Antioxidants—protective effect
		Increase collagen synthesis
Depigmenting agents	Hydroquinone (Neostrata HQ®, Ultraquin), monobenzone (Benoquin®)	Bleach hyperpigmented areas

Topical Retinoids

Regular use of products containing retinoic acid/all-trans-retinoic acid may improve some signs of photoaging and chronological aging. In the epidermis, retinoic acid increases keratinocyte cell division, replacing damaged and unorganized cells with new, organized cells, and reduces melanin production. In the dermis, it enhances the formation of new collagen and elastic fibers. The skin's appearance can be changed, becoming visibly smoother and thicker, with significant flattening/diminishing or even disappearance of fine wrinkles; lightening or disappearance of solar lentigines (age spots); regression or disappearance of precancerous lesions, that is, solar keratosis (but this is not the preferred treatment for precancerous lesions).[48]

Keep in mind that beneficial effects of retinoic acid are gradual and may take several months to be noticeable, with maximal improvement occurring within the first year of treatment where delaying of the aging process as well as repairing of already-damaged skin occur. Continuing treatment for more than a year may further delay the aging process, although further repair of damaged skin cannot be expected.[48]

Side effects of retinoic acid include an initial dryness with slight scaling occurring within 2 weeks to 3 months of use. To minimize this common problem, a cream-based formulation should be selected rather than a gel formulation, when a choice is available. Gels tend to dry skin to a greater

extent and should be used only on oily skin. A moisturizer may be applied during the day if needed, or a second option would be to use retinoic acid every other night alternating with a moisturizer.[48] There may also be an initial redness and mild stinging which usually disappears within 2 to 3 months. If this becomes too irritating, try an alternate day or every third day dosing or temporary discontinuation of treatment.[48] There is also a phototoxicity concern[49] with increased risk of sunburn, thus broad spectrum sunscreen use with an SPF of 30 or higher is recommended. (Refer to Chapter e17 of this edition of *Pharmacotherapy* for a discussion about sunburn and the use of sunscreens.)

Oral retinoids are known teratogens and have absolute contraindications for use during pregnancy; if used in women of childbearing age, there must be effective contraception in place reliably used. Is this also a concern with the topical use of retinoids? The topical retinoids may also be teratogenic, thus the same precautions should apply. For example, topical tretinoin (Stieva-A) is "not recommended during pregnancy or in women of childbearing years without the proper use of an effective method of contraception."[49] This statement from the manufacturer was based on case reports of temporally associated congenital abnormalities during topical tretinoin use in pregnancy (eg, holoprosencephaly),[49] although observational studies of 1,535 women presumed exposed to topical tretinoin during the first trimester did not detect an increased incidence of congenital abnormality.[49] Nonclinical reproductive toxicity studies have detected developmental toxicity at doses ≥80-fold of the anticipated topical tretinoin clinical dose.[49] Although systemic absorption from topical tretinoin is between 1% and 6% when properly used, risk cannot be excluded as other factors may lead to increased systemic absorption (eg, loss of skin barrier integrity, inappropriate dosing, concurrent use with other products, hypervitaminosis A, dietary vitamin A intake, and/or provitamin A [beta-carotene]).[49]

Keratolytics

Keratolytics exfoliate or "peel" the top layer of dead skin, resulting in smoother, nonscaly skin, lessening fine lines, and normalizing pigmentation. Keratolytics include alpha-hydroxy acids (AHAs), beta-hydroxy acids (BHAs), and polyhydroxy acids.

AHAs are water soluble; the most common AHAs in cosmetic products include glycolic acid (from sugar cane), lactic acid (from milk), citric acid (from citrus fruits), and malic acid (from apples).[50] AHAs slough off dead skin cells and promote cell turnover. Regular use may help to "brighten" skin and improve the look of photoaged skin or blotchy complexions.[50] They may cause dryness and skin irritation which may be compounded if used with other agents having similar side effects.

BHAs are organic acids of which the most commonly known is salicylic acid; others include trophic acid and beta-hydroxybutanoic acid.[51] BHAs are more lipid soluble than AHAs and can penetrate more deeply into the skin and skin pores, thus having a greater keratolytic effect: dissolving/removing keratin, breaking up dead top skin cells in thickened skin, loosening cell adhesion in the upper epidermis, and removing excess material blocking the outlet of sebaceous glands and hair follicles.[51] Salicylic acid has a prolonged keratolytic effect within skin pores and may also have an anti-inflammatory effect on acne lesions.[51] For chemical peeling, salicylic acid can be used alone in concentrations up to 30%, or it may be used in combination with AHAs.[51] Skin irritation can be minimized by a gradual increase in frequency as tolerated, beginning with every other night dosing.

Polyhydroxy acids are water soluble compounds including lactobionic acid, galactose, and gluconolactone.[51] They function similar to AHAs and may be used as humectants, increasing the moisture level of the skin.[51] Since they have higher molecular weights than AHAs, they may take longer to penetrate skin, thus cause less irritation, and may be useful as mild exfoliants in people with sensitive skin or skin conditions such as rosacea.[51]

Vitamins

Vitamin C is one of the most powerful antioxidants in the skin, protecting against photoaging, UV-induced immunosuppression, and photocarcinogenesis. It may increase collagen synthesis, stabilizing collagen fibers, and reducing collagen degradation—thus producing an antiaging effect.[52] A placebo-controlled study using ultrasonographic evaluation has shown that a vitamin C-based moisturizer cream was highly efficient in rejuvenation therapy in healthy female volunteers between 20 and 75 years old, inducing significant collagen synthesis in all age groups with minimal side effects.[53]

Depigmenting Agents

Chemical depigmentation is not always a desired effect. Occupational leukoderma was first reported as an occupational hazard in 1939, due to the monobenzyl ether of hydroquinone (MBEH) which translocated from rubber gloves worn by workers, causing a vitiligo-like depigmentation.[54,55] Later, MBEH (10%-30%) lotions and ointments and bleaching creams using hydroquinone (2%) were used to treat hyperpigmentation,[54] but can also result in leukoderma.[56] Hydroquinone is a depigmentation treatment in patients with widespread but incomplete vitiligo, to improve their overall appearance.

At the same time, hydroquinone is also a hyperpigmentation treatment in patients with age spots ("liver spots") and may be used alone or together with retinoic acid for this indication; spots may gradually fade over several months of use.[57] Laser and intense pulsed light therapy for two to three sessions may destroy melanocytes and also result in fading of spots over several months.[57] Cryotherapy ("freezing") using liquid nitrogen on a cotton swab may be useful on a single age spot or a small grouping of age spots, but there is a slight risk of permanent scarring or discoloration.[57]

SKIN CANCERS AND PRECANCEROUS CONDITIONS

Actinic keratoses are precursors to the development of skin cancers. UV radiation (with UVA a greater risk than UVB) may induce abnormal keratinocyte changes. These present as actinic keratoses. Lesions can develop into squamous cell or basal cell carcinomas.

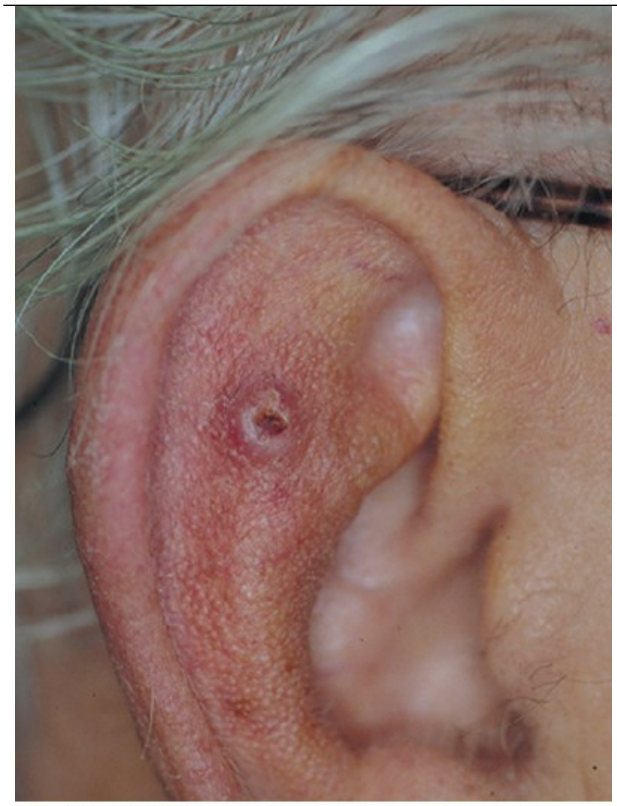
Actinic keratoses are most often found in elderly fair-skinned individuals and on chronically sun-exposed areas, such as hands, forearms, head, and neck.

11 Skin cancers include squamous cell carcinoma, basal cell carcinoma, and malignant melanoma.

Squamous cell carcinoma (SCC) is a skin cancer most commonly seen in older patients (Fig. e121-7). Risk factors include fair complexion, prolonged sun exposure, UV radiation (including PUVA [psoralens plus UVA] used for treatment of psoriasis), and long-term immunosuppression (including the use of biologic response modifiers for treatment of conditions such as psoriasis). Most SCCs present as firm, flesh-colored, or erythematous papules or plaques. Treatment is primarily via surgical excision.

FIGURE e121-7

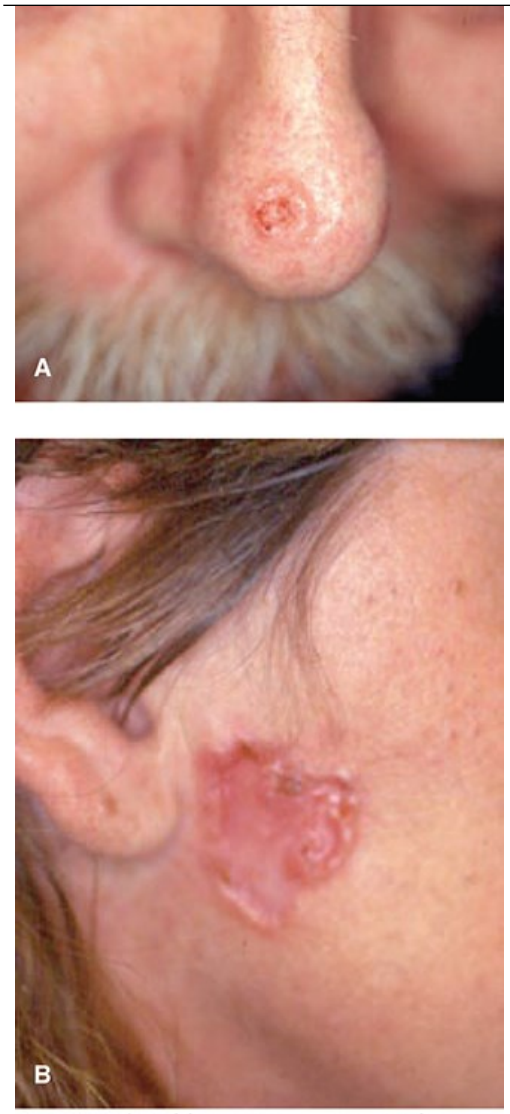
Squamous cell carcinoma. This case of squamous cell carcinoma must be differentiated in diagnosis from chondrodermatitis nodularis helicis, which, unlike carcinoma, is painful. *(Reprinted, with permission, from Grossman D, Leffell DJ. Squamous cell carcinoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:738.)*



Basal cell carcinoma (BCC) is a common skin disorder (Fig. e121-8). BCC most commonly presents as a pigmented nodule on the head and neck. Treatment may vary based on histology and may involve surgical excision as well as the use of topical agents such as imiquimod, or antineoplastic agents such as 5-fluorouracil.

FIGURE e121-8

Basal cell carcinoma. (*A*) Basal cell carcinoma, nodular type. (*B*) An ulcerated nodular basal cell carcinoma. *(Reprinted, with permission, from Carucci JA, Leffell DJ. Basal cell carcinoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:749.)*



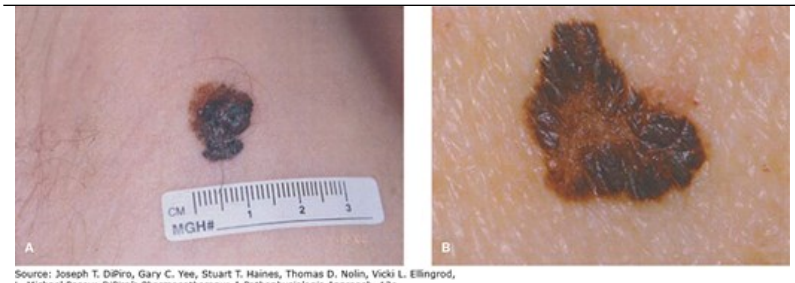
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Malignant melanoma, unless detected early and excised, often produces systemic metastases. Thus, early detection is crucial. The incidence of melanoma has increased over the past few decades, with an estimated one in 65 Americans developing melanoma during their lifetimes.[58]

A changing mole (dysplastic nevus) is often a harbinger of melanoma. These are detected by skin examination; dermatologists often have melanoma clinics for this purpose. Moles are examined for asymmetry, irregular borders, variegated colors, and size (Fig. e121-9). Full-body skin examinations are important in screening for melanoma because it can occur anywhere on the skin.[58] Refer to Chapter e17 for further discussion about dysplastic nevi.

FIGURE e121-9

Melanomas. These two superficial spreading melanomas illustrate the ABCDs of melanoma. (*A*) Asymmetry. The lesions are not symmetrical and often have irregular borders. (*B*) Border. Note the highly irregular, uneven, and notched border. (*C*) Color. The color is variegated with different shades of brown, black, and tan. (*D*) Diameter. The diameter is usually (but not always) more than 6 mm in melanomas. *(Reprinted, with permission, from Langley RGB, Barnhill RL, Mihm MC Jr, et al. Neoplasms: Cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw Hill, 2003:925.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Other risk factors include prolonged sun exposure and the ability to tan, family history, and drug treatments such as PUVA or biologic response modifiers used for psoriasis.

Suspicious pigmented lesions should be fully excised as soon as possible rather than biopsied; malignant melanomas are best diagnosed and microstaged with an excisional biopsy of the entire lesion.[59] Delayed diagnosis of malignant melanoma directly affects patient survival adversely.[59] Treatment may also include systemic antineoplastic therapy, such as temozolomide or dacarbazine, for metastatic melanoma.

SPECIAL PATIENT POPULATIONS

There are signs or symptoms relating to skin disorders that may need to be assessed and/or managed differently in specific patient populations such as the pregnant woman. Pharmacists should be aware of these situations before deciding to recommend OTC products—in some cases, a referral to a medical practitioner is needed. If in doubt, a referral would be prudent.

Pregnancy

Pruritus affects up to 20% of pregnant women and may affect sleep and quality of life.[60] Pruritic skin disorders unique to pregnancy include intrahepatic cholestasis of pregnancy (ICP), pruritic urticarial papules and plaques of pregnancy (PUPPP), pemphigoid gestationis (PG), and atopic eruption of pregnancy.[60,61]

ICP presents as a sudden onset of severe pruritus that begins on palms and soles then quickly becomes more generalized, with *no rash*; the pruritus may worsen at night.[60] This *should not* be managed with dry skin care and the patient should be immediately referred to her physician. ICP is caused by elevated serum bile acids and the treatment is ursodeoxycholic acid. ICP has been associated with adverse fetal outcomes including preterm labor and fetal death.[60]

PUPPP are pruritic, erythematous, urticarial papules/plaques that often begin in abdominal stretch marks then spread to buttocks/thighs, but sparing the umbilicus.[60] This is a self-limiting condition that resolves spontaneously after delivery; low potency topical corticosteroids can be recommended to provide relief.[60]

PG is a bullous disorder that presents with intense pruritus followed by pruritic, erythematous, urticarial papules/plaques that subsequently blister. Lesions are clustered around the umbilicus and may spread to the extremities but sparing the face, palms, and soles.[60] This is a self-limiting condition that presents after the 20th week of gestation but may appear postpartum.[60] Treatment is usually with systemic corticosteroids to control the blisters, thus a referral would be appropriate.[60]

Atopic eruption of pregnancy describes many benign pruritic conditions of pregnancy that occur in patients with a history of atopy. These can usually be managed with short courses of topical corticosteroids.[60]

Children

Chronic pruritus is associated with many skin disorders in children including chronic spontaneous urticaria (csU), psoriasis, and atopic dermatitis (AD). Although the differential diagnoses and specific discussions are beyond the scope of this chapter, it must be emphasized that adequate control of the pruritus is important in each condition. For example, children with AD and chronic pruritus may be at increased risk for anxiety, depression,

attention deficit hyperactivity disorder, and other such conditions.[62] The quality of life of the children and their caregivers is affected.

Management strategies include identifying and minimizing causative factors in addition to dry skin care and pharmacotherapy with topical corticosteroids and/or other agents. Oral antihistamines have limited efficacy in AD but may be useful in some children with histaminergic pruritus associated with csU.[62] (Refer to Chapter 119, "Atopic Dermatitis," for further discussion about managing pruritus in patients with this condition.)

MUCOCUTANEOUS MANIFESTATIONS OF COVID-19 INFECTION

When the coronavirus disease 2019 (COVID-19) pandemic first began in early 2020, there was little awareness that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could cause skin signs and symptoms; the focus was mostly respiratory/cardiovascular and gastrointestinal effects. However, since SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2) receptors and these are present in the skin, it is not surprising that there would be mucocutaneous manifestations. By spring 2020, there were enough clinical cases that cutaneous manifestations were classified by a nationwide consensus study in Spain with 375 cases.[63] The most common type found was maculopapular (47%), followed by pseudochilblain (19%), urticarial (19%), vesicular (9%), and livedo or necrosis (6%).[63] Other studies followed, including assessments in specific populations (eg, hospitalized patients, children, "long haulers") and specific types of skin manifestations (eg, pseudo-chilblains or "COVID toes").

An October 2020 US study in hospitalized children and adolescents who developed multisystem inflammatory syndrome found 47% (9/19) had rash and/or mucositis, including erythema, morbilliform pattern, retiform purpura, targetoid and urticarial patterns, acral edema, lip mucositis, tongue papillitis, and conjunctivitis.[64] They further noted that patients with rash had less respiratory symptoms, thus less pediatric ICU admission or invasive ventilation, and had shorter hospital stays.[64] This correlation with severity of illness differs from a July 2021 study in Spain that found mucocutaneous manifestations in 42% (21/50) of hospitalized children that posed a higher risk of pediatric ICU admissions.[65] The manifestations included maculopapular, conjunctival hyperemia, and red cracked lips or strawberry tongue.[65] A study in 296 hospitalized adult COVID patients in the United States also reported a more severe course of illness in patients with skin eruptions (about one of every nine patients). The types of lesions included ulcer (37%), purpura (26%), necrosis (14%), non-specific erythema (11%), morbilliform eruptions (11%), pernio-like lesions (11%), and vesicles (3%).[66]

The discrepancies reported when relating hospitalized patients with mucocutaneous lesions to severity of disease may reflect small sample sizes, COVID variants, illness on admission (eg, the Spain study reported higher incidence in older children, but they were brought to the hospital when their COVID illness had progressed further),[65] and other factors. Regardless, these studies have provided evidence that the SARs-CoV-2 virus has many associated mucocutaneous manifestations.

Additional studies assessing a specific type of mucocutaneous manifestation are numerous. For example, a case series in patients with COVID-19 described purpuric ulcers with epidermal necrosis and subepidermal vesiculation.[67] Scattered varicella-like lesions that are minimally pruritic have also been reported in a case series, associated with moderate COVID-19 severity.[68] The phenomenon of "long COVID" is also seen in the skin, with mean durations of up to 28 days for urticaria and 20 days for papulosquamous lesions.[69]

The well-known "COVID toes" deserve special mention. These are pernio- or chilblains-like lesions that may be painful and pruritic. While these lesions are most commonly seen in the toes, the fingers and heels or tips of ears may be involved.[70] In a May 2020 study of 505 patients with confirmed or suspected COVID-19, 318 (63%) had pernio-like lesions. These patients were generally young and healthy with relatively mild COVID-19 symptoms or the pernio-like lesions were their only symptom (55% of patients).[70] If patients had other COVID symptoms, "COVID toes" were usually a late presentation.[70] The conclusion was that "pernio-like skin changes of the feet and hands, without another explanation, may suggest COVID-19 infection and should prompt confirmatory testing."[70] However, testing negative does not rule out COVID-19 infection. A series of 40 consecutive patients with chilblain-like lesions were negative for SARS-CoV-2 on PCR tests, and only 12 patients (30%) showed positive SARS-CoV-2 serology. The serology showed IgM in 1 patient and IgA in 8 and IgG in 5 patients.[71]

CONCLUSION

This chapter has discussed patient-specific lesion assessment, drug-induced skin reactions, contact dermatitis (both irritant and allergic), photoaging, common skin cancers, and skin conditions in special patient populations. Other common skin disorders are covered in the other chapters in the

Dermatology section of this edition of Pharmacotherapy and in the skin care Chapter e17 in the self-care section of this work. Skin and soft tissue infections and parasitic diseases are detailed in the Infectious Diseases section of this chapter. See Appendix A for additional discussion about SJS/TEN, which will be useful for the drug-induced reactions case (TEN) in the casebook.

ABBREVIATIONS

ACD	allergic contact dermatitis
AD	atopic dermatitis
ADR	adverse drug reaction
AGEP	acute generalized exanthematous pustulosis
AHA	alpha-hydroxy acids
BCC	basal cell carcinoma
BHA	beta-hydroxy acids
BSA	body surface area
COVID-19	coronavirus disease of 2019
CPIC	Clinical Pharmacogenetics Implementation Consortium
CSU	chronic spontaneous urticaria
DHS	drug hypersensitivity syndrome
EM	erythema multiforme
DRESS	drug reaction with eosinophilia and systemic symptoms
FDA	US Food and Drug Administration
HLA	human leukocyte antigen
ICD	irritant contact dermatitis
ICP	intrahepatic cholestasis of pregnancy
IVIG	IV immunoglobulin
LFA-1	lymphocyte function-associated antigen
LMW	low molecular weight
LTT	lymphocyte transformation tests
MBEH	monobenzyl ether of hydroquinone

MCI	methylchloroisothiazolinone
MHC	major histocompatibility
MI	methylisothiazolinone
MRSA	methicillin-resistant *Staphylococcus aureus*
NHP	natural health product
NRL	natural rubber latex
NSAID	nonsteroidal anti-inflammatory agent
OTC	over-the-counter medication
PG	pemphigoid gestationis
PUPPP	pruritic, urticarial papules and plaques of pregnancy
PUVA	psoralens + ultraviolet A light
ROAT	repeat open application test
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SCARs	severe cutaneous adverse reactions to drugs
SCC	squamous cell carcinoma
SCOTEN	Severity of Illness Score for Toxic Epidermal Necrolysis
SJS	Stevens–Johnson syndrome
SPF	a sun protection factor
TEN	toxic epidermal necrolysis
UV	ultraviolet
UVA	ultraviolet A

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is a risk factor for hypersensitivity adverse drug reactions of the skin?

   A. Serum drug level increases

   B. Topical medication administration

   C. Skin dryness or abrasion

   D. No known drug allergies

2. SJS/TEN is classified as what type of cutaneous drug eruption?

A. Urticarial

B. Pustular

C. Exanthemous

D. Blistering

3. Which of the following eruptions lacks the presence of a fever?

A. AGEP

B. Acneiform

C. DRESS

D. Serum sickness-like reaction

4. Which of the following drug classes is a common cause of maculopapular skin reactions?

A. Beta blockers

B. Analgesics

C. CNS bepressants

D. Sulfonamides

5. Which of the following medications has been shown to halt disease progression, decrease mortality, and enhance recovery in patients with SJS or TEN?

A. Calcium channel blockers

B. Vancomycin

C. IVIG

D. Normal saline

6. Pharmacogenomics testing indicates a patient is positive for HLA-B*15:02. What is the most appropriate next step before initiation of carbamazepine therapy?

A. Increase starting dose by 20%

B. Use alternate therapy

C. Decrease starting dose by 10%

D. Conduct additional testing

7. Beta-hydroxy acids (BHAs) are agents in what pharmacologic class that is indicated for the treatment of photoaging?

A. Keratolytics

B. Topical retinoids

C. Depigmenting agents

D. Vitamins

8. ICP is treated using which of the following agents?

   A. Hydroquinone

   B. Salicylic acid

   C. Topical retinoids

   D. Ursodeoxycholic acid

9. Which of the following risk factors increases the risk of serious skin reactions with allopurinol therapy?

   A. Low blood pressure

   B. Renal impairment

   C. Loop diuretic use

   D. Liver impairment

10. What is the most important first step in managing a suspected drug-induced skin reaction?

    A. Apply cool compress

    B. Administer corticosteroids

    C. Discontinue suspected drug

    D. Conduct a skin patch test

11. Phenytoin is metabolized predominately by which of the following CYP enzymes?

    A. 2C9

    B. 1A2

    C. 2D6

    D. 3A4

12. What class of medications is considered the mainstay of treatment for allergic contact dermatitis?

    A. Vitamins

    B. Depigmenting agents

    C. Topical corticosteroids

    D. Keratolytics

13. Which of the following factors is used to calculate the SCOTEN score?

    A. Blood glucose

    B. Absence of malignancy

    C. Pulse <120 beats/min

D. BSA >10% affected

14. Which of the following topical agents may be used to treat basal cell carcinoma?

    A. Imiquimod

    B. Benzoyl peroxide

    C. Triamcinolone acetonide

    D. Mupirocin

15. Which of the following is indicated to treat age-related hyperpigmentation (i.e., age spots)?

    A. Salicylic acid

    B. Hydroquinone

    C. Sunscreen

    D. Ursodeoxycholic acid

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Serum drug level increases are a risk factor for hypersensitivity adverse drug reactions of the skin. B, C, and D are not known risk factors.

2. **D.** SJS/TEN is a type of blistering cutaneous drug eruption characterized by presence of a fever.

3. **B.** Acneiform is the only eruption that occurs without a fever present. AGEP, DRESS, and Serum sickness-like reactions all occur in the setting of a fever.

4. **D.** Sulfonamides are known to cause maculopapular skin reactions. It is usually a delayed reaction that resolves with discontinuation of the drug or completion of the course of therapy.

5. **C.** IVIG is the only medication shown to halt disease progression, decrease mortality, and enhance recovery in patients with SJS or TEN. Corticosteroids is an incorrect response as these agents may increase mortality.

6. **B.** If testing indicates that the patient is positive for HLA-B*15:02, the product labeling states that carbamazepine should not be used unless the benefits clearly outweigh the risks. “Use alternative therapy” is the most appropriate option here.

7. **A.** BHAs are keratolytic agents.

8. **D.** Ursodeoxycholic acid is the treatment of choice for ICP. Other therapies listed are used for the management of photoaging.

9. **B.** For patients taking allopurinol, several factors increase the risk of serious skin reactions: renal impairment, hypertension, and use of thiazide diuretics or excessive allopurinol doses (ie, not dose adjusted for renal impairment). Liver impairment is not a risk factor for serious skin reactions with allopurinol use.

10. **C.** Discontinuing the suspected drug is critical in nearly all cases of a suspected drug-induced skin reaction to remove continued exposure. Administering corticosteroids may be appropriate in limited cases. Patch tests are a diagnostic technique for contact allergens. Applying a cool compress does not address the cause of the drug-induced skin reaction.

11. **A.** CYP 2C9 is the main metabolizing enzyme for phenytoin.

12. **C.** Topical corticosteroids are considered the mainstay of treatment. Higher potency topical steroids are used, with a taper to lower potency topical corticosteroids as needed as the condition improves.

13. **D.** BSA >10% affected is a factor used to calculate the SCOTEN score. All other options are represented in the score; however, the benchmark for inclusion for each is incorrect in the answer options. Blood glucose must be greater than 252 mg/dL, malignancy must be present, and pulse should be greater than 120 beats per min.

14. **A.** Surgical excision, along with the use of imiquimod, is an appropriate treatment option for basal cell carcinoma. All other answer options are incorrect as these are not indicated for topical treatment of basal cell carcinoma and are used for minor skin conditions.

15. **B.** Hydroquinone is a hyperpigmentation treatment option for patients with age spots ("liver spots") and may be used alone or with retinoic acid. Sunscreen is a preventive measure against the development of hyperpigmentation. Salicylic acid and ursodeoxycholic acid are not appropriate treatment options for age-related hyperpigmentation.

APPENDIX A: TOXIC EPIDERMAL NECROLYSIS

Toxic epidermal necrolysis (TEN) typically presents with a prodrome of multiple symptoms including malaise, rash (may be pruritic), fever, cough, arthralgias, myalgias, rhinitis, headache, anorexia, pharyngitis, conjunctivitis, nausea, vomiting, and/or diarrhea. The rash may be morbilliform (a fine, discrete maculopapular exanthema), or may consist of atypical targetoid macules.[72] This is followed by acute persistent fevers, flaccid bullae, generalized epidermal sloughing, and extensive sloughing of both internal and external mucocutaneous membranes. Blisters can extend laterally on pressure (Asboe–Hansen sign) and the skin can peel off in sheets with minor manipulation (Nicolsky sign).[73]

Complications include painful stomatitis and mucositis, with erosions throughout the gastrointestinal tract and there may be gastrointestinal hemorrhage. Ocular complications included conjunctiva hyperemia, palpebral synechiae, and symblepharon formation (adhesions of the eyelids).[73] Genitourinary complications, including acute renal failure, may also occur. Pulmonary complications including acute respiratory distress syndrome, bronchiolitis obliterans, and subcutaneous emphysema have been documented.[72] Twenty-five percent of patients with TEN develop early pulmonary dysfunction with hypoxemia, dyspnea, and bronchial mucosal sloughing seen on fiberoptic bronchoscopy.[72] Other complications include anemia, leukopenia, transient increase in liver function tests (LFTs), hepatitis, severe abdominal pain, hypoalbuminemia, hyponatremia, encephalopathy, and myocarditis.[72]

The conditions erythema multiforme (EM), Stevens–Johnson syndrome (SJS), and TEN are often discussed together. TEN and SJS have similar clinical presentations and have been considered variants within a continuous spectrum or overlapping conditions.[72,74] Although EM also has a similar clinical presentation, current concepts support EM as a specific disease different from the SJS/TEN spectrum.[72,74] Detachment of <10% of the body surface area (BSA) defines SJS, and detachment of more than 30% of the BSA classically defines TEN.[72,74] The overlap between SJS and TEN refers to detachment of 10% to 30% of the BSA.

As the epidermis sloughs off in large sheets, it leaves a characteristic moist, denuded dermis. Denudation and erosions of mucous membranes precede epidermal necrolysis.[58,60] A positive Nikolsky sign is typical of SJS/TEN: the epidermis separates easily when slight pressure is applied laterally to the skin.[72,74]

Prognostic factors to assess disease severity include assessing mortality risk using the Severity of Illness Score for Toxic Epidermal Necrolysis (SCOTEN) score, which is calculated based on summation of the single points assigned for each of the following[72]:

- Age older than 40 years
- Presence of malignancy
- Pulse >120 beats/min
- Blood glucose >252 mg/dL (14 mmol/L)
- Blood urea nitrogen >28 mg/dL (10 mmol/L)

- Serum bicarbonate <20 mEq/L (mmol/L)
- BSA >10% affected

Based on the calculated SCOTEN score, mortality risks can be estimated as follows: score of 0 to 1, mortality risk of 3.2%; score 2, risk 12.1%; score 3, risk 35.3%; score 4, risk 58.3%; and with a SCOTEN score of 5 to 7, the estimated mortality risk is 90%.[72]

To optimize its predictive value for mortality and to inform patient care, the SCOTEN score should be calculated within 24 hours of admission and repeated on day 3 of admission.[72]

Mortality rate for TEN in adults have been variously estimated and may be between 25% and 30%[72] or between 30% and 50%,[75] but is significantly lower in children[61] and higher in the elderly. Mortality for SJS is significantly lower (less BSA involvement, etc.) and estimates are between 1% and 3%.

SJS and TEN have been reported worldwide and in all age groups including children, infants, and even newborns.[75,76] The worldwide incidence of TEN has been estimated at about 1.5 to 2 cases per million persons per year in most countries.[76] However, in the United States, the annual frequency of TEN is reported to be 0.22 to 1.23 cases per 100,000 population; with a higher incidence (1 per 1,000 per year) among patients living with human immunodeficiency virus infections.[72] An estimate of SJS was 1 to 7 cases per million persons per year.[75] In children, TEN occurs equally frequently in boys and girls, but in adults the frequency of men to women is 2:3 or 1:2.[75] Persons older than 60 years of age are more likely to develop TEN.[75]

TEN can be drug induced, caused by other inciting factors such as infection, or be idiopathic; medications are by far the major cause.[72,75,76] Drugs are implicated in an estimated 60% to 94% of cases of TEN in the general population (mostly adult patients).[62] Antibacterial sulfonamides are among the most frequently cited causative agents.[75,76] One large international case-control study which separated short-term use drugs (days to weeks) versus long-term use drugs (months to years) in their assessment of risks for SJS/TEN found that the highest risk in the short-term use group was for trimethoprim-sulfomethoxazole (TMP-SMX) and other sulfonamide antibiotics.[77] The crude relative risk was 172 (95% confidence interval 75-396), and TMP/SMX accounted for 69% of the cases, with a median unbiased relative risk estimate of 160.[77] A pooled analysis in children and teens younger than 15 years of age showed strong association with SJS/TEN for anti-infective sulfonamides, phenobarbital, lamotrigine, and carbamazepine, with other drugs including valproic acid, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs) also increasing the risk; this study is further discussed below.[78] A 2008 multinational case-control study (conducted in France, Germany, Italy, the Netherlands, Austria, and Israel between 1997 and 2001) evaluated the risk of medications inducing severe cutaneous adverse reactions (SCAR), which include SJS/TEN.[79] This assessment (the EuroSCAR study) emphasized on the risk from recently marketed drugs as well as reviewing all drug causes. The study reported that among more recently marketed drugs, the strongest associations with SCAR were nevirapine and lamotrigine, followed by weak associations with sertraline, pantoprazole, and tramadol. Among all drugs, strong associations with SCAR were confirmed for anti-infective sulfonamides, allopurinol, carbamazepine, phenobarbital, phenytoin, and oxicam-type NSAIDs.[79]

Sulfonamides warrant additional discussion since they are the most commonly implicated drugs in SCAR. They can be structurally classified into two distinct groups: sulfanilamides and nonsulfanilamides. Sulfanilamides have a sulfonamide moiety attached to a benzene ring, with an unsubstituted amine (–NH2) at the N4 position. Sulfanilamides include the antibacterial sulfonamides (sulfadiazine, sulfamethoxazole, sulfisoxazole, and sulfapyridine) and protease inhibitors (amprenavir, fosamprenavir).[80]

Nonsulfanilamides are structurally distinct; these include COX-2 inhibitors, carbonic anhydrase inhibitors, diuretics (eg, furosemide, indapamide), sulfonylureas (eg, glyburide, glipizide), and others (eg, ibutilide, sotalol, topiramate).[80] Thus, a person with an allergic reaction to TMP/SMX might cross-react to another sulfanilamide but likely not with all sulfonamides. However, genetic factors are associated with severe drug hypersensitivity reactions (SCARs) such as TEN, and this is a predisposition to allergic reactions independent of the cross-sensitivity risk. Thus, hypersensitivity reactions may infrequently occur with nonsulfanilamides, or with other drugs, and these are not true cross-reactivities. For patients with serious allergic reactions to a sulfonamide, or with multiple medication allergies, nonsulfonylarylamine or sulfonamide moiety-containing medications should be avoided. Patients with a history of allergic reactions to drugs may be at increased risk for all drug-induced allergic reactions.

Genetic predispositions are known to exist. SJS/TEN is associated with an impaired capacity in some patients to detoxify reactive intermediate drug metabolites, which react with host tissues to form an antigenic complex, triggering the immune response that results in SJS/TEN.[81] This defect was

shown in patients with sulfonamide or anticonvulsant allergies and were constitutional and inherited.[82] Patients with particular HLA subtypes are at higher risk for SJS/TEN, and there are racial differences.[81] For example, Asians and East Indians with HLA-B*1502 exposed to carbamazepine, Han Chinese and some Europeans with HLA-B*5801 exposed to allopurinol, and whites and African Americans with HLA-B*5701 exposed to abacavir are all at higher risk of SJS/TEN[81]; the US Food and Drug Administration currently recommends genotyping of all Asians before treatment with carbamazepine.[81] The genetic predisposition may have relevance for the patient's first-degree relatives as well.[82]

There are also nonmedication risk factors for TEN. The pooled analysis in children and teens younger than 15 years of age discussed above also identified nonmedication risk factors.[78] Significant nonmedication risk factors were fever or an upper respiratory tract infection; no other nonmedication risk factors were significant, including recent herpes infection (11% cases vs 10% controls). With regard to medication risks, cases were exposed to more drugs (mean = 2.4) than controls (mean = 0.75). Seventy percent of cases and 15% of controls were exposed to at least one suspected drug. Highly suspected drugs were taken by 39% of cases and fewer than 1% of controls. Among the highly suspected drugs, anti-infective sulfonamides, phenobarbital, lamotrigine, and carbamazepine were strongly associated with SJS/TEN. There was only one case of exposure to phenytoin, and no children were exposed to allopurinol, nevirapine, or oxicam-NSAIDs. Among the other suspected drugs, valproic acid, acetaminophen, and NSAIDs as a group were found to increase the risk of SJS/TEN in children.[78]

Treatment of TEN is vital for survival and is necessarily multipronged; it includes immediate pharmacologic and nonpharmacologic life support measures such as maintaining airway patency and therapies to prevent long-term sequelae (eg, ocular damage).[72-74,83,84] In addition, any complication that arises during the skin healing period (eg, bacteremia) must be promptly treated. Furthermore, nutritional support is required.[74]

An interprofessional collaborative team approach to care as used at a burn center in a major Canadian acute care teaching hospital (Sunnybrook Health Sciences Centre in Toronto), which has a strong dermatology team, was published in 2018.[85] Evidence-based United Kingdom guidelines for the management of SJS/TEN in adults were published in 2016.[86] The use of biologic agents such as etanercept is efficacious in both an adult[84] and a child[87] and has been incorporated into some treatment protocols.[85] Refer to the *Pharmacotherapy Casebook* for treatment of a TEN case.

Although acute mortality from TEN can be reduced with better management and treatment guidelines, other issues including prevention, reduction of risk factors, and treatment of long-term sequelae also need to be addressed. For long-term morbidity, ocular lesions are considered the most frequent severe sequelae of TEN, as lesions can remain active for years and too often result in severe disabilities, including blindness.[88]