The Generalized Rash: Part I. Differential Diagnosis

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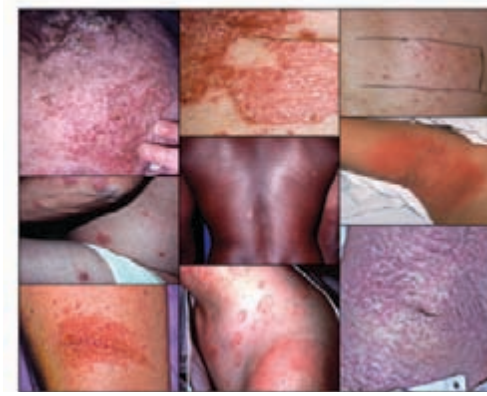
Physicians often have difficulty diagnosing a generalized rash because many different conditions produce similar rashes, and a single condition can result in different rashes with varied appearances. A rapid and accurate diagnosis is critically important to make treatment decisions, especially when mortality or significant morbidity can occur without prompt intervention. When a specific diagnosis is not immediately apparent, it is important to generate an inclusive differential diagnosis to guide diagnostic strategy and initial treatment. In part I of this two-part article, tables listing common, uncommon, and rare causes of generalized rash are presented to help generate an inclusive differential diagnosis. The tables describe the key clinical features and recommended tests to help accurately diagnose generalized rashes. If the diagnosis remains unclear, the primary care physician must decide whether to observe and treat empirically, perform further diagnostic testing, or refer the patient to a dermatologist. This decision depends on the likelihood of a serious disorder and the patient's response to treatment. (*Am Fam Physician*. 2010;81(6):726-734. Copyright © 2010 American Academy of Family Physicians.)



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This is part I of a two-part article on generalized rashes. Part II, "Diagnostic Approach," appears in this issue of *AFP* on page 735.

Generalized rashes are among the most common conditions seen by primary care physicians,[1,2] and the most common reason for new patient visits to dermatologists.[3] Diagnostic errors involving generalized rashes are common.[4,5] However, accurate diagnosis is important because treatment varies depending on the etiology, and because some rashes can be life-threatening if not treated promptly. Some generalized rashes have distinctive features that allow immediate recognition, such as psoriasis (silvery white scale on the knees and elbows), pityriasis rosea (herald patch), and atopic dermatitis (lichenified skin in flexural areas). But these conditions, like many others, can present with similar appearances and can be mistaken for each other.

It is difficult to comprehensively review generalized rashes because the topic is so broad. Previous reviews have been limited to narrower topics, such as viral exanthems,[6] drug eruptions,[7] and rashes associated with fever.[8,9] Physicians, however, cannot limit their considerations; they must constantly guard against premature closure of the diagnostic process.[10] Therefore, a broad perspective is maintained in this article. Generalized rashes that manifest only as purpura or petechiae will not be discussed, with the exception of meningococcemia and Rocky Mountain spotted fever (because these conditions often present initially with nonspecific maculopapular rashes before becoming purpuric). Rashes that primarily affect pregnant women, newborns, immunocompromised persons, and persons living outside North America are also excluded. Part I of this two-part article focuses on differential diagnosis of generalized rashes. Part II focuses on the clinical features that can help distinguish these rashes.[11]

Differential Diagnosis

The causes of a generalized rash are numerous, but most patients have common diseases *(Table 1)*.[12-26] Many common rashes improve

Table 1. Common Causes of Generalized Rash

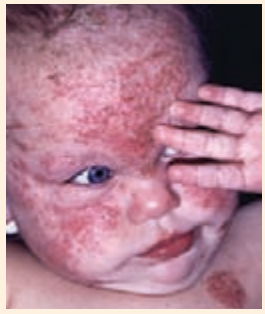
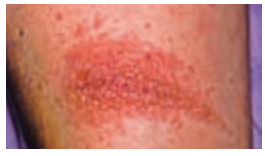
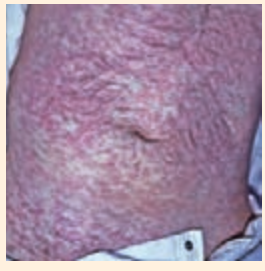
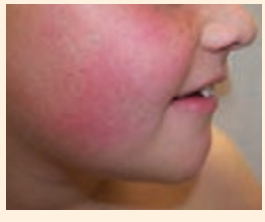
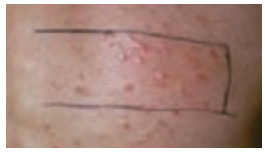
Condition	*Key clinical features*	*Tests*
Atopic dermatitis 	Dry skin; pruritus; erythema; erythematous papules; excoriations; scaling; lichenification; accentuation of skin lines; keys to diagnosis are pruritus, eczematous appearance of lesions, and personal or family history of atopy[12]	Skin biopsy is nonspecific and not often done*
Contact dermatitis 	Erythema; edema; vesicles; bullae in linear or geometric pattern; common causes include cosmetics, topical medications, metal, latex, poison ivy, textiles, dyes, sunscreens, cement, food, benzocaine, neomycin[13]; keys to diagnosis are linear or geometric pattern and distribution of lesions	Skin biopsy is nonspecific and not often done,* but it can help exclude other conditions
Drug eruption† 	Many patterns, but most commonly maculopapular (95% of cases)[14]; common in patients taking allopurinol (Zyloprim), beta-lactam antibiotics, sulfonamides, anticonvulsants, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, hypoglycemics, and thiazide diuretics, but can occur with almost any drug[14]; usually appears within 1 to 4 weeks of initiating drug; key to diagnosis is timing of rash appearance in relation to drug use[14]	Skin biopsy is usually nonspecific and not often done*[15]
Erythema multiforme	Round, dusky red lesions that evolve into target (iris) lesions over 48 hours; starts on backs of hands and feet and on extensor surfaces of arms and legs; symmetric; may involve palms, soles, oral mucous membranes, or lips; key to diagnosis is presence of target lesions	Skin biopsy is generally diagnostic and occasionally done; biopsy should be taken from the erythematous (not blistered) portion of the target[16]
Fifth disease (i.e., erythema infectiosum)† 	"Slapped cheek" appearance with sparing of periorbital areas and nasal bridge; unique fishnet pattern; erythema on extremities, trunk, and buttocks; keys to diagnosis in children are slapped cheek appearance and net-like rash, and in adults are arthralgias and history of exposure to affected child	Parvovirus B19 serology; skin biopsy is nonspecific and rarely done*
Folliculitis 	Multiple small pustules localized to hair follicles on any body surface; key to diagnosis is hair follicle at center of each lesion	Skin biopsy is often diagnostic but not often done*

Table 1 continues

Table 1. Common Causes of Generalized Rash *(continued)*

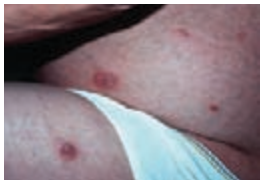
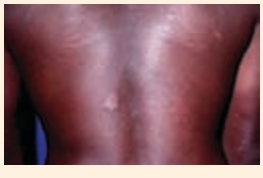
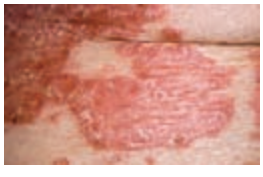
Condition	*Key clinical features*	*Tests*
Guttate psoriasis	Pinpoint to 1-cm scaling papules and plaques on trunk and extremities; often preceded by streptococcal pharyngitis 1 to 2 weeks before eruption[17]; keys to diagnosis are scaling and history of streptococcal pharyngitis[17]	Throat culture; antistreptolysin O titer; early skin biopsy may not be diagnostic and is not often done*
Insect bites	Urticarial papules and plaques; keys to diagnosis are outdoor exposure (usually) and distribution of lesions where insects are likely to bite	Skin biopsy is nonspecific and not often done*
Keratosis pilaris	Pinpoint follicular papules and pustules on posterolateral upper arms, cheeks, anterior thighs, or buttocks[18]; keys to diagnosis are upper arm distribution, absence of comedones, and tiny palpable lesions	Skin biopsy can be diagnostic but is not often done*
Lichen planus	Violaceous flat-topped papules and plaques; commonly on ankles and wrists; 5 P's (pruritic, planar, polygonal, purple plaques); Wickham striae (reticular pattern of white lines on surface of lesions)[19]; lacy white buccal mucosal lesions; Koebner phenomenon (development of typical lesions at the site of trauma); keys to diagnosis are purple color and distribution of lesions[20]	Skin biopsy is diagnostic and often done
Miliaria rubra (i.e., prickly heat, heat rash)	Erythematous nonfollicular papules associated with heat exposure or fever; lesions on back, trunk, neck, or occluded areas; keys to diagnosis are history of heat exposure and distribution of lesions	Skin biopsy can be diagnostic but is not often done*
Nummular eczema 	Sharply defined, 2- to 10-cm, coin-shaped, erythematous, scaled plaques; lesions on dorsal hands and feet, extensor surfaces of arms and legs, flanks, and hips; key to diagnosis is sharply defined, round, erythematous, scaled lesions	Skin biopsy is nonspecific and not often done,* but it may help exclude other diagnoses
Pityriasis rosea 	Discrete, round to oval, salmon pink, 5- to 10-mm lesions; "Christmas tree" pattern on back; often (17 to 50%) preceded by solitary 2- to 10-cm oval, pink, scaly herald patch[21]; keys to diagnosis are oval shape, orientation with skin lines, and distinctive scale	Skin biopsy is nonspecific and not often done,* but it may help exclude other diagnoses; rapid plasma reagin testing is optional to rule out secondary syphilis
Psoriasis (plaque psoriasis) 	Thick, sharply demarcated, round or oval, erythematous plaques with thick silvery white scale; lesions on extensor surfaces, elbows, knees, scalp, central trunk, umbilicus, genitalia, lower back, or gluteal cleft; positive Auspitz sign (removal of scale produces bleeding points); Koebner phenomenon; keys to diagnosis are distinctive scale and distribution of lesions[22]	Skin biopsy can be diagnostic but is not often done*
Roseola (i.e., exanthem subitum, sixth disease)	Sudden onset of high fever without rash or other symptoms in a child younger than 3 years; as fever subsides, pink, discrete, 2- to 3-mm blanching macules and papules suddenly appear on trunk and spread to neck and extremities; key to diagnosis is high fever followed by sudden appearance of rash as fever abruptly resolves[23]	Skin biopsy is nonspecific and not often done*

Table 1 continues

Table 1. Common Causes of Generalized Rash *(continued)*

Condition	*Key clinical features*	*Tests*
Scabies	Discrete, small burrows, vesicles, papules, and pinpoint erosions on fingers, finger webs, wrists, elbows, knees, groin, buttocks, penis, scrotum, axillae, belt line, ankles, and feet; keys to diagnosis are distribution of lesions, intense pruritus, and positive mineral oil mount	Mineral oil mount is routinely done to identify mites or eggs; skin biopsy is usually nonspecific and not often done*
Seborrheic dermatitis	Erythematous patches with greasy scale; lesions behind ears or on scalp and scalp margins, external ear canals, base of eyelashes, eyebrows, nasolabial folds, central chest, axillae, inframammary folds, groin, and umbilicus; keys to diagnosis are greasy scale and distribution of lesions	Skin biopsy is nonspecific and not often done*
Tinea corporis	Flat, red, scaly lesions progressing to annular lesions with central clearing or brown discoloration; keys to diagnosis are annular lesions with central clearing and positive KOH preparation	KOH preparation is routinely done; skin biopsy can be diagnostic[24] but is not often done*
Urticaria (i.e., hives)	Discrete and confluent, raised, edematous, round or oval, waxing and waning lesions with large variation in size; may have erythematous border (flare) and pale center (wheal); patient may have history of drug, food, or substance exposure; key to diagnosis is distinctive appearance of edematous lesions	Skin biopsy is nonspecific and not often done*
Varicella†	Vesicles on erythematous papules ("dewdrop on rose petal" appearance); all stages (papules, vesicles, pustules, crusts) are present at the same time and in close proximity; keys to diagnosis are crops of lesions in different stages, systemic illness, and exposure to persons with the infection	Diagnosis is usually clinical, but real-time polymerase chain reaction assay of skin lesion or direct fluorescent antibody testing of skin scrapings could be done[25]; skin biopsy is often diagnostic but cannot distinguish herpes zoster or herpes simplex, and is not often done*
Viral exanthem, nonspecific	Blanchable, red, sometimes confluent macules and papules; may be indistinguishable from drug eruptions[26]; keys to diagnosis are nonspecific generalized maculopapular rash in a child with systemic symptoms (fever, diarrhea, headache, fatigue)	Skin biopsy is nonspecific and not often done*

KOH = potassium hydroxide.

**—Skin biopsy is often not performed because the histology is nonspecific or because a biopsy is usually not needed for diagnosis.*

†*—Rashes that can have serious consequences for the patient or pregnant contacts of the patient.*

Information from references 12 through 26.

spontaneously or with simple measures, such as discontinuing a medication. Life-threatening rashes are rare in the United States, so they can be easily missed because they are not considered.

Because of the large number of conditions that can manifest as a generalized rash, it is not reasonable to expect physicians to generate a complete differential diagnosis from memory at the point of care. Consulting a list of potential causes allows the physician to narrow the possibilities by noting salient clinical features and test results *(Table 1*[12-26], *Table 2*[27-39], and *Table 3*[40]*)*. If the diagnosis remains unclear, the physician must decide whether to treat the patient symptomatically, pursue further testing, or consult a dermatologist.

Patients with acute generalized maculopapular rashes and no systemic symptoms are often treated symptomatically without a definitive diagnosis. If the rash does not resolve spontaneously, skin biopsy and blood testing (e.g., serologies, complete blood count) may be indicated. There are no widely accepted guidelines that address indications for skin biopsy, but *Table 1*[12-26], *Table 2*[27-39], and *Table 3*[40] include common practices.

Table 2. Uncommon Causes of Generalized Rash

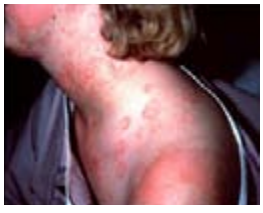
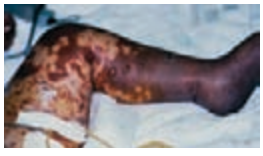
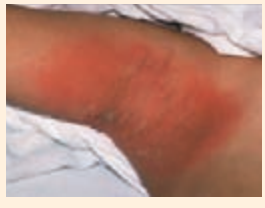
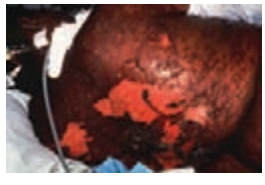
Condition	*Key clinical features*	*Tests*
Bullous pemphigoid	Generalized bullae, especially on trunk and flexural areas; patient usually older than 60 years[27]; Nikolsky sign (easy separation of epidermis from dermis with lateral pressure) usually negative	Skin biopsy with direct and indirect immunofluorescence is diagnostic and usually done
Dermatitis herpetiformis	Symmetric, pruritic, urticarial papules and vesicles that are often excoriated and isolated or grouped on extensor surfaces (knees, elbows), buttocks, and posterior scalp; most patients have celiac disease, but it is often asymptomatic; diagnosis is often delayed[28]	Skin biopsy with direct immunofluorescence is diagnostic and routinely done
HIV acute exanthem*	Diffuse, nonspecific, erythematous, maculopapular, nonpruritic lesions[29]; fever, fatigue, headache, lymphadenopathy, pharyngitis, myalgias, and gastrointestinal disturbances	Measurement of quantitative plasma HIV-1 RNA levels (viral load) by polymerase chain reaction[30]; HIV serology (delay at least 1 month after acute illness); skin biopsy is nonspecific and not often done†
Id reaction	Follicular papules or maculopapular or vesiculopapular rash involving forearms, thighs, legs, trunk, or face; associated with active dermatitis (e.g., stasis dermatitis) or fungal infection elsewhere	KOH preparation to diagnose dermatophyte infection; skin biopsy is nonspecific and not often done†
Kawasaki disease*	Erythematous rash on hands and feet starting 3 to 5 days after onset of fever in children younger than 8 years (usually younger than 4 years); blanching macular exanthem on trunk, especially groin and diaper area; hyperemic oral mucosa and red, dry, cracked, bleeding lips	CBC to detect elevated white blood cell and platelet counts; measurement of C-reactive protein level and erythrocyte sedimentation rate[31]; skin biopsy is nonspecific and not often done†
Lupus (subacute cutaneous lupus erythematosus) 	Papulosquamous or annular pattern, mainly on trunk and sun-exposed face and arms; can be drug induced[32]	Antinuclear antibody testing; skin biopsy with direct immunofluorescence is diagnostic and often done
Lyme disease*	Erythema migrans at site of tick bite, progressing to generalized macular lesions on proximal extremities, chest, and creases (median lesion size, 15 cm); history of outdoor activities; most common in northeastern U.S. seaboard, Minnesota, and Wisconsin[33]	Serology; skin biopsy is nonspecific and not often done†
Meningococcemia* 	Nonblanching petechiae and palpable purpura, which may have gunmetal gray necrotic centers[34]; usually spares palms and soles; may start as erythematous papules or pink macules	Positive cultures of blood, lesions, and cerebrospinal fluid; positive buffy coat Gram stain; skin biopsy is usually nonspecific and not often done†
Mycosis fungoides (i.e., cutaneous T-cell lymphoma)	Flat erythematous macules evolving into red scaly plaques with indistinct edges and poikiloderma (atrophy, white and brown areas, telangiectasia); can present as erythroderma (Sézary syndrome); diagnosis is often delayed; often confused with eczema[35]	Skin biopsy is diagnostic and routinely done

Table 2 continues

Table 2. Uncommon Causes of Generalized Rash *(continued)*

Condition	*Key clinical features*	*Tests*
Rocky Mountain spotted fever*	2- to 6-mm macules that spread centrally from wrists and ankles and that progress to papules and petechiae; often involves palms and soles; fever, severe headache, photophobia, myalgias, abdominal pain, nausea, and vomiting; history of outdoor activities in endemic area (e.g., Oklahoma, Tennessee, Arkansas, southern Atlantic states)	Serology; skin biopsy with direct fluorescent antibody testing is diagnostic and often done, if available[36]
Scarlet fever*	Blanching sandpaper-like texture follows streptococcal pharyngitis or skin infection; Pastia lines (petechiae in antecubital and axillary folds); fever, vomiting, headache, and abdominal pain; most common in children	Antistreptolysin O titer; throat culture; skin biopsy is nonspecific and not often done†
Secondary syphilis*	Variable morphology, but usually red-brown scaly papules with involvement of the palms and soles; oral and genital mucosa also commonly affected	Positive syphilis serology (usually done); skin biopsy can be nonspecific and is not often done†
Staphylococcal scalded skin syndrome* 	Starts with painful, tender sandpaper-like erythema favoring flexural areas, and progresses to large, flaccid bullae[37]; positive Nikolsky sign; most common in children younger than 6 years	Skin biopsy is diagnostic and routinely done to distinguish from toxic epidermal necrolysis, which is rare in infancy and childhood; frozen section biopsy should be considered; eyes, nose, throat, and bullae should be cultured for *Staphylococcus aureus*
Stevens-Johnson syndrome* Toxic epidermal necrolysis* 	Stevens-Johnson syndrome: vesiculobullous lesions on the eyes, mouth, genitalia, palms, and soles; usually drug induced Toxic epidermal necrolysis: life-threatening condition with diffuse erythema, fever, and painful mucosal lesions; positive Nikolsky sign	Skin biopsy is diagnostic and routinely done for toxic epidermal necrolysis; frozen section biopsy should be considered[38]
Sweet syndrome (i.e., acute febrile neutrophilic dermatosis)	Red, tender papules that evolve into painful erythematous plaques and annular lesions on upper extremities, head, neck, backs of hands, and back; most common in middle-aged and older women	Skin biopsy is diagnostic and routinely done[39]
Toxic shock syndrome*	Diffuse erythema (resembling sunburn); fever, malaise, myalgia, nausea, vomiting, hypotension, diarrhea, and confusion; conjunctival injection, mucosal hyperemia (oral or genital); late desquamation, especially on palms and soles; most common in menstruating women or postoperative patients	CBC to detect thrombocytopenia; blood cultures; skin biopsy is nonspecific and not often done†

CBC = complete blood count; HIV = human immunodeficiency virus; KOH = potassium hydroxide.

**—Rashes that can have serious consequences for the patient or pregnant contacts of the patient.*

†—*Skin biopsy is often not performed because the histology is nonspecific or because a biopsy is usually not needed for diagnosis.*

Information from references 27 through 39.

Table 3. Rare Causes of Generalized Rash

Condition	*Key clinical features*	*Tests*
Lichen nitidus	1- to 3-mm, skin-colored, raised, flat-topped papules on trunk, flexor surfaces of extremities, dorsal hands, or genitalia	Skin biopsy is diagnostic and often done
Pityriasis lichenoides	2- to 10-mm, round or oval, red-brown papules progressing to hemorrhagic lesions on trunk, thighs, or upper arms	Skin biopsy is diagnostic and routinely done
Pityriasis rubra pilaris	Red or orange follicular papules on fingers, elbows, knees, trunk, or scalp; often mistaken for psoriasis; characterized by "skip areas" of normal skin	Skin biopsy is occasionally nonspecific but can help exclude other conditions, and is routinely done
Rickettsialpox	Initial lesion, which may not be noticed by patient, begins as papule and evolves to vesicle, then crusts; generalized maculopapular vesicular exanthem can involve palms and soles; most common in large cities[40]	Serology (immunoglobulin G for *Rickettsia rickettsii* and *Rickettsia akari*); biopsy with direct fluorescent antibody testing may be diagnostic but is not often done*
Rubella†	Round, pink macules and papules starting on forehead, neck, and face, then spreading to trunk and extremities, including palms and soles	Serology; skin biopsy is nonspecific and not often done*
Rubeola	Maculopapular purple-red lesions that may become confluent; start on face and behind ears and at anterior hairline; Koplik spots (i.e., tiny red or white spots with red halo on buccal mucosa)	Serology; skin biopsy is usually nonspecific and not often done*

**—Skin biopsy is often not performed because the histology is nonspecific or because a biopsy is usually not needed for diagnosis.*
†—Rashes that can have serious consequences for the patient or pregnant contacts of the patient.
Information from reference 40.

The patient should be referred to a dermatologist if the rash is progressive or does not resolve with observation or empiric treatment. For example, mycosis fungoides (cutaneous T-cell lymphoma) mimics eczema in its early stages and is rarely diagnosed correctly at initial presentation.[41] Reevaluation and possible referral are imperative in chronic eczematous conditions that do not respond to therapy.

It is important to look beyond the appearance of the rash itself and search for clues from the patient's history, physical examination, laboratory tests, and skin biopsy. Because of busy schedules and perceived patient expectations, physicians often feel pressured to quickly arrive at a diagnosis. However, unless the diagnosis is obvious, it is usually more productive to start with a differential diagnosis that includes all reasonable possibilities.[4,42,43] Before making a final diagnosis, the physician could also refer to a list of rashes that are often confused with each other *(Table 4)*.[4,8,26]

Although it is important to begin with an

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Skin biopsy is helpful in diagnosing the following conditions: • Bullous pemphigoid • Dermatitis herpetiformis • Erythema multiforme • Lichen planus • Mycosis fungoides (i.e., cutaneous T-cell lymphoma) • Psoriasis • Rocky Mountain spotted fever • Staphylococcal scalded skin syndrome • Subacute cutaneous lupus erythematosus • Sweet syndrome (i.e., acute febrile neutrophilic dermatosis) • Toxic epidermal necrolysis	C	16, 20, 22, 28, 35, 36, 38, 39

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 4. Rashes That Are Often Confused with Each Other

Condition	*Similar rashes (distinguishing features)*
Atopic dermatitis	Contact dermatitis (not associated with dry skin) Keratosis pilaris (nonpruritic, involves posterolateral upper arms) Mycosis fungoides (lesion borders sharper, fixed size and shape) Psoriasis (well-defined plaques, silvery white scale, involves extensor surfaces) Scabies (involves genitalia, axillae, finger webs) Seborrheic dermatitis (nonpruritic, greasy scale, characteristic distribution)
Contact dermatitis	Atopic dermatitis (symmetric distribution, history of hay fever or asthma, flexural areas, hyperlinear palms, family history, not limited to area of exposure, dry skin and itching precede skin lesions rather than follow them) Dermatitis herpetiformis (vesicles on extensor surfaces, enteropathy, burning pain) Psoriasis (patches on knees, elbows, scalp, and gluteal cleft; pitted nails) Seborrheic dermatitis (greasy scale on eyebrows, nasolabial folds, or scalp)
Drug eruption (morbilliform)	Erythema multiforme (target lesions) Viral exanthem (more common in children, less intense erythema and pruritus, less likely to be dusky red, more focal systemic symptoms, less likely to be polymorphic, less likely to be associated with eosinophilia)[8,26]
Pityriasis rosea	Drug eruption (no scale, lesions coalesce) Erythema multiforme (target lesions) Guttate psoriasis (thicker scale, history of streptococcal pharyngitis) Lichen planus (violaceous, involves wrists and ankles) Nummular eczema (larger round [not oval] lesions, do not follow skin lines) Psoriasis (thick white scale, involves extensor surfaces) Secondary syphilis (positive serology; involves palms and soles) Tinea corporis (positive KOH preparation, scale at peripheral border of lesions rather than inside border) Viral exanthem (no scale, lesions coalesce)
Psoriasis	Atopic dermatitis (atopic features, flexural areas, lichenification) Lichen planus (violaceous, minimal scale, involves wrists and ankles) Mycosis fungoides (lesion borders less distinct) Pityriasis rubra pilaris (islands of normal skin) Seborrheic dermatitis (greasy scale, involves anterior face) Secondary syphilis (red-brown lesions on palms and soles) Tinea corporis (thinner peripheral scale, positive KOH preparation)
Seborrheic dermatitis	Atopic dermatitis (nongreasy scale, atopic history, pruritic) Psoriasis (silver scale, sharply demarcated lesions on extensor surfaces of extremities; involvement of scalp commonly extends onto forehead, whereas seborrheic dermatitis of scalp stops at scalp margin)

KOH = potassium hydroxide.

Information from references 4, 8, and 26.

inclusive differential diagnosis, the possibilities must be quickly narrowed down by taking a focused history and looking for key clinical features of the rash. These features are discussed in part II of this article.[11]

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