The Generalized Rash: Part I. Differential Diagnosis

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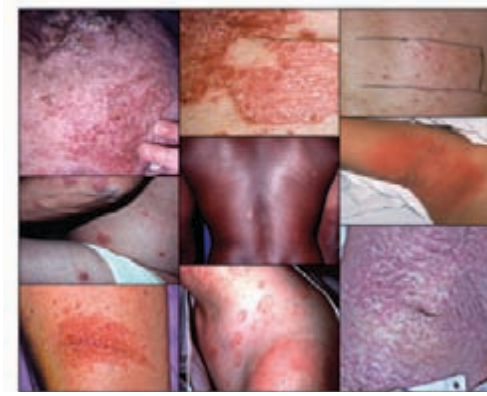
Physicians often have difficulty diagnosing a generalized rash because many different conditions produce similar rashes, and a single condition can result in different rashes with varied appearances. A rapid and accurate diagnosis is critically important to make treatment decisions, especially when mortality 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

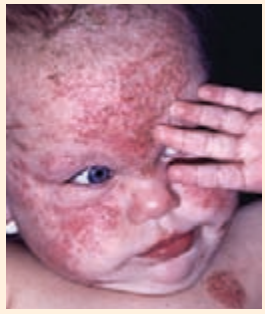
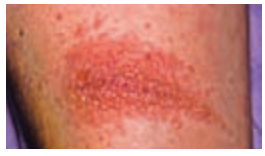
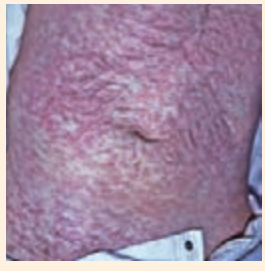
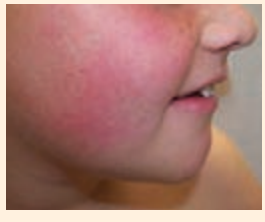
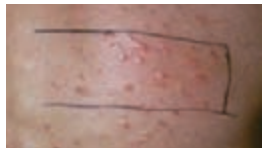
Condition	*Key clinical features*	*Tests*
Atopic dermatitis 	Dry skin; pruritus; erythema; erythematous papules; excoriations; scaling; lichenification; accentuation of skin lines; keys to diagnosis are pruritus, eczematous appearance of lesions, and personal or family history of atopy[12]	Skin biopsy 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)*

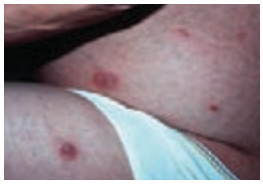
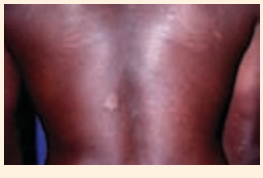
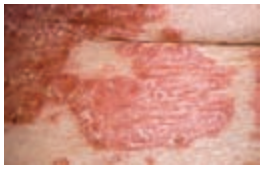
Condition	*Key clinical features*	*Tests*
Guttate psoriasis	Pinpoint to 1-cm scaling papules and plaques on trunk and extremities; often preceded by streptococcal pharyngitis 1 to 2 weeks before eruption[17]; keys to diagnosis are scaling and history of streptococcal pharyngitis[17]	Throat culture; antistreptolysin 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

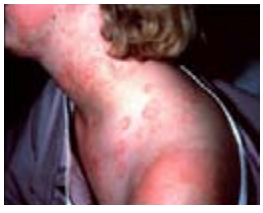
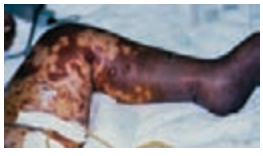
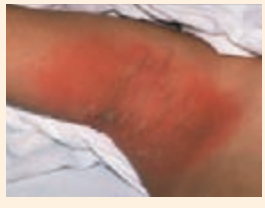
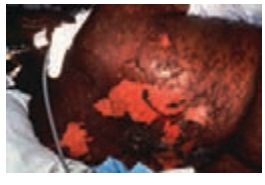
Condition	*Key clinical features*	*Tests*
Bullous pemphigoid	Generalized bullae, especially on trunk and flexural areas; patient usually older than 60 years[27]; Nikolsky sign (easy separation of epidermis from dermis with lateral pressure) usually negative	Skin biopsy with direct and indirect immunofluorescence 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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The Generalized Rash: Part II. Diagnostic Approach

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Although it is important to begin the evaluation of generalized rash with an inclusive differential diagnosis, the possibilities must be narrowed down by taking a focused history and looking for key clinical features of the rash. Part I of this two-part article lists the common, uncommon, and rare causes of generalized rashes. In part II, the clinical features that help distinguish these rashes are described. These features include key elements of the history (e.g., travel, environmental exposures, personal or family history of atopy); characteristics of individual lesions, such as color, size, shape, and scale; areas of involvement and sparing, with particular attention to palms, soles, face, nails, sun-exposed areas, and extensor and flexor surfaces of extremities; pruritic or painful lesions; systemic symptoms, especially fever; and dermatologic signs, such as blanching, and the Koebner phenomenon. (*Am Fam Physician.* 2010;81(6):735-739. Copyright © 2010 American Academy of Family Physicians.)

This is part II of a two-part article on generalized rashes. Part I, "Differential Diagnosis," appears in this issue of *AFP* on page 726.

Accurate diagnosis of the generalized rash can be difficult because of the nonspecific appearance of many rashes. If the diagnosis is not obvious, the physician must resist the common tendency to prematurely close the diagnostic process and instead generate an inclusive differential diagnosis. Part I of this two-part article discusses the common, uncommon, and rare causes of generalized rashes.[1] Part II describes the clinical features that help distinguish these rashes.

Keys to Diagnosis

HISTORY

When the diagnosis of a generalized rash is not obvious, patients should be asked about recent travel, insect and plant exposure, drug exposure (including over-the-counter drugs, alternative medications, and illicit drugs), contact with persons who are ill, pets, hobbies, occupational exposures, chemical exposure, chronic illness, sexual history, and recent systemic symptoms, especially fever *(Table 1)*. Patients should be asked about pruritus, painful lesions, the initial site of involvement, and any personal or family history of atopy (e.g., asthma, allergic rhinitis, childhood eczema).

The patient's age may help narrow the possible diagnoses. For example, acute maculopapular rashes in children are usually caused by viral infections, whereas in adults they are usually caused by drug reactions.[2] Some rashes are rare in children (e.g., nummular eczema, lichen planus, dermatitis herpetiformis), whereas others are rare in adults (e.g., roseola, Kawasaki disease, scarlet fever).

Patients should be asked about pruritus, because some conditions routinely cause intense pruritus (e.g., scabies, urticaria, atopic dermatitis), whereas others are usually nonpruritic (e.g., seborrheic dermatitis, secondary syphilis, many viral exanthems; *Table 2*). Most generalized rashes are not painful, but Sweet syndrome, Kawasaki disease, and Stevens-Johnson syndrome are exceptions.

Systemic symptoms, especially fever, can help narrow the differential diagnosis.[3,4] Rashes accompanied by fever are most commonly associated with infections, but drug eruptions and rheumatologic diseases can also cause fever. Although most maculopapular rashes that are associated with fever are caused by self-limited viral infections, empiric antibiotics and laboratory testing are indicated when the history, geography, demographics, and systemic manifestations

Table 1. Generalized Rash: Conditions Suggested by Patient History

Historical finding	*Conditions*
Chemicals	Contact dermatitis
Chronic illness	Dermatitis herpetiformis
	Seborrheic dermatitis
Contact with ill persons	Fifth disease (i.e., erythema infectiosum)
	Meningococcemia
	Roseola (i.e., exanthem subitum, sixth disease)
	Rubella
	Rubeola
	Scarlet fever
	Varicella
	Viral exanthem, nonspecific
Drug exposure	Lupus (subacute cutaneous lupus erythematosus)
	Drug eruption
	Urticaria (i.e., hives)
Hobbies	Contact dermatitis
Insect and arthropod exposure	Insect bites
	Lyme disease
	Rickettsialpox
	Rocky Mountain spotted fever
	Scabies
Occupational exposures	Contact dermatitis
Plant exposure	Contact dermatitis
Recent systemic symptoms, fever	Fifth disease (i.e., erythema infectiosum)
	HIV acute exanthem
	Kawasaki disease
	Meningococcemia
	Roseola (i.e., exanthem subitum, sixth disease)
	Rubella
	Rubeola
	Scarlet fever
	Varicella
	Viral exanthem, nonspecific
Sexual history	HIV acute exanthem
	Secondary syphilis
Travel	Insect bites
	Lyme disease
	Rickettsialpox
	Rocky Mountain spotted fever

HIV = human immunodeficiency virus.

Table 2. Generalized Rash: Conditions Associated with Pruritus

Common	**Variable**	**Absent or rare**
Atopic dermatitis	Drug eruption*	Fifth disease (i.e., erythema infectiosum)*
Contact dermatitis	Erythema multiforme	HIV acute exanthem*
Insect bites	Folliculitis	Keratosis pilaris
Lichen planus	Guttate psoriasis	Lyme disease*
Nummular eczema	Kawasaki disease*	Meningococcemia*
Scabies	Pityriasis rosea	Miliaria rubra (i.e., prickly heat, heat rash)
Urticaria (i.e., hives)	Psoriasis (plaque psoriasis)	Rocky Mountain spotted fever*
Varicella*	Tinea corporis	Roseola (i.e., exanthem subitum, sixth disease)
	Toxic epidermal necrolysis*	Rubella*
	Toxic shock syndrome (late)*	Scarlet fever*
	Viral exanthem, nonspecific	Seborrheic dermatitis
		Secondary syphilis*
		Staphylococcal scalded skin syndrome*
		Stevens-Johnson syndrome*

NOTE: *Table includes all common rashes and all rashes that can have serious consequences for the patient or pregnant contacts of the patient (designated by *).*

HIV = human immunodeficiency virus.

suggest a more serious infection (e.g., meningococcemia, Lyme disease, Rocky Mountain spotted fever). Petechial rashes require immediate decisions about empiric antibiotics, but life-threatening infections characterized by petechiae (e.g., meningococcemia, Rocky Mountain spotted fever) can start as nonspecific maculopapular rashes.[5]

PHYSICAL EXAMINATION

Characteristics of the rash itself can help narrow the differential diagnosis. In dermatologic diagnosis, it is often helpful to focus on the clinical appearance of the rash after determining the patient's primary symptom, but before taking a more focused history.[6] This approach may not be intuitive to primary care physicians, who would normally take a complete history first and then perform a physical examination. The size of individual lesions can vary from pinpoint to total-body redness (i.e., erythroderma; *Table 3)*. The shape of individual lesions and their tendency to cluster can also provide important clues. For example, linear patterns of erythema or vesicles are typical of poison ivy; oval lesions are typical of pityriasis rosea; round lesions are typical of nummular eczema; annular lesions are typical of tinea corporis; and geometric patterns may imply a contact component. The color of the lesions should also be noted. Although most generalized rashes are pink or red, lichen planus is characterized by violaceous lesions, and secondary syphilis by red-brown lesions.

In addition to the rash itself, the physician should evaluate the patient's lymph nodes, neurologic status, body temperature, and general appearance. Patients with fever and toxic appearance require prompt evaluation and possibly empiric treatment before reaching a definitive diagnosis.

Dermatologic Signs. Several dermatologic signs may help narrow the differential diagnosis. For example, the Koebner phenomenon (i.e., development of typical lesions at the site of trauma) is characteristic of psoriasis and lichen planus.[7] The Nikolsky sign (i.e., easy separation of the epidermis from the dermis with lateral pressure) is associated with staphylococcal scalded skin syndrome and toxic epidermal necrolysis.[8] The value of the Auspitz sign (i.e., the appearance of bleeding points when scale is removed from psoriatic lesions) in the diagnosis of patients with psoriasis has been questioned because of its low sensitivity and specificity.[9] Blanching of erythematous lesions with brief downward pressure implies that the erythema is the result of vasodilation rather than dermal hemorrhage. Blanching is characteristic of drug eruptions, viral exanthems, Kawasaki

Table 3. Generalized Rash: Conditions Suggested by Size of Lesions

Size of lesions	*Conditions*
Pinpoint	Folliculitis
	Keratosis pilaris
	Scarlet fever*
1 mm to 1 cm	Guttate psoriasis
	Insect bites†
	Lichen planus
	Miliaria rubra (i.e., prickly heat, heat rash)
	Rocky Mountain spotted fever*
	Roseola (i.e., exanthem subitum, sixth disease)
	Rubella*
	Scabies
	Varicella*
1 to 25 cm	Lyme disease*
	Nummular eczema
	Tinea corporis
	Urticaria (i.e., hives)
Variable	Atopic dermatitis
	Contact dermatitis
	Drug eruption*
	Erythema multiforme
	Fifth disease (i.e., erythema infectiosum)*
	HIV acute exanthem*
	Kawasaki disease*
	Meningococcemia*
	Pityriasis rosea
	Psoriasis (plaque psoriasis)
	Seborrheic dermatitis
	Secondary syphilis*
	Staphylococcal scalded skin syndrome*
	Stevens-Johnson syndrome*
	Toxic epidermal necrolysis*
	Viral exanthem, nonspecific
Erythroderma possible	Atopic dermatitis
	Drug eruption*
	Psoriasis (plaque psoriasis)
	Sézary syndrome (i.e., chronic cutaneous T-cell lymphoma)
	Toxic shock syndrome*

NOTE: *Table includes all common rashes and all rashes that can have serious consequences for the patient or pregnant contacts of the patient (designated by *).*

HIV = human immunodeficiency virus.

†—Some insect bites may be larger than 1 cm.

Table 4. Generalized Rash: Involvement of Palms and Soles

Common	Variable	Absent or rare
Contact dermatitis	Atopic dermatitis	Fifth disease (i.e., erythema infectiosum)*
Erythema multiforme	Drug eruption*	Folliculitis
Kawasaki disease*	HIV acute exanthem*	Guttate psoriasis
Rocky Mountain spotted fever*	Lichen planus	Insect bites
Rubella*	Meningococcemia*	Keratosis pilaris
Scabies (in infants)	Psoriasis (plaque psoriasis)	Lyme disease*
Secondary syphilis*	Urticaria (i.e., hives)	Miliaria rubra (i.e., prickly heat, heat rash)
Staphylococcal scalded skin syndrome*		Nummular eczema
Stevens-Johnson syndrome*		Pityriasis rosea
Tinea corporis		Roseola (i.e., exanthem subitum, sixth disease)
Toxic epidermal necrolysis*		Scarlet fever*†
Toxic shock syndrome*		Seborrheic dermatitis
		Varicella*
		Viral exanthem, nonspecific

NOTE: *Table includes all common rashes and all rashes that, if left untreated, can have serious consequences for the patient or pregnant contacts of the patient (designated by *).*

HIV = human immunodeficiency virus.

†—Palms and soles can desquamate.

disease, roseola, and scarlet fever, whereas the lesions of meningococcemia and the late petechial stage of Rocky Mountain spotted fever do not blanch. The physician should note the presence and quality of scale (e.g., psoriasis, tinea corporis, pityriasis rosea); whether the lesions are evanescent (e.g., urticaria) or stable (e.g., erythema multiforme); and whether lesions tend to become confluent (e.g., urticaria) or remain discrete (e.g., insect bites). When atopic dermatitis is considered, the physician should search for other signs of atopy, such as palmar hyperlinearity, infraorbital folds (Dennie-Morgan lines), dry skin, and lichenification.[10,11]

Rash Location. Many rashes tend to avoid or favor certain regions of the body. Physicians should note whether the rash involves the palms, soles, mucous membranes, face, scalp, or extensor or flexor surfaces of extremities. For example, psoriasis usually does not involve the central face, and many generalized rashes avoid the palms and soles, whereas secondary syphilis, erythema multiforme, and rickettsial infections typically include the palms and soles *(Table 4)*. Keratosis pilaris commonly involves the posterolateral upper arms. Scabies involves the fingers, finger webs, wrists, elbows, knees, groin, buttocks, penis, axillae, belt line, ankles, and feet. Seborrheic dermatitis most often involves the scalp margins, the area behind the ears, external ear canals, base of eyelashes, eyebrows, nasolabial folds, and central chest. Patients should be asked where the rash first appeared, because some rashes have a characteristic progression. For example, pityriasis rosea often starts with a relatively large herald patch on the trunk or proximal extremity several days before the smaller oval lesions appear. Rocky Mountain spotted fever often starts on the wrists and ankles before spreading centrally.[5]

TESTS

Blood tests that may be helpful include a complete blood count to determine the presence of leukocytosis or thrombocytopenia, and serologic studies to identify various infectious causes. Mineral oil mounts and potassium hydroxide scrapings can be helpful when scabies or dermatophytes are considered. Skin biopsy, with or without direct or indirect immunofluorescence, is often helpful, especially to confirm lichen planus, dermatitis herpetiformis, mycosis fungoides, and staphylococcal scalded skin syndrome.[12]

"Don't-Miss" Rashes

"Don't-miss" rashes are those that can have serious consequences for the patient or pregnant contacts of the patient. These rashes include various infectious diseases, such as meningococcemia, Lyme disease, and Rocky

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Systemic symptoms, and involvement of palms, soles, and nails can help distinguish various rashes.	C	3, 4
When evaluating generalized rash, physicians should determine the patient's primary symptom, then focus on the clinical appearance of the rash before taking a more focused history to help narrow down the differential diagnosis.	C	6

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.

Mountain spotted fever. Many of these rashes are associated with fever and manifest as petechiae or purpura.[4] However, there are notable exceptions, such as Lyme disease, which is not petechial, and drug eruptions, which may not be associated with systemic symptoms. Don't-miss rashes can usually be ruled out on the basis of clinical features and demographics, but sometimes further testing is indicated. Some patients should be treated immediately, before a diagnosis can be established. For example, toxic-appearing children and adults with petechiae should be treated immediately for presumed meningococcemia, before undergoing any further evaluation.[13] Patients from Oklahoma, Tennessee, Arkansas, or the southern Atlantic states who present in the spring or summer with fever, myalgia, and headache—with or without a rash—should be strongly considered for antibiotic treatment of Rocky Mountain spotted fever while awaiting the results of serology or skin biopsy.[14,15] If the physician cannot distinguish between meningococcemia and Rocky Mountain spotted fever on clinical grounds (a common occurrence), patients should be treated for both before undergoing diagnostic tests.[4,16]

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