

Introduction

Fever and Rash

• Skin lesions are frequently present in acutely ill patients with serious infectious diseases and may provide important clues that aid in early diagnosis and treatment

 Patients with skin lesions or rashes consistent with a communicable infectious disease (e.g., invasive meningococcal infection) should be immediately placed on appropriate isolation precautions (i.e., contact, droplet, airborne, or special precautions for highly communicable diseases, such as viral hemorrhagic fevers)

Serious bacterial infections with skin lesions include

- Staphylococcus aureus (toxic shock syndrome [TSS], scalded skin syndrome [4S])
- Streptococcus pyogenes (TSS)
- Salmonella Typhi
- Neisseria meningitidis

Potentially serious viral infections with skin lesions include:

- Measles
- Rubella
- Epstein-Barr virus infection
- Cytomegalovirus
- Human herpesvirus 6, and
- Viral hemorrhagic fevers

- Life-threatening drug reactions may result from antibiotic therapy for disorders such as:
- Stevens-Johnson syndrome/toxic epidermolysis necrosis
- Drug reaction with eosinophilia and systemic symptoms (DRESS)

Key aspects of skin lesions that aid in a proper diagnosis include

- (1) primary type(s) of skin lesions,
- (2) distribution of the lesions,
- (3) pattern of progression of the rash, and
- (4) timing of onset of the rash relative to the onset of fever and other systemic signs

 Consideration should be given to biopsy of skin lesions, if present, in acutely ill immunocompromised patients for appropriate stains (e.g., Gram stain, fungal stain) and cultures and for pathologic study

History and physical examination

Acutely ill patients with a potential infectious disease and skin lesions (or rash) should have a history obtained that elicits the following:

- Recent drug ingestion (drug-drug interaction)
- Travel outside the local area
- Potential occupational exposures
- Recent immunizations
- Risk factors for human immunodeficiency virus infection
- Immunocompromising conditions (leukemia cutis, histiocytosis, GVHD)
- Prior allergies to antibiotics
- Recent exposures to febrile or ill persons
- Exposure to rural habitats, insects, arthropods, and wild animals
- Exposure to pets or animals

Physical examination should focus on the following

- 1. Vital signs
- 2. General appearance (Awareness, Tone, playing, Interactivity, Consolability, Look/gaze, Crying/speech)
- 3. Presence and location of adenopathy
- 5. Presence and morphology of genital, mucosal, or conjunctival lesions
- 6. Detection of hepatosplenomegaly
- 7. Presence of arthritis
- 8. Signs of nuchal rigidity, meningismus, or neurologic dysfunction

Key points

- (1) the primary type(s) of skin lesions present,
- (2) the location and distribution of the eruption,
- (3) the number and size of the lesions,
- (4) the pattern of progression of the rash, and
- (5) the timing of the onset of the rash relative to the onset of fever and other signs of systemic illness

- It is important for physicians who observe a rash to carefully document the characteristics or take images of the skin lesions in the medical record to aid other providers in the later care of the patient
 - ➤It may be transient
 - >It may be progress
 - ➤It may be a reminder!



Improve your skill ...

- Palpable purpura, the hallmark feature of leukocytoclastic vasculitis, is the prototypic early finding in
 - Meningococcemia
- Rapidly enlarging but asymptomatic red dermal nodules suggest
 - Candidemia
- Skin nodules noted on very deep palpation are probably located within the subcutaneous fat, suggesting one of several types of *panniculitis*, including
 - Erythema nodosum

Distribution or direction of spread

- The rash of acute meningococcal infection, most often begins on the lower extremities and then spreads centrally (*centripetally*)
- Most drug- and viral-infection associated eruptions¹ begin on the face or trunk and spread outward (*centrifugally*)
- "Streaky" facial involvement, usually without other skin findings, is characteristic of infection due to parvovirus B19 (fifth disease, erythema infectiosum)

¹ With the exception of those caused by echoviruses and coxsackieviruses

Timing of the rash

• With the exception of urticarial eruptions, which usually occur within a few minutes to a few hours of the administration of a systemic agent, the more typical generalized maculopapular or morbilliform drug eruption typically occurs within the first 7 to 14 days of the first dose of the offending agent, suggesting the need for a very careful drug history (including start and stop dates for all medications taken within 30 days of the onset of eruption)

Adverse drug reaction

- Between 5% and 15% of all patients to whom a drug is administered experience an adverse reaction
- Adverse cutaneous reactions to drugs are frequent (0% to 8%)
 - >2% to 3% of all hospitalized patients
 - ≥20% of emergency department visits
 - \geq 2% of adverse cutaneous reactions are severe and very few fatal

P@INT



- The rate of cutaneous reactions to drugs is highest for antibiotics (1%–8% depending on the class of antibiotic), mainly penicillins and cephalosporins
- Exanthems (75%–95%) and urticaria (5%–6%) account for most drug reactions
- A drug reaction must be considered in any patient with a generalized maculopapular rash, especially if associated with palmoplantar involvement

Severe drug reactions

- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Hypersensitivity syndromes (urticaria, angioedema, anaphylaxis)
- Small vessel vasculitis
- Serum sickness
- Drug reaction with eosinophilia and systemic symptoms (DRESS)



Approach to the patient

- If the patient is well enough to provide further history or whether cardiorespiratory support is required?
- Is whether the nature and presentation of the rash demands immediate institution of isolation precautions?
- If skin lesions suggest a life-threatening infection, such as <u>bacterial</u> sepsis, <u>staphylococcal or streptococcal toxic shock</u>, <u>Kawasaki disease</u>, <u>necrotizing fasciitis</u>, <u>toxic epidermal necrolysis</u>?
- Is there any possibility that the patient has an exotic disease acquired as a result of travel or the intentional release of an agent of bioterrorism (viral hemorrhagic fevers)?

Fever and rash

Morphologic approach

2 Diagnostic approach

3 Etiologic approach

Treatment approach

Fever and rash

Etiologic approach

Systemic Infections With Prominent Cutaneous Manifestations					
ORGANISM/DISEASE	MACULES, PAPULES	VESICLES, BULLAE	PETECHIAE, PURPURA		
Viruses					
Human immunodeficiency virus type 1	X				
Echoviruses	X	X	X		
Coxsackieviruses	X	X	X		
Rubeola (measles)	X				
Atypical measles	Χ		X		
Adenovirus	X		X		
Lymphocytic choriomeningitis	Χ				
Dengue	X		X		
Zika virus	Χ				
West Nile virus	X				
Viral hemorrhagic fevers			X		
Rubella (German measles)	X		X		
Colorado tick fever	X				
Yellow fever			X		
Varicella-zoster (disseminated)		X			
Herpes simplex (disseminated)		X			
Varicella (chickenpox)		Χ			
Vaccinia		X			

Systemic Infections With Prominent Cutaneous Manifestations				
ORGANISM/DISEASE	MACULES, PAPULES	VESICLES, BULLAE	PETECHIAE, PURPURA	
Variola		X	X	
Cytomegalovirus	X			
Congenital cytomegalovirus			X	
Epstein-Barr virus	X		X	
Hepatitis B virus	X		X (as palpable purpura)	
Monkeypox	X			
Parvovirus B19 (erythema infectiosum)	Χ			
Human herpesvirus 6	Χ			
Human herpesvirus 7	X			

ORGANISM/DISEASE	MACULES, PAPULES	VESICLES, BULLAE	PETECHIAE, PURPURA
Bacteria			
Chlamydia psittaci	Χ	Χ	
Mycoplasma pneumoniae	X		
Ehrlichia spp.	Χ		
Rickettsia rickettsii (RMSF)	X		Χ
Rickettsia akari (rickettsialpox)	Χ	Χ	
Rickettsia prowazekii (epidemic/louse-borne typhus)	X		X
Rickettsia typhi (endemic/murine typhus)	Χ		
Rickettsia tsutsugamushi (scrub typhus)	X		
Bartonella henselae	X		
Bartonella quintana	Χ		
Salmonella enterica serovar Typhi	X		
Francisella tularensis	X		
Streptobacillus moniliformis (rat-bite fever)	Χ		X
Treponema pallidum (secondary syphilis)	X		
Mycobacterium haemophilum	Χ		
Neisseria gonorrhoeae	Χ		Χ
Neisseria meningitidis			Χ
Leptospira spp.	Χ		
Listeria monocytogenes		X (rare)	

ORGANISM/DISEASE	MACULES, PAPULES	VESICLES, BULLAE	PETECHIAE, PURPURA
Bartonella bacilliformis	X		
Borrelia spp. (relapsing fever)	Χ		Χ
Borrelia burgdorferi (Lyme disease)	X (annular)		
Pseudomonas aeruginosa	Χ		
Spirillum minus (rat-bite fever)	Х		Χ
Staphylococcus aureus	X		Х
Streptococci—group A (scarlet fever)	Χ		
Capnocytophaga canimorsus			X
Vibrio vulnificus		X	
Fungi (Disseminated Infection)			
Candida spp.	X		
Cryptococcus neoformans	X		
Histoplasma capsulatum	X		
Blastomyces dermatitidis	Χ		
Coccidioides immitis	Χ		
Fusarium spp. (agents of mucormycosis)	X		
Protozoa			
Plasmodium falciparum (malaria)			Х

Fever and rash

Morphologic approach

Characteristics of the Lesion

- 1. Macules are flat, nonpalpable lesions in the plane of the skin
- 2. Papules are small, solid, palpable lesions elevated above the plane of the skin
- 3. Nodules: masses that are located deeper within or below the skin
- 4. Vesicles and bullae are small and large blisters, respectively
- 5. Pustules are usually small, palpable lesions filled with pus
- 6. Plaques are large, flat lesions, usually greater than 1 cm in diameter, that are palpable

For purposes of the management, it is useful to divide eruptions into the:

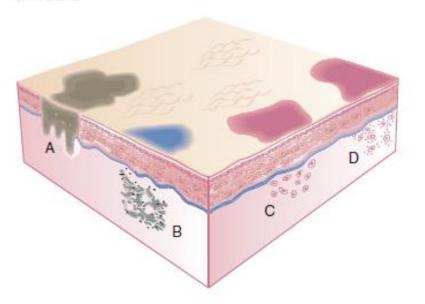
- Maculopapular rash
- Nodular rash
- Erythematous rash
- Vesiculobullous rash, and
- Purpuric rash

The appearance of skin lesions may be very useful in the diagnosis of specific infectious diseases

- Maculopapular rashes are usually seen in viral illnesses, drug eruptions, and immune complex—mediated diseases
- Nodular lesions are suggestive of mycobacterial or fungal infections
- Diffuse erythema suggests scarlet fever, TSS, Kawasaki disease, or Stevens-Johnson syndrome/toxic epidermal necrolysis
- Bullous lesions suggest streptococcal erysipelas with necrotizing fasciitis, ecthyma gangrenosum, and Vibrio infections
- Petechial eruptions suggest gram-negative sepsis, invasive N. meningitidis infection, rickettsial infections, and viral hemorrhagic fever



Macule

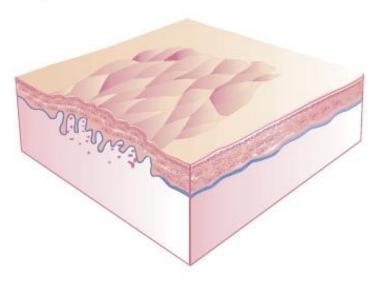


A flat lesion <1 cm in diameter

Leukocytoclastic vasculitis



Plaque

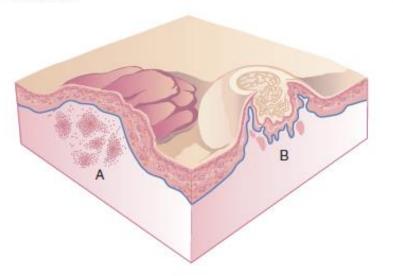


A raised lesion with a flat top >1 cm in diameter

Verucca vulgaris



Nodule

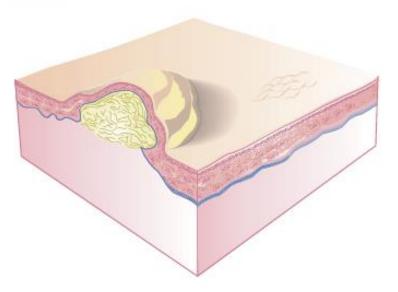


A raised lesion >1 cm in diameter

Erythema nodosum



Vesicle

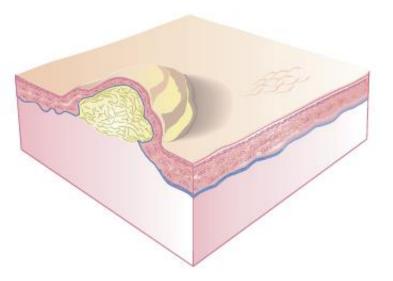


A clear fluid-filled lesion <1 cm in diameter

Herpes zoster



Bullae

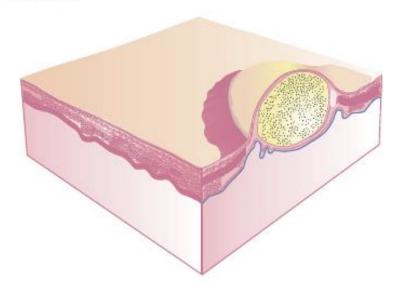


A fluid-filled lesion >1 cm in diameter

Impetigo



Pustule



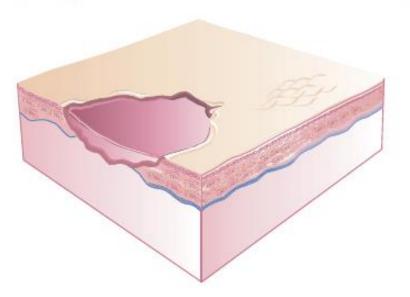
A cloudy fluid-filled lesion <1 cm in diameter

Neonatal staphylococcal pustulosis



(continued)

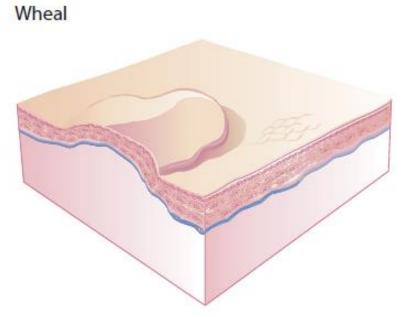
Erosion



A loss of the epidermis (superficial)

Streptococcal intertrigo





A transient edematous lesion, often with blanching or pallor centrally with surrounding erythema

Urticaria



Ulcer

A loss of the epidermis and part of the dermis and sometimes the subcutis (deep)

Echthyma gangrenosum



Fissure

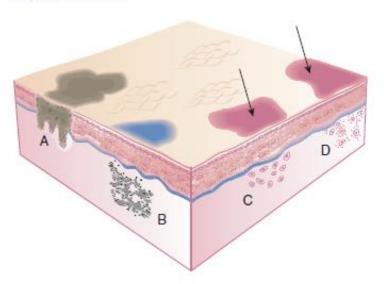


A linear cleft or ulcer

Angular chelistis (Candida albicans)



Erythroderma



Confluent erythema resulting from vasodilation or capillary leak

Toxic epidermal necrolysis



Nonblanchable erythema or violaceous areas

Cutaneous vasculitis



Excoriation

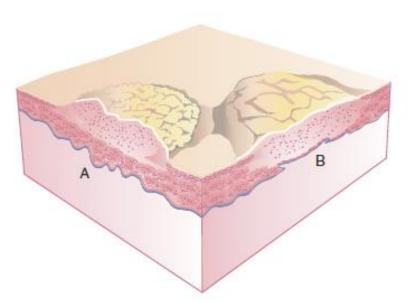


A superficial abrasion, often self-induced from scratching

Scabies



Scale



Superficial epidermal desquamation

Tinia facei



Crust

Dried exudate

Impetigo



Shape and configuration

Individual

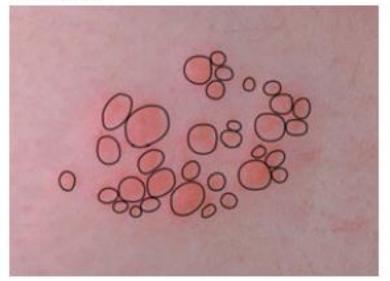


Singly dispersed lesions

Ecthyma, S. aureus



Grouped

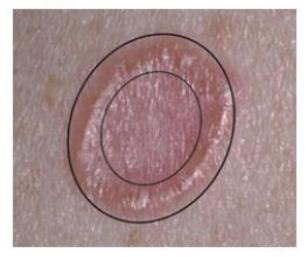


Multiple similar lesions present within a localized area

Herpes simplex virus infection



Annular



Ring-shaped

Urticaria



Targetoid



"Bulls-eye" appearance with central dusky zone surrounded by a ring of pallor (edema) and a peripheral rim of erythema

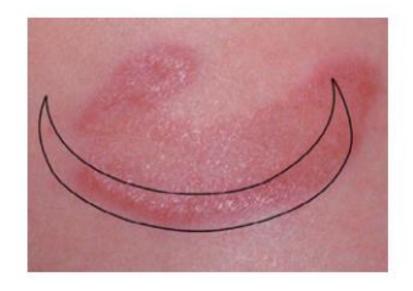
Erythema multiforme



Arcuate

Incomplete rings and arcs

Urticaria





Polycyclic

Linked ring-shaped lesions

Urticaria



Dermatomal L3 L3 Confined to one or more areas of cutaneous sensory nerve innervation

Herpes zoster



Acral

Affecting the distal extremities and sometimes the head

Gianotti-Crosti syndrome



Palmoplantar

Affecting the palms and soles

Erythema multiforme



Photodistributed

Affecting areas exposed to sunlight; commonly the face, upper extremities

Polymorphous light eruption



Intertriginous

Affecting skinfold areas such as the groin, axillae, and neck

Candidal intertrigo



Periorificial

Affecting the periorbital, perioral, and sometimes the perianal areas

Acrodermatitis enteropathica



Clinical cases













Cutaneous manifestations of covid-19

- Vesicular Eruption
- Urticarial Eruption
- Maculopapular eruption
- Pityriasis rosea-like
- Perifollicular eruption
- Erythema multiforme-like
- Pseudo-vesicullar

- Purpuric eruptions
- Bilateral axillary purpuric eruption
- Morbilliform eruptions
- Palmar erythema
- Enanthem
- Livedoid or necrotic lesions

5 predominant morphological patterns of COVID-19 associated rashs

- 1. Maculopapular
- 2. Urticarial
- 3. Pseudo-chilblain (also known as COVID-19 toes)
 - ± SARS-CoV-2 infection
 - tend to affect younger, asymptomatic patients
 - often late in the evolution of COVID-19 disease
 - late-phase immune response or be associated with failure to trigger humoral immunity
- 4. Vesicular
- 5. Livedoid (likely complement mediated vasculopathy that may portend systemic thrombosis)













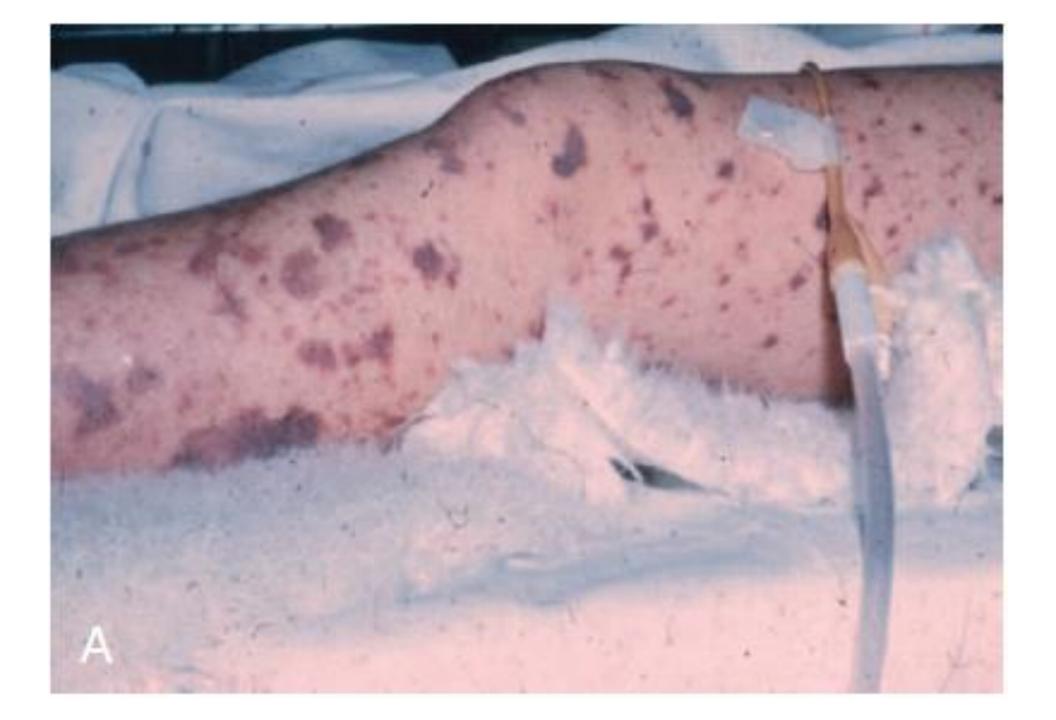














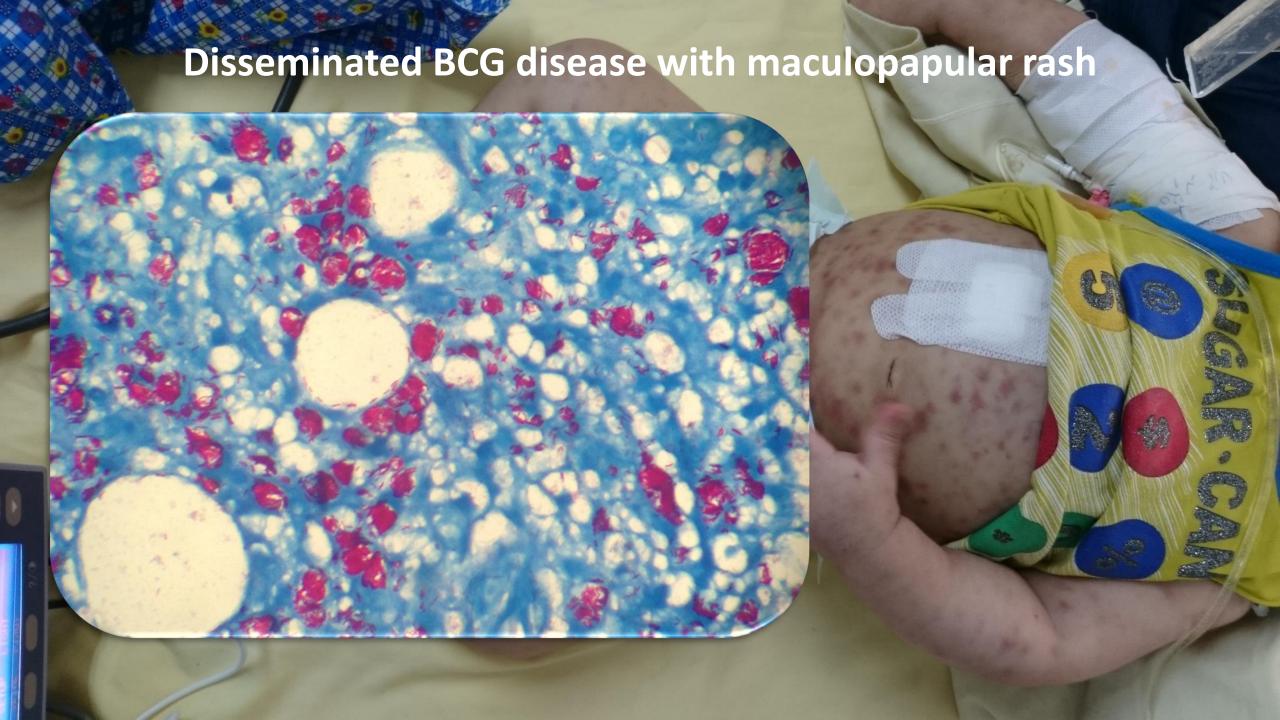


Embolic lesions on a palm secondary to meningococcal sepsis



Because of Its High Morbidity and Mortality, Meningococcemia is The Most Important Consideration in the Child With a New-onset Purpuric Rash

Acutely febrile child with skin purpuric rash =
Lumbar puncture in addition to sepsis work up and
prompt proper antibiotic therapy
(consider contact precaution)



Ecthyma gangrenosum Pseudomonas aeruginosa



Aspergillus terreus, back



Candida tropicalis, arm



Fusarium, leg





Mucormycosis



Mucormycosis

Hypersensitivity to Leukoplast tape



Fever and rash

Diagnostic approach



- Although histologic findings from skin biopsies may help to confirm some diagnoses, the patterns observed are frequently not specific for a single organism, the presence of infectious agents may not always be detectable, and laboratory studies often require at least 24 hours to complete
 - ➤ Suitable location (margin/center, fluid/base, hemorrhagic [blood is inhibitor])
 - ➤ Suitable media (N/S; formalin)
 - Suitable request (AF, gram, geimsa, PAS, MB, CFW, MSS, Tzank, KOH)
 - ➤ Suitable diagnostic test (Culture/PCR), ...

Selected Diagnostic Tests of Importance in the Evaluatio	n of	f a Rash	
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Diagnostic Test	Procedure	Comments
Potassium hydroxide (KOH) preparation	 Clean skin with alcohol pad Use a #15 blade or a glass slide to scrape the scale from the lesion; use tangential motion Place scrapings on a glass slide Add 10% KOH; either warm the slide gently with a flame or allow to sit at room temperature for 5 minutes to facilitate dissolution of epithelial cells. Examine under 10× power; make sure the condenser is on low 	Useful in confirming a candidal or malassezia or dermatophyte infection of the skin. Candida species will appear as budding yeast. Dermatophyte species will appear as refreactile, branching hyphae. The characteristic "spaghetti and meatballs" appearance of clusters of spores in association with septate hyphae is seen with tinea versicolor infections caused by Malassezia furfur.
Fungal culture	 Use a toothbrush or culture swab to rub the lesion briskly Plate on mycobiotic agar (contains chlorhexidine to inhibit nondermatophyte molds) 	Useful for confirmation of superficial infections with dermatophyte molds and Candidal species.
Scabies preparation	 Use a #15 blade to briskly scrape 3–4 lesions; pick a fresh lesion Place a drop of mineral oil on a glass slide Spread the scrapings on the slide and examine under 4× power 	Scabies mites, eggs, and scybylla (feces) can be easily seen in positive preparations. To increase diagnostic yield, scrape several lesions.
Bacterial culture	 Swab the skin with alcohol first; allow the skin to dry Puncture or unroof the pustule with a sterile needle or #11 blade Obtain specimen with culture swab 	Most laboratories can culture and identify common pathogenic organisms such as Staphylococcus, Streptococcus, and Pseudomonas species. Uncommon organisms may require special culture media or growth conditions. Check with your clinical laboratory if you have any questions or are trying to isolate an unusual organism.

Tzanck preparation	 Choose an intact vesicle or pustule, if possible Unroof lesion Briskly scrape the base of the lesion with 	The presence of multinucleated giant cells suggests a herpes virus infection such as herpes simplex virus (HSV) or varizella zoster virus (VZV).
	a #15 blade and smear onto a glass slide 4. Stain with Wright's or Giemsa stain	Mainly of historical interest and largely supplanted by rapid diagnostic tests such as direct fluorescent antibody test (DFA) and polymerase chain reaction (PCR).
HSV/VZV direct fluorescent antibody	 Choose an intact vesicle or pustule, if possible 	Check with your clinical laboratory to verify how the specimen should be transported.
test (DFA), PCR, and	2. Unroof lesion with a #15 blade	PCR not available in all clinical laboratories.
viral culture	3. Briskly scrape the base of the lesion with a Dacron swab4. Place in viral culture media or smear	Viral cultures may take several days to grow. Do not delay treatment if HSV or VZV infection is suspected.
	immediately on a glass slide	
Skin biopsy	May be performed as a shave biopsy for superficial epidermal processes or as a punch biopsy for processes suspected to	Consult dermatologist who can select appropriate skin lesion and perform procedure.
	involve the dermis or subcutis	Special immunohistochemical stains, immunofluorescence, and in situ PCR as well as bacterial, fungal, viral, and mycobacterial cultures may be performed if indicated.
Nikolsky's sign	Using your index finger, firmly stroke away from the lateral border of a bullae	Epidermal blistering processes, such as Staphylooccal-scalded skin disease and toxic epidermal necrolysis, will demonstrate additional shearing of the skin and lateral extension of the blister.
Dermatographism	Using the wooden end of a cotton-tipped applicator, briskly stroke the skin of the upper back	Often positive in children with urticaria or atopic dermatitis; essentially a form of pressure urticaria.

Fever and rash

Treatment approach

آیا در ارزیابی سریع و اولیه حداقل یکی از نکات زیر وجود دارد؟

- شک به مننژیت یا سپتی سمی
 - اختلال هو شیاری
- اختلال همودینامیک (افت فشار خون، پرفوزیون و کاهش cap. filling)
 - راشهای سریعا پیشرونده
- در زمان طغیان مننگو کو ک و یا تماس با بیمار مبتلا به مننگو کو ک، تب هموراژیک و ...
 - وجود بثورات جلدی در بیمار با نقص ایمنی
 - خونریزی از مخاطات
 - همراهی با عوارض شدید و یا در گیری شدید یک ارگان
 - اریترودرمی
 - پتشی و پورپورا محدود به سرو گردن نباشد

الف) یک یا چند نشانه وجود دارد

- 1. فورا اقدام نمایید
- تجویز اکسیژن، برقراری راه هوایی و وریدی و stable کردن بیمار و در صورت نیاز برقراری راه هوایی
 - 2. مانیتور کردن علایم حیاتی
 - 3. تاریخچه و معاینه بالینی دقیق بعد از ثبات علایم حیاتی
 - 4. آنتی بیوتیک و یا آنتی ویرال مناسب
 - آزمایشات اولیه
- B/C ،ESR/CRP ،CBC diff و الکترولیتها، ABG, کشت از ضایعات، بررسی CSF (در صورتیکه ممنوع نباشد)، تستهای کبدی، تستهای انعقادی، تستهای و یرولوژیک و PCR در صورت نیاز
 - 6. کورتیکواستروئید در موارد لازم
 - 7. اقدامات بعدی تشخیصی و یا درمانی و مدیریت درازمدت بر اساس تاریخچه، معاینه و آزمایشات

ب) عدم وجود علایم و نشانه های خطر

• تاریخچه و معاینه دقیق، سن، بررسی لینک های اپیدمیولوژیک، سابقه تماس و علایم همراه و تعیین لیست شکایات و در نظر گرفتن علل بر اساس نوع ضایعه و تظاهرات بالینی

> در نظر گرفتن علل عفونی و غیر عفونی قابل درمان • علل قابل درمان مطرح است درخواست آزمایشات در صورت نیاز و شروع درمان مناسب

> > بررسی مجدد

در صورت عدم وجود علایم اختصاصی درمان حمایتی انجام شود • علل قابل درمان مطرح نمیباشد مراجعه مجدد بعد از ۴۸ تا ۷۲ ساعت

• تذكر علايم هشدار

- در صورتی که اقدام درمانی فوری و ضروری باشد باید در کنار درمان تجربی اقدام های تشخیصی ضروری را نیز انجام داد.
 - در صورتی که اقدام درمانی فوری و ضروری نباشد، می توان درمان را تا مشخص شدن نتیجه اقدام های تشخیصی به تعویق انداخت. گاه تحت نظر گرفتن بیمار و مانیتور نمودن وی از نظر علائم و نشانه های هشدار کافی است

١-ضايعات ماكولريا ماكولوپاپولر:

ه.عفونی با درمان اختصاصی: مننگوکوکسی، هموفیلوس آنفلوانزا، پنوموکوک، مایکوپلاسما پنومونیه، بیماری لایم، سالمونلا، لیستریا منوسیتوژن، سیفیلس ثانویه و آرکانوباکتر همولیتیکوم

ل.غیر عفونی با درمان اختصاصی: بیماری کاوازاکی، واکنش داروئی، ARF و ARF (اریتم مارژیناتوم)

Lebv ورمان اختصاصی: سرخک، سرخجه، روزئولا اینفانتوم، اریتما انفکتیوزوم، EBV، آنتروویرسها، هپاتیت HIV، B و آدنوویروس

۲-ضایعات پتشی و پورپورا:

- **a. عفونی با درمان اختصاصی:** مننگوکوکسمی، سپتی سمی های غیر مننگوکوکی (هموفیلوس آنفلوانزا، سودوموناس، پنوموکوک)، آندوکاردیت، تب های هموراژیک ویروسی (تب کریمه کنگو، تب دانگ هموراژیک)، تب کوههای راکی، تیفوس اپیدمیک
- **له غیر عفونی با درمان اختصاصی:** ضایعات واسکولیتی غیر عفونی (SLE و هنوخ شوئن لاین)، واکنش دارویی و ...
- **ح. بدون درمان اختصاصی:** سرخک آتیپیک، انتروویروس ها، TORCHs ،HIV، پاروویروس B19، پاروویروس B19 (بیماری دستکش و جوراب پاپولوهموراژیک)

٣- ضايعات اريترودرمي:

- **a. عفونی با درمان اختصاصی:** تب مخملک (Scarlet fever) (استافیلوکوکی و استرپتوکوکی) و کاندیدا آلبیکانس
- **ل.غیر عفونی با درمان اختصاصی:** درمان سندرم افزایش حساسیتی وابسته به داروهای ضد Redman syndrome
 - C. بدون درمان اختصاصی: ویروس ها و داروها

٤-ضايعات وزيكولوبولوز:

- a. عفونى با درمان اختصاصى: SSSS و زرد زخم، HSV، آبله مرغان، زونا
 - **d.** غير عفوني با درمان اختصاصي: TEN و استيون جانسون
 - **C.** بدون درمان اختصاصی: داروها و علل ویروسی مثل انتروویروس ها

٥- ضايعات كهيرى:

a.عفونی با درمان اختصاصی: مایکوپلاسما پنومونیه، استرپ گروه **A،** شیگلا، یرسینیا و انگل

d.غیر عفونی با درمان اختصاصی: واکنش داروئی و گزش حشرات

C. بدون درمان اختصاصى: EBV ، هپاتیت B، HIV و انتروویروس ها



