10 - 21 Fever and Rash

21 Fever and Rash

can aggravate the condition of patients with preexisting impairment of cardiac, pulmonary, or CNS function. Children with a history of febrile or nonfebrile seizure should be aggressively treated to reduce fever. However, it is unclear what triggers the febrile seizure, and there is no correlation between absolute temperature elevation and onset of a febrile seizure in susceptible children. In hyperpyrexia, the use of cooling blankets facilitates the reduc tion of temperature; however, cooling blankets should not be used without oral antipyretics. In hyperpyretic patients with CNS disease or trauma (CNS bleeding), reducing core temperature mitigates the detrimental effects of high temperature on the brain. For a discussion of treatment for hyperthermia, see Chap. 478. ■ ■FURTHER READING Dinarello CA et al: Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nature Rev 11:633, 2012. Gattorno M et al: Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 78:1025, 2019. Kullenberg T et al: Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology 55:1499, 2016. Sakkat A et al: Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials. J Crit Care 61:89, 2021. Elaine T. Kaye, Kenneth M. Kaye

Fever and Rash The acutely ill patient with fever and rash often presents a diagnostic challenge for physicians, yet the distinctive appearance of an eruption in concert with a clinical syndrome can facilitate a prompt diagnosis and the institution of life-saving therapy or critical infection-control interventions. Representative images of many of the rashes discussed in this chapter are included in Chap. A1. APPROACH TO THE PATIENT Fever and Rash A thorough history of patients with fever and rash includes the following relevant information: immune status, medications taken within the previous month, specific travel history, immunization status, exposure to domestic pets and other animals, history of animal (including arthropod) bites, recent dietary exposures, exis tence of cardiac abnormalities, presence of prosthetic material, recent exposure to ill individuals, and sexual exposures. The history should also include the site of onset of the rash and its direction and rate of spread. PHYSICAL EXAMINATION A thorough physical examination entails close attention to the rash, with an assessment and precise identification of its salient features. First, it is critical to determine what type of lesions make up the eruption. Macules are flat lesions defined by an area of changed color (i.e., a blanchable erythema). Papules are raised, solid lesions <5 mm in diameter; plaques are lesions >5 mm in diameter with a flat, plateau-like surface; and nodules are lesions >5 mm in diameter with a more rounded configuration. Wheals (urticaria, hives) are papules or plaques that are pale pink and may appear annular (ring like) as they enlarge; classic (nonvasculitic) wheals are transient, lasting only 24 h in any defined area. Vesicles (<5 mm) and bullae

(>5 mm) are circumscribed, elevated lesions containing fluid. Pus tules are raised lesions containing purulent exudate; vesicles such as due to varicella or herpes simplex may evolve to pustules. Nonpal pable purpura is a flat lesion that is due to bleeding into the skin. If <3 mm in diameter, the purpuric lesions are termed petechiae; if

> 3 mm, they are termed ecchymoses. Palpable purpura is a raised lesion that is due to inflammation of the vessel wall (vasculitis) with subsequent hemorrhage. An ulcer is a defect in the skin extending at least into the upper layer of the dermis, and an eschar (tâche noire) is a necrotic lesion covered with a black crust. Fever and Rash CHAPTER 21 Other pertinent features of rashes include their configuration (i.e., annular or target), the arrangement of their lesions, and their distribution (i.e., central or peripheral). For further discussion, see Chaps. 59, 61, 127, and 134. ■ ■CLASSIFICATION OF RASH This chapter reviews rashes that reflect systemic disease, but it does not include localized skin eruptions (i.e., cellulitis, impetigo) that may also be associated with fever (Chap. 134). The chapter is not intended to be all-inclusive, but it covers the most important and most common diseases associated with fever and rash. Rashes are classified herein on the basis of lesion morphology and distribution. For practical pur poses, this classification system is based on the most typical disease presentations. However, morphology may vary as rashes evolve, and the presentation of diseases with rashes is subject to many variations (Chap. 61). For instance, the classic petechial rash of Rocky Mountain spotted fever (Chap. 192) may initially consist of blanchable ery thematous macules distributed peripherally; at times, however, the rash associated with this disease may not be predominantly acral, or no rash may develop at all. Diseases with fever and rash may be classified by type of eruption: centrally distributed maculopapular, peripheral, confluent desquama tive erythematous, vesiculobullous, urticaria-like, nodular, purpuric, ulcerated, or with eschars. Diseases are listed by these categories in Table 21-1, and many are highlighted in the text. However, for a more detailed discussion of each disease associated with a rash, the reader is referred to the chapter dealing with that specific disease. (Reference chapters are cited in the text and listed in Table 21-1.) ■ ■CENTRALLY DISTRIBUTED MACULOPAPULAR ERUPTIONS Centrally distributed rashes, in which lesions are primarily truncal, are the most common type of eruption. The rash of rubeola (measles) starts at the hairline 2–3 days into the illness and moves down the body, typically sparing the palms and soles (Fig. 21-1; see also Fig. A1-3) (Chap. 211). It begins as discrete erythematous lesions, which become confluent as the rash spreads. Koplik’s spots (1- to 2-mm white or blu ish lesions with an erythematous halo on the buccal mucosa) (Fig. A1-2) are pathognomonic for measles and are generally seen during the first 2 days of symptoms. They should not be confused with Fordyce’s spots (ectopic sebaceous glands), which have no erythematous halos and are found in the mouth of healthy individuals. Koplik’s spots may briefly overlap with the measles exanthem. Rubella (German measles) (Fig. A1-4) also spreads from the hairline downward; unlike that of

> measles, however, the rash of rubella tends to clear from originally affected areas as it migrates, and it may be pruritic (Chap. 212). Forchheimer spots (palatal petechiae) may develop but are nonspecific because they also develop in infectious mononucleosis (Chap. 199), scarlet fever (Chap. 153), and Zika virus infection (Chap. 215) (Fig. A1-51A-D). Postauricular and suboccipital adenop athy and arthritis are common among adults with rubella. Exposure of pregnant women to ill individuals should be avoided, as rubella causes severe congenital abnormalities. Numerous strains of enteroviruses (Chap. 210), primarily echoviruses and coxsackieviruses, cause non specific syndromes of fever and eruptions that may mimic rubella or measles. Patients with infectious mononucleosis caused by Epstein-Barr virus (Chap. 199) or with primary HIV infection (Fig. A1-6; see also

TABLE 21-1 Diseases Associated with Fever and Rash DISEASE ETIOLOGY DESCRIPTION Centrally Distributed Maculopapular Eruptions Acute meningococcemiaa — — — —

Drug reaction with eosinophilia and systemic symptoms (DRESS); also termed drug-induced hypersensitivity syndrome (DIHS)b; Chikungunyac; COVID-19c — — — —

PART 2 Cardinal Manifestations and Presentation of Diseases Rubeola (measles, first disease) (Fig. 21-1,

Fig. A1-2, Fig. A1-3) Paramyxovirus Discrete lesions that become confluent as rash spreads from hairline downward, usually sparing palms and soles; lasts

≥3 days; Koplik’s spots Rubella (German measles, third disease) (Fig. A1-4) Togavirus Spreads from hairline downward, clearing as it spreads; Forchheimer spots (palatal petechiae) Erythema infectiosum (fifth disease) (Fig. A1-1) Human parvovirus B19 Bright-red “slapped-cheeks” appearance followed by lacy reticular rash that waxes and wanes over 3 weeks; rarely, papularpurpuric “gloves-and-socks” syndrome on hands and feet Exanthem subitum (roseola, sixth disease) (Fig. A1-5) Human herpesvirus 6 or, less commonly, the closely related human herpesvirus 7 Diffuse maculopapular eruption over trunk and neck; resolves within 2 days Primary HIV infection

(Fig. A1-6) HIV Nonspecific diffuse macules and papules most commonly on upper thorax, face, collar region; less commonly, urticarial or vesicular lesions; oral or genital ulcers Infectious mononucleosis Epstein-Barr virus Diffuse maculopapular eruption historically in ~5% of cases increasing to ~90% of cases when antibiotics, particularly ampicillin, given, but recent observed rates of ~20% without antibiotics and little increase with antibiotics; urticaria, petechiae in some cases; periorbital edema (50%); palatal petechiae (25%) Other viral exanthems Echoviruses 2, 4, 9, 11, 16, 19, 25; coxsackieviruses A9, B1, B5; etc. Wide range of skin findings that may mimic rubella or measles Exanthematous druginduced eruption

(Fig. A1-7) Drugs (antibiotics, anticonvulsants, diuretics, etc.) Intensely pruritic, bright-red macules and papules, symmetric on trunk and extremities; may become confluent Epidemic typhus Rickettsia prowazekii Maculopapular eruption appearing in axillae, spreading to trunk and later to

extremities; usually spares face, palms, soles; evolves from blanchable macules to confluent eruption with petechiae; rash evanescent in recrudescent typhus

(Brill-Zinsser disease) Endemic (murine) typhus Rickettsia typhi Maculopapular eruption, usually sparing palms, soles Scrub typhus Orientia tsutsugamushi Diffuse macular rash starting on trunk; eschar at site of mite bite

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Nonimmune individuals Cough, conjunctivitis, coryza, severe prostration

Nonimmune individuals Adenopathy, arthritis

Most common among children 3–12 years old; occurs in winter and spring Mild fever; arthritis in adults; rash following resolution of fever

Usually affects children <3 years old Rash following resolution of fever; similar to Boston exanthem (echovirus 16); febrile seizures may occur

Individuals recently infected with HIV Pharyngitis, adenopathy, arthralgias

Adolescents, young adults Hepatosplenomegaly, pharyngitis, cervical lymphadenopathy, atypical lymphocytosis, heterophile antibody

Affects children more commonly than adults Nonspecific viral syndromes

Occurs 2–3 days after exposure in previously sensitized individuals; otherwise, after 2–3 weeks (but can occur anytime, even shortly after drug is discontinued) Variable findings: fever and eosinophilia

Exposure to body lice; occurrence of recrudescent typhus as relapse after

30–50 years Headache, myalgias; mortality rates 10–40% if untreated; milder clinical presentation in recrudescent form

Exposure to rat or cat fleas Headache, myalgias

Endemic in South Pacific, Australia, Asia; transmitted by mites Headache, myalgias, regional adenopathy; mortality rates up to 30% if untreated

(Continued)

(Continued) TABLE 21-1 Diseases Associated with Fever and Rash DISEASE ETIOLOGY DESCRIPTION Rickettsial spotted fevers (Fig. 21-8) Rickettsia conorii (boutonneuse fever), Rickettsia australis (North Queensland tick typhus), Rickettsia sibirica (Siberian tick typhus), Rickettsia africae (African tick-bite fever), and others Eschar common at bite site; maculopapular (rarely, vesicular and petechial) eruption on proximal extremities, spreading to trunk and face Human monocytotropic ehrlichiosisd Ehrlichia chaffeensis Maculopapular eruption (40% of cases), involves trunk and extremities; may be petechial Leptospirosis Leptospira interrogans and other Leptospira species

Maculopapular eruption; conjunctivitis; scleral hemorrhage in some cases Lyme disease (Fig. A1-8) Borrelia burgdorferi (sole cause in U.S.), Borrelia afzelii, Borrelia garinii Papule expanding to erythematous

annular lesion with central clearing (erythema migrans; average diameter,

15 cm), sometimes with concentric rings, sometimes with indurated or vesicular center; multiple secondary erythema migrans lesions in some cases Southern tick-associated rash illness (STARI, Master's disease) Unknown (possibly Borrelia lonestari or other Borrelia spirochetes) Similar to erythema migrans of Lyme disease with several differences, including: multiple secondary lesions less likely; lesions tending to be smaller (average diameter, ~8 cm); central clearing more likely Typhoid fever (Fig. A1-9) Salmonella typhi Transient, blanchable erythematous macules and papules, 2–4 mm, usually on trunk (rose spots) Dengue fevere (Fig. A1-53) Dengue virus

(4 serotypes; flaviviruses) Rash in 50% of cases; initially diffuse flushing; midway through illness, onset of maculopapular rash, which begins on trunk and spreads centrifugally to extremities and face; pruritus, hyperesthesia in some cases; after defervescence, petechiae on extremities may occur Rat-bite fever (sodoku) Spirillum minus Eschar at bite site; then blotchy violaceous or red-brown rash involving trunk and extremities Relapsing fever Borrelia species Central rash at end of febrile episode; petechiae in some cases Erythema marginatum (rheumatic fever) Group A Streptococcus Erythematous annular papules and plaques occurring as polycyclic lesions in waves over trunk, proximal extremities; evolving and resolving within hours Systemic lupus erythematosus (SLE)

(Fig. A1-10, Fig. A1-11,

Fig. A1-12) Autoimmune disease Macular and papular erythema, often in sun-exposed areas; discoid lupus lesions (local atrophy, scale, pigmentary changes); periungual telangiectasis; malar rash; vasculitis sometimes causing urticaria, palpable purpura; oral erosions in some cases Still's disease (Fig. A1-13) Autoimmune disease Transient 2- to 5-mm erythematous papules appearing at height of fever on trunk, proximal extremities; lesions evanescent

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Exposure to ticks; R. conorii in Mediterranean region, India, Africa; R. australis in Australia; R. sibirica in Siberia, Mongolia; R. africae in Africa, Caribbean Headache, myalgias, regional adenopathy

Fever and Rash CHAPTER 21 Tick-borne; most common in U.S. Southeast, southern Midwest, and midAtlantic regions Headache, myalgias, leukopenia

Exposure to water contaminated with animal urine Myalgias; aseptic meningitis; fulminant form: icterohemorrhagic fever (Weil's disease)

Bite of Ixodes tick vector Headache, myalgias, chills, photophobia occurring acutely; CNS disease, myocardial disease, arthritis weeks to months later in some cases

Bite of tick vector Amblyomma americanum (Lone Star tick); often found in regions where Lyme disease is uncommon, including southern United States Compared with Lyme disease: fewer

constitutional symptoms, tick bite more likely to be recalled; other Lyme disease sequelae lacking

Ingestion of contaminated food or water (rare in U.S.) Variable abdominal pain and diarrhea; headache, myalgias, hepatosplenomegaly

Occurs in tropics and subtropics; transmitted by mosquito Headache; musculoskeletal pain (“breakbone fever”); leukopenia; occasionally biphasic (“saddleback”) fever

Rat bite; primarily found in Asia; rare in U.S. Regional adenopathy; recurrent fevers if untreated

Exposure to ticks or body lice Recurrent fever, headache, myalgias, hepatosplenomegaly

Patients with rheumatic fever Pharyngitis preceding polyarthritis, carditis, subcutaneous nodules, chorea

Most common in young to middleaged women; flares precipitated by sun exposure Arthritis; cardiac, pulmonary, renal, hematologic, and vasculitic disease

Children and young adults High spiking fever, polyarthritis, splenomegaly; erythrocyte sedimentation rate

> “ 100 mm/h — (Continued)

TABLE 21-1 Diseases Associated with Fever and Rash (Continued) DISEASE ETIOLOGY DESCRIPTION African trypanosomiasis (Fig. A1-47) Trypanosoma brucei rhodesiense/gambiense Blotchy or annular erythematous macular and papular rash (trypanid), primarily on trunk; pruritus; chancre at site of tsetse fly bite may precede rash by several weeks Arcanobacterial pharyngitis Arcanobacterium (Corynebacterium) haemolyticum Diffuse, erythematous, maculopapular eruption involving trunk and proximal extremities; may desquamate PART 2 Cardinal Manifestations and Presentation of Diseases West Nile virus infection West Nile virus Maculopapular eruption involving the trunk, extremities, and head or neck; rash in 20–50% of cases Zika virus infection

(Fig. A1-51) Zika virus Pruritic macular and papular erythema; rash may begin on trunk and descend to lower body; conjunctival injection; palatal petechiae may occur Peripheral Eruptions Chronic meningococcemia, disseminated gonococcal infection,a human parvovirus B19 infection,f RIMEg — — — — 160, 161, 202 Rocky Mountain spotted fever (Fig. 21-2, Fig. A1-16) Rickettsia rickettsii Rash beginning on wrists and ankles and spreading centripetally; appears on palms and soles later in disease; lesion evolution from blanchable macules to petechiae Secondary syphilis

(Fig. A1-18, Fig. A1-19,

Fig. A1-20, Fig. A1-21) Treponema pallidum Coincident primary chancre in 10% of cases; copper-colored, scaly papular eruption, diffuse but prominent on palms and soles; rash never vesicular in adults; condyloma latum, mucous patches, and alopecia in some cases Chikungunya fever

(Fig. A1-54) Chikungunya virus Maculopapular eruption; typically occurs on trunk, but also occurs on extremities and face Hand-foot-and-mouth disease (Fig. A1-22) Coxsackievirus A16 and enterovirus 71 most common causes; coxsackievirus A6 associated with atypical syndrome Tender vesicles, erosions in mouth; 0.25- to 1-cm papules on hands and feet with rim of erythema evolving into tender vesicles; shedding of nails (onychomadesis) can occur 1–2 months after acute illness; coxsackievirus A6 lesions may also be maculopapular, petechial, purpuric, or erosive; atypical form often extends to perioral area, extremities, trunk, buttocks, genitals, and areas affected by eczema (eczema coxsackium) Erythema multiforme (EM) (Fig. A1-24) Infection, drugs, idiopathic causes Target lesions (central erythema surrounded by area of clearing and another rim of erythema) up to 2 cm; symmetric on knees, elbows, palms, soles; spreads centripetally; papular, sometimes vesicular; when extensive and involving mucous membranes, termed EM major

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Tsetse fly bite in eastern (T. brucei rhodesiense) or western (T. brucei gambiense) Africa Hemolymphatic disease followed by meningoencephalitis; Winterbottom’s sign (posterior cervical lymphadenopathy)

(T. brucei gambiense)

Children and young adults Exudative pharyngitis, lymphadenopathy

Mosquito bite; rarely, blood transfusion or transplanted organ Headache, weakness, malaise, myalgia, neuroinvasive disease (encephalitis, meningitis, flaccid paralysis)

Mosquito bite; sexual transmission or blood transfusion less common Arthralgia (especially of small joints), myalgia, lymphadenopathy, headache, low-grade fever; illness in pregnancy may cause severe birth defects, including microcephaly; neurologic complications, including Guillain-Barré, may occur

Tick vector; widespread but more common in southeastern and southwest-central U.S. Headache, myalgias, abdominal pain; mortality rates up to 40% if untreated

Sexually transmitted Fever, constitutional symptoms

Aedes aegypti and A. albopictus mosquito bites; tropical and subtropical regions Severe polyarticular, migratory arthralgias, especially involving small joints (e.g., hands, wrists, ankles)

Summer and fall; primarily children

<10 years old; multiple family members; coxsackievirus A6 infection also occurs in young adults Transient fever; enterovirus 71 can be associated with brainstem encephalitis, flaccid paralysis resembling polio, or aseptic meningitis

Herpes simplex virus or Mycoplasma pneumoniae infection; drug intake (i.e., sulfa, phenytoin, penicillin) 50% of patients <20 years old; fever more common in most severe form, EM major, which can be confused with StevensJohnson syndrome (but EM major lacks prominent skin sloughing) —h (Continued)

(Continued) TABLE 21-1 Diseases Associated with Fever and Rash DISEASE ETIOLOGY DESCRIPTION Rat-bite fever (Haverhill fever) Streptobacillus moniliformis Maculopapular eruption over palms, soles, and extremities; tends to be more severe at joints; eruption sometimes becoming generalized; may be purpuric; may desquamate Bacterial endocarditis (Fig. A1-23) Streptococcus, Staphylococcus, etc. Subacute course (e.g., viridans streptococci): Osler's nodes (tender pink nodules on finger or toe pads); petechiae on skin and mucosa; splinter hemorrhages. Acute course (e.g., Staphylococcus aureus): Janeway lesions (painless erythematous or hemorrhagic macules, usually on palms and soles) COVID-19 (Fig. A1-57) SARS-CoV-2 Mild or asymptomatic COVID-19: Pernio (macules, papules, or plaques that are tender, erythematous/violaceous; acral, feet more common than hands). Moderate/ severe COVID-19: Vesicles, urticaria, maculopapular erythema; often pruritic; occur on trunk, extremities. Severe

COVID-19: Retiform purpura (net-like, purple patches/plaques often with necrosis); lesions often asymptomatic; occur on extremities, buttocks. Multisystem inflammatory syndrome in children (MIS-C): Findings similar to Kawasaki disease Confluent Desquamative Erythemas Scarlet fever (second disease) (Fig. A1-25) Group A Streptococcus (pyrogenic exotoxins

A, B, C) Diffuse blanchable erythema beginning on face and spreading to trunk and extremities; circumoral pallor; "sandpaper" texture to skin; accentuation of linear erythema in skin folds (Pastia's lines); enanthem of white evolving into red "strawberry" tongue; desquamation in second week Kawasaki disease

(Fig. A1-29) Idiopathic Rash similar to scarlet fever (scarlatiniform) or EM; fissuring of lips, strawberry tongue; conjunctivitis; edema of hands, feet; desquamation later in disease Streptococcal toxic shock syndrome Group A Streptococcus (associated with pyrogenic exotoxin A and/or B or certain

M types) When present, rash often scarlatiniform May occur in setting of severe group A streptococcal infections (e.g., necrotizing fasciitis, bacteremia, pneumonia) Staphylococcal toxic shock syndrome S. aureus (toxic shock syndrome toxin 1, enterotoxins B and others) Diffuse erythema involving palms; pronounced erythema of mucosal surfaces; conjunctivitis; desquamation 7–10 days into illness Staphylococcal scaldedskin syndrome (Fig. A1-28) S. aureus, phage group II Diffuse tender erythema, often with bullae and desquamation; Nikolsky's sign Exfoliative erythroderma syndrome (Fig. A1-27) Underlying psoriasis, eczema, drug eruption, mycosis fungoides Diffuse erythema (often scaling) interspersed with lesions of underlying condition

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Rat bite, ingestion of contaminated food Myalgias; arthritis (50%); fever recurrence in some cases

Abnormal heart valve (e.g., viridans streptococci), intravenous drug use New or changing heart murmur

Fever and Rash CHAPTER 21 Infection with SARSCoV-2; MIS-C in older children/adolescents Ranging from asymptomatic to mild/ moderate with loss of taste/smell, pharyngitis, cough, fever, to severe with dyspnea, ARDS; complications include thrombosis, especially with retiform purpura; lesions

may be delayed compared to other COVID-19 symptoms; MIS-C occurs ~2-6 weeks following acute (often asymptomatic) infection Most common among children 2–10 years old; usually follows group A streptococcal pharyngitis Fever, pharyngitis, headache

Children <8 years old Cervical adenopathy, pharyngitis, coronary artery vasculitis 61, 375 Multiorgan failure, hypotension; mortality rate 30%

Colonization with toxin-producing

S. aureus Fever >39°C (>102°F), hypotension, multiorgan dysfunction

Colonization with toxin-producing

S. aureus; occurs in children <10 years old (termed Ritter's disease in neonates) or adults with renal dysfunction Irritability; nasal or conjunctival secretions

Usually occurs in adults over age 50; more common among men Fever, chills (i.e., difficulty with thermoregulation); lymphadenopathy 61, 63 (Continued)

TABLE 21-1 Diseases Associated with Fever and Rash (Continued) DISEASE ETIOLOGY DESCRIPTION DRESS (drug reaction with eosinophilia and systemic symptoms; also known as drug-induced hypersensitivity syndrome [DIHS]) (Fig. A1-48) Aromatic anticonvulsants; other drugs, including sulfonamides, minocycline Maculopapular eruption (mimicking exanthematous drug rash), sometimes progressing to exfoliative erythroderma; profound edema, especially facial; pustules may occur PART 2 Cardinal Manifestations and Presentation of Diseases Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (Fig. 21-3,

Fig. A1-26) Drugs (80% of cases; often allopurinol, anticonvulsants, antibiotics), infection, idiopathic factors Erythematous and purpuric macules, sometimes targetoid, or diffuse erythema progressing to bullae, with sloughing and necrosis of entire epidermis; Nikolsky's sign; involves mucosal surfaces; TEN (>30% epidermal necrosis) is maximal form; SJS involves <10% of epidermis; SJS/TEN overlap involves 10–30% of epidermis Vesiculobullous or Pustular Eruptions Hand-foot-andmouth syndromec; staphylococcal scaldedskin syndromeb; TENb; DRESS/DIHSb; COVID-19c — — — — —h Varicella (chickenpox) (Fig. 21-4, Fig. A1-30) Varicella-zoster virus (VZV) Macules (2–3 mm) evolving into papules, then vesicles (sometimes umbilicated), on an erythematous base ("dewdrops on a rose petal"); pustules then forming and crusting; lesions appearing in crops; may involve scalp, mouth; intensely pruritic Pseudomonas "hot-tub" folliculitis (Fig. A1-55) Pseudomonas aeruginosa Pruritic erythematous follicular, papular, vesicular, or pustular lesions that may involve axillae, buttocks, abdomen, and especially areas occluded by bathing suits; can manifest as tender isolated nodules on palmar or plantar surfaces (the latter designated "Pseudomonas hot-foot syndrome") Variola (smallpox)

(Fig. A1-50) Variola major virus Red macules on tongue and palate evolving to papules and vesicles; skin macules evolving to papules, then vesicles, then pustules over 1 week, with subsequent lesion crusting; lesions initially appearing on face and spreading centrifugally from trunk to extremities; differs from varicella in that (1) skin lesions in any given area are at same stage of development and (2) there is a prominent distribution of lesions on face and extremities

(including palms, soles) Mpox (Fig. A1-59) Monkeypox virus Classically, lesions similar in morphology and distribution to those of variola (smallpox); 2022 outbreak: macules evolve to papules, vesicles, and pustules, with subsequent crusting over 1–2 weeks; often umbilicated; unlike traditional Mpox, lesions may be in different stages of development and typically number fewer than 20; lesions often painful; mucosal lesions (anorectal, oropharyngeal, ocular) may occur at sites of inoculation; disease may be severe and progressive in advanced HIV

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Individuals genetically unable to detoxify arene oxides (anticonvulsant metabolites), patients with slow N-acetylating capacity (sulfonamides) Lymphadenopathy, multiorgan failure (especially hepatic), eosinophilia, atypical lymphocytes; HHV6 viremia; mimics sepsis

Uncommon among children; more common among people living with HIV systemic lupus erythematosus, certain HLA types, or slow acetylators Dehydration, sepsis sometimes resulting from lack of normal skin integrity; mortality rates up to 30%

Usually affects children; 10% of adults susceptible; most common in late winter and spring; incidence down by 90% in U.S. as a result of varicella vaccination Malaise; generally mild disease in healthy children; more severe disease with complications in adults and immunocompromised children

Bathers in hot tubs or swimming pools; occurs in outbreaks Earache, sore eyes and/ or throat; fever may be absent; generally self-limited

Nonimmune individuals exposed to smallpox Prodrome of fever, headache, backache, myalgias; vomiting in 50% of cases S4 Nonimmune individuals exposed to monkeypox; virus endemic to Central and West Africa; 2022 outbreak: among nonendemic countries including Europe, U.S.; most cases in men who have sex with men Classically, similar to smallpox, though with lymphadenopathy and typically milder; 2022 outbreak: fever, lymphadenopathy, headache, proctitis, or pharyngitis

(Continued)

(Continued) TABLE 21-1 Diseases Associated with Fever and Rash DISEASE ETIOLOGY DESCRIPTION Primary herpes simplex virus (HSV) infection (Fig. A1-58) HSV Erythema rapidly followed by hallmark painful grouped vesicles that may evolve into pustules that ulcerate, especially on mucosal surfaces; lesions at site of inoculation: commonly gingivostomatitis for HSV-1 and genital lesions for HSV-2; recurrent disease milder (e.g., herpes labialis typically does not involve oral mucosa) Disseminated herpesvirus infection (Fig. A1-31,

Fig. A1-58D) VZV or HSV Generalized nongrouped vesicles that can evolve to pustules and ulcerations; individual lesions similar for VZV and HSV. Zoster cutaneous dissemination:

25 lesions extending outside involved dermatome. HSV: extensive, progressive mucocutaneous lesions may occur in absence of dissemination; HSV may disseminate in eczematous skin (eczema herpeticum); HSV visceral dissemination may occur with only localized mucocutaneous disease; in disseminated HSV neonatal disease, skin lesions diagnostically helpful when present, but rash absent in a substantial minority of cases Rickettsialpox (Fig. A1-33) Rickettsia akari Eschar found at site of mite bite; generalized rash involving face, trunk, extremities; may involve palms and soles; <100 papules and plaques (2–10 mm); centers of papules develop vesicles or pustules Acute generalized exanthematous pustulosis (Fig. A1-49) Drugs (mostly anticonvulsants or antimicrobials); also viral Tiny, sterile, nonfollicular pustules on erythematous, edematous skin; begins on face and in body folds, then becomes generalized Disseminated Vibrio vulnificus infection V. vulnificus Erythematous lesions evolving into hemorrhagic bullae and then into necrotic ulcers Ecthyma gangrenosum (Fig. A1-34) P. aeruginosa, other gram-negative rods, fungi Indurated plaque evolving into hemorrhagic bulla or pustule that sloughs, resulting in eschar formation; erythematous halo; most common in axillary, groin, perianal regions Reactive infectious mucocutaneous eruption (RIME) (this generalized term encompasses multiple infectious etiologies, and includes Mycoplasma pneumoniae–induced rash and mucositis [MIRM]) M. pneumoniae, Chlamydia pneumoniae, human metapneumovirus, parainfluenzavirus 2, rhinovirus, influenza B virus, SARS-CoV-2 Severe mucositis of at least two sites (e.g., oropharynx, ocular, genital) with nearly universal hemorrhagic crusting of lips; sparse, vesiculobullous, or atypical targetoid rash over <10% of body; lesions typically on extremities but can be truncal; rash sometimes absent Urticaria-Like Eruptions COVID-19c Urticarial vasculitis

(Fig. 21-5, Fig. A1-35) Serum sickness, often due to infection (including acute hepatitis B, enteroviral, parasitic), drugs; connective tissue disease Erythematous, edematous “urticarialike” plaques, pruritic or burning; unlike urticaria: typical lesion duration >24 h (up to 5 days) and lack of complete lesion blanching with compression due to hemorrhage

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Primary infection most common among children and young adults for HSV-1 and among sexually active young adults for HSV-2; no fever in recurrent infection Regional lymphadenopathy

Fever and Rash CHAPTER 21 Patients with immunosuppression, eczema; neonates Visceral organ involvement (e.g., liver, lungs) in some cases; neonatal disease particularly severe 143, 197, 198 Seen in urban settings; transmitted by mouse mites Headache, myalgias, regional adenopathy; mild disease

Appears 2–21 days after start of drug therapy, depending on whether patient has been sensitized Acute fever, pruritus, leukocytosis

Patients with cirrhosis, diabetes, renal failure; exposure by ingestion of contaminated saltwater, seafood Hypotension; mortality rate 50%

Usually affects neutropenic patients; occurs in up to 28% of individuals with Pseudomonas bacteremia Clinical signs of sepsis

More common in males; usually children (mean age 11–12 years old) Cough, respiratory infection symptoms often precede rash by ~1 week, good prognosis; distinct from SJS/TEN Patients with serum sickness (including acute hepatitis B), connective tissue disease Fever variable; arthralgias/ arthritis 375h (Continued)

TABLE 21-1 Diseases Associated with Fever and Rash (Continued) DISEASE ETIOLOGY DESCRIPTION Nodular Eruptions Disseminated infection (Fig. 21-6, Fig. A1-36,

Fig. A1-37, Fig. A1-38) Fungal infections (e.g., candidiasis, histoplasmosis, cryptococcosis, sporotrichosis, coccidioidomycosis); mycobacteria Subcutaneous nodules (up to 3 cm); fluctuance, draining common with mycobacteria; necrotic nodules (extremities, periorbital or nasal regions) common with Aspergillus, Mucor PART 2 Cardinal Manifestations and Presentation of Diseases Erythema nodosum (septal panniculitis)

(Fig. A1-39) Infections (e.g., streptococcal, fungal, mycobacterial, yersinial); drugs (e.g., sulfas, penicillins, oral contraceptives); sarcoidosis; idiopathic causes Large, violaceous, nonulcerative, subcutaneous nodules; exquisitely tender; usually on lower legs but also on upper extremities Sweet syndrome (acute febrile neutrophilic dermatosis) (Fig. A1-40) Yersinia infection; upper respiratory infection; inflammatory bowel disease; pregnancy; malignancy (usually hematologic); drugs (G-CSF) Tender red or blue edematous nodules giving impression of vesiculation; usually on face, neck, upper extremities; when on lower extremities, may mimic erythema nodosum Bacillary angiomatosis Bartonella henselae,

B. quintana Many forms, including erythematous, smooth vascular nodules; friable, exophytic lesions; erythematous plaques (may be dry, scaly); subcutaneous nodules (may be erythematous) Purpuric Eruptions Rocky Mountain spotted fever, rat-bite fever, endocarditisc; epidemic typhusf; dengue fevere,f; human parvovirus B19 infectionf; COVID-19c — — — — —h Acute meningococcemia Neisseria meningitidis Initially pink maculopapular lesions evolving into petechiae; petechiae rapidly becoming numerous, sometimes enlarging and becoming vesicular; trunk, extremities most commonly involved; may appear on face, hands, feet; may include purpura fulminans (see below) reflecting DIC Purpura fulminans

(Fig. A1-41) Severe DIC Large ecchymoses with sharply irregular shapes evolving into hemorrhagic bullae and then into black necrotic lesions Chronic meningococcemia

(Fig. A1-42) N. meningitidis Variety of recurrent eruptions, including pink maculopapular; nodular (usually on lower extremities); petechial (sometimes developing vesicular centers); purpuric areas with pale blue-gray centers Disseminated gonococcal infection (Fig. A1-43) Neisseria gonorrhoeae Papules (1–5 mm) evolving over 1–2 days into hemorrhagic pustules with gray necrotic centers; hemorrhagic bullae occurring rarely; lesions (usually <40) distributed peripherally near joints (more commonly on upper extremities) Enteroviral petechial rash Usually echovirus 9 or coxsackievirus

A9 Disseminated petechial lesions (may also be maculopapular, vesicular, or urticarial) Viral hemorrhagic fever Arenaviruses, bunyaviruses, filoviruses (including Ebola), flaviviruses (including dengue) Petechial rash Residence in or travel to endemic areas, other virus exposure

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Immunocompromised hosts (e.g., bone marrow transplant recipients, patients undergoing chemotherapy, HIVinfected patients) Features vary with organism —h More common among females 15–30 years old Arthralgias (50%); features vary with associated condition —h More common among women and among persons 30–60 years old; 20% of cases associated with malignancy (men and women equally affected in this group) Headache, arthralgias, leukocytosis

Immunosuppressed individuals, especially those with advanced HIV infection Peliosis of liver and spleen in some cases; lesions sometimes involving multiple organs; bacteremia

Most common among children, individuals with asplenia or terminal complement component deficiency (C5–C8) Hypotension, meningitis (sometimes preceded by upper respiratory infection)

Individuals with sepsis (e.g., involving N. meningitidis), malignancy, or massive trauma; asplenic patients at high risk for sepsis Hypotension 160, 315 Individuals with complement deficiencies Fevers, sometimes intermittent; arthritis, myalgias, headache

Sexually active individuals (more often females), some with complement deficiency Low-grade fever, tenosynovitis, arthritis

Often occurs in outbreaks Pharyngitis, headache; aseptic meningitis with echovirus 9

Triad of fever, shock, hemorrhage from mucosa or gastrointestinal tract 215, 216 (Continued)

(Continued) TABLE 21-1 Diseases Associated with Fever and Rash DISEASE ETIOLOGY DESCRIPTION Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome Idiopathic, bloody diarrhea caused by Shiga toxin– generating bacteria (e.g., Escherichia coli O157:H7), deficiency in ADAMTS13 (cleaves von Willebrand factor), drugs (e.g., quinine, chemotherapy, immunosuppression) Petechiae Individuals with Shiga toxin producing bacterial (commonly E. coli O157:H7) gastroenteritis (especially children), cancer chemotherapy, HIV infection, autoimmune diseases, pregnant/postpartum women, those with ADAMTS13 deficiency Cutaneous smallvessel vasculitis (leukocytoclastic vasculitis) (Fig. 21-7,

Fig. A1-44) Infections (including group A streptococcal infection, hepatitis B or C), drugs, idiopathic factors Palpable purpuric lesions appearing in crops on legs or other dependent areas; may become vesicular or ulcerative Eruptions with Ulcers and/or Eschars Scrub typhus, rickettsial spotted fevers, ratbite fever, African trypanosomiasisf; rickettsialpox, ecthyma gangrenosumg — — — — —h Tularemia (Fig. A1-45,

Fig. A1-46) Francisella tularensis Ulceroglandular form: erythematous, tender papule evolves into necrotic, tender ulcer with raised borders; in 35% of cases, eruptions (maculopapular, vesiculopapular, acneiform, or urticarial; erythema nodosum; or EM) may occur Anthrax (Fig. A1-52) Bacillus anthracis Pruritic papule enlarging and evolving into a 1- by 3-cm painless ulcer

surrounded by vesicles and then developing a central eschar with edema; residual scar aSee “Purpuric Eruptions.” bSee “Confluent Desquamative Erythemas.” cSee “Peripheral Eruptions.” dRash is rare in human granulocytotropic ehrlichiosis or anaplasmosis (caused by Anaplasma phagocytophilum; most common in the upper midwestern and northeastern United States). eSee “Viral hemorrhagic fever” under “Purpuric Eruptions” for dengue hemorrhagic fever/dengue shock syndrome. fSee “Centrally Distributed Maculopapular Eruptions.” gSee “Vesiculobullous or Pustular Eruptions.” hSee etiology-specific chapters. Abbreviations: ARDS, acute respiratory distress syndrome; CNS, central nervous system; DIC, disseminated intravascular coagulation; G-CSF, granulocyte colonystimulating factor; HLA, human leukocyte antigen. Chapter 208) may exhibit pharyngitis, lymphadenopathy, and a non specific maculopapular exanthem. The rash of erythema infectiosum (fifth disease), which is caused by human parvovirus B19, primarily affects children 3–12 years old; it develops after fever has resolved as a bright blanchable erythema on the cheeks (“slapped cheeks”) (Fig. A1-1A) with perioral pallor (Chap. 202). A more diffuse rash (often pruritic) appears the next day on the trunk and extremities and then rapidly develops into a lacy reticular eruption (Fig. A1-1B) that may wax and wane (especially with temperature change) over 3 weeks. Adults with fifth disease often have arthritis, and fetal hydrops can develop in association with this condi tion in pregnant women. Exanthem subitum (roseola) is caused by human herpesvirus 6, or less commonly by the closely related human herpesvirus 7, and is most common among children <3 years of age (Chap. 200). As in erythema infectiosum, the rash usually appears after fever has subsided. It con sists of 2- to 3-mm rose-pink macules and papules that coalesce only rarely, occur initially on the trunk (Fig. A1-5) and sometimes on the extremities (sparing the face), and fade within 2 days. Although drug reactions have many manifestations, including urti caria, exanthematous drug-induced eruptions (Chap. 63) (Fig. A1-7) are most common and are often difficult to distinguish from viral

GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS CLINICAL SYNDROME CHAPTER Fever (not always present), microangiopathic hemolytic anemia, thrombocytopenia, renal dysfunction, neurologic dysfunction; coagulation studies normal 61, 105, 120, 166, 172 Fever and Rash CHAPTER 21 Occurs in a wide spectrum of diseases, including connective tissue disease, cryoglobulinemia, malignancy, HenochSchönlein purpura (HSP); more common among children Fever (not always present), malaise, arthralgias, myalgias; systemic vasculitis in some cases; renal, joint, and gastrointestinal involvement common in HSP

Exposure to ticks, biting flies, infected animals Fever, headache, lymphadenopathy

Exposure to infected animals or animal products, other exposure to anthrax spores Lymphadenopathy, headache S4 exanthems. Eruptions elicited by drugs are usually more intensely erythematous and pruritic than viral exanthems, but this distinction is not reliable. A history of new medications and an absence of prostra tion may help to distinguish a drug-related rash from an eruption of another etiology. Rashes may persist for up to 2 weeks after admin istration of the offending agent is discontinued. Certain populations are more prone than others to drug rashes. Of people living with HIV, 50–60% develop a rash in response to sulfa drugs. Rickettsial illnesses (Chap. 192) should be considered in the evalua tion of individuals with centrally distributed maculopapular eruptions. The usual setting for epidemic typhus is a site of war or natural disaster in which people are exposed to body lice. Endemic typhus or leptospirosis (the latter caused by a spirochete) (Chap. 189) may be seen in urban environments where rodents proliferate. Outside the

United States, other rickettsial diseases cause a spotted-fever syndrome and should be consid ered in residents of or travelers to endemic areas. Similarly, typhoid fever, a nonrickettsial disease caused by Salmonella typhi (Chap. 171) (Fig. A1-9), is usually acquired during travel outside the United States. Dengue fever (Fig. A1-53), caused by a mosquito-transmitted flavivirus, occurs in tropical and subtropical regions of the world (Chap. 215). Some centrally distributed maculopapular eruptions have distinc tive features. Erythema migrans (Fig. A1-8), the rash of Lyme disease

PART 2 Cardinal Manifestations and Presentation of Diseases FIGURE 21-1 Centrally distributed, maculopapular eruption on the trunk in a patient with measles. (From EJ Mayeaux Jr et al: Measles, in Usatine RP et al [eds]: Color Atlas and Synopsis of Family Medicine, 3rd ed. New York, McGraw-Hill, 2019, p. 797, Figure 132-2. Reproduced with permission from Richard P. Usatine, MD.) (Chap. 191), typically manifests as single or multiple annular lesions. Untreated erythema migrans lesions usually fade within a month but may persist for more than a year. Southern tick-associated rash illness (STARI) (Chap. 191) has an erythema migrans–like rash but is less severe than Lyme disease and often occurs in regions where Lyme is not endemic. Erythema marginatum, the rash of acute rheumatic fever (Chap. 371), has a distinctive pattern of enlarging and shifting tran sient annular lesions. Collagen vascular diseases may cause fever and rash. Patients with systemic lupus erythematosus (Chap. 368) typically develop a sharply defined, erythematous eruption in a butterfly distribution on the cheeks (malar rash) (Fig. A1-10) as well as many other skin manifes tations (Figs. A1-11, A1-12). Still’s disease presents as an evanescent, salmon-colored rash on the trunk and proximal extremities that coin cides with fever spikes (Fig. A1-13). Hemophagocytic lymphohistiocytosis may be familial or triggered by infection, autoimmunity, or neoplasia. Cutaneous manifestations are protean and can present as an erythematous maculopapular erup tion, pyoderma gangrenosum, purpura, panniculitis, or Stevens-Johnson syndrome. Zika virus is a mosquito-transmitted flavivirus that is associated with severe birth defects (Chap. 215). Zika is widespread among tropi cal and subtropical regions of the world. The eruption of Zika virus infection (Fig. A1-51A, A1-51B) is typically pruritic and often accom panied by conjunctival injection (Fig. A1-51C). ■ ■PERIPHERAL ERUPTIONS These rashes are alike in that they are most prominent peripherally or begin in peripheral (acral) areas before spreading centripetally. Early diagnosis and therapy are critical in Rocky Mountain spotted fever (Chap. 192) because of its grave prognosis if untreated. Lesions (Fig. 21-2; see also Fig. A1-16) evolve from macular to petechial, start on the wrists and ankles, spread centripetally, and appear on the palms and soles only later in the disease. The rash of secondary syphilis (Chap. 187), which may be generalized (Fig. A1-18) but is prominent on the palms and soles (Fig. A1-19), should be considered in the differ ential diagnosis of pityriasis rosea, especially in sexually active patients.

FIGURE 21-2 Peripheral eruption on the wrist and palm exhibiting erythematous macules in the process of evolving into petechial lesions in a patient with Rocky Mountain spotted fever. (From K Wolff et al [eds]: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York, McGraw-Hill, 2017, p. 562, Figure 25-50; with permission.) Chikungunya fever (Chap. 215), which is transmitted by mosquito bite in tropical and subtropical regions, is associated with a maculopapular eruption (Fig. A1-54) and severe polyarticular small-joint arthralgias. Hand-foot-and-mouth disease (Chap. 210), most commonly caused by coxsackievirus A16 or enterovirus 71, is distinguished by tender vesicles distributed on the hands and feet and in the mouth (Fig. A1-22); coxsackievirus A6 causes an atypical syndrome with more extensive lesions. The classic target lesions of erythema multiforme (Fig. A1-24A) appear symmetrically on the elbows, knees, palms,

soles, and face. In severe cases, these lesions spread diffusely and involve mucosal surfaces (Fig. A1-24B, C). Lesions may develop on the hands and feet in endocarditis (Fig. A1-23) (Chap. 133). Pernio, tender violaceous lesions that are acral (Fig. A1-57), occur most commonly on the feet in asymptomatic or mild COVID-19. Vesicles, urticaria, or maculopapu lar eruptions, often pruritic, may occur on the trunk and extremities in moderate or severe disease, whereas retiform purpura occurs on the extremities and buttocks in severe COVID-19. ■ ■CONFLUENT DESQUAMATIVE ERYTHEMAS These eruptions consist of diffuse erythema frequently followed by desquamation. The eruptions caused by group A Streptococcus or Staphylococcus aureus are toxin-mediated. Scarlet fever (Chap. 153) (Fig. A1-25) usually follows pharyngitis; patients have a facial flush, a "strawberry" tongue, and accentuated petechiae in body folds (Pastia's lines). Kawasaki disease (Fig. A1-29) (Chaps. 61 and 375) presents in the pediatric population as fissuring of the lips, a strawberry tongue, conjunctivitis, adenopathy, and sometimes cardiac abnormalities. Streptococcal toxic shock syndrome (Chap. 153) manifests with hypo tension, multiorgan failure, and, often, a severe group A streptococ cal infection (e.g., necrotizing fasciitis). Staphylococcal toxic shock syndrome (Chap. 152) also presents with hypotension and multiorgan failure, but usually only S. aureus colonization—not a severe S. aureus infection—is documented. Staphylococcal scalded-skin syndrome (Fig. A1-28) (Chap. 152) is seen primarily in children and in immu nocompromised adults. Generalized erythema is often evident during the prodrome of fever and malaise; profound tenderness of the skin is distinctive. In the exfoliative stage, the skin can be induced to form bul lae with light lateral pressure (Nikolsky's sign) (Fig. A1-28B). In a mild form, a scarlatiniform eruption mimics scarlet fever, but the patient

FIGURE 21-3 Confluent desquamation in a patient with toxic epidermal necrolysis. (From KS-M Kane et al: Color Atlas & Synopsis of Pediatric Dermatology, 3rd ed. New York, McGraw Hill, 2017, Figure 15-6; with permission.) does not exhibit a strawberry tongue or circumoral pallor. In contrast to the staphylococcal scalded-skin syndrome, in which the cleavage plane is superficial in the epidermis, toxic epidermal necrolysis (Chap. 63), a maximal variant of Stevens-Johnson syndrome, involves sloughing of the entire epidermis (Fig. 21-3, see also Fig. A1-26), resulting in severe disease. Exfoliative erythroderma syndrome (Chaps. 61 and 63) is a serious reaction associated with systemic toxicity that is often due to eczema, psoriasis (Fig. A1-27), a drug reaction, or mycosis fungoides. Drug reaction with eosinophilia and systemic symptoms (DRESS) (also termed drug-induced hypersensitivity syndrome [DIHS]), often due to antiepileptic or antibiotic agents (Chap. 63), initially appears similar to an exanthematous drug reaction (Fig. A1-48) but may progress to exfoliative erythroderma; it is accompanied by multiorgan failure and has an associated mortality rate of ~10%. ■ ■VESICULOBULLOUS OR PUSTULAR ERUPTIONS Varicella (Chap. 198) is highly contagious, often occurring in winter or spring, and is characterized by pruritic lesions that, within a given region of the body, are in different stages of development at any point in time (Fig. 21-4; see also Fig. A1-30). In immunocompromised FIGURE 21-4 Vesicular and pustular lesions on the chest in a patient with varicella. (From K Wolff et al [eds]: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York, McGraw-Hill, 2017, p. 695, Figure 27-48; with permission.)

hosts, varicella vesicles may lack the characteristic erythematous base or may appear hemorrhagic. Lesions of Pseudomonas "hot-tub" folliculi tis (Chap. 170) are also pruritic and may appear similar to those of varicella (Fig. A1-55). However, hot-tub folliculitis generally occurs in outbreaks after bathing in hot tubs or swimming pools, and lesions occur in regions occluded by bathing suits. Lesions of variola (smallpox) (Chap. S4) also appear similar to those of varicella but

are all at the same stage of development in a given region of the body (Figs. A1-50B and A1-50C). Variola lesions are most prominent on the face (Fig. A1-50A) and extremities, while varicella lesions are most promi nent on the trunk. Mpox, endemic to Africa, can present similarly to variola, although with lower mortality. A 2022 Mpox outbreak in nonendemic nations was characterized by presence of fewer lesions (Fig. A1-59) and milder disease. Herpes simplex virus infection (Chap. 197) is characterized by hallmark grouped vesicles on an erythematous base. Primary herpes infection (Fig. A1-58A, B) is accompanied by fever and toxicity, while recurrent disease (Fig. A1-58C) is milder. Rickettsialpox (Chap. 192) is often documented in urban settings and is characterized by vesicles followed by pustules (Figs. A1-33B, A1-33C). It can be distinguished from varicella by an eschar at the site of the mouse-mite bite (Fig. A1-33A) and the papule/plaque base of each vesicle. Acute generalized exanthematous pustulosis (Fig. A1-49) should be considered in individuals who are acutely febrile and are taking new medications, especially anticonvulsant or antimicrobial agents (Chap. 63). Disseminated Vibrio vulnificus infection (Chap. 173) or ecthyma gangrenosum due to Pseudomonas aeruginosa (Fig. A1-34) (Chap. 170) should be considered in immunosuppressed individuals with sepsis and hemorrhagic bullae. In children, reactive infectious mucocutaneous eruption (RIME, encompasses MIRM) can occur with Mycoplasma pneumoniae or other respiratory pathogen infection

(Fig. A1-56) and is characterized by a sparse, often vesiculobullous eruption with prominent oral, ocular, or urogenital mucositis.

Fever and Rash CHAPTER 21 ■ ■URTICARIA-LIKE ERUPTIONS Individuals with classic urticaria (“hives”) (Fig. 21-5; see also Fig. A1-35) usually have a hypersensitivity reaction without associated fever. In the presence of fever, urticaria-like eruptions are most often due to urticarial vasculitis (Chap. 375). Unlike individual lesions of classic urticaria, which last up to 24 h, these lesions may last 3–5 days. Etiologies include serum sickness (often induced by drugs such as penicillins, sulfas, salicylates, or FIGURE 21-5 Urticarial eruption. (From K Wolff et al [eds]: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York, McGraw-Hill, 2017, p. 299, Figure 14-2; with permission.)

barbiturates), connective-tissue disease (e.g., systemic lupus erythema tosus or Sjögren’s syndrome), and infection (e.g., with hepatitis B virus, enteroviruses, or parasites). Malignancy, especially lymphoma, may be associated with fever and chronic urticaria (Chap. 61).

■ ■NODULAR ERUPTIONS In immunocompromised hosts, nodular lesions often represent dis seminated infection. Patients with disseminated candidiasis (Fig. A1-37) (often due to Candida tropicalis) may have a triad of fever, myalgias, and eruptive nodules (Chap. 222). Disseminated cryptococcosis lesions (Fig. 21-6; see also Fig. A1-36) (Chap. 221) may resemble molluscum contagiosum (Chap. 201). Necrosis of nodules should raise the sus picion of aspergillosis (Fig. A1-38) (Chap. 223) or mucormycosis (Chap. 224). Erythema nodosum presents with exquisitely tender nodules on the lower extremities (Fig. A1-39). Sweet syndrome (Chap. 61) should be considered in individuals with multiple nod ules and plaques, often so edematous (Fig. A1-40) that they give the appearance of vesicles or bullae. Sweet syndrome may occur in indi viduals with infection, inflammatory bowel disease, or malignancy and can also be induced by drugs. PART 2 Cardinal Manifestations and Presentation of Diseases ■ ■PURPURIC ERUPTIONS Acute meningococcemia (Chap. 160) classically presents in children as a petechial eruption, but initial lesions may appear

as blanchable mac ules or urticaria. Rocky Mountain spotted fever should be considered in the differential diagnosis of acute meningococcemia. Echovirus 9 infection (Chap. 210) may mimic acute meningococcemia; patients should be treated as if they have bacterial sepsis because prompt dif ferentiation of these conditions may be impossible. Large ecchymotic areas of purpura fulminans (Fig. A1-41) (Chaps. 160 and 315) reflect severe underlying disseminated intravascular coagulation, which may be due to infectious or noninfectious causes. The lesions of chronic meningococcemia (Fig. A1-42) (Chap. 160) may have a variety of morphologies, including petechial. Purpuric nodules may develop on the legs and resemble erythema nodosum but lack its exquisite tender ness. Lesions of disseminated gonococcemia (Chap. 161) are distinctive, sparse, countable hemorrhagic pustules (Fig. A1-43), usually located near joints. The lesions of chronic meningococcemia and those of gonococcemia may be indistinguishable in terms of appearance and FIGURE 21-6 Nodular eruption on the face due to disseminated Cryptococcus in a patient living with HIV. (From K Wolff et al [eds]: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York, McGraw-Hill, 2017, p. 641, Figure 26-57. Used with permission from Loïc Vallant, MD.)

FIGURE 21-7 Purpuric lesions of cutaneous small vessel vasculitis in a patient with Henoch-Schonlein purpura. (Courtesy of Peter Lio, MD; with permission) distribution. Viral hemorrhagic fever (Chaps. 215 and 216) should be considered in patients with an appropriate travel history and a pete chial rash. Thrombotic thrombocytopenic purpura (Chaps. 61, 105, and 120) and hemolytic-uremic syndrome (Chaps. 120, 166, and 172) are closely related and are noninfectious causes of fever and petechiae. Cutaneous small-vessel vasculitis (leukocytoclastic vasculitis) typically manifests as palpable purpura (Fig. 21-7, see also Fig. A1-44) and has a wide variety of causes (Chap. 61). ■ ■ERUPTIONS WITH ULCERS OR ESCHARS The presence of an ulcer or eschar (Fig. 21-8) in the setting of a more widespread eruption can provide an important diagnostic clue. For FIGURE 21-8 Eschar with surrounding erythema at the site of a tick bite in a patient with African tick-bite fever. (From K Wolff et al [eds]: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York, McGraw-Hill, 2017, p. 561, Figure 25-49; with permission.)

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