

# Fever and Rash



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## KEYWORDS

- Rash • Fever • Emergency medicine • Exanthem • Toxic shock syndrome
- Rocky Mountain spotted fever • Arbovirus • Meningococemia

## KEY POINTS

- When evaluating fever and rash, an exhaustive history and head-to-toe skin examination are cornerstones of diagnosis.
- Fever with rash can herald life-threatening infection and imminent clinical decompensation.
- Particular attention should be directed toward identifying petechiae and bullae.
- Many life-threatening causes of infectious fever and rash remain clinical diagnoses, and laboratory confirmation should not delay life-saving antimicrobial therapy and supportive care.
- The differential diagnosis for fever and rash differential also includes life-threatening, noninfectious causes and indolent infectious diseases.

## INTRODUCTION

Emergency department (ED) visits for rash comprise up to 8% of annual ED visits.<sup>1</sup> Timely outpatient visits to a primary care physician or dermatologist are particularly difficult to obtain for underinsured patients in the United States, requiring ED evaluation for what is often a benign skin condition.<sup>2,3</sup> However, cutaneous manifestations of infection can carry higher risk, with up to 18% of ED patients requiring dermatology consultation also needing hospital admission.<sup>1</sup> Rash plus fever poses even greater concern; the combination may herald life-threatening infectious disease and imminent hemodynamic collapse.<sup>4–6</sup> Many of these infections can cause fatal illness long before laboratory confirmation, highlighting the need for a fundamental knowledge of the most dangerous cutaneous diagnoses and a well-developed clinical gestalt. The importance of rapid management is highlighted by increased mortality when appropriate antibiotics and supportive therapy is delayed.<sup>7,8</sup> Emergency providers additionally play a critical role in the fight against communicable diseases; prompt recognition, isolation, and disease reporting can prevent outbreaks in the community as well among ED staff.

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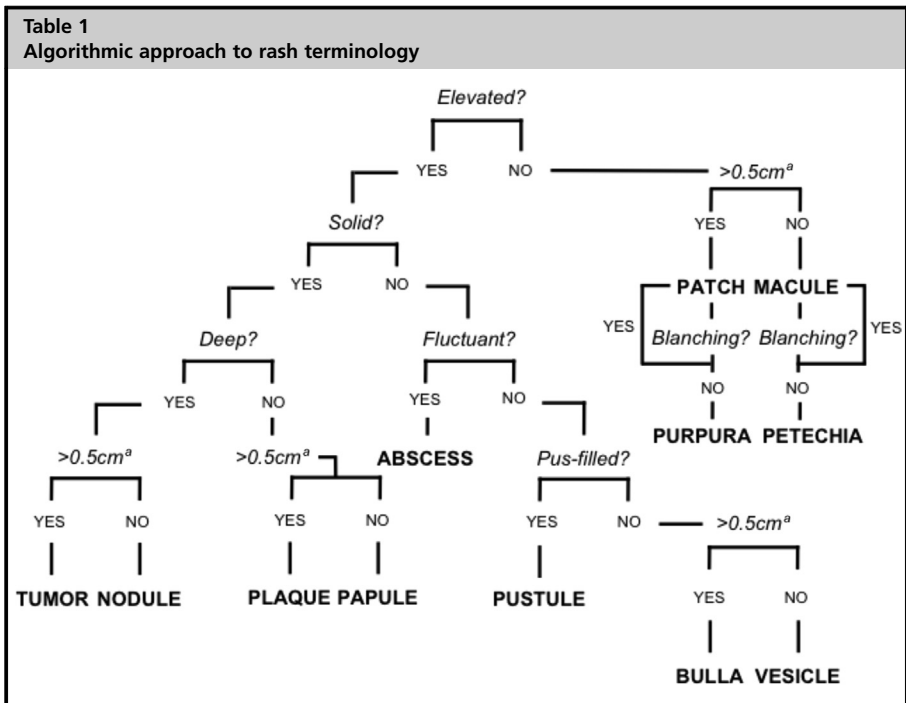
The differential for fever and rash is enormous, contributing to the diagnostic challenge of distinguishing benign, self-limited disease from life-threatening infection. This review article provides a basic approach to fever and rash in the ED and focuses on several infectious causes of fever and rash associated with significant morbidity and mortality.

## DEFINITIONS, MORPHOLOGY, AND PATHOPHYSIOLOGY

Fluency in rash morphology and terminology is essential both to create an algorithmic differential and communicate effectively with consultants (Table 1).<sup>9,10</sup>

*Maculopapular* (also referred to as morbilliform, meaning “measles-like”) rashes comprise the most common cutaneous manifestation of infection. Maculopapular rashes are usually generalized and thought to result from local or diffuse perivascular lymphocytic infiltration into the dermis, usually without capillary leak, as virus infects various cellular components of skin.<sup>11–13</sup> Maculopapular rashes are most commonly caused by one of the numerous childhood viruses (the so-called viral exanthems) (Table 2).<sup>10,14,15</sup> This is also the main type of arbovirus rash since skin is the primary site of viral replication in arbovirus infection.<sup>11,14</sup>

*Erythroderma* is a generalized “sunburn” like rash. When infectious, it corresponds to the diffuse nature of the responsible toxin or bacteremia, superantigens, and



General definitions of rashes based on descriptive factors broken into an algorithmic approach.

<sup>a</sup>Diameter of lesion.

Data from Walls RM, Hockberger RS, Gausche-Hill M. Rosen's emergency medicine: concepts and clinical practice. Ninth edition. ed. Elsevier; 2018:2 volumes (xxviii, 2443, 1-88 pages); and Santistevan J, Long B, Koyfman A. Rash Decisions: An Approach to Dangerous Rashes Based on Morphology. *J Emerg Med.* Apr 2017;52(4):457-47.

	Central	Peripheral
Febrile	Lyme disease (erythema migrans) Viral exanthem	Meningococcemia RMSF Syphilis Lyme disease (erythema migrans) Targetoid Stevens-Johnson Syndrome Erythema multiforme
Afebrile	Drug reaction Pityriasis	Psoriasis Scabies Eczema

Maculopapular exanthem body distribution in the setting of febrile versus afebrile rash (excluding diffuse rashes).

Data from Refs. <sup>10,14,15</sup>

immune-mediated cytokine release.<sup>6</sup> This leads to a generalized capillary dilation, endothelial dysfunction, and extravasation of blood components into interstitial tissue, as seen in toxic shock syndrome (TSS).<sup>16,17</sup>

*Vesiculobullous* rash results from fluid accumulation between the dermis and epidermis, manifesting as vesicles, which can coalesce to bullae and eventually desquamate.<sup>16,18</sup> This process is secondary to a compromised dermal–epidermal junction, often from toxin-mediated cleavage of junctional proteins.

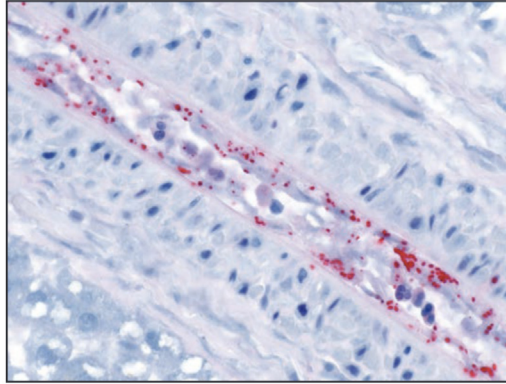
*Petechiae* are small, 0.5 cm red–brown lesions that do not blanch when pressure is applied.<sup>10,18</sup> They can be flat or palpable. Petechiae often coexist with maculopapular rashes, representing further endothelial dysfunction, capillary leak, and microvascular dysfunction.<sup>19,20</sup> Petechiae can be toxin-mediated or from direct bacterial invasion of vascular endothelium and smooth muscle cells, causing mononuclear cell infiltration, vasculitis, capillary leak, coagulation dysfunction, and platelet consumption (**Fig. 1**).<sup>21,22</sup> Petechiae can increase in size and coalesce, resulting in *purpura*.

## INITIAL EVALUATION

### History

A careful and thorough history is the cornerstone for correct rash diagnosis. Questions about health habits and travel should include outdoor activity, geographic location of any recent travel, urban versus rural travel, routine and travel-related vaccination status, travel-related chemoprophylaxis and adherence, contact with fresh or saltwater, livestock contact, and types of foods eaten.<sup>23,24</sup> A sexual history is mandatory as many sexually transmitted infections (STIs) have cutaneous manifestations (**Table 3**).<sup>25–31</sup> Questions about past medical history should focus on comorbidities that affect immunocompetence, including HIV, diabetes, complement deficiency, and use of chemotherapeutic and immunomodulating agents.<sup>32–34</sup> Medication history is critical since new medications are frequent triggers of serious and potentially fatal noninfectious rashes, which can be accompanied by fever (**Table 4**).<sup>35–39</sup>

The emergency provider must elicit a specific history of the fever and rash, including their temporal relationship with one another.<sup>40,41</sup> They should create a historical narrative of rash morphology, location, migration, and evolution. Categorize location and evolution as local versus generalized and centripetal versus centrifugal.



Photo/CDC

**Fig. 1.** Immunohistochemical staining of invading *Rickettsia rickettsii* (red) in endothelial cells of blood vessels. (Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis - United States. *MMWR Recomm Rep.* 2016;65(2):1-44. Published 2016 May 13. <https://doi.org/10.15585/mmwr.rr6502a1>. Fig. 20 in series.)

Note whether it is pruritic or painful.<sup>42</sup> Other prodromal and associated symptoms can help differentiate between infections with similar morphology, particularly maculopapular rashes.<sup>10,13,14,43</sup> In the case of travel, determine the possible incubation period from exposure to fever and rash onset.

### **Physical Examination**

A head-to-toe dermatologic examination is an essential part of the evaluation. Patients must be fully undressed in a hospital gown, and placed in a well-lit examination room. Visually inspect all body locations systematically, including the palms, soles, axilla, intertriginous areas, and flexor and extensor surfaces.<sup>16</sup> Note rash morphology and location, whether it involves extremities (acral vs central), sun-exposed areas, and dermatomes. Examine for involvement of ocular, oropharyngeal, and genital mucosal surfaces (termed enanthem).

Palpation follows visual inspection. Use a gloved hand to palpate whether lesions are flat or raised. The “glass test” provides a window to assess whether lesions blanch with pressure or maintain color as with petechiae (**Fig. 2**).<sup>5</sup> Interrogate vesicles or bullae with a gloved hand, assessing for the Nikolsky sign, in which superficial skin shears easily from underlying layers with lateral pressure, signifying dermal–epidermal junction lysis and higher morbidity.<sup>18</sup>

Providers must maintain a particular awareness of skin of color and its effect on correct diagnosis. Several studies have highlighted the tendency to feature photographs of lighter skin in medical education and dermatology literature.<sup>44,45</sup> Research has demonstrated providers’ difficulty identifying life-threatening pathology such as Rocky Mountain spotted fever (RMSF) and meningococemia in darker-skinned patients.<sup>7,46,47</sup>

### **Laboratory Testing**

Laboratory testing can be used to assess illness severity and evolution and prognosticate patient deterioration and organ failure.<sup>13,41,48,49</sup> Appropriate initial laboratory

Table 3

## Cutaneous manifestations of sexually transmitted infections

STI	Description	Pain/Pruritus	Lymph Nodes
Disseminated gonococcal infection	Very nonspecific, need high index of suspicion based on history. Erythematous, 1–2 mm pustules, fluctuant furuncle-like nodules, indurated abscesses, shallow erosions, indurated ulcers of varying size.	No	Rarely
Syphilis	Primary syphilis: a 1–2 cm ulcer with raised indurated margins called a chancre. Secondary syphilis: can be almost any form so high index of suspicion required but classically a diffuse symmetric macular or papular eruption involving trunk and extremities that does NOT spare the palms and soles. May present as pustular. Atypical presentations common with concomitant AIDS. Tertiary syphilis/individuals with HIV: gummas may present as ulcers or granulomatous lesions with round, irregular, or serpiginous shape.	Usually painless	Firm, nontender, regionally enlarged nodes
Herpes	Multiple small grouped ulcers, erythematous base. Vesicles can be open and form ulcers/erosions that coalesce.	Usually painful	Reactive, painful nodes
Scabies	Multiple small, erythematous papules often excoriated. Distribution is key to diagnosis: interdigital spaces, skinfolds including wrists, elbows, axilla, waist, knee, buttocks.	Pruritic	Uncommon
Primary HIV	Erythematous maculopapular eruption, over the trunk, collar, face and sometimes the palms and soles. May become confluent. May include oral/genital lesions.	Unusual	Nontender adenopathy often present
Mpox	Progresses through stages. Macules to papules, vesicles, then umbilicated pseudo-pustules (so named due to containing cell debris rather than pus or fluid). Eventually crust and fall off. Found in anogenital, perioral areas as well as sometimes acral/truncal.	Often painful and pruritic	Uncommon

Cutaneous manifestations of common sexually transmitted infection.

Data from Refs.<sup>25,26,28–31</sup>

Table 4 Emergent noninfectious causes of fever and rash		
Name	Pathophysiology	Rash Morphology
DRESS	T-cell-mediated hypersensitivity reaction generally due to an immune response to an offending drug. Incompletely understood.	Maculopapular eruption progressing to a coalescing erythema with purpura, infiltrated plaques, pustules, exfoliative dermatitis, and target-like lesions. Symmetrically distributed on trunk and extremities. Facial edema, mild mucosal involvement present in majority of cases. Skin detachment uncommon.
SJS/TEN	Suggestions of a cell-mediated cytotoxic reaction against keratinocytes both directly and indirectly. Incompletely understood. SJS is a less severe condition (>30%).	Coalescing, erythematous macules with target lesions, <sup>a</sup> blisters, erosions, skin detachment, and severe mucosal involvement in multiple sites of body
Graft-versus-host disease	Immune cells transplanted from a nonidentical donor recognize transplant recipient as foreign, causing an immune reaction in recipient.	First clinical manifestation often maculopapular rash. Involves neck, ears, shoulders, palms of hand, and soles of feet and can spread to whole integument. Classically described as a sunburn, pruritic, and painful. Severe forms involve formation of bullous lesions similar to TEN.
Pemphigus vulgaris	Acantholysis due to binding of autoantibodies to epithelial cell surface antigens due to both genetic and environmental factors.	Mucosal, often oral, blisters which are painful and rupture easily with resultant bleeding. Nikolsky sign positive.
Erythema multiforme	Cell-mediated immune process against pathogen (viral [often HSV]/drug) antigens deposited in skin. Generally transient condition. Incompletely understood.	Cutaneous lesions in a symmetric distribution on extensor surfaces of extremities, spreads centripetally. Classically target lesions: a dusky central area or blister with a pale ring of edema and finally an erythematous halo on periphery of lesion. Can involve mucosa.
Kawasaki disease	Likely inflammatory cell infiltration into vascular tissues often triggered by transmissible agents. Incompletely understood.	1 of 5 diagnostic criteria are a polymorphous rash. Begins as perineal erythema and desquamation, then macular, morbilliform lesions of trunk and extremities. Children can develop diffuse erythema of palms/soles.

Fatal and emergent noninfectious etiologies of fever and rash.

*Abbreviations:* DRESS, drug reaction eosinophilia and systemic symptoms, HSV, herpes simplex virus; SJS, Stevens–Johnson syndrome, TEN, toxic epidermal necrolysis, GVHD, graft versus host disease.

<sup>a</sup> See erythema multiforme for description.

Data from Refs.<sup>35–39</sup>



**Fig. 2.** An example of the glass test, which can be used to identify petechiae. Current image from a patient with meningococemia. ([https://doi.org/10.1016/S0140-6736\(07\)61016-2](https://doi.org/10.1016/S0140-6736(07)61016-2) Reprinted with permission from Elsevier. *The Lancet*, 2007;369(9580):2196-2210.)

studies include complete blood count (CBC) with differential, CMP, erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP), coagulation studies, and creatine kinase (CK). Troponin, kidney function and liver function tests, and indicators of disseminated intravascular coagulation (DIC), can indicate organ system failure and coagulation disruption.

While laboratory tests and infectious etiologic testing can help establish diagnosis and prognosis, they should not delay expeditious antibiotic treatment when indicated. Rapid treatment has been associated with improved outcomes and decreased mortality in many infections that present with rash.<sup>7,50</sup> While blood, urine, and body fluid Gram stain and cultures should be obtained, providers must recognize their sensitivity may be limited, particularly in toxin-mediated exanthem.<sup>6,17,41,51,52</sup> Polymerase chain reaction (PCR) viral testing offers high sensitivity and specificity for viral etiologies, though it may take days to return.<sup>43,53,54</sup> On occasion, skin biopsy of lesions or petechiae may reveal dermal bacterial invasion.<sup>55,56</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for fever and rash is intimidatingly long, encompassing the entire gamut of infectious, toxic, metabolic, vascular, and autoimmune pathology. Within this long differential are several life-threatening but noninfectious causes, which must always be considered given their potential high mortality, worsened by diagnostic delay (see **Table 4**).<sup>35–39</sup> While this article focuses specifically on rapidly progressive infections, it is important to recognize the numerous indolent but important infections that manifest with fever and rash (**Table 5**).<sup>57,58</sup>

## ROCKY MOUNTAIN SPOTTED FEVER

### *Epidemiology, Transmission, and Pathophysiology*

First identified in 1896 in Western Montana, RMSF is the most common rickettsial illness in the United States with an incidence of 8.9 per million cases.<sup>4,21,59</sup> Since 2000, RMSF has increased in incidence, peaking in 2017.<sup>21</sup> This increase is in part due to change in nomenclature and creation of the larger, generally less fatal spotted fever group rickettsiosis (SFG) categorization. The case fatality rate for confirmed RMSF, however, remains high at 5% to 10%.<sup>21</sup> This is higher for specific populations, including children, which comprise two-thirds of total cases, Latino, and Native American populations.<sup>4,60–62</sup>

Disease	Incubation Period
Syphilis	9–90 d
Blastomyces	30–45 d
Coccidioides	7–21 d
Disseminated gonococcal infection	7 d to mo
Epstein–Barr virus (EBV)	30–50 d
Human immunodeficiency virus (HIV)	28–180 d
Infective endocarditis	7–90 d

General time course of indolent causes of fever and rash.

From Sanders CVN, L.T. The Skin and Infection: A Color Atlas and Text. Williams & Wilkins; 1995:325; and N'Guyen Y, Duval X, Revest M, et al. Time interval between infective endocarditis first symptoms and diagnosis: relationship to infective endocarditis characteristics, microorganisms and prognosis. *Ann Med.* Mar 2017;49(2):117-125. <https://doi.org/10.1080/07853890.2016.1235282>.

While RMSF occurs throughout the United States, 60% of cases occur in the South-east.<sup>21</sup> RMSF is transmitted predominantly through *Dermacentor variabilis* and *Dermacentor andersoni* ticks. It is highly seasonal, with 90% of cases occurring between April and September, when up to 3% of ticks can be infected in endemic areas.<sup>4</sup> However, with recent identification of *Rhipicephalus sanguineus* as a potential vector in the Southwestern United States and Central America, infections have been increasingly observed throughout the year in these regions.<sup>61,63</sup>

RMSF is caused by the spirochete *Rickettsia rickettsii*, an obligate, intracellular, gram-negative spirochete. Ticks act as the primary vector with humans an incidental host.<sup>21</sup> Upon initiating feeding, ticks can transmit rickettsial species within 4 to 6 hours of attachment. Transmission can also occur through tick fluids, feces, and handling of crushed tissue.<sup>4,21,64</sup> The spirochete has a tropism for endothelial capillary cells, which spreads centripetally from the inoculation site, causing direct cellular damage and subsequent vascular injury and endothelial permeability.<sup>65</sup>

### **Signs and Symptoms**

The RMSF initial incubation period ranges from 3 to 12 days, followed by fever, headache, myalgias, conjunctival injection, and photophobia. Fever is a hallmark symptom, present in 80% to 94% of patients, and included in the Centers for Disease Control and Prevention (CDC) case definition.<sup>4,21,63,66</sup> Abrupt illness onset and headache are classically described. In a report on American tribal land outbreaks, a myriad of nonspecific symptoms were also observed, potentially leading to confusion with other viral illnesses.<sup>63</sup> Children are more likely to present with initial abdominal pain and periorbital edema.<sup>14,21,67</sup> Other manifestations include meningitis, myocarditis, pneumonitis, muscle necrosis, rhabdomyolysis, and kidney injury.<sup>21</sup>

### **Rash in Rocky Mountain Spotted Fever**

RMSF produces a generalized rash in up to 95% of patients. In the classic presentation, which may occur in only 58%, rash appears 2 to 5 days after fever onset as a blanching, several millimeter macular rash on the wrist and ankles, and can also include the palms and soles.<sup>4,42,65,66</sup> Other peripheral sites of rash presentation have been described.<sup>4,42,67</sup> The rash then travels centripetally toward the neck, torso, and back. It may take on a papular appearance, with subsequent central petechia as endothelial dysfunction

commences (Fig. 3). By day 5 to 6, the rash develops a petechial predominance, echoing further endothelial dysfunction and coagulation cascade disturbance, with purpura fulminans in the end stages.<sup>4,64</sup> Microvascular thrombosis depletes coagulation factors and consumes platelets, leading to tissue necrosis and extremity ischemia.<sup>7,66</sup>

### Diagnosis

Because treatment delay is associated with higher mortality and definitive diagnostic testing may take days to return, RMSF requires a high index of suspicion and low threshold for empirical treatment.<sup>4,21</sup> Misdiagnosis remains high, with up to 75% of patients misdiagnosed on initial physician encounter.<sup>67</sup> The triad of fever, headache, and rash manifests in only 3% of patients by day 3 and must be abandoned as a requisite for ED diagnosis.<sup>4,21</sup> While over 90% of individuals manifest a rash, only 50% produce a characteristic exanthem by day 3.<sup>68</sup> Known tick exposures, found in only 50%, cannot be relied on for diagnosis.<sup>68</sup> Providers must consider geographic location, time of year, and the patient's behavioral risk for tick exposure. In the right epidemiologic setting, a provisional diagnosis of RMSF may be appropriate if there is fever without rash or known tick bite.

Laboratory evaluation has a limited role in initial diagnosis of RMSF, though certain findings may provide important diagnostic clues and assist in gauging severity of disease. Appropriate initial laboratories include CBC, comprehensive metabolic panel (CMP), prothrombin time, International normalized ratio (PT/INR), liver function tests (LFTs), CK, and blood cultures. Thrombocytopenia and hyponatremia with normal white blood cell count (WBC) count has been classically described, though can be absent early in disease.<sup>21,64</sup> If lumbar puncture is performed, cerebrospinal fluid (CSF) can show pleocytosis with lymphocytic predominance, normal glucose, and elevated protein.<sup>21,64</sup>



**Fig. 3.** (A, B) Rocky Mountain spotted fever petechial rash with involvement of palms and soles. (Courtesy of Dr. Amina Ahmed, Professor, Wake Forest University School of Medicine and Atrium Health.)

Formal testing options include enzyme-linked immunoassay (ELISA) and antibody immunoglobulin G, immunoglobulin M (IgG/IgM) testing. These take weeks to return, do not distinguish from other species in the spotted fever group *Rickettsia* (SFGR), and should not delay appropriate treatment.<sup>21</sup>

### **Treatment**

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Immediate treatment with antimicrobials is critical in RMSF. Doxycycline provides effective therapy, reducing mortality from 23% to 6% when given within 5 days of symptom onset.<sup>4,7,21</sup> Early treatment has additionally been associated with reduced risk of permanent neurologic sequelae.<sup>60</sup> Yet rates of delayed doxycycline administration remain high, with studies reporting just 44% of cases being treated by day 5, despite being seen by a physician prior to diagnosis in 90%.<sup>7</sup> Another study found only 35% of physicians would correctly prescribe doxycycline when tested on RMSF clinical scenarios.<sup>69</sup> A primary reason for prescription avoidance is the pervasive myth that doxycycline is contraindicated in children.<sup>70</sup> Association with tooth discoloration has been disproven, and doxycycline therapy is currently recommended by the American Association of Pediatrics for RMSF treatment.<sup>21,71</sup>

### **Prognosis and Prevention**

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Despite improved outcomes with early antibiotic therapy, RMSF mortality remains at 5% to 10%.<sup>21,67</sup> Patients at higher risk for complications include those less than 8 years or more than 40 year old, those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, alcohol use disorder, and Native Americans.<sup>4,63</sup> Currently, no vaccines exist for SFGR, and disease prevention focuses on tick avoidance and protection.<sup>4,21</sup>

## **DENGUE, ZIKA, AND CHIKUNGUNYA**

### **Introduction**

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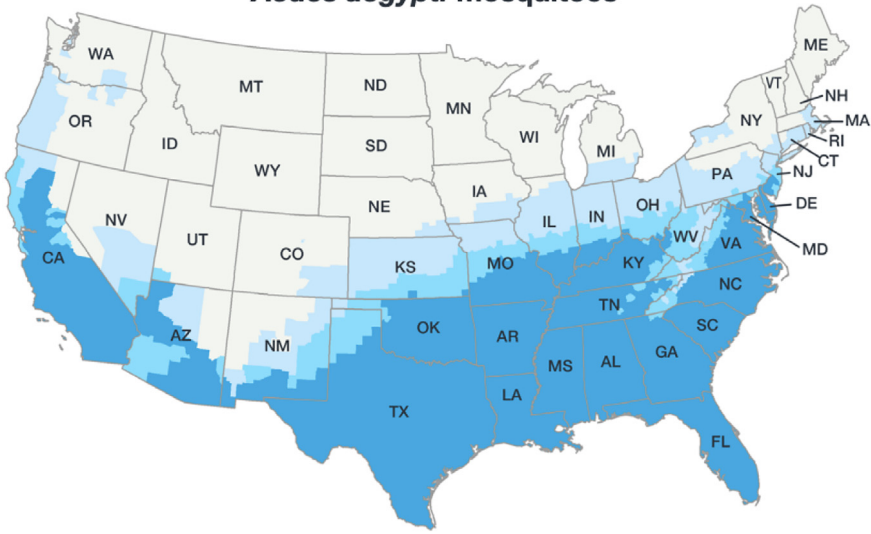
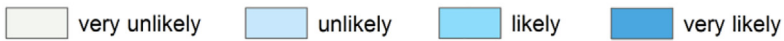
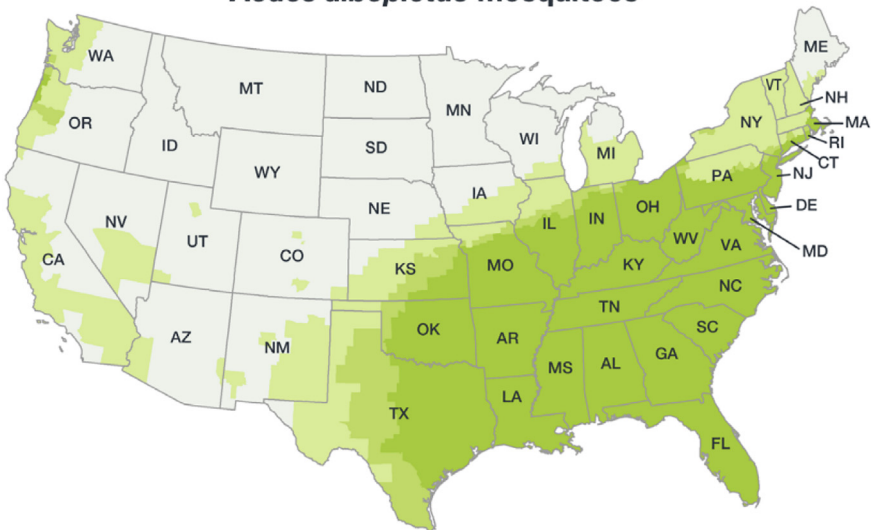
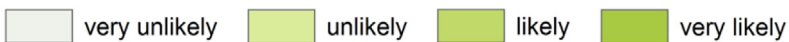
Increased intercontinental travel and globalization have brought novel mosquito-borne illness to the Americas. A trio of viral fevers, dengue, Zika and chikungunya, which constitute a disease triptych, have become the fastest spreading arboviruses of the New World.<sup>13,43,53,72</sup> Initially carried by the mosquito *Aedes aegypti*, these viruses are now found in *Aedes albopictus*, whose tolerance for colder climates has expanded the species' habitat to nearly half of the United States (**Fig. 4**).<sup>43,73–75</sup> Previously seen only in returning travelers, US autochthonous transmission has now been described.<sup>43,53,76–78</sup> The majority of US outbreaks occur in Caribbean and Pacific territories with infection peaks from June to October.<sup>78,79</sup> Since the trio shares the same mosquito vector and the initial clinical presentation of each is almost indistinguishable, the diagnosis of dengue, Zika, and chikungunya should be simultaneously considered (**Table 6**).<sup>54</sup> While only dengue carries a significant risk of mortality in adults, Zika is linked to devastating teratogenicity and chikungunya can lead to debilitating chronic arthropathy.

## **DENGUE**

### **Epidemiology and Transmission**

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With descriptions dating back to the third century, “Breakbone Fever,” or dengue, has become a global hemorrhagic fever responsible for significant mortality.<sup>80,81</sup> Dengue is the most common and fastest growing arbovirus in the world, with up to 100 million cases and 20,000 deaths per year worldwide, and 2.4 million cases in the Americas in 2015.<sup>13,80</sup> A total of 2016 US cases of dengue were reported to the CDC in 2022, the majority in returning travelers, but with autochthonous infection (acquired in the geographic location where the patient lives) in US island territories, Florida, and Arizona.<sup>79</sup>

***Aedes aegypti* mosquitoes****Mosquitoes' ability to live and reproduce*****Aedes albopictus* mosquitoes****Mosquitoes' ability to live and reproduce**

**Fig. 4.** Estimated potential range of *A. aegypti* and *A. albopictus* in the United States, 2017. (<https://www.cdc.gov/zika/pdfs/Zika-mosquito-maps.pdf> ESTIMATED potential range of *Aedes aegypti* and *Aedes albopictus* in the United States, 2017\*. Retrieved from: <https://www.cdc.gov/zika/pdfs/zika-mosquito-maps.pdf>.)

Table 6

## Characteristics of arboviral infections

	Dengue	Zika	Chikungunya
Transmission	Vector: mosquito. Can be vertical/blood-borne. No sexual.	Vector: mosquito. Can be vertical/blood-borne/sexual.	Vector: mosquito. Can be vertical/blood-borne. No sexual.
Symptomatic postinfection?	20% manifesting disease.	20% manifesting disease.	85% manifesting disease.
Incubation	Symptoms 2–7 d postinfection	Symptoms 3–12 d postinfection	Symptoms 1–12 d postinfection, most by day 3
Rash morphology	Maculopapular and morbilliform rash	Generally papular NOT macular rash	Maculopapular rash
Pruritic	Sometimes	Often	Sometimes
Rash distribution	Starts on dorsum of hands and feet, spreads centripetally; 30% with mucosal involvement.	Mostly face, upper limbs, and trunk.	Starts on limbs and trunk, can involve face, may be patchy or diffuse; 25% with mucosal involvement.
Sequelae	Prior infection predisposes to more severe future infection	Severe neonatal teratogenicity if vertical transmission occurs	Chronic postinfectious arthropathy common in 10%–60% of cases. Infection grants lifelong immunity.

General characteristics of mosquito-borne arboviral infections.

From Refs. <sup>12,13,19</sup>

Four serotypes of dengue exist, labeled DENV1-4, all carrying potential for severe disease, and transmitted via the aforementioned *Aedes* mosquito vectors, with potential for vertical and blood-borne transmission.<sup>32,82</sup> Sexual transmission has not been described.<sup>43,79</sup> Most infections remain asymptomatic, with approximately 20% causing symptomatic disease.<sup>32,43,80</sup>

### **Signs and Symptoms**

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Dengue is divided into 3 phases: febrile, critical, and recovery. Febrile phase occurs 2 to 7 days after infection, with high fever, myalgias, headache, nausea, vomiting, and a diffuse maculopapular rash.<sup>80</sup> Dengue critical phase occurs in 5% of febrile phase individuals, usually by day 4 to 5. Critical phase is characterized by diffuse endothelial dysfunction, leading to hypotension from distributive shock, pulmonary edema, ascites, and multiorgan system failure. Concurrent coagulation pathway disruption occurs, leading to hemorrhagic complications.<sup>80</sup> Using preexisting risk factors along with characteristic warning signs, the CDC has developed an algorithm to guide providers in predicting progression to the critical phase (Fig. 5). One such physical examination finding, the tourniquet test, provides an effective method to differentiate dengue from Zika and chikungunya (Fig. 6).<sup>83</sup> Recovery phase manifests as resorption of fluids and normalization of the coagulation pathway. This period may manifest as sudden pulmonary edema and congestive heart failure if IV fluid resuscitation was excessive during critical phase.<sup>80</sup>

### **Rash in Dengue Fever**

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Dengue rash occurs during the febrile phase, between days 2 and 7 of illness, developing in 30% to 80% of cases, and more commonly in young patients.<sup>19,33,84</sup> It is characterized by a pruritic, dense, diffuse maculopapular, or morbilliform rash, described as an “isles of white on a sea of red” appearance (Fig. 7).<sup>19,85</sup> Thirty percent of individuals will display mucosal involvement, including aphthous ulcers, posterior oropharyngeal erythema, and petechiae.<sup>19,84</sup> Patients who progress to the critical phase are more likely to have petechiae, reflecting endothelial dysfunction and coagulation disturbance.<sup>80</sup>

### **Diagnosis**

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The initial provisional diagnosis of dengue, Zika, or chikungunya relies on recognition of typical symptoms and signs in individuals residing in or traveling from an endemic area. Dengue is further identified and risk stratified by the high-risk physical examination and laboratory findings included in the CDC algorithm, which predict progression to the critical phase (see Fig. 5). Characteristic laboratory findings include elevated hematocrit, leukopenia, and thrombocytopenia, with leukopenia being unique to dengue as compared to Zika or chikungunya.<sup>19,80</sup> Increased liver function tests and ferritin have been associated with severe disease.<sup>19</sup>

Definitive diagnostic tests will depend on the time from symptom onset, cost and availability considerations, and the need to also test for Zika. In the first 7 days of symptoms, molecular tests (nucleic acid antigen tests and PCR) are preferred and highly accurate.<sup>48,86</sup> A viral antigen test can also be used in this time period. Beyond 7 days, IgM serologic testing is preferred and can remain positive for months. However, the results can be complicated by previous dengue infection, and false positives may result from other flavivirus infections.<sup>48,80</sup> In most cases, testing for both dengue and Zika is performed together. The CDC has additionally introduced a multiplex PCR assay for all 3 viruses, for use in areas with habitat overlap.<sup>87</sup> Since testing decisions

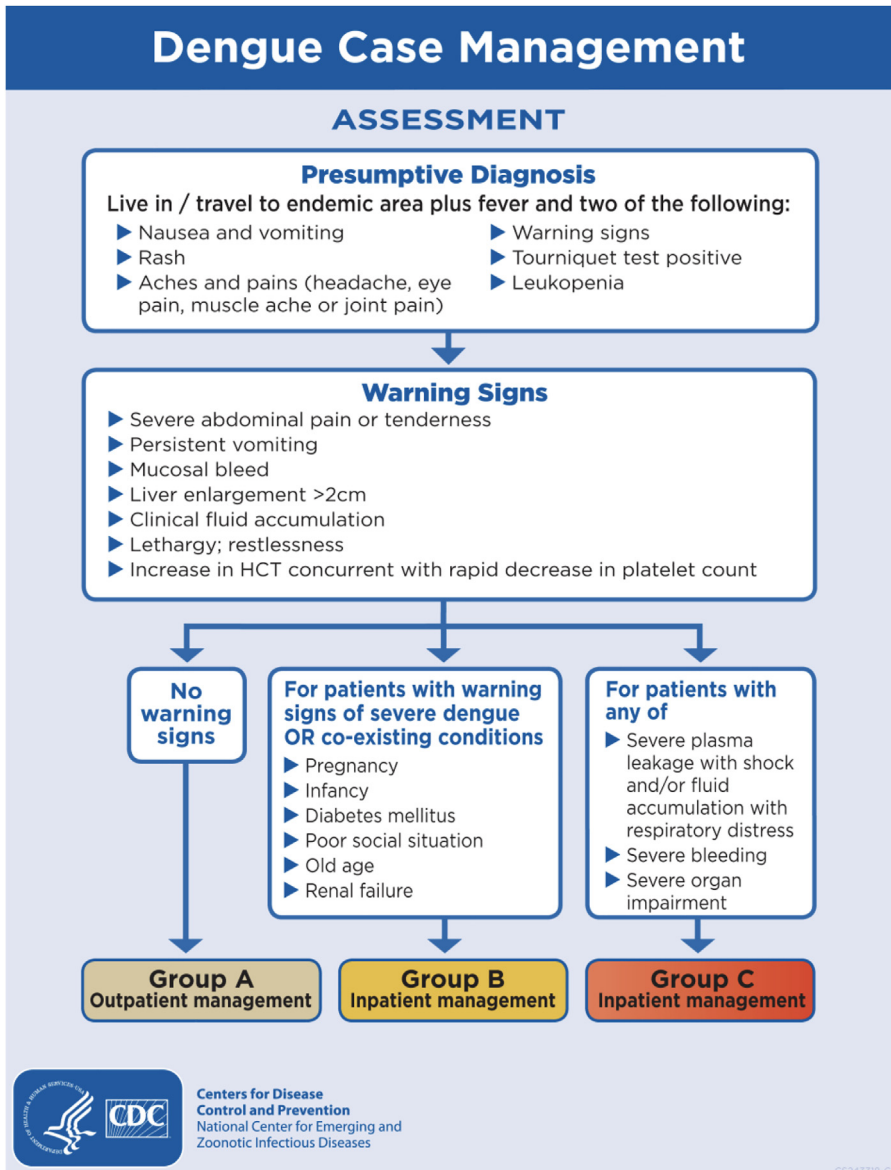


Fig. 5. [http://www.cdc.gov/dengue/resources/DENGUE-clinician-guide\\_508.pdf](http://www.cdc.gov/dengue/resources/DENGUE-clinician-guide_508.pdf) Dengue Case Management. Retrieved from: [https://www.cdc.gov/dengue/resources/DENGUE-clinician-guide\\_508.pdf](https://www.cdc.gov/dengue/resources/DENGUE-clinician-guide_508.pdf).

can be complex, US emergency providers should generally consult an infectious disease or public health officer for assistance.

### ***Treatment, Prognosis, and Prevention***

Dengue treatment remains supportive. Given the potential for dengue-induced coagulation disturbance and thrombocytopenia, non-steroidal anti-inflammatory



**Fig. 6.** The tourniquet test is done by inflating a blood pressure cuff for 5 minutes, halfway between the systolic and diastolic pressures. A petechial rash below the cuff (as seen in the patient's left arm) defines a positive test. Notice the maculopapular, morbilliform rash on the contralateral arm, characteristic of dengue. (Feder HM Jr, Plucinski M, Hoss DM. Dengue with a morbilliform rash and a positive tourniquet test. *JAAD Case Rep.* 2016 Nov 9;2(5):422-423. <https://doi.org/10.1016/j.jdc.2016.07.010>. PMID: 27872891; PMCID: PMC5107725.)

drugs (NSAIDs) should be avoided while dengue fever is being considered.<sup>80,88</sup> Early recognition of warning signs, with appropriate hospitalization and use of intensive care, can reduce mortality from 20% to under 1% in patients proceeding to critical phase. In general, mortality has steadily decreased since 2010.<sup>33,80</sup>

Risk factors for increased mortality include underlying diabetes and hypertension.<sup>33</sup> Prior dengue infection also increases the risk of severe disease and mortality.<sup>80</sup> Termed the dengue antibody-dependent enhancement hypothesis, this phenomena is thought to be due to preexisting antibodies binding new viral particles, causing upregulated phagocytosis and accelerated viral replication,<sup>82</sup> with increased risk of progression to critical phase. A history of prior infection is thus important when considering the need for hospitalization or vaccination.

A CDC and FDA-approved vaccine became available in 2022. Dengvaxia, a tetravalent dengue vaccine for all 4 dengue serotypes, is currently available to children and



**Fig. 7.** "Isles of white on a sea of red" characteristic appearance of morbilliform dengue rash. (Printed, with permission, from: Thomas EA, John M, Kanish B. Mucocutaneous manifestations of dengue fever. *Indian J Dermatol.* 2010;55(1):79-85. <https://doi.org/10.4103/0019-5154.60359>.)

adolescents ages 9 to 16 years who have laboratory-confirmed previous dengue infection and live in dengue-endemic US territories.<sup>86</sup>

## ZIKA

### *Epidemiology and Transmission*

Identified in 1947, Zika remained a sporadic disease in Africa and Asia until sustained transmission was recorded in 2007.<sup>13</sup> After reaching the Americas in 2015, Zika distribution exploded to 89 countries. US cases peaked in 2017 with cases of autochthonous spread described in Florida and Texas.<sup>89–91</sup> Despite its extremely low mortality rate, among pregnant mothers, Zika virus carries a risk of devastating neurocognitive teratogenicity.<sup>92</sup>

Zika virus is predominantly vector-borne, with most US infections occurring in returning travelers from endemic areas.<sup>93</sup> However, sexual transmission in the United States has been described.<sup>13,54,78</sup>

### *Signs and Symptoms*

Like dengue, the majority of Zika infections remain asymptomatic, with only 20% of individuals manifesting disease.<sup>54</sup> The incubation period lasts 3 to 14 days.<sup>13,91</sup> Symptoms are generally nonspecific, including low-grade fever, arthralgias, dysesthesias, conjunctivitis, and rash (**Fig. 8**).<sup>13,94–96</sup>

### *Zika Rash*

A pruritic, generalized, papular rash is the hallmark of Zika infection, occurring in up to 98% of symptomatic patients, and is included in the WHO case definition.<sup>40,91,97,98</sup> Eruption occurs within 48 hours of symptom onset, can last up to 6 days, and may be the only significant symptom.<sup>11,95,99</sup> Areas most frequently affected include the face, upper limbs, and trunk, followed by abdomen and lower limbs, covering on average 45% of total body surface area (**Fig. 9**).<sup>13</sup> Zika rash may involve palms and soles and about one-half exhibit acral edema.<sup>94,95</sup> A dengue-like macular rash with petechiae has been described, but should not result in a positive tourniquet test.<sup>94</sup>



**Fig. 8.** Conjunctivitis in Zika. Notice the associated faint maculopapular facial rash. (Borrowed from Martinez JD, Garza JAC, Cuellar-Barboza A. *Going Viral* 2019: Zika, Chikungunya, and Dengue. *Dermatol Clin.* 2019;37(1):95-105. <https://doi.org/10.1016/j.det.2018.07.008>)



**Fig. 9.** Maculopapular rash in Zika. (Borrowed from Martinez JD, Garza JAC, Cuellar-Barboza A. *Going Viral 2019: Zika, Chikungunya, and Dengue. Dermatol Clin.* 2019;37(1):95-105. <https://doi.org/10.1016/j.det.2018.07.008>.)

### **Diagnosis**

Given its similarity to other arbovirus infections, Zika diagnosis on clinical grounds is difficult. Simultaneous testing for Zika and dengue, and sometimes also for chikungunya, should be undertaken together. Tests and testing strategies are similar as described earlier for dengue. Pregnant patients who may have been infected or with suggestive symptoms should undergo both molecular and serologic testing as soon as possible.

### **Treatment, Prognosis, and Prevention**

Treatment of Zika is supportive. NSAIDs should be avoided until dengue has been ruled out or symptoms resolve. Mortality remains extremely low, well under 1%.<sup>32</sup> The seriousness of Zika virus infection lies primarily in its teratogenicity. The US Zika Pregnancy and Infancy Registry reports a 6.1% rate of brain and eye disorders among infants born to women with laboratory-confirmed Zika. Given that two-thirds of maternal cases report no symptoms, prevention involves a combination of education, avoidance of mosquito exposure, and isolation strategies in individuals desiring pregnancy.<sup>92</sup>

Zika infection in adults carries 2.4/10,000 risk of neurologic sequelae occurring within 6 days of symptom onset, including encephalitis, transverse myelitis, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy.<sup>100</sup> Currently, there are no approved Zika vaccines, though multiple vaccine trials are in progress.<sup>101</sup>

## CHIKUNGUNYA

### *Epidemiology and Transmission*

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Identified in Tanzania in 1953, chikungunya translates to “that which bends up,” describing the arthralgias and chronic arthropathy associated with infection.<sup>102</sup> Like other New World arboviruses, reports of chikungunya were confined to Africa until explosive outbreaks occurred in India and Southeast Asia in the 2000s.<sup>43</sup> Chikungunya reached the Americas in 2013, with 2 million total cases reported from 44 countries in 2020, and an increase in associated mortality reported in 2023.<sup>72</sup> As with dengue and Zika, US autochthonous transmission has recently been described.<sup>43,103</sup>

Infections are predominantly *Aedes* mosquito vector-borne, with occasional cases reported from blood donation.<sup>12,104</sup> Vertical transmission, which carries serious neonatal risk, occurs most frequently at time of delivery.<sup>105</sup>

### *Signs and Symptoms*

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Unlike other arboviruses, infection with chikungunya infection is usually symptomatic, with up to 85% of infected individuals developing symptoms 1 to 12 days after infection and usually by day 3.<sup>12,43,53,74,106</sup> Symptoms include fever, headache, myalgias, and vomiting.<sup>107–109</sup> The hallmark of chikungunya infection is a severe, usually symmetric, polyarthralgia syndrome, which occurs in 80% of patients.<sup>74,107</sup>

The risk of neonatal infection from an acutely infected mother is as high as 50%.<sup>105,106</sup> Infection will manifest 3 to 7 days after birth as neonatal encephalopathy, with eventual cerebral palsy or other neurocognitive sequelae.<sup>110</sup>

### *Rash in Chikungunya*

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Chikungunya rash develops in 25% to 90% of individuals.<sup>43,74,107–109,111</sup> Rash is more common in younger patients, occurring in 100% of infected infants.<sup>112</sup> Typically, it is a fine maculopapular exanthem that appears about 48 hours after fever onset.<sup>108,109,113</sup> It may start at the site of inoculation, followed by generalized spread, eventually covering up to 90% of total body surface area and involving the palms and soles.<sup>43</sup> It is pruritic in 80% of patients.<sup>108,109,113</sup> Twenty-five percent of patients develop perianal, genital, or oral mucosal involvement.<sup>108</sup> Vesiculobullous transformation has been described in infants.<sup>114</sup> Unique to chikungunya is delayed development of a hyperpigmented, predominantly malar rash in the days to weeks after infection.<sup>108</sup>

### *Diagnosis*

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Chikungunya infection remains a largely clinical diagnosis, with laboratories helpful in distinguishing it from dengue and Zika. Lymphopenia has been described, though it is neither sensitive nor specific for diagnosis.<sup>115</sup> Definitive diagnosis is considered less critical than for dengue and Zika, and testing for chikungunya should generally be coupled with dengue and Zika testing. Both molecular and serologic tests for chikungunya are available, including the multiplex PCR test for all 3 arboviruses.<sup>13</sup>

### *Treatment, Prognosis, and Prevention*

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As with dengue and Zika, the initial treatment is supportive, with avoidance of NSAIDs until dengue has been excluded. Most infections are self-limited, ending within 7 to 10 days.<sup>53</sup> While mortality from chikungunya remains under 0.1%, rare cases of myocarditis and encephalitis, with high associated mortality, have been described.<sup>116</sup> However, morbidity from a postinfectious, sometimes chronic arthropathy, can be significant. This occurs in 10% to 60% of cases, more commonly in elderly patients, those with immunosuppression, and diabetes.<sup>117,118</sup> Unlike dengue, chikungunya infection grants lifelong immunity. Several vaccine studies are in Phase III trials as of December 2022.<sup>119</sup>

## STAPHYLOCOCCAL TOXIC SHOCK SYNDROME

### *Introduction, Epidemiology, and Pathophysiology*

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TSS is a rapidly-progressive, toxin-mediated syndrome of hypotension and organ dysfunction caused by *Staphylococcus aureus* and invasive Group A Strep infections. The 2 forms of TSS differ. Streptococcal TSS occurs in the setting of invasive soft tissue infection, pregnancy-related infection, or respiratory infection, often with associated bacteremia, and carries high mortality. Streptococcal TSS rash is uncommon. Staphylococcal TSS has a lower rate of associated bacteremia and lower—albeit significant—mortality and it is distinguished by an erythroderma rash, which may later desquamate.<sup>16</sup> This discussion focuses primarily on staphylococcal TSS.

Staphylococcal TSS was first described in 1978 by Todd and colleagues, and awareness of it increased after cases were described associated with superabsorbent tampon use in the early 1980s.<sup>41,120</sup> Current TSS incidence is 6.65 per million persons, with both streptococcal and staphylococcal cases increasing in recent years.<sup>121,122</sup> Warnings were issued by the CDC in 2022 for streptococcal TSS in Minnesota and Colorado pediatric populations.<sup>122</sup> Risk factors for the disease include female sex, Asian race, and extremes of age (<5 years and >65 years).<sup>121</sup>

*S aureus* infection and subsequent TSS occur after staphylococcal entry through a compromised epidermal or mucosal barrier.<sup>17</sup> Cases have been associated with post-surgical and postpartum wound infections, burns, cutaneous and oropharyngeal abscess, insect bites, implanted prosthetics, breast augmentation, abdominoplasty, and liposuction.<sup>17,123–125</sup> Recurrent TSS has been described.<sup>126,127</sup> Increasing vaginal pH during menstruation and changes in local oxygen and carbon dioxide levels with tampon introduction contribute to menstruation staphylococcal TSS. This form carries a unique risk profile and is separately categorized in case definition as menstruation-associated TSS.<sup>121,128</sup>

In staphylococcal TSS, the production of exotoxins, which act as superantigens, plays an important role in pathogenesis. These exotoxins include staphylococcal toxic shock syndrome toxin-1 (TSST-1) and enterotoxin. These result in direct *t*-cell activation, leading to diffuse cytokine release, further recruitment of immune cells, and a subsequent feedback loop resulting in the syndrome's rapidly progressive capillary leak, hypotension, shock, and multiorgan system failure.<sup>16,129</sup>

### **Signs and Symptoms**

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TSS poses a diagnostic challenge, with initially nonspecific symptoms that can rapidly progress to fulminant disease. Chesney describes a 24 to 48 hour symptom progression with initial high fever and severe myalgias found in all patients, vomiting in 90%, diarrhea in 80%, odynophagia and arthralgias in 83%, with altered mentation in nearly 60%, respectively.<sup>41,126</sup> Symptoms quickly decompensate to distributive shock, tissue ischemia, fulminant liver failure, acute kidney injury, cardiac dysfunction, and average time from symptom onset to mortality is 48 hours.<sup>41,126,130</sup>

### **Rash in Toxic Shock Syndrome**

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The rash of staphylococcal TSS is definitive, found in all patients, incorporated into the CDC case definition, and present as inclusion criteria in most studies.<sup>121,131–133</sup> The rash is described as a diffuse “sunburn” erythroderma, with a fine, confluent macular or scarlatiniform presentation.<sup>10,16,111,126</sup> The rash can have flexural accentuation when involving extremities, may involve the palms and soles, and has a predilection for the trunk in hypotensive patients.<sup>16,111,120</sup> TSS rash presents early in disease onset, usually within 24 hours of illness presentation, and 2 to 4 days in cases associated with

postoperative infections.<sup>17,126,127</sup> Mucosal involvement has been described, though appears later in disease presentation.<sup>41</sup> Tissue desquamation is a late finding in survivors of TSS and should not be used in initial diagnostic criteria.<sup>6,41</sup>

### **Diagnosis**

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Because of potential for rapid progression and significant mortality when treatment is delayed, TSS remains a clinical diagnosis, relying heavily on a history of surgical, menstrual, or other infectious risk factors. Physical examination should include the vagina and other body cavities, searching for a potential infection nidus. Cross-sectional imaging should be considered.

Laboratory testing is used to assess for organ dysfunction and identification of DIC. Associated abnormalities include azotemia, lymphopenia, hypocalcemia, hypoalbuminemia, disruption of coagulation studies, elevated liver function tests, and elevated creatine kinase.<sup>41</sup> The white blood cell count may be normal.<sup>130</sup> In a largely toxin-mediated disease, blood cultures are rarely positive in staphylococcal TSS.<sup>17,41,130,134</sup> Skin and wound cultures may be obtained and can be helpful, but reports have described minimal or no purulent drainage at operative wound sites.<sup>130</sup> The CDC has created diagnostic criteria for TSS, which are used for research and not for initial diagnosis.<sup>135,136</sup>

### **Treatment and Prognosis**

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Considerations in selecting empirical antibiotic therapy include the following: streptococcal and staphylococcal TSS may be difficult to discern early in disease; methicillin-resistant *S aureus* has been implicated in TSS, an agent that reduces toxin production may be beneficial; and most cases will initially warrant treatment for sepsis of unclear cause.<sup>137,138</sup> Given these considerations, the combination of vancomycin, clindamycin, and a broad-spectrum beta-lactam is reasonable.<sup>6,139</sup> Clindamycin and linezolid reduce toxin production within hours of administration, and clindamycin has been associated with improved outcomes in both staphylococcal and invasive streptococcal TSS.<sup>140,141</sup> Meta-analysis suggest that there is mortality benefit with intravenous immunoglobulin (IVIG) administration in streptococcal TSS.<sup>140,142</sup>

Mortality remains high for staphylococcal TSS at approximately 10%.<sup>121,130</sup> Associations with mortality include coagulopathy, significant hepatic dysfunction, elderly age, and respiratory failure.

## **MENINGOCOCCEMIA**

### **Introduction, Epidemiology, Transmission, and Pathophysiology**

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*Neisseria meningitidis*, a gram-negative diplococcus that colonizes human respiratory mucosa, is responsible for invasive meningococcal disease (IMD). IMD manifests primarily as 2 diseases: meningitis and the less common meningococemia, with hematogenous spread resulting in the classic presentation of petechial rash and shock. This discussion will focus primarily on meningococemia, though much of the epidemiology and treatment is similar. With its rapid progression from symptom onset to fulminant disease and high rate of misdiagnosis, meningococemia requires early recognition by emergency providers, followed by immediate antibiotic treatment, resuscitation and supportive care, appropriate patient isolation, and close contact notification.<sup>8</sup>

IMD incidence was 0.11/100,000 cases in the United States in 2020.<sup>143</sup> However, IMD remains a more common cause of epidemic infection in Africa, where rates can reach 1/1000 during peak epidemics.<sup>144</sup> Within the United States, infection occurs

most commonly in the winter months of January to March, disproportionately affecting infants, adolescents age 16 to 23 years, and elderly over 80 years of age.<sup>143,145</sup>

*N meningitidis* colonizes approximately 10% of the human population, which can increase to 25% during active epidemics.<sup>5,146,147</sup> Any social behavior that increases population density increases carriage rate, including the first week of university and annual Hajj Mecca pilgrimage, with rates as high as 71% reported in military dormitories.<sup>148–150</sup> *N meningitidis* is divided into 13 serogroups, categorized by individual polysaccharide characteristics, 6 producing fatal disease.<sup>51</sup> These serogroups are important in geographic and infection trends and population-targeted vaccine campaigns.<sup>51,143</sup> Serogroups B, C, W, and Y are most commonly found in the United States.<sup>143,144</sup>

Transmission occurs through close or intimate contact with carriers through saliva and respiratory secretions, followed by colonization and replication in the upper respiratory mucosa.<sup>22</sup> Factors that increase colonization include dry air, smoking, concurrent upper respiratory tract infections, cocaine, and methamphetamine use.<sup>5,151</sup> Risk factors for progression to disease include waning maternal immunity in infants, genetic complement deficiency or impaired complement formation, and asplenia.<sup>46,148,152</sup> HIV results in a 10-fold increased infection risk.<sup>34</sup>

Many of the devastating manifestations of meningococemia result from lipooligosaccharide endotoxin embedded in the bacterial capsule. Hematogenous spread, rapid bacterial division, activation of host immune cells by the endotoxin, and production of pro-inflammatory cytokines all result in an explosive inflammatory cascade, widespread endothelial dysfunction, and vascular collapse.<sup>153</sup>

### **Signs and Symptoms**

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Time from colonization to disease manifestation takes 1 to 14 days.<sup>22</sup> Initial symptoms that herald the onset of meningococemia are vexingly nonspecific, including fevers, myalgias, headache, and upper respiratory infection symptoms. Young children exhibit a more characteristic early presentation of abdominal pain, leg pain, abnormal skin color, and cold hands and feet.<sup>8,154</sup> The patient can deteriorate within 24 hours, with onset of shock, hemodynamic collapse, and tissue ischemia.<sup>5,155</sup>

### **Meningococemia Rash**

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Rash develops in 28% to 77% of patients with meningococemia and is more common in pediatric patients. Time from symptom onset to rash is 9 to 16 hours, with earlier onset in younger patients.<sup>8</sup> Up to 11% of children presenting to the ED with a nonblanching rash may have meningococemia.<sup>5,156,157</sup> The exanthem begins as faint macules measuring less than 5 mm, evolving within hours to palpable petechiae, which coalesce into purpura, an indicator of poor prognosis (**Fig. 10**).<sup>5,20,47</sup> End-stage cutaneous manifestations include desquamation and purpura fulminans.<sup>5,155</sup> Petechiae are not invariably present, with 15% of cases showing only maculopapular findings.<sup>155</sup> Petechiae may be few, with 71% of patients having less than 12 petechiae on initial presentation, underscoring the need for a thorough head-to-toe skin examination.<sup>155</sup> Petechiae isolated to the distribution of the superior vena cava (upper chest, neck, and face) are negatively associated with meningococemia.<sup>156</sup>

### **Diagnosis**

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Given the short time between symptom onset and shock, the emergency provider must maintain a high index of suspicion for IMD and meningococemia. Unfortunately, only about half of patients with meningococemia are sent to the ED after initial



**Fig. 10.** Subtle violaceous mottling of foot, with early necrosis on dorsum of toe in an infant with meningococemia. (Borrowed from Shanmugavadivel D, Liu JF, Buonsenso D, Davis T, Roland D. Assessing Healthcare Professionals' Identification of Pediatric Dermatologic Conditions in Darker Skin Tones. *Children (Basel)*. 2022 Nov 15;9(11):1749. <https://doi.org/10.3390/children9111749>. PMID: 36421198; PMCID: PMC9688675.)

outpatient physician contact, and median time to hospital admission from symptom onset was 19 hours in one study.<sup>8</sup>

Diagnostic tests can aid in meningococcal identification, particularly laboratory findings indicating DIC (elevated PT, low platelet count, and low fibrinogen) with prolonged PT associated with higher mortality.<sup>157</sup> Blood culture sensitivity ranges from 50% to 92%, depending in part on whether antibiotics were given before cultures were drawn.<sup>144,158</sup> Suspected meningococemia is an instance where administration of empirical antibiotics should precede obtaining blood cultures. Skin biopsy and Gram stain of petechial lesions can aid in diagnosis.<sup>55,56</sup> Meningococcal PCR testing has high sensitivity and is unaffected by antibiotic administration.<sup>159</sup>

### ***Treatment, Prognosis, and Prevention***

Early antibiotic therapy, at the time of first physician encounter, has been repeatedly shown to reduce mortality, with reductions from 80% to 15% with effective antimicrobials.<sup>8,14,144,160</sup> Penicillin and fluoroquinolone-resistant strains of *N meningitidis* have been identified in the United States, and ceftriaxone remains the first-line agent.<sup>143</sup> The early administration of ceftriaxone increases bacterial doubling time, and plasma endotoxin levels drop within 2 hours of antibiotic delivery. However, one-third of patients do not receive antibiotic therapy before laboratory-confirmed diagnosis.<sup>160–162</sup>

Despite significant reductions in mortality through early diagnosis, antibiotic treatment, and vaccination, mortality remains nearly 14%.<sup>5,145,157</sup> The predictors of poor outcome include extremes of age, meningococemia without meningitis, decreased mental status, hypotension, leukopenia, thrombocytopenia, and evidence of DIC. The progression of rash to purpura fulminans imparts poor prognosis.<sup>20</sup>

Chemoprophylaxis is recommended for individuals who have had close contact with the patient from 1 week before symptom onset until 24 hours after antibiotic administration. This includes health care providers with oral secretion exposure (such as performing intubation).<sup>20,51,52</sup> A single dose of oral ciprofloxacin or intramuscular

ceftriaxone reduces the risk of illness by 89% and is most effective when given within 24 hours of identification of a confirmed case.<sup>163</sup>

*N meningitidis* vaccination campaigns have reduced the incidence of IMD worldwide. In the United States, MenACWY vaccines have resulted in a nearly 90% decline in IMD incidence among adolescents since being introduced in 2005.<sup>143,145</sup> In 2014, a MenB vaccine was also introduced. The current CDC guidelines recommend vaccination for adolescents ages 12 to 18 years as well as for certain other high-risk populations, including: military recruits, asplenic patients, HIV-positive patients, or those working with *N meningitidis* in laboratories.<sup>143,145</sup> Recent IMD outbreaks in communities of men who have sex with men in the United States highlight the persistent risk of this infection and the importance of public health surveillance and targeted vaccination in high-risk cohorts as recommended by the CDC.<sup>164</sup>

## CLINICS CARE POINTS

- ED physicians must develop a framework for discerning life-threatening from benign exanthems, which comprise the majority of ED presentations.
- Comprehensive history and physical examination are essential for diagnoses of emergent fever and rash so as to not delay antimicrobial and supportive care.
- Rocky Mountain spotted fever is the most common rickettsial illness in the United States; it is frequently misdiagnosed and doxycycline remains the choice antimicrobial in both adults and pediatrics.
- Dengue, Zika, and chikungunya are now endemic arboviruses to the Americas with similar symptomatic presentation; all 3 must be simultaneously considered with a focus on assessment of dengue given higher risk of mortality. Triple PCR testing exists through the CDC.
- Early antimicrobial coverage is necessary for treatment and reduced mortality for the rapidly progressive staphylococcal TSS; 100% of patients will present with erythroderma.
- Meningococemia poses high risk to targeted populations and areas of concentrated human congregation. Reduced infection rates are successful through vaccination campaigns and early chemoprophylaxis.

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