Rash in the Severely Ill Patient

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INTRODUCTION

Early in the disease process, life-threatening rashes may occur in relatively well-appearing patients. However, these patients may deteriorate rapidly, and early resuscitative measures, including pressure support with central venous access, aggressive respiratory care, and broad-spectrum antibiotic therapy, are crucial. Early recognition of these potentially lethal rashes is facilitated by morphologic classification and refined by serial physical examination.

KEY POINTS

- Identification of rash morphology is paramount for elucidating the differential diagnoses of potentially lethal rashes.
- History taking must include occupation, travel, medications, comorbid conditions, and immune status.
- Complete and serial physical examinations are needed for proper evaluation of any patient with a potentially lethal rash.
- Blood cultures and early antibiotic administration are crucial because most potentially lethal rashes have an infectious cause.
- The clinical manifestations of Rocky Mountain spotted fever and meningococcemia are very similar. With any diagnostic uncertainty, treat for both.
- Petechial and purpuric rashes are marked by high morbidity and mortality.
- Petechiae and fever are very concerning. These patients may decompensate rapidly and require aggressive care.
- Palpable petechiae are due to vasculitides and may have an infectious cause.
- Nonpalpable petechiae are most often associated with thrombocytopenia.
- Hemorrhagic bullae are ominous.
- Patients with toxic epidermal necrolysis and other skin-sloughing diseases desquamate extensively and may require admission to a burn unit.

PATHOPHYSIOLOGY

The pathophysiology of rashes in severely ill patients is broad and depends on the cause. Most of these rashes result from devastating bacterial infections, viral infections, tick bites, drug reactions, vasculitides, or environmental triggers. Many of these diseases also have a high predisposition in those with comorbid conditions.

PRESENTING SIGNS AND SYMPTOMS

HISTORY TAKING

The history is of paramount importance in the diagnosis of a patient with a rash. Of particular concern is an accounting of any recent travel, the patient’s own geographic location, medical and occupational history, animal exposure, and medication regimens. Table 192.1 classifies rashes in severely ill patients by exposure to geographic regions and animals.

PHYSICAL EXAMINATION

At the start it is very important to evaluate the vital signs of toxic-appearing patients with rashes. Fever and hypotension are of particular concern and mandate expedited and intensive care. A complete examination should include evaluation for any new-onset heart murmur, changes in mental status, and nuchal rigidity. Of particular importance are the onset and progression of the rash; involvement of the palms, soles, and mucous membranes; and the age of the patient. An algorithmic approach can aid greatly in the identification of systematically ill patients with a rash. Table 192.2 categorizes rash characteristics in severely ill patients.

PHYSICAL SIGNS

Two signs are important in the evaluation of these rashes, the Nikolsky sign and the Asboe-Hansen sign. A positive Nikolsky sign (Fig. 191.1) is noted when slight rubbing of the skin results in exfoliation of the outermost layer with lateral extension of the erosion into intact skin. The area of denuded skin is pink and tender. The Asboe-Hansen sign (indirect Nikolsky sign or Nikolsky II sign) is extension of a blister into normal skin with the application of light pressure on top of the blister. All patients with tender, blistering, or sloughing skin should be evaluated serially for these important signs.
Differential Diagnosis and Medical Decision Making

Algorithmic Approach to Classification

It is helpful to first define the rash into one of four types: erythematous, maculopapular, vesiculobullous, or petechial/purpuric (see Chapter 191 for more detailed review). Erythematous rashes can then be further classified into those with or without a positive Nikolsky sign. Maculopapular rashes may be subdivided into those with or without target lesions. Vesiculobullous rashes should be differentiated into those with a localized or a diffuse distribution. Petechial/purpuric rashes should be classified into those with palpable or non-palpable rash morphology (Table 192.3).

Erythematous Rashes

Erythematous rashes are characterized by diffuse redness of the skin as a result of capillary congestion. Toxic patients with an erythematous rash may have specific signs that narrow the differential diagnosis. The combination of an erythematous rash in a toxic patient with a positive Nikolsky sign reduces the differential diagnosis substantially, usually to toxic epidermal necrolysis (TEN) in adults and staphylococcal scalded skin syndrome (SSSS).
in infants and young children. Alternatively, the differential diagnosis for toxic and febrile patients with an erythematous rash as well as a negative Nikolsky sign includes toxic shock syndrome (TSS), Kawasaki disease, and erythroderma (see Table 192.3). Table 192.4 details the symptoms, signs, mortality, and treatment of the aforementioned erythematous rashes. SSSS, TSS, and Kawasaki disease are also covered in Chapter 18.

**Table 192.3** Differential Diagnoses of Severely Ill, Febrile/Toxic Patients with a Rash

<table>
<thead>
<tr>
<th>ERYTHEMATOUS</th>
<th>MACULOPAPULAR</th>
<th>VESSEICULOBULLOUS</th>
<th>PETECHIAL/PURPURIC RASH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Nikolsky Sign</strong></td>
<td><strong>Negative Nikolsky Sign</strong></td>
<td><strong>Positive Target Lesions</strong></td>
<td><strong>Negative Target Lesions</strong></td>
</tr>
<tr>
<td>TEN (adults)</td>
<td>TSS</td>
<td>SJS</td>
<td>RMSF</td>
</tr>
<tr>
<td>SSSS (children)</td>
<td>Kawasaki disease (children)</td>
<td>Lyme disease (erythema migrans)</td>
<td>Syphilis</td>
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<tr>
<td>Erythroderma</td>
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DIC, Disseminated intravascular coagulopathy; RMSF, Rocky Mountain spotted fever; SJS, Stevens-Johnson syndrome; SSSS, staphylococcal scalded skin syndrome; TEN, toxic epidermal necrolysis; TSS, toxic shock syndrome; TTP, thrombotic thrombocytopenic purpura

**Table 192.4** Selected Erythematous Rashes

<table>
<thead>
<tr>
<th>TOXIC EPIDERMAL NECROLYSIS</th>
<th>STAPHYLOCOCCAL SCALDED SKIN SYNDROME</th>
<th>TOXIC SHOCK SYNDROME</th>
<th>ERYTHRODERMA (RED MAN SYNDROME)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associations and triggers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfa drugs</td>
<td>Common illness:</td>
<td>Tampon use</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Children</td>
<td>Nasal packing</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Neonates</td>
<td>Surgical wounds</td>
<td>Medications</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Rare in adults:</td>
<td>Postpartum</td>
<td>Cancer</td>
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<tr>
<td>Allopurinol</td>
<td>Chronic illness</td>
<td></td>
<td>Skin disorders</td>
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<tr>
<td></td>
<td>Renal failure</td>
<td></td>
<td>Many drugs</td>
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<td></td>
<td>Immune deficiency</td>
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<td>Heavy metals</td>
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| **Predispositions or increased risk**<sup>2</sup> | | | |
| Women | Children < 5 yr | Recent varicella infection | Generalized erythema |
| HIV infection | Males 2:1 | Soft tissue infections | Scaling, sloughing |
| Head injury patients | | Major surgery | Nail, hair loss |
| Brain tumor patients | | | |
| Lupus patients | | | |

| **Symptoms** | | | |
| Sudden diffuse erythema | Scarlatiniform | Shock | >90% skin exfoliation |
| Toxic appearing | Abrupt fever | Fever | Large tissue loss |
| Tender skin, blistering | Very tender skin | Diffuse erythematosus rash | Fever, chills<sup>1</sup> |
| Skin sloughing | Blisters, sloughing | Desquamation of extremities | Fatigue<sup>2</sup> |
| Significant mucous membrane involvement | No mucous membrane involvement | | Intense pruritis<sup>3</sup> |

| **Clinical signs** | | | |
| Positive Asboe-Hansen sign | Positive Nikolsky sign | Negative Nikolsky sign | Negative Nikolsky sign |

| **Mortality** | | | |
| 30-35% with optimal care | Children (<5%) | 30-70% | 20-40% |
| Adults (50-60%)<sup>4,5</sup> | Secondary to end-organ and multisystem organ damage |

| **Treatment** | | | |
| Stop offending agent | Antibiotics | Remove infective material | Cancer work-up |
| Wound care | Fluid, electrolyte balance | IV antibiotics | Admission |
| Eye care | Wound care | Fluid resuscitation | Fluid, electrolyte balance |
| Fluid, electrolyte balance | ICU admission | ICU admission | Wound care |
| ICU or burn unit | Consider IVIG | | Topical steroids<sup>6</sup> |
| | | | Antihistamines |

HIV, Human immunodeficiency virus; ICU, intensive care unit; IV, intravenous; IVIG, intravenous immune globulin; NSAIDs, nonsteroidal antiinflammatory drugs.
TEN (Lyell disease) is the most serious cutaneous drug reaction. It is most commonly associated with sulfonamides; however, it has other important triggers as well. TEN is manifested as the sudden onset of diffuse erythema with tender skin and blistering. The skin cleavage is full thickness with positive Nikolsky and Asboe-Hansen signs and significant skin sloughing (Fig. 192.1). These patients are toxic and exhibit significant mucous membrane involvement. Symptoms occur first around the eyes, spread caudally (shoulders and upper extremities), and then progress to involve the entire body. Several populations are predisposed to TEN and others are at high risk (see Table 192.4). However, one group deserves expanded mention. It is important to consider that patients infected with human immunodeficiency virus (HIV) who are on a chronic regimen of trimethoprim-sulfamethoxazole prophylaxis and other polypharmacy have a 1000 times greater risk for TEN than do those without HIV.2,7

Staphylococcal Scalded Skin Syndrome
Also known as Ritter disease or dermatitis exfoliativa neonatorum,4 SSSS is manifested as a scarlatiniform, erythematous rash caused by a staphylococcal infection that blisters and sloughs (positive Nikolsky sign). Children younger than 5 years are at highest risk.

Toxic Shock Syndrome
This toxin-mediated staphylococcal or streptococcal infection is historically associated with tampon use, although any staphylococcal or streptococcal source can precipitate TSS. Up to 45% of cases are unrelated to menses. Patients are overtly toxic, febrile, and in shock with a diffuse erythematous rash that eventually leads to desquamation of the hands and feet. The mortality associated with TSS is 30% to 70% and is usually due to multisystem organ failure and end-organ damage. Complications include azotemia, rhabdomyolysis, encephalopathy, thrombocytopenia, and liver dysfunction.

Kawasaki Disease
This childhood illness is also known as mucocutaneous lymph node syndrome or infantile polyarteritis. It is a vasculitis of unknown cause, although infective and autoimmune theories abound. It affects many organ systems, including the skin, mucous membranes, lymph nodes, and blood vessels. Diagnostic criteria include high fever for at least 5 days, diffuse erythoderma of the skin, strawberry tongue, significant cervical lymphadenopathy, conjunctival injection, peeling of the fingers and toes, and edema of the extremities.5 Thrombocytosis may also be present. By far the most serious complication is vasculitis of the coronary arteries, which leads to coronary vessel aneurysms, myocarditis, and myocardial infarction (even in the very young). Treatment consists of high-dose aspirin (given immediately), hospitalization with supportive care, and very importantly, intravenous immune globulin (IVIG) because Kawasaki disease does not respond to antibiotics.8,9

Erythroderma
Erythroderma, also known as exfoliative dermatitis, is an erythematosus, scaling rash that involves more than 90% of the skin.10 Erythroderma is also termed red man syndrome when a primary cause cannot be identified.10 The rash begins as a very generalized erythema. The skin begins to scale and slough, along with nails and hair.11 The skin is inflamed and may lose pigmentation in dark-skinned individuals. This is an overwhelming disease process in which large tissue burdens of exfoliated scales are lost en masse daily; these patients are, in essence, “burn victims.” They have marked increases in skin perfusion and profound temperature dysregulation that result in significant heat loss, increased basal metabolic rate, fluid loss, edema, and hypoalbuminemia.10 Although this disease primarily affects adults, it does occur in younger populations who have other skin or connective tissue disorders (lupus, sarcoid, psoriasis, SSSS, atopic dermatitis, or seborrheic dermatitis). Patients with rapid disease progression usually have a history of cancer or SSSS or an inciting medication reaction. Those with gradual symptomatology generally have a skin disorder history. The work-up for these patients should be conducted in close consultation with a dermatologist, who can aid in identification of the primary lesions, which can be a difficult task. All patients warrant cancer evaluation and treatment of the underlying cause. Laboratory studies include a sedimentation rate, complete blood count, comprehensive metabolic panel, HIV testing, skin scrapings, skin biopsies, and wound cultures.6 All patients warrant admission. In pediatric patients, erythroderma and fever are predictors of hypotension and may reflect TSS.12 Systemic steroids are controversial and may worsen psoriasis and SSSS. Recovery is long and recurrences common in the case of red man syndrome. Mortality ranges from 20% to 40% and in many instances is due to factors unrelated to the disease process itself.3,15

MACULOPAPULAR RASHES
The term maculopapule is a portmanteau of macule and papule. Maculopapular rashes are differentiated according to the distribution of the rash and systemic toxicity (Table 192.5). Patients who appear toxic and febrile have a wide differential; however, it is paramount that patients living in endemic areas be assessed for Lyme disease. Target lesions (see Fig. 191.4) are pathognomonic for Stevens-Johnson Syndrome (SJS) and erythema multiforme (EM). Refer to Chapter 191 for review of EM. A full discussion of
TEN was presented in the previous section (erythematous rashes); however, TEN and Lyme disease may also be associated with target lesions. Toxic patients with a maculopapular rash but no target lesions require emergency evaluation for Rocky Mountain spotted fever (RMSF), syphilis, and meningococcemia (see Table 192.3).

**Stevens-Johnson Syndrome**

SJS is often a drug reaction, although infections and malignancies have been implicated. Previously, SJS was thought to be linked with EM, but it has recently been reclassified on the spectrum with TEN. These patients have diffusely distributed target lesions that include the palms and soles. Significant mucous membrane involvement is present as well (Fig. 192.2). Patients with SJS are toxic with many constitutional symptoms. Treatment involves discontinuation of the offending agent and optimization of fluid and electrolyte status. Steroid treatment is controversial. Both SJS and TEN have greater mortality (10% and 30%, respectively) than do EM major (mortality less than 5%) and minor (negligible morbidity and mortality). Patients with SJS require intensive care unit (ICU) admission.

**Lyme Disease**

This tick-borne illness is caused by *Borrelia burgdorferi*. The patient generally has erythema migrans (a large annular target lesion with a dark red border and central clearing) at the site of the tick bite (Fig. 192.3). The rash begins with tick inoculation and may therefore be central or peripheral in location. As the infection spreads hematogenously over a period of days to weeks, the patient may experience a variety of systemic symptoms, including a secondary rash (annular lesions), fever, meningitis, atrioventricular nodal block, migratory arthralgias, and myalgias. Neuritis occurs as well and is often manifested as Bell palsy (which may be bilateral); however, any nerve can be affected. The diagnosis is made clinically, although biopsy of the site of the tick bite is often diagnostic. Serologic tests are positive after several weeks but do not differentiate active from inactive infection. Though rarely lethal, Lyme disease can be accompanied by significant morbidity, usually related to neurologic and rheumatic complications. Doxycycline is first-line treatment in nonpregnant adult patients. Children may be treated with amoxicillin. Ceftriaxone is indicated for those with significant neurologic or cardiac involvement.

<table>
<thead>
<tr>
<th>Table 192.5 Maculopapular Rashes</th>
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</thead>
<tbody>
<tr>
<td><strong>ROCKY MOUNTAIN SPOTTED FEVER</strong></td>
</tr>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Clinical signs</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
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AV, Atrioventricular; CV, cerebrovascular; GI, gastrointestinal; HIV, human immunodeficiency virus.
Annular erythema migrans spreading centrifugally.

- Rocky Mountain Spotted Fever

This tick-borne illness (*Rickettsia rickettsii*) has been recorded from Canada to Mexico and in every mainland state in the union except Vermont and Maine. Although history taking is essential, only 50% can recall a tick bite. The RMSF-associated erythematous, maculopapular rash begins on the wrists and ankles and spreads over the entire body (including the palms and soles). In its early stage the rash consists of reddish macules that blanch, only to become petechial and purpuric later. In up to 20% of patients, the rash is absent (spotless fever). Regardless of whether the rash is present, these patients are highly febrile and toxic. The diagnosis is clinical! Do not await confirmatory antibody tests to begin treatment (they will be negative in the acute period). These patients may appear to have meningococcemia. If the clinician is unsure of the diagnosis, it is essential to treat for both diseases. Lumbar puncture in a patient with RMSF will show leukocytosis with 25% neutrophils, elevated protein, and low to normal glucose. If not recognized and treated early, the mortality associated with RMFS is higher than 30%. However, mortality decreases to 5% with prompt appropriate antibiotic therapy. The neurologic deficits are permanent in 15% of cases. Doxycycline is the drug of choice in all nonpregnant patients, even children. Pregnant patients may be treated with chloramphenicol, although doxycycline may also be considered in especially sick pregnant patients because chloramphenicol simply does not work as well.

- Secondary Syphilis

Syphilis is an infection caused by the spirochete *Treponema pallidum*. Primary syphilis is characterized by a painless chancre (punched-out base with rolled edges). It resolves completely and without scar formation in about 3 to 6 weeks. Secondary syphilis develops about 4 to 10 weeks after emergence of the chancre. The patient will have many constitutional symptoms: malaise, headache, sore throat, fever, joint and muscle aches, decreased oral intake, meningial symptoms, generalized lymphadenopathy, and a rash. The rash of secondary syphilis is maculopapular, symmetric, nonpruritic, and diffuse. It may also involve the palms and soles, as well as the oral mucosa. Patients may also have other skin findings, including condylomata lata (painless, gray to white verrucous lesions in the groin and other moist regions) and patchy alopecia. These patients can become very ill, with gastrointestinal distress, hepatitis, arthritis, optic neuritis, proctitis, and nephropathy. The diagnosis is made clinically, and a high index of suspicion is required. Testing for HIV is also recommended. The sensitivity of the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests approaches 100% for secondary syphilis. Because false-positive testing does occur, confirmatory fluorescent treponemal antibody absorption testing (FTA-ABS) is also performed. The sensitivity of FTA-ABS for secondary syphilis also approaches 100%. Treatment consists of intramuscular administration of penicillin G for all patients. Bicillin LA is preferred over Bicillin CR due to increased concentrations of benzathine penicillin G. Penicillin G is also the only treatment for pregnant women. Pregnant patients with allergies should undergo desensitization and then treatment with penicillin. Nonpregnant patients allergic to penicillin may be treated with doxycycline.

- Meningococcemia

Meningococcemia is caused by infection with *Neisseria meningitidis*, a gram-negative intracellular diplococci that causes fulminant septicemia and has a predilection for adolescents and children younger than 4 years. Without proper treatment, meningococcemia is invariably fatal; mortality remains at 10% to 20% even with immediate therapy. Patients are ill appearing, febrile, and in shock and have changes in mental status and a rash that develops within 24 hours of toxicity. The rash is initially erythematous and maculopapular (beginning on the wrists and ankles) and then spreads (sparing the palms and soles) and becomes a petechial vasculitis that is palpable. Early in the illness, meningococcemia can be mistaken for RMSF. Treatment of both is mandatory when there is any diagnostic uncertainty. The diagnosis is confirmed by Gram stain and blood or CSF culture. Gram staining of a specimen from a meningococcal skin lesion is more sensitive than a CSF Gram stain (72% versus 22%, respectively). Lumbar puncture in patients with meningitis will show leukocytosis with a predominance of neutrophils, low glucose, and high protein. Complications include disseminated intravascular coagulopathy (DIC), acute respiratory distress syndrome, renal failure, multisystem organ failure, and adrenal hemorrhage (Waterhouse-Friderichsen syndrome). Ceftriaxone is first-line therapy. Vancomycin should be added in cases of diagnostic uncertainty to cover resistant streptococcal meningitis. Dexamethasone has been shown to reduce neurologic sequelae if administered early (before antibiotics, if possible). Rifampin prophylaxis for close contacts is recommended; alternatives include single-dose ciprofloxacin and intramuscular ceftriaxone. A vaccine is available and is now recommended routinely for children 11 to 18 years of age.
Meningococcal purpura fulminans involves the sudden onset of fever, severe headache, nausea, malaise, and meningococcal meningitis. It results in a silent viremia for 2 weeks, followed by the carrier state. It is spread by inhalation or direct contact. Infected individuals may not have symptoms, and the disease is most common in children, pneumonia (most common in adults), and perinatal varicella (30% mortality rate).

Smallpox

Smallpox (varicella-zoster virus or herpesvirus 3) is usually a benign, self-limited infection with an incubation period of 10 to 21 days. Infectivity is present 48 hours before the onset of fever and continues until all lesions have crusted. Symptoms include conjunctival and catarrhal manifestations followed by a rash. The rash appears in various stages at same time (papules, vesicles, crusted) and is described historically as "dew drops on a rose petal." Children should not be given aspirin for fever because of concerns related to Reye syndrome. All patients should avoid those who are pregnant, elderly, or immunocompromised. Complications from smallpox include staphylococcal or streptococcal secondary infections, visceral complications (15% mortality rate in the immunocompromised), neurologic complications (most common in children), pneumonia (most common in adults), and perinatal varicella (30% mortality rate). Prevention involves immunization, which decreases the rate of occurrence and severity. Please refer to Chapter 18 for further review of varicella.

Smallpox

Few differential considerations invoke more fear or dread than smallpox. Although smallpox was eradicated in 1980, isolates still exist in the United States and Russia. Moreover, nearly 50% of the U.S. population has never been vaccinated against smallpox. Infection by the variola virus is manifested in two forms (major and minor), and only humans are infected (no carrier state). It is spread by inhalation or direct contact. Infection results in a silent viremia for 2 weeks, followed by the sudden onset of fever, severe headache, nausea, malaise, and a sore throat. During this time an enanthem that is fine, erythematous, and macular may be found on the posterior pharynx, soft palate, and tongue. It is followed by the enanthem, which begins on the face and spreads centrifugally to encompass the entire body (including the palms and soles in 50%) within 24 hours. These lesions start as macules, then papules, and finally pustules that crust over in several weeks. The lesions are always in the same stage of development. Any suspected cases should be reported to the Centers for Disease Control and Prevention at once. Vaccinated personnel should obtain viral swabs of the patient’s throat or pustular skin lesions. Strict respiratory and contact isolation is mandatory. Supportive care with attention to eye care (keratitis) is indicated. The mortality rate positively correlates with the extent of the rash (10% to 80%; mean, 30%). Death usually occurs as a result of overwhelming toxemia. Complications include blindness and diffuse scarring.

Purpura Fulminans/Disseminated Intravascular Coagulopathy

This acutely life-threatening disorder is associated with previous infection (often meningococcus or gram-negative organisms), sepsis, pregnancy, massive trauma, end-stage malignant disease, hepatic failure, snake bites, transfusion reactions, or anything that can precipitate DIC. It is characterized by fever, shock, rapid subcutaneous hemorrhage (echymotic purpura, hemorrhagic bullae), tissue necrosis, widespread petechiae, bleeding from multiple sites, widespread organ failure, and DIC (Fig. 192.4). The pathophysiology of this disease spectrum involves activation of the coagulation cascade with thrombin and fibrin formation. This leads to occlusion of vessels and end-organ damage with the consumption of platelets and clotting factors. Overactivation of the fibrinolytic system then occurs with resultant endogenous fibrinopeptide A production and bleeding. Laboratory findings include thrombocytopenia, schistocytes, prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT), increases in fibrin degradation products and D-dimer levels, and a decrease in fibrinogen levels. The lower the fibrinogen levels, the higher the mortality. Emergency hematology/
PETECHIAL/PURPURIC RASHES

These rashes can be especially challenging and are associated with devastating differential diagnoses. However, an algorithmic approach can help the physician narrow the diagnosis with confidence (see Table 192.3). It is helpful to determine early whether the rash is palpable or nonpalpable. Palpable (raised) purpura occurs in vasculitic diseases secondary to inflammation or infection. In toxic and febrile patients with palpable petechial/purpuric lesions, the differential diagnoses include RMSF, endocarditis, and meningococcemia. Non-palpable purpura (flat, subcutaneous hemorrhages) occurs in thrombocytopenic conditions. Toxic and febrile patients with petechiae or purpura but without palpable lesions may have purpura fulminans/DIC or thrombotic thrombocytopenic purpura (TTP).

Bacteremic Endocarditis

Endocarditis is a systemic infectious process caused most commonly by Streptococcus viridans, coagulase-negative staphylococci, and S. aureus. Patients with endocarditis have various constitutional symptoms that mimic other diseases (tuberculosis, heart failure, and malignancy). Early in its course, patients may not appear to be toxic. However, the symptoms progress to fever, new cardiac murmurs, weakness, anemia, fatigue, malaise, weight loss, and rash. Risk factors include valvular disorders, intravenous drug use, immunodeficiency, dialysis, poor dental hygiene, and chronic in-dwelling vascular access. Associated skin findings are pathognomonic and include petechiae (most common finding and may involve the eyelids and conjunctiva), Roth spots (exudative, edematous hemorrhagic retinal septic emboli), splinter hemorrhages, Janeway lesions (macular erythematous or hemorrhagic spots on the palms and soles), and Osler nodes (painful, violaceous nodules on the pulp pads of finger and toes). The diagnosis is confirmed with transesophageal echocardiography and by identification of valvular vegetations. Treatment consists of broad-spectrum antibiotics to cover methicillin-resistant S. aureus (MRSA) and, thereafter, guidance by culture of blood (three sets) obtained before antibiotic therapy. Endocarditis is associated with significant morbidity; mortality is 25% to 40% for S. aureus endocarditis and 19% for S. viridans endocarditis.

Thrombotic Thrombocytopenic Purpura

Patients with TTP have fever, jaundice, and a diffuse, nonpalpable petechial/purpuric rash in a distinct manifestation. The classic pentad of symptoms includes fever, thrombocytopenia, hemolytic anemia, neurologic deficits, and renal failure. It is more common, however, to observe the clinical triad of thrombocytopenia, hemolytic anemia, and elevated lactate dehydrogenase. This triad of findings alone is sufficient for the diagnosis and initiation of treatment. Numerous conditions are associated with TTP, including HIV infection, lupus, pregnancy, malignancy, and transplantation. Drugs associated with TTP include clopidogrel, cyclosporine, and quinine. Laboratory studies reveal that unlike DIC, the PT, PTT, and fibrin level are often normal. Schistocytes and helmets cells are seen on blood smears and indicate hemolysis. The pathophysiology of TTP involves platelet aggregation and thrombus formation with diffuse organ and tissue damage. Treatment includes emergency hematology/oncology consultation, plasmapheresis, FFP, ICU admission, and treatment of the underlying cause. Importantly, FFP can be used as a temporizing measure, but patients with TTP should be transferred to a facility with the capability of performing plasmapheresis. Platelet administration is to be avoided because it will precipitate more thrombus formation. The mortality associated with TTP is higher than 90% if not properly treated. Exchange transfusion can decrease the mortality to 10%. Facilities without the ability to perform exchange transfusions must consider emergency transfer to an appropriate facility.

TREATMENT

ERYTHEMATOUS RASHES

Treatment of these rashes can be found in Table 192.4. These highly lethal rashes require intensive treatment and continuous monitoring for complications. Patients with TEN may benefit from IVIG, although this indication is not yet approved by the FDA. Most physicians recommend against steroid use. Sulfadiazine should not be used on the wounds because sulfis is the most common offending agent. Treatment of SSSS in young, well-appearing patients with minimal skin sloughing may be conducted on an outpatient basis (mortality < 5%). By contrast, adult SSSS has a mortality that can be as high as 60%. Treatment of Kawasaki disease involves hospitalization, supportive care, and immediate high-dose aspirin to prevent coronary artery vasculitis, coronary vessel aneurysms, myocarditis, and myocardial infarction. Importantly, IVIG must be administered because Kawasaki disease does not respond to antibiotics. Treatment of erythroderma involves recognition that recovery is long and recurrences common.

MACULOPAPULAR RASHES

Treatment of these rashes can be found in Table 192.5. Though rarely lethal, Lyme disease can be associated with significant morbidity, usually related to neurologic and rheumatic complications. Doxycycline is the first-line treatment of Lyme disease in nonpregnant adult patients. Children may be treated with amoxicillin. Ceftriaxone is indicated for those with significant neurologic or cardiac involvement. Treatment of RMSF consists of doxycycline. It is the drug of choice in all nonpregnant patients, even children. Pregnant patients may be treated with chloramphenicol, although doxycycline may also be considered in especially sick pregnant patients because chloramphenicol simply does not work as well.
cases of diagnostic uncertainty to cover resistant streptococcal meningitis. Dexamethasone reduces neurologic sequelae if administered early.

**VESSELCULOBULLOUS RASHES**

Treatment of necrotizing fasciitis involves prompt surgical débridement, broad-spectrum antibiotics, and fluid resuscitation. Adjunctive hyperbaric oxygen therapy significantly reduces mortality and amputation rates. Varicella is a self-limited illness in most patients, although complications can be devastating. Treatment of varicella is reviewed in Chapter 18. Smallpox is a devastating illness whose care is primarily supportive, with attention to eye care for keratitis. Death usually occurs as a result of overwhelming toxemia. In a similar manner, purpura fulminans is a disease with high morbidity and mortality. First-line therapy involves treatment of the underlying cause and administration of blood products (FFP, cryoprecipitate, platelets, and red blood cells). Folate, vitamin K, and heparin are also given. Antithrombin III is a promising investigational drug that has not yet been approved by the FDA. A metaanalysis of trials showed a reduction in mortality from 47% to 32% with the administration of antithrombin. Hematologist consultation is essential.

**PETECHIAL/PURPURIC RASHES**

Treatment of RMSF, meningococcemia, and purpura fulminans was discussed in a previous section. Bacterial endocarditis is a disease that requires consultation with cardiology and infectious disease specialists. Treatment consists of broad-spectrum antibiotics to cover MRSA and, thereafter, guidance by culture of blood (three sets) obtained before antibiotic therapy. Treatment of TTP includes ICU admission, emergency hematologic consultation, plasmapheresis, FFP, and treatment of the underlying cause. Importantly, FFP is only a temporizing measure. Patients must be treated definitively with plasmapheresis (exchange transfusion) or be transferred. Platelet administration will precipitate more thrombus formation.

**FOLLOW-UP AND PATIENT EDUCATION**

Most of these illnesses are devastating with significant morbidity and mortality. Invariably, most patients will require close follow-up not only with their primary care provider (PCP) but also with infectious disease specialists, dermatologists, and cardiologists, and some will require surgical interventions.

**ERYTHEMATOUS RASHES**

Patients with TEN require primary care follow-up, wound care, and dermatologic referral. Ophthalmologic consultation is needed for eye involvement. Those infected with HIV also require infectious disease follow-up. Patients with SSSS require PCP follow-up, as well as wound care and referral for any evidence of end-organ damage. Patients recovering from TSS require wound care and PCP monitoring during recovery and surveillance for end-organ damage. Recovery from Kawasaki disease requires PCP follow-up and cardiology referral. Patients with erythroderma require PCP follow-up, dermatologic referral, and wound care. Recovery is long for these patients, and recurrences are common.

**MACULOPAPULAR RASHES**

Patients recovering from SJS require PCP and dermatologic follow-up. Significant mortality and morbidity are associated with SJS, and monitoring for end-organ damage is required. Patients discharged with a diagnosis of either Lyme disease, RMSF, syphilis, or meningococcemia require close PCP follow-up, as well as continued monitoring by an infectious disease specialist.

**VESSELCULOBULLOUS RASHES**

Patients with necrotizing fasciitis require continued surgical monitoring, wound care, and possibly adjunctive hyperbaric oxygen therapy. Those in whom varicella is diagnosed require PCP follow-up and wound care as needed. Those with smallpox will require management by an infectious disease physician. Patients with purpura fulminans need continuous, close monitoring with a PCP and a hematologist.

**TIPS AND TRICKS**

Drug reactions: Stop the offending agent and all related compounds at once. This will reduce the risk for death by 30% daily!

Toxic epidermal necrolysis and Stevens-Johnson syndrome: Usually caused by drugs.

Endocarditis, meningococcemia, and Rocky Mountain spotted fever: May be manifested as either a maculopapular (early) or petechial/purpuric rash (late) morphology. Serial examinations are mandatory!

Meningitis: The gold standard for diagnosis is cerebrospinal fluid analysis.

Meningitis prophylaxis: Should be given to close contacts, including classmates, household members, and medical personnel who had contact with respiratory droplets.

Rocky Mountain spotted fever: Doxycycline is the drug of choice, even in children. Pregnant patients may be treated with chloramphenicol, but doxycycline should be considered if the patient is especially ill.

Meningitis versus Rocky Mountain spotted fever: If the diagnosis is not clear, treat both!

Streptococcal toxic shock syndrome: 80% have an associated skin or soft tissue infection. Look for it early because drainage is a critical component of treatment.

Necrotizing fasciitis: Pain out of proportion to findings on examination. Always complete a full genitourinary examination on all ill-appearing patients because many are too toxic to adequately relate symptoms.

Fingers and toes: Must be evaluated for signs of endocarditis (Janeway lesions, Osler nodes, splinter hemorrhages).

Tissue samples: Can be of immense value in certain instances. Tzanck smears are sensitive for herpes infections. Potassium hydroxide preparations can identify yeast infections. Gram stains will identify gonococci and anthrax organisms. Punch biopsies with a Gram stain will aid in the identification of meningococcemia and Rocky Mountain spotted fever.
PETECHIAL/PURPURIC RASHES
Patients with RMSF or meningococcemia will require PCP follow-up in conjunction with an infectious disease specialist. Those with TTP or purpura fulminans/DIC need close PCP follow-up, as well as close monitoring by a hematologist. Patients treated for endocarditis will require PCP and cardiology follow-up.

SUGGESTED READINGS

REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.