The physician treating the acutely ill febrile patient must be able to recognize infections that require emergent attention. If such infections are not adequately evaluated and treated at initial presentation, the opportunity to alter an adverse outcome may be lost. In this chapter, the clinical presentations of and approach to patients with relatively common infectious disease emergencies are discussed. These infectious processes and their treatments are discussed in detail in other chapters.

**APPRAOCH TO THE PATIENT:**

**Acute Febrile Illness**

Before the history is elicited and a physical examination is performed, an immediate assessment of the patient’s general appearance can yield valuable information. The perceptive physician’s subjective sense that a patient is septic or toxic often proves accurate. Visible agitation or anxiety in a febrile patient can be a harbinger of critical illness.

**HISTORY**

Presenting symptoms are frequently nonspecific. Detailed questions should be asked about the onset and duration of symptoms and about changes in severity or rate of progression over time. Host factors and comorbid conditions may increase the risk of infection with certain organisms or of a more fulminant course than is usually seen. Lack of splenic function, alcoholism with significant liver disease, IV drug use, HIV infection, diabetes, malignancy, organ transplantation, and chemotherapy all predispose to specific infections and frequently to increased severity. The patient should be questioned about factors that might help identify a nidus for invasive infection, such as recent upper respiratory tract infections, influenza, or varicella; prior trauma; disruption of cutaneous barriers due to lacerations, burns, surgery, body piercing, or decubiti; and the presence of foreign bodies, such as nasal packing after rhinoplasty, tampons, or prosthetic joints. Travel, contact with pets or other animals, or activities that might result in tick or mosquito exposure can lead to diagnoses that would not otherwise be considered. Recent dietary intake, medication use, social or occupational contact with ill individuals, vaccination history, recent sexual contacts, and menstrual history may be relevant. A review of systems should focus on any neurologic signs or sensorium alterations, rashes or skin lesions, and focal pain or tenderness and should also include a general review of respiratory, gastrointestinal, or genitourinary symptoms.

**PHYSICAL EXAMINATION**

A complete physical examination should be performed, with special attention to several areas that are sometimes given short shrift in routine examinations. Assessment of the patient’s general appearance and vital signs, skin and soft tissue examination, and the neurologic evaluation are of particular importance.

The patient may appear either anxious and agitated or lethargic and apathetic. Fever is usually present, although elderly patients and compromised hosts (e.g., patients who are uremic or cirrhotic and those who are taking glucocorticoids or nonsteroidal anti-inflammatory drugs) may be afibrile despite serious underlying infection. Measurement of blood pressure, heart rate, and respiratory rate helps determine the degree of hemodynamic and metabolic compromise. The patient’s airway must be evaluated to rule out the risk of obstruction from an invasive oropharyngeal infection.

The etiologic diagnosis may become evident in the context of a thorough skin examination (Chap. 24). Petechial rashes are typically seen with meningococcemia or Rocky Mountain spotted fever (RMSF; see Fig. 25e-16); erythromelias is associated with toxic shock syndrome (TSS) and drug fever. The soft tissue and muscle examination is critical. Areas of erythema or diskiness, edema, and tenderness may indicate underlying necrotizing fasciitis, myositis, or myonecrosis. The neurologic examination must include a careful assessment of mental status for signs of early encephalopathy. Evidence of nuchal rigidity or focal neurologic findings should be sought.

**DIAGNOSTIC WORKUP**

After a quick clinical assessment, diagnostic material should be obtained rapidly and antibiotic and supportive treatment begun. Blood (for cultures; baseline complete blood count with differential; measurement of serum electrolytes, blood urea nitrogen, serum creatinine, and serum glucose; and liver function tests) can be obtained at the time an IV line is placed and before antibiotics are administered. The blood lactate concentration also should be measured. Three sets of blood cultures should be performed for patients with possible acute endocarditis. Asplenic patients should have a buffy coat examined for bacteria; these patients can have >10⁶ organisms per milliliter of blood (compared with 10³/mL in patients with an intact spleen). Blood smears from patients at risk for severe parasitic disease, such as malaria or babesiosis (Chap. 250e), must be examined for the diagnosis and quantitation of parasitemia. Blood smears may also be diagnostic in ehrlichiosis and anaplasmosis.

Patients with possible meningitis should have cerebrospinal fluid (CSF) drawn before the initiation of antibiotic therapy. Focal findings, depressed mental status, or papiledema should be evaluated by brain imaging prior to lumbar puncture, which, in this setting, could initiate herniation. Antibiotics should be administered before imaging but after blood for cultures has been drawn. If CSF cultures are negative, blood cultures will provide the diagnosis in 50–70% of cases. Molecular diagnostic techniques (e.g., broad-range 16S rRNA gene polymerase chain reaction testing for bacterial meningitis pathogens) are of increasing importance in the rapid diagnosis of life-threatening infections.

Focal abscesses necessitate immediate CT or MRI as part of an evaluation for surgical intervention. Other diagnostic procedures, such as wound cultures, should not delay the initiation of treatment for more than minutes. Once emergent evaluation, diagnostic procedures, and (if appropriate) surgical consultation (see below) have been completed, other laboratory tests can be conducted. Appropriate radiography, computed axial tomography, MRI, urinalysis, erythrocyte sedimentation rate and C-reactive protein determination, and transthoracic or transesophageal echocardiography all may prove important.

**TREATMENT**

The acutely ill patient, empirical antibiotic therapy is critical and should be administered without undue delay. Increased prevalence of antibiotic resistance in community-acquired bacteria must be considered when antibiotics are selected. Table 147-1 lists first-line empirical regimens for infections considered in this chapter. In addition to the rapid initiation of antibiotic therapy, several of these infections require urgent surgical attention. Neurosurgical evaluation for subdural empyema, otolaryngologic surgery for possible mucormycosis, and cardiothoracic surgery for critically ill patients with acute endocarditis are as important as antibiotic therapy. For infections such as necrotizing fasciitis and clostridial myonecrosis, rapid surgical intervention supersedes other diagnostic or therapeutic maneuvers.

Adjuvant treatments may reduce morbidity and mortality rates and include dexamethasone for bacterial meningitis or IV immunoglobulin for TSS and necrotizing fasciitis caused by group A Streptococcus. Adjunctive therapies should usually be initiated within the first hours of treatment; however, dexamethasone for
Infectious Diseases

**PART 8**

### Table 147-1: Empirical Treatment for Common Infectious Disease Emergencies*

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Possible Etiologies</th>
<th>Treatment</th>
<th>Comments</th>
<th>See Chap(s.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sepsis without a Clear Focus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td><em>Pseudomonas</em> spp., gram-negative enteric bacilli, <em>Staphylococcus</em> spp., <em>Streptococcus</em> spp.</td>
<td>Vancomycin (15/mg/kg q12h)* plus gentamicin (5 mg/kg per day) <strong>plus either</strong></td>
<td>Adjust treatment when culture data become available.</td>
<td>172, 173, 186, 189, 325</td>
</tr>
<tr>
<td>Overwhelming post-splenectomy sepsis</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Neisseria meningitidis</em></td>
<td>Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)*</td>
<td>If a β-lactam-sensitive strain is identified, vancomycin can be discontinued.</td>
<td>325</td>
</tr>
<tr>
<td>Babesiosis</td>
<td><em>Babesia microti</em> (U.S.), <em>B. divergens</em> (Europe)</td>
<td>Clindamycin (600 mg q8h) plus quinine (650 mg q8h)</td>
<td>Atovaquone and azithromycin can be used in less severe disease and are associated with fewer side effects. Treatment with doxycycline (100 mg bid) for potential co-infection with <em>Borrelia burgdorferi</em> or <em>Anaplasma</em> spp. may be prudent.</td>
<td>246e, 249</td>
</tr>
</tbody>
</table>

| **Sepsis with Skin Findings**           |                                                                                     |                                                                                                                    |                                                                                                |              |
| Meningococcemia                        | *N. meningitidis*                                                                    | Penicillin (4 mU q4h) or ceftriaxone (2 g q12h)                                                              | Consider protein C replacement, if available, in fulminant meningococcemia. Drotrecogin alfa (activated) is no longer produced. | 180          |
| Rocky Mountain spotted fever (RMSF)    | *Rickettsia rickettsii*                                                              | Doxycycline (100 mg bid)                                                                                    | If both meningococcemia and RMSF are being considered, use ceftriaxone (2 g q12h) plus doxycycline (100 mg bid). If RMSF is diagnosed, doxycycline is the proven superior agent. | 211          |
| Purpura fulminans                      | *S. pneumoniae*, *H. influenzae*, *N. meningitidis*                                  | Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)                                                      | If a β-lactam-sensitive strain is identified, vancomycin can be discontinued.                   | 171, 180, 182, 325 |
| Erythroderma: toxic shock syndrome      | *Group A Streptococcus*, *Staphylococcus aureus*                                    | Vancomycin (15 mg/kg q12h)* plus clindamycin (600 mg q8h)                                                 | If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 2 mg q4h; or oxacillin, 2 g IV q4h). The site of toxicigenic bacteria should be debrided; IV immunoglobulin can be used in severe cases.  | 172, 173   |

| **Sepsis with Soft Tissue Findings**    |                                                                                     |                                                                                                                    |                                                                                                |              |
| Necrotizing fasciitis                   | *Group A Streptococcus*, mixed aerobic/anaerobic flora, *CA-MRSA*                   | Vancomycin (15 mg/kg q12h)* plus clindamycin (600 mg q8h) plus gentamicin (5 mg/kg q8h) | Urgent surgical evaluation is critical. Adjust treatment when culture data become available. | 156, 172, 173 |
| Clostridial myonecrosis                 | *Clostridium perfringens*                                                            | Penicillin (2 μU q4h) plus clindamycin (600 mg q8h)                                                        | Urgent surgical evaluation is critical.                                                        | 179          |

| **Neurologic Infections**               |                                                                                     |                                                                                                                    |                                                                                                |              |
| Bacterial meningitis                    | *S. pneumoniae*, *N. meningitidis*                                                   | Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)*                                                      | If a β-lactam-sensitive strain is identified, vancomycin can be discontinued. If the patient is >50 years old or has comorbid disease, add ampicillin (2 g q4h) for *Listeria* coverage. Dexamethasone (10 mg q6h x 4 days) improves outcome in adults with meningitis (especially pneumococcal) and cloudy CSF, positive CSF Gram’s stain, or a CSF leukocyte count >1000/mL. | 164          |
| Brain abscess, suppurative intracranial infections | *Streptococcus* spp., *Staphylococcus* spp., *anaerobes*, gram-negative bacilli | Vancomycin (15 mg/kg q12h)* plus metronidazole (500 mg q8h) plus ceftriaxone (2 g q12h) | Urgent surgical evaluation is critical. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 μg q4h; or oxacillin, 2 g q4h). | 164          |
| Cerebral malaria                        | *Plasmodium falciparum*                                                              | Artesunate (2.4 mg/kg IV at 0, 12, and 24 h; then once daily)* or quinine (IV loading dose of 20 mg salt/kg; then 10 mg/kg q8h) | Do not use glucocorticoids. Use IV quinidine if IV quinine is not available. During IV quinidine treatment, blood pressure and cardiac function should be monitored continuously and blood glucose periodically. | 246e, 248   |
| Spinal epidural abscess                 | *Staphylococcus* spp., gram-negative bacilli                                       | Vancomycin (15 mg/kg q12h)* plus ceftriaxone (2 g q24h)                                                   | Surgical evaluation is essential. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 μU q4h; or oxacillin, 2 g q4h). | 456          |

| **Focal Infections**                    |                                                                                     |                                                                                                                    |                                                                                                |              |
| Acute bacterial endocarditis            | *S. aureus*, β-hemolytic *streptococci*, HACEK group*                               | Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)*                                                      | Adjust treatment when culture data become available. Surgical evaluation is essential.       | 155          |

*These empirical regimens include coverage for gram-positive pathogens that are resistant to β-lactam antibiotics. Local resistance patterns should be considered and may alter the need for empirical vancomycin. 1β-lactam antibiotic loading dose of 20–25 mg/kg can be considered in critically ill patients. 2β-Lactam antibiotics may exhibit unpredictable pharmacodynamics in severe sepsis. Prolonged or continuous infusions can be considered. 3The optimal dose of IV immunoglobulin has not been determined, but the median dose in observational studies is 2 g/kg (total dose administered for 1–5 days). 4Community-acquired methicillin-resistant *S. aureus*. 5In the United States, artesunate must be obtained through the Centers for Disease Control and Prevention. For patients diagnosed with severe malaria, full doses of parenteral antimalarial treatment should be started with whichever recommended antimalarial agent is first available. 6*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella* corrodens, and *Klebsiella* aerogenes.
bacterial meningitis must be given before or at the time of the first dose of antibiotic. Glucocorticoids can also be harmful, sometimes resulting in worse outcomes—e.g., when given in the setting of cerebral malaria or viral hepatitis.

**SPECIFIC PRESENTATIONS**

The infections considered below according to common clinical presentation can have rapidly catastrophic outcomes, and their immediate recognition and treatment can be life-saving. Recommended empirical therapeutic regimens are presented in Table 147-1.

**SEPSIS WITHOUT AN OBVIOUS FOCUS OF PRIMARY INFECTION**

Patients initially have a brief prodrome of nonspecific symptoms and signs that progresses quickly to hemodynamic instability with hypotension, tachycardia, tachypnea, respiratory distress, and altered mental status. Disseminated intravascular coagulation (DIC) with clinical evidence of a hemorrhagic diathesis is a poor prognostic sign.

**Septic Shock** *(See also Chap. 325)* Patients with bacteremia leading to septic shock may have a primary site of infection (e.g., pneumonia, pyelonephritis, or cholangitis) that is not evident initially. Elderly patients with comorbid conditions, hosts compromised by malignancy and neutropenia, and patients who have recently undergone a surgical procedure or hospitalization are at increased risk for an adverse outcome. Gram-negative bacteremia with organisms such as *Pseudomonas aeruginosa* or *Escherichia coli* and gram-positive infection with organisms such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) or group A streptococci can present as intractable hypotension and multiorgan failure. Treatment can usually be initiated empirically on the basis of the presentation, host factors *(Chap. 325)*, and local patterns of bacterial resistance. Outcome is worse when antimicrobial treatment is delayed or when the responsible pathogen ultimately proves not to be susceptible to the initial regimen. Broad-spectrum antimicrobial agents are therefore recommended and should be instituted rapidly, preferably within the first hour after presentation. Risk factors for fungal infection should be assessed, as the incidence of fungal septic shock is increasing. Biomarkers such as C-reactive protein and procalcitonin have not proved reliable diagnostically but, when measured over time, can facilitate appropriate de-escalation of therapy. Glucocorticoids should be considered only for patients with severe sepsis who do not respond to fluid resuscitation and vasopressor therapy.

**Overwhelming Infection in Asplenic Patients** *(See also Chap. 325)* Patients without splenic function are at risk for overwhelming bacterial sepsis. Asplenic adult patients succumb to sepsis at 58 times the rate of the general population. Most infections are thought to occur within the first 2 years after splenectomy, with a mortality rate of >30%, especially in patients with underlying comorbid or immunosuppressive conditions. Plague occurs infrequently in the United States *(Chap. 196)*, primarily after contact with ground squirrels, prairie dogs, or chipmunks, but is endemic in other parts of the world, with >90% of all cases occurring in Africa. The septic form is particularly rare and is associated with shock, multiorgan failure, and a 30% mortality rate. These infections should be considered in the appropriate epidemiologic setting. The Centers for Disease Control and Prevention lists *Francisella tularensis* and *Yersinia pestis* *(the agents of tularemia and plague, respectively)* along with *Bacillus anthracis* *(the agent of anthrax)* as important organisms that might be used for bioterrorism *(Chap. 261)*.

**SEPSIS WITH SKIN MANIFESTATIONS** *(See also Chap. 24)* Maculopapular rashes may reflect early meningococcal or rickettsial disease but are usually associated with noninfectious conditions. Exanthems are usually viral. Primary HIV infection commonly presents with a rash that is typically maculopapular and involves the upper part of the body but can spread to the palms and soles. The patient is usually febrile and can have lymphadenopathy, severe headache, dysphagia, diarrhea, myalgias, and arthralgias. Recognition of this syndrome provides an opportunity to prevent transmission and to institute treatment and monitoring early on.

Petechial rashes caused by viruses are seldom associated with hypotension or a toxic appearance, although there can be exceptions (e.g., severe measles or arboviral infection). Petechial rashes limited to the distribution of the superior vena cava are rarely associated with severe disease. In other settings, petechial rashes require more urgent attention.

**Meningococcemia** *(See also Chap. 180)* Almost three-quarters of patients with *N. meningitidis* bacteria have a rash. Meningococcemia most often affects young children (i.e., those 6 months to 5 years old). In sub-Saharan Africa, the high prevalence of serogroup A meningococcal disease has been a threat to public health for more than a century. Thousands of deaths occur annually in this area, which is known as the “meningitis belt,” and large epidemic waves occur approximately every 8–12 years. Serogroups W135 and X are also important emerging pathogens in Africa. In the United States, sporadic cases and outbreaks occur in day-care centers, schools *(grade school through college, particularly among college freshmen living in residential halls)*, and army barracks. Household contacts of index cases are at 400–800 times greater risk of disease than the general population. Patients may exhibit fever, headache, nausea, vomiting, myalgias, changes in mental status, and meningismus. However, the rapidly progressive form of disease is not usually associated with meningitis. The rash is initially pink, blanching, and maculopapular, appearing on the trunk and extremities, but then becomes hemorrhagic, forming petechiae. Petechiae are first seen at the ankles, wrists, axillae, mucosal surfaces, and palpebral and bulbar conjunctiva, with subsequent spread on the lower extremities and to the trunk. A cluster of petechiae may be seen at pressure points—e.g., where a blood pressure cuff has been inflated. In rapidly progressive meningococcemia *(10–20% of cases)*, the petechial rash quickly becomes purpuric *(see Fig. 70-5)*, and patients develop DIC, multiorgan failure, and shock; 50–60% of these patients die, and survivors often require extensive debridement or amputation of gangrenous extremities.
Hypotension with petechiae for <12 h is associated with significant mortality. Cyanosis, coma, oliguria, metabolic acidosis, and elevated partial thromboplastin time also are associated with a fatal outcome. Correction of protein C deficiency may improve outcome. Antibiotics given in the office by the primary care provider before hospital evaluation and admission may improve prognosis; this observation suggests that early initiation of treatment may be life-saving. Meningococcal conjugate vaccines are protective against serogroups A, C, Y and W135 and are recommended for children 11–18 years of age and for other high-risk patients.

**Rocky Mountain Spotted Fever** (See also Chap. 211) RMSF is a tick-borne disease caused by *Rickettsia rickettsii* that occurs throughout North and South America. Up to 40% of patients do not report a history of a tick bite, but a history of travel or outdoor activity (e.g., camping in tick-infested areas) can often be ascertained. For the first 3 days, headache, fever, malaise, myalgias, nausea, vomiting, and anorexia are documented. By day 3, half of patients have skin findings. Blanching macules develop initially on the wrists and ankles and then spread over the legs and trunk. The lesions become hemorrhagic and are frequently petechial. The rash spreads to palms and soles later in the course.

The centripetal spread is a classic feature of RMSF but occurs in a minority of patients. Moreover, 10–15% of patients with RMSF never develop a rash. The patient can be hypotensive and develop noncardiogenic pulmonary edema, confusion, delirium, and encephalitis progressing to coma. The CSF contains 10–100 cells/μL, usually with a predominance of mononuclear cells. The CSF glucose level is often normal; the protein concentration may be slightly elevated. Renal and hepatic injury as well as bleeding secondary to vascular damage are noted. For untreated infections, mortality rates are 20–30%. Delayed recognition and treatment are associated with a greater risk of death; Native Americans, children 5–9 years of age, adults >70 years old, and persons with underlying immunosuppression also are at increased risk of death.

Other rickettsial diseases cause significant morbidity and mortality worldwide. *Mediterranean spotted fever* caused by *Rickettsia conori* is found in Africa, southwestern and southwestern Asia, and southern Europe. Patients have fever, flu-like symptoms, and an inoculation eschar at the site of the tick bite. A maculopapular rash develops within 1–7 days, involving the palms and soles but sparing the face. Elderly patients or those with diabetes, alcoholism, uremia, or congestive heart failure are at risk for severe disease characterized by neurologic involvement, respiratory distress, and gangrene of the digits. Mortality rates associated with this severe form of disease approach 50%. *Epidemic typhus*, caused by *Rickettsia prowazekii*, is transmitted in louse-infested environments and emerges in conditions of extreme poverty, war, and natural disaster. Patients experience a sudden onset of high fevers, severe headache, cough, myalgias, and abdominal pain. A maculopapular rash develops (primarily on the trunk) in more than half of patients and can progress to petechiae and purpura. Serious signs include delirium, coma, seizures, noncardiogenic pulmonary edema, skin necrosis, and peripheral gangrene. Mortality rates approached 60% in the preantibiotic era and continue to exceed 10–15% in contemporary outbreaks. *Scrub typhus*, caused by *Orientia tsutsugamushi* (a separate genus in the family Rickettsiaceae), is transmitted by larval mites or chiggers and is one of the most common infections in southeastern Asia and the western Pacific. The organism is found in areas of heavy scrub vegetation (e.g., along riverbanks). Patients may have an inoculation eschar and may develop a maculopapular rash. Severe cases progress to pneumonia, meningoencephalitis, DIC, and renal failure. Mortality rates range from 1% to 35%.

If recognized in a timely fashion, rickettsial disease is very responsive to treatment. Doxycycline (100 mg twice daily for 3–14 days) is the treatment of choice for both adults and children. The newer macrolides and chloramphenicol may be suitable alternatives, but mortality rates are higher when a tetracycline-based treatment is not given.

**Purpura Fulminans** (See also Chaps. 180 and 325) Purpura fulminans is the cutaneous manifestation of DIC and presents as large ecchymotic areas and hemorrhagic bullae. Progression of petechiae to purpura, ecchymoses, and gangrene is associated with concomitant heart failure, septic shock, acute renal failure, acidosis, hypoxia, hypotension, and death. Purpura fulminans has been associated primarily with *N. meningitidis* but, in splenectomized patients, may be associated with *S. pneumoniae, H. influenzae*, and *S. aureus*.

**Ecthyma Gangrenosum** Septic shock caused by *P. aeruginosa* or *Aeromonas hydrophila* can be associated with ecthyma gangrenosum (see Figs. 189-1 and 25e-35): hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration. These gram-negative bacteremias are most common among patients with neutropenia, extensive burns, and hypogammaglobulinemia.

**Other Emergent Infections Associated with Rash** *Vibrio vulnificus* and other noncholera *Vibrio* bacteremic infections (Chap. 193) can cause focal skin lesions and overwhelming sepsis in hosts with chronic liver disease, iron storage disorders, diabetes, renal insufficiency, or other immunocompromising conditions. After ingestion of contaminated raw shellfish, typically oysters from the Gulf Coast, there is a sudden onset of malaise, chills, fever, and hypotension. The patient develops bullous or hemorrhagic skin lesions, usually on the lower extremities, and 75% of patients have leg pain. The mortality rate can be as high as 50–60%, particularly when the patient presents with hypotension. Outcomes are improved when patients are treated with tetracycline-containing regimens. Other infections, caused by agents such as *Anarmonas, Klebsiella*, and *E. coli*, can cause hemorrhagic bullae and death due to overwhelming sepsis in cirrhotic patients. *Capnocytophaga canimorsus* can cause septic shock in asplenic patients. Infection typically follows a dog bite. Patients present with fever, chills, myalgia, vomiting, diarrhea, dyspnea, confusion, and headache. Findings can include an exanthem or erythema multiforme (see Figs. 70-9 and 25e-35), cyanotic mottling or peripheral cyanosis, petechiae, and ecchymoses. About 30% of patients with this fulminant form die of overwhelming sepsis and DIC, and survivors may require amputation because of gangrene.

**Erythoderma** TSS (Chaps. 172 and 173) is usually associated with erythoderma. The patient presents with fever, malaise, myalgias, nausea, vomiting, diarrhea, and confusion. There is a sunburn-type rash that may be subtle and paretic but is usually diffuse and is found on the face, trunk, and extremities. Erythoderma, which desquamates after 1–2 weeks, is more common in *Staphylococcus*-associated than in *Streptococcus*-associated TSS. Hypotension develops rapidly—often within hours—after the onset of symptoms. Multiorgan failure occurs. Early renal failure may precede hypotension and distinguishes this syndrome from other septic shock syndromes. There may be no indication of a primary focal infection, although possible cutaneous or mucosal portals of entry for the organism can be ascertained when a careful history is taken. Colonization rather than overt infection of the vagina or a postoperative wound, for example, is typical with staphylococcal TSS, and the mucosal areas appear hyperemic but not infected. Streptococcal TSS is more often associated with skin or soft tissue infection (including necrotizing fasciitis), and patients are more likely to be bacteremic. TSS caused by *Clostridium sordellii* is associated with childbirth or with skin injection of black-tar heroin. The diagnosis of TSS is defined by the clinical criteria of fever, rash, hypotension, and multiorgan involvement. The mortality rate is 5% for menstruation-associated TSS, 10–15% for nonmenstrual TSS, 30–70% for streptococcal TSS, and up to 90% for obstetric *C. sordellii* TSS.

**Viral Hemorrhagic Fevers** Viral hemorrhagic fevers (Chaps. 233 and 234) are zoonotic illnesses caused by viruses that reside in either animal reservoirs or arthropod vectors. These diseases occur worldwide and are restricted to areas where the host species live. They are caused by four major groups of viruses: Arenaviridae (e.g., Lassa fever in Africa), Bunyaviridae (e.g., Rift Valley fever in Africa; hantavirus hemorrhagic fever with renal syndrome in Asia; or Crimean-Congo hemorrhagic fever, which has an extensive geographic distribution), Filoviridae (e.g., Ebola and Marburg virus infections in Africa), and Flaviridae (e.g., yellow fever in Africa and South America and dengue in Asia, Africa, and the Americas). Lassa fever...
and Ebola and Marburg virus infections are also transmitted from person to person. The vectors for most viral fevers are found in rural areas; dengue and yellow fever are important exceptions. After a prodrome of fever, myalgia, and malaise, patients develop evidence of vascular damage, petechiae, and local hemorrhage. Shock, multisystemic hemorrhaging, and neurologic signs (e.g., seizures or coma) predict a poor prognosis. Dengue (Chap. 233) is the most common arboviral disease worldwide. More than half a million cases of dengue hemorrhagic fever occur each year, with at least 12,000 deaths. Patients have a triad of symptoms: hemorrhagic manifestations, evidence of plasma leakage, and platelet counts of <100,000/μL. Mortality rates are 10–20%. If dengue shock syndrome develops, mortality rates can reach 40%. Supportive care to maintain blood pressure and intravascular volume with careful volume-replacement therapy is key to survival. Ribavirin also may be useful against Arenaviridae and Bunyaviridae.

**Sepsis with a Soft Tissue/Muscle Primary Focus**

See also Chap. 156.

**Necrotizing Fasciitis**  This infection is characterized by extensive necrosis of the subcutaneous tissue and fascia. It may arise at a site of minimal trauma or postoperative incision and may also be associated with recent varicella, childbirth, or muscle strain. The most common causes of necrotizing fasciitis are group A streptococci alone (Chap. 173), the incidence of which has been increasing for the past two decades, and a mixed facultative and anaerobic flora (Chap. 156). Diabetes mellitus, IV drug use, chronic liver or renal disease, and malignancy are associated risk factors. Physical findings are initially minimal compared with the severity of pain and the degree of fever. The examination is often unrewarding except for soft tissue edema and erythema. The infected area is red, hot, shiny, swollen, and exquisitely tender. In untreated infection, the overlying skin develops blue-gray patches after 36 h, and cutaneous bullae and necrosis develop after 3–5 days. Necrotizing fasciitis due to a mixed flora, but not that due to group A streptococci, can be associated with gas production. Without treatment, pain decreases because of the small blood vessels and destruction of the peripheral nerves—an ominous sign. The mortality rate is 15–34% overall, >70% in association with TSS, and nearly 100% without surgical intervention. Necrotizing fasciitis may also be due to *Clostridium perfringens* (Chap. 179); in this condition, the patient is extremely toxic and the mortality rate is high. Within 48 h, rapid tissue invasion and systemic toxicity associated with hemolysis and death ensue. The distinction between this entity and clostridial myonecrosis is made by muscle biopsy. Necrotizing fasciitis caused by community-acquired MRSA also has been reported.

**Clostridial Myonecrosis**  (See also Chap. 179) Myonecrosis is often associated with trauma or surgery but can develop spontaneously. The incubation period is usually 12–24 h long, and massive necrotizing gangrene develops within hours of onset. Systemic toxicity, shock, and death can occur within 12 h. The patient’s pain and toxic appearance are out of proportion to physical findings. On examination, the patient is febrile, apathetic, tachycardic, and tachypneic and may express a feeling of impending doom. Hypotension and renal failure develop later, and hyperalertness is evident predeterminedly. The skin over the affected area is bronze-brown, mottled, and edematous. Bullous lesions with serosanguineous drainage and a mousy or sweet odor can develop. Crepitus can occur secondary to gas production in muscle tissue. The mortality rate is >65% for spontaneous myonecrosis, which is often associated with *Clostridium septicum* or *C. tertium* and underlying malignancy. The mortality rates associated with truncal and limb infection are 63% and 12%, respectively, and any delay in surgical treatment increases the risk of death.

**Neurologic Infections with or Without Septic Shock**

**Bacterial Meningitis**  (See also Chap. 164) Bacterial meningitis is one of the most common infectious disease emergencies involving the central nervous system. Although hosts with cell-mediated immune deficiency (including transplant recipients, diabetic patients, elderly patients, and cancer patients receiving certain chemotherapeutic agents) are at particular risk for *Listeria monocytogenes* meningitis, most cases in adults are due to *S. pneumoniae* (30–60%) and *N. meningitidis* (10–35%). The classic presentation of fever, meningismus, and altered mental status is seen in only one-half to two-thirds of patients. The elderly can present without fever or meningeal signs. Cerebral dysfunction is evidenced by confusion, delirium, and lethargy that can progress to coma. In some cases, the presentation is fulminant, with sepsis and brain edema; papilledema at presentation is unusual and suggests another diagnosis (e.g., an intracranial lesion). Focal signs, including cranial nerve palsies (IV, VI, VII), can be seen in 10–20% of cases; 50–70% of patients have bacteremia. A poor outcome is associated with coma, hypotension, a pneumococcal etiology, respiratory distress, a CSF glucose level of <0.6 mmol/L (<0.1 mg/dL), a CSF protein level of >2.5 g/L, a peripheral white blood cell count of <5000/μL, and a serum sodium level of <135 mmol/L. Rapid initiation of treatment is essential; the odds of an unfavorable outcome may increase by 30% for each hour that treatment is delayed. Mortality also increases linearly with age of the patient.

**Septic Intracranial Infections**  (See also Chap. 164) In suppurative intracranial infections, rare intracranial lesions present along with sepsis and hemodynamic instability. Rapid recognition of the toxic patient with central neurologic signs is crucial to improvement of the dismal prognosis of these entities. *Subdural empyema* arises from the paranasal sinus in 60–70% of cases. Microaerophilic streptococci and staphylococci are the predominant etiologic organisms. The patient is toxic, with fever, headache, and nuchal rigidity. Of all patients, 75% have focal signs and 6–20% die. Despite improved survival rates, 15–44% of patients are left with permanent neurologic deficits. *Septic cavernous sinus thrombosis* follows a facial or sphenoid sinus infection; 70% of cases are due to staphylococci (including MRSA), and the remainder are due primarily to aerobic or anaerobic streptococci. A unilateral or retroorbital headache progresses to a toxic appearance and fever within days. Three-quarters of patients have unilateral periorbital edema that becomes bilateral and then progresses to ptosis, proptosis, ophthalmoplegia, and papilledema. The mortality rate is as high as 30%. *Septic thrombosis of the superior sagittal sinus* spreads from the ethmoid or maxillary sinuses and is caused by *S. pneumoniae*, other streptococci, and staphylococci. The fulminant course is characterized by headache, nausea, vomiting, rapid progression to confusion and coma, nuchal rigidity, and brainstem signs. If the sinus is totally thrombosed, the mortality rate exceeds 80%.

**Brain Abscess**  (See also Chap. 164) Brain abscess often occurs without systemic signs. Almost half of patients are febrile, and presentations are more consistent with a space-occupying lesion in the brain; 70% of patients have headache and/or altered mental status, 50% have focal neurologic signs, and 25% have papilledema. Abscesses can present as single or multiple lesions resulting from contiguous foci or hematogenous infection, such as endocarditis. The infection progresses over several days from cerebritis to an abscess with a mature capsule. More than half of infections are polymicrobial, with an etiology consisting of aerobic bacteria (primarily streptococcal species) and anaerobes. Abscesses arising hematogenously are especially apt to rupture into the ventricular space, causing a sudden and severe deterioration in clinical status and a high mortality rate. Otherwise, mortality is low but morbidity is high (30–55%). Patients presenting with stroke and a parameningeal infectious focus, such as sinusitis or otitis, may have a brain abscess, and physicians must maintain a high level of suspicion. Prognosis worsens in patients with a fulminant course, delayed diagnosis, abscess rupture into the ventricles, multiple abscesses, or abnormal neurologic status at presentation.

**Cerebral Malaria**  (See also Chap. 248) This entity should be urgently considered if patients who have recently traveled to areas endemic for malaria present with a febrile illness and lethargy or other neurologic signs. Fulminant malaria is caused by *Plasmodium falciparum* and is associated with temperatures of >40°C (>104°F), hypotension, jaundice, adult respiratory distress syndrome, and bleeding. By definition, any patient with a change in mental status or repeated
Infectious Diseases

Infectious Diseases

In the setting of fulminant malaria has cerebral malaria. In adults, this nonspecific febrile illness progresses to coma over several days; occasionally, coma occurs within hours and death within 24 h. Nuchal rigidity and photophobia are rare. On physical examination, symmetric encephalopathy is typical, and upper motor neuron dysfunction with decorticate and decerebrate posturing can be seen in advanced disease. Unrecognized infection results in a 20–30% mortality rate.

Intracranial and Spinal Epidural Abscesses  (See also Chap. 456) Spinal and intracranial epidural abscesses (SEAs and ICEAs) can result in permanent neurologic deficits, sepsis, and death. At-risk patients include those with diabetes mellitus; IV drug use; chronic alcohol abuse; recent spinal trauma, surgery, or epidural anesthesia; and other comorbid conditions, such as HIV infection. Fungal epidural abscesses and meningitis can follow epidural or paraspinal glucocorticoid infections. In the United States and Canada, where early treatment of otitis and sinusitis is typical, ICEA is rare but the number of cases of SEA is on the rise. In Africa and areas with limited access to health care, SEAs and ICEAs cause significant morbidity and mortality. ICEAs typically present as fever, mental status changes, and neck pain, while SEAs often present as fever, localized spinal tenderness, and back pain. ICEAs are typically polymicrobial, whereas SEAs are most often due to hematogenous seeding, with staphylococci the most common etiologic agent. Early diagnosis and treatment, which may include surgical drainage, minimize rates of mortality and permanent neurologic sequelae. Outcomes are worse for SEA due to MRSA, infection at a higher vertebral-body level, impaired neurologic status on presentation, and dorsal rather than ventral location of the abscess. Elderly patients and persons with renal failure, malignancy, and other comorbidities also have less favorable outcomes.

Other Focal Syndromes with a Fulminant Course Infection at virtually any primary focus (e.g., osteomyelitis, pneumonia, pyelonephritis, or cholangitis) can result in bacteraemia and sepsis. Lembiere’s disease—jugular septic thrombophlebitis caused by *Fusobacterium necrophorum*—is associated with metastatic infectious emboli (primarily to the lung) and sepsis, with mortality rates of >15%. TSS has been associated with focal infections such as septic arthritis, peritonitis, sinusitis, and wound infection. Rapid clinical deterioration and death can be associated with destruction of the primary site of infection, as is seen in endocarditis and in infections of the oropharynx (e.g., Ludwig’s angina or epiglottitis, in which edema suddenly compromises the airway).

Rhinoencephalitis Mucormycosis  (See also Chap. 242) Individuals with diabetes or immunocompromising conditions are at risk for invasive rhinocerebral mucormycosis. Patients present with low-grade fever, dull sinus pain, diplopia, decreased mental status, decreased ocular motion, chemosis, proptosis, dusky or necrotic nasal turbinates, and necrotic hard-palate lesions that respect the midline. Without rapid recognition and intervention, the process continues on an inexorable invasive course, with high mortality rates.

Acute Bacterial Endocarditis  (See also Chap. 155) This entity presents with a much more aggressive course than subacute endocarditis. Bacteria such as *S. aureus, S. pneumoniae, L. monocytogenes, Haemophilus* species, and streptococci of groups A, B, and G attack native valves. Native-valve endocarditis caused by *S. aureus* (including MRSA strains) is increasing, particularly in health care settings. Mortality rates range from 10% to 40%. The host may have comorbid conditions such as underlying malignancy, diabetes mellitus, IV drug use, or alcoholism. The patient presents with fever, fatigue, and malaise <2 weeks after onset of infection. On physical examination, a changing murmur and congestive heart failure may be noted. Hemorrhagic macules on palms or soles (Janeway lesions) sometimes develop. Petechiae, Roth’s spots, splinter hemorrhages, and splenomegaly are unusual. Rapid valvular destruction, particularly of the aortic valve, results in pulmonary edema and hypotension. Myocardial abscesses can form, eroding through the septum or into the conduction system and causing life-threatening arrhythmias or high-degree conduction block. Large friable vegetations can result in major arterial emboli, metastatic infection, or tissue infarction. Older patients with *S. aureus* endocarditis are especially likely to present with nonspecific symptoms—a circumstance that delays diagnosis and worsens prognosis. Rapid intervention is crucial for a successful outcome.

Inhalatinal Anthrax  (See also Chap. 261e) Inhalational anthrax, the most severe form of disease caused by *B. anthracis*, had not been reported in the United States for more than 25 years until the use of this organism as an agent of bioterrorism in 2001. Patients presented with malaise, fever, cough, nausea, drenching sweats, shortness of breath, and headache. Rhinorrhea was unusual. All patients had abnormal chest roentgenograms at presentation. Pulmonary infiltrates, mediastinal widening, and pleural effusions were the most common findings. Hemorrhagic meningitis was seen in 38% of these patients. Survival was more likely when antibiotics were given during the prodromal period and when multidrug regimens were used. In the absence of urgent intervention with antimicrobial agents and supportive care, inhalational anthrax progresses rapidly to hypotension, cyanosis, and death.

Avian and Swine Influenza  (See also Chap. 224) Human cases of avian influenza have occurred primarily in Southeast Asia, particularly Vietnam (H5N1) and China (H7N9). Avian influenza should be considered in patients with severe respiratory tract illness, particularly if they have been exposed to poultry. Patients present with high fever, an influenza-like illness, and lower respiratory tract symptoms; this illness can progress rapidly to bilateral pneumonia, acute respiratory distress syndrome, multiorgan failure, and death. Early antiviral treatment with neuraminidase inhibitors should be initiated along with aggressive supportive measures. Unlike avian influenza, for which human-to-human transmission has been rare so far and has not been sustained, a novel swine-associated influenza A/H1N1 virus has spread rapidly throughout the world. Patients most at risk of severe disease are children <5 years of age, elderly persons, patients with underlying chronic conditions, and pregnant women. Obesity also has been identified as a risk factor for severe illness.

Hantavirus Pulmonary Syndrome  (See also Chap. 233) Hantavirus pulmonary syndrome has been documented in the United States (primarily the southwestern states), Canada, and South America. Most cases occur in rural areas and are associated with exposure to rodents. Patients present with a nonspecific viral prodrome of fever, malaise, myalgias, nausea, vomiting, and dizziness that may progress to pulmonary edema and respiratory failure. Hantavirus pulmonary syndrome causes myocardial depression and increased pulmonary vascular permeability; therefore, careful fluid resuscitation and use of pressor agents are crucial. Aggressive cardiopulmonary support during the first few hours of illness can be life-saving. The early onset of thrombocytopenia may help distinguish this syndrome from other febrile illnesses in an appropriate epidemiologic setting.

CONCLUSION

Acutely ill febrile patients with the syndromes discussed in this chapter require close observation, aggressive supportive measures, and—in most cases—admission to intensive care units. The most important task of the physician is to distinguish these patients from other infected febrile patients whose illness will not progress to fulminant disease. The alert physician must recognize the acute infectious disease emergency and then proceed with appropriate urgency.