05 - 127 Approach to the Acutely Ill Infected Febrile Patient

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Approach to the Acutely

Ill Infected Febrile Patient The physician treating the acutely ill febrile patient must be able to recognize infections that require emergent attention. If such infec tions are not adequately evaluated and treated at initial presenta tion, the opportunity to alter an adverse outcome may be lost. In this chapter, the clinical presentations of and approach to patients with infectious disease emergencies are discussed. These infec tious processes and their treatments are discussed in detail in other chapters. APPROACH TO THE PATIENT Acute Febrile Illness Before the history is elicited and a physical examination is per formed, an immediate assessment of the patient's general appear ance can yield valuable information. The perceptive physician's subjective sense that a patient is septic or toxic often proves accu rate. Visible agitation or anxiety in a febrile patient can be a harbin ger of critical illness. HISTORY Presenting symptoms are frequently nonspecific. Detailed ques tions should be asked about the onset and duration of symptoms and about changes in severity or rate of progression over time. Host factors, such as extremes of age 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 func tion, alcoholism with significant liver disease, IV drug use, HIV infection, diabetes, malignancy, morbid obesity, organ transplan tation, 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 infec tion, 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 or prosthetic devices. Travel, presence during a natural disaster such as a hurricane or tsunami, contact with pets or other animals, or activities that might result in tick or mosquito exposure can lead to diagnoses that would not other wise 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. Pregnancy might increase the risk and severity of some illnesses, such as influenza or COVID-19, or increase the risk of significant morbidity for the fetus, as in Listeria or Zika virus infection. A

detailed review of systems should include any neurologic signs or sensorium alterations, rashes or skin lesions, and focal pain or tenderness. PHYSICAL EXAMINATION A complete physical examination should be performed, with spe cial attention to several areas that are sometimes given short shrift in routine examinations such as assessment of the patient’s general appearance and a detailed skin, soft tissue, and neurologic evaluation. 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 cir rhotic and those who are taking glucocorticoids or nonsteroidal anti-inflammatory drugs) may be afebrile despite serious under lying infection. Critically ill patients may be hypothermic, with a high risk of organ failure and mortality. Mortality at 30 days decreases with increasing temperature at presentation. Measure ment of blood pressure, heart rate, and respiratory rate and oxy gen saturation helps determine the degree of hemodynamic and metabolic compromise. The etiologic diagnosis may become evident in the context of a thorough skin examination (Chap. 21). Petechial rashes are typically seen with meningococcemia or Rocky Mountain spotted fever (RMSF; see Fig. A1-16); erythroderma is associated with toxic shock syndrome (TSS). On soft tissue and muscle examina tion, areas of erythema or duskiness, 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. CHAPTER 127 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; liver function tests and serum lac tate; and d-dimer) can be obtained at the time an IV line is placed and before antibiotics are administered. Three sets of blood cultures should be performed for patients with possible acute endocarditis. Blood smears from patients at risk for severe parasitic disease, such as malaria or babesiosis (Chaps. 231, 232, and A2), must be examined for the diagnosis and quantitation of parasitemia. Blood smears may also be diagnostic in ehrlichiosis and anaplasmosis. Testing of a nasopharyngeal sample for COVID-19 or influenza may be indicated. Approach to the Acutely Ill Infected Febrile Patient Patients with possible meningitis should have cerebrospinal fluid (CSF) obtained before the initiation of antibiotic therapy. Focal findings, depressed mental status, or papilledema 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., broadrange 16S rRNA gene polymerase chain reaction testing for bacte rial meningitis pathogens) are of increasing importance in the rapid diagnosis of life-threatening infections. CT or MRI may be necessary to evaluate focal processes that require urgent surgical intervention. Other diagnostic procedures, such as wound cultures,

should not delay the initiation of treatment for more than minutes. Once emergent evaluation, diagnostic pro cedures, and (if appropriate) surgical consultation (see below) have been completed, other laboratory tests can be conducted. Appropri ate radiography; CT and/or MRI imaging; urinalysis; measurement of the erythrocyte sedimentation rate, C-reactive protein, and/or procalcitonin; and transthoracic or transesophageal echocardiogra phy all may prove important.

TREATMENT The Acutely Ill Patient In the acutely ill patient, empirical antibiotic therapy for presumed bacterial or fungal infection is critical and should be administered without undue delay in addition to fluid resuscitation and vasopres sor support as needed. Increased prevalence of antibiotic resistance in community-acquired bacteria must be considered when antibiot ics are selected. Table 127-1 lists first-line empirical regimens for infections considered in this chapter. In addition to the rapid initia tion of antibiotic therapy, several of these infections require urgent surgical attention. Neurosurgical evaluation for subdural empyema, otolaryngologic surgery for possible mucormycosis, and cardiotho racic 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. Adjunctive treatments may reduce morbidity and mortality rates and include dexamethasone for bacterial meningitis or IV immu noglobulin for TSS. Adjunctive therapies should usually be initiated within the first hours of treatment; however, dexamethasone for bacterial meningitis must be given before or at the time of the first dose of antibiotic. Glucocorticoids may also be harmful—e.g., when given in the setting of cerebral malaria or viral hepatitis. SPECIFIC PRESENTATIONS The infections considered below according to common clinical pre sentation can have rapidly catastrophic outcomes, and their immediate recognition and treatment can be life-saving. PART 5 Infectious Diseases ■ ■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 hypoten sion, 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. 315) 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 who may have atypical presentations and often have comorbid conditions, hosts compromised by malignancy and neutro penia, and patients who have recently undergone a surgical procedure or hospitalization are at increased risk for an adverse outcome. Gramnegative 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 hypo tension and multiorgan failure. Treatment can usually be initiated empirically on the basis of the presentation, host factors (Chap. 315), and local patterns of bacterial resistance. Outcomes are worse when antimicrobial treatment is delayed or when the responsible pathogen ultimately proves not to be susceptible to the initial regimen. The increasing prevalence of multidrug-resistant organisms makes this especially relevant. Broad-spectrum antimicrobial agents are therefore recommended and should be instituted rapidly, preferably within the first hours after presentation with septic shock. Pharmacodynamics are altered in sepsis due to increased volume of distribution and renal clearance, so it is important to adequately dose antimicrobials. Risk fac tors for fungal infection should be assessed, as the incidence of fungal septic shock is increasing. Nonbacterial causes of shock, such as den gue virus infection, should be considered in endemic areas. Glucocor ticoids are often considered for patients with severe sepsis who do not respond to fluid

resuscitation and vasopressor therapy, but conclusive evidence for efficacy in this setting is lacking. Overwhelming Infection in Asplenic Patients (See also Chap. 315) Patients without splenic function are at risk for

overwhelming bacterial sepsis compared with the general population. The median interval between splenectomy and sepsis is 4–6 years, with a range of 1–19 years. Almost 50% or more of these infections occur within the first l or 2 years, but the increased risk persists throughout life. Encapsulated bacteria cause the majority of infections. Strepto coccus pneumoniae is the most common isolate, causing 40–70% of cases. Children less than 5 years of age are at 15 times higher risk of invasive pneumococcal disease than adults, who are more likely to have antibody to these organisms. The risk of infection with Haemophilus influenzae or Neisseria meningitidis also is greater in patients without splenic function, but reported cases are declining. Severe clinical mani festations of infections due to other organisms, such as E. coli, S. aureus, Bordetella holmesii, Capnocytophaga, Babesia, and Plasmodium species, have been described. Babesiosis (See also Chap. 232) A history of recent travel to endemic areas raises the possibility of infection with Babesia. Cases are increasing in the United States, particularly in the Northeast. Between 1 and 4 weeks after a tick bite, the patient experiences chills, fatigue, anorexia, myalgia, arthralgia, shortness of breath, nausea, and neuro logic symptoms such as headache, confusion, delirium or impaired consciousness; ecchymosis and/or petechiae are occasionally seen. The tick that most commonly transmits Babesia, Ixodes scapularis, also transmits Borrelia burgdorferi (the agent of Lyme disease) and Anaplasma; co-infection can occur and may result in more severe disease. Infection with the European species Babesia divergens is more frequently fulminant than that due to the U.S. species Babesia microti. B. divergens causes a febrile syndrome with hemolysis, jaundice, hemo globinemia, and renal failure and is associated with a mortality rate as high as 40%. Severe babesiosis is especially common in asplenic hosts but does occur in hosts with normal splenic function, particularly those >60 years of age and those with underlying immunosuppres sive conditions such as HIV infection or malignancy. Complications include renal failure, acute respiratory failure, heart failure, DIC, and splenic rupture. Other Sepsis Syndromes Tularemia (Chap. 175) has been reported in every U.S. state except Hawaii. This disease is associated with wild rabbit, tick, horse-fly, and tabanid fly contact. It can be transmitted by arthropod bite, handling of infected animal carcasses, consumption of contaminated food and water, or inhalation. The typhoidal form can be associated with gram-negative septic shock and a mortality rate of >30%, especially in patients with underlying comor bid or immunosuppressive conditions. Plague occurs infrequently in the United States (Chap. 176), primarily after contact with ground squirrels, prairie dogs, or chipmunks, but is endemic in other parts of the world; >90% of all cases occur in Africa with Madagascar especially affected. The septic form is particularly rare and is associated with shock, multiorgan failure, and a 30% mortality rate. Pneumonic plague is rapidly progressive and fatal without treatment. These infections should be considered in the appropriate epidemiologic setting. The Centers for Disease Control and Prevention (CDC) 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. S4). ■

■SEPSIS WITH SKIN MANIFESTATIONS

(SEE ALSO CHAP. 21) Sepsis can be associated with diverse skin findings. In one study, almost 18% of patients with severe sepsis had secondary skin findings, such as purpura, petechiae, or ecchymoses. Maculopapular rashes may reflect early meningococcal or rickettsial disease but are

usually associated with nonemergent infections. Exanthems are usually viral. Primary HIV infection commonly presents with a rash that is typically maculo papular and involves the upper part of the body but can spread to the palms and soles. The patient is usually febrile and can have lymphade nopathy, severe headache, dysphagia, diarrhea, myalgias, and arthral gias. Recognition of this syndrome provides an opportunity to prevent transmission and to institute early treatment.

TABLE 127-1 Empirical Treatment for Common Infectious Disease Emergenciesa CLINICAL SYNDROME POSSIBLE ETIOLOGIES TREATMENT COMMENTS SEE CHAP(S) Sepsis without a Clear Focus Septic shock Pseudomonas spp., gramnegative enteric bacilli, Staphylococcus spp., Streptococcus spp. Vancomycin (15 mg/kg q12h)b plus either Piperacillin/tazobactam (4.5 g) q8h via extended infusion (EI)c or cefepime (2 g) q8h via EI Overwhelming postsplenectomy sepsis Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)b If a β-lactam–sensitive strain is identified, vancomycin can be discontinued and a narrower-spectrum agent, such as penicillin, considered based on susceptibility testing. Babesiosis Babesia microti (U.S.),

B. divergens (Europe) Atovaquone (750 mg q12h) plus azithromycin (500 mg q24h) Sepsis with Skin Findings Meningococcemia N. meningitidis Ceftriaxone (2 g q12h) or penicillin (4 mU q4h) 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, ceftriaxone can be discontinued. Purpura fulminans S. pneumoniae, H. influenzae, N. meningitidis Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)b If a β-lactam-sensitive strain is identified, vancomycin can be discontinued. Erythroderma: toxic shock syndrome Group A Streptococcus, Staphylococcus aureus Vancomycin (15 mg/kg q12h)b plus clindamycin (600 mg q8h) Sepsis with Soft Tissue Findings Necrotizing fasciitis Group A Streptococcus, mixed aerobic/anaerobic flora Vancomycin (15 mg/kg q12h)b plus piperacillin/tazobactam (4.5 q q8h via EI)c plus clindamycin (600 mg q8h) Clostridial myonecrosis Clostridium perfringens Penicillin (2 mU q4h) plus clindamycin (600 mg q8h) Neurologic Infections Bacterial meningitis S. pneumoniae,

N. meningitidis Ceftriaxone (2 g q12h) plus vancomycin (15 mg/kg q12h)b 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 for 4 days) started before, or at the time of, the first dose of antibiotic improves outcome in adults with meningitis (especially pneumococcal). Brain abscess, suppurative intracranial infections Streptococcus spp., Staphylococcus spp., anaerobes, gram-negative bacilli Vancomycin (15 mg/kg q12h)b plus metronidazole (500 mg q8h) plus ceftriaxone (2 g q12h) Cerebral malaria Plasmodium falciparum Artesunate (2.4 mg/kg IV at 0, 12, and 24 h; then once daily) Spinal epidural abscess Staphylococcus spp., gram-negative bacilli Vancomycin (15 mg/kg q12h)b plus either Piperacillin/tazobactam (4.5 g q8h via EI) or cefepime (2 g q8h via EI)c Focal Infections Acute bacterial endocarditis Ceftriaxone (2 g q12h) or cefepime (2 g q8h via EI)c plus vancomycin (15 mg/kg q12h)b S. aureus, β-hemolytic streptococci, HACEK group,e Neisseria spp.,

S. pneumoniae aThese 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 or for expanded coverage for antibiotic-resistant gram-negative

pathogens. bA vancomycin loading dose of 20–25 mg/kg can be considered in critically ill patients. Dosing must be adjusted based on pharmacokinetic/pharmacodynamic monitoring. Daptomycin (10 mg/kg once daily) can be considered in place of vancomycin as alternate coverage for β-lactam resistant gram-positive organisms. Data for use in central nervous system infections are limited but emerging. cEI, extended infusion. β-Lactam antibiotics may exhibit unpredictable pharmacodynamics in sepsis. Prolonged or continuous infusions are often used. dThe 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). eHaemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae.

Empirical therapy should be tailored to local resistance patterns. Carbapenem or aminoglycoside antibiotics should be considered for empirical therapy when rates of multidrugresistant gram-negative organisms are high or for patients with risk factors for resistant organisms. Adjust treatment when culture data become available. 152, 153, 166, 170, 315

Clindamycin (600 mg q8h) plus quinine (650 mg q8h) can be used in severe disease not responding to atovaquone and azithromycin. Treatment with doxycycline (100 mg bid) for potential co-infection with Borrelia burgdorferi or Anaplasma spp. may be prudent. 229, 232 Ceftriaxone eradicates nasopharyngeal carriage of the organism. Close contacts require chemoprophylaxis with rifampin (600 mg q12h for 2 days) or ciprofloxacin (a single dose, 500 mg).

151, 160, 162,

CHAPTER 127 If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 2 mU q4h; or oxacillin, 2 g IV q4h). The site of toxigenic bacteria should be debrided; IV immunoglobulin can be used in severe cases.d 152, 153 Urgent surgical evaluation is critical. Empirical therapy should be tailored to local resistance patterns. For mixed aerobic/anaerobic infections, clindamycin can be discontinued. Adjust treatment when culture data become available. 134, 152, 153 Approach to the Acutely Ill Infected Febrile Patient Urgent surgical evaluation is critical.

Urgent surgical evaluation is critical. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 mU q4h; or oxacillin, 2 g q4h).

Avoid glucocorticoids. Until IV artesunate is available, treatment can be initiated with oral artemether-lumefantrine. Atovaquone-proguanil, quinine, and mefloquine are other options. 229, 231

Surgical evaluation is essential. If a β-lactam–sensitive strain is isolated, oxacillin, 2 g q4h or cefazolin 2 gm IV q8h is superior to vancomycin. Adjust treatment when culture data become available. Evaluation by cardiology and cardiothoracic surgery is essential.

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. 160) Almost three-quarters of patients with N. meningitidis bacteremia have a rash. Meningococ cemia 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. In the setting of aggressive vaccination programs against serogroup A, disease due to other serogroups, such as serogroups C, W135, and X, are increasing. Outside Africa, out breaks for the past 50 years reported in the United States and Europe are caused primarily by serogroup C (approximately 60%) followed by serogroup B (29%). 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. Outbreaks have also been described in people expe riencing homelessness. People with underlying comorbidities, such as cancer, renal or liver disease, or solid organ transplant recipients, are at increased risk. Household contacts of index cases are at 400–800 times greater risk of disease than the general population. Patients may have 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 extremi ties, 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 extremi ties 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. A1-41), and patients develop DIC, multiorgan failure, and shock; 50–60% of these patients die, and survi vors 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. 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 lifesaving. Members of the patient’s household and other persons with close contact should receive antibiotic prophylaxis with ciprofloxacin, rifampin, or ceftriaxone. Meningococcal conjugate vaccines are protec tive against serogroups A, C, Y, and W135 and are recommended for children 11–12 years of age with a booster dose at 16 years of age, and for other high-risk patients. Vaccines active against serogroup B are recommended for high-risk individuals ≥10 years of age and may be appropriate for teens and young adults (16 through 23 years of age). PART 5 Infectious Diseases Rocky Mountain Spotted Fever and Other Rickettsial Dis eases (See also Chap. 192) RMSF is a tickborne disease that occurs throughout North and South America. It is caused primarily by Rickettsia rickettsii but can be caused by other rickettsiae (e.g., R. parkeri, R. akari). 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, lethargy, 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 pro tein concentration may be slightly elevated. Renal and hepatic injury as well as bleeding secondary to vascular damage are noted. Delayed recognition and treatment are associated with a greater risk of death; mortality rates are 20–35% if treatment is delayed or not prescribed compared with ~4% when treated with doxycycline within 5 days of onset. Native Americans, Alaskan natives, Pacific Islanders, children 5–9 years of age, adults >70 years old, and persons with underlying immunosuppression are at increased risk of death as well. Other rickettsial diseases cause significant morbidity and mortality worldwide. Mediterranean spotted fever caused by Rickettsia conorii is found in Africa, southwestern and south-central 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 or purpura fulminans. Mortality rates associated with this severe form of disease approach 50% without treatment, but a single day of doxycycline is associated with much improved outcomes. Epidemic typhus, caused by Rickettsia prowazekii, is transmitted in louse-infested environments and emerges in conditions of extreme poverty, war, refugee camps, and natural disaster. Patients experience a sudden onset of high fevers, severe headache, cough, myalgias, and abdominal pain. A maculo papular 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 con temporary 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 south eastern Asia and the western Pacific. The organism is found in areas of heavy scrub vegetation (e.g., along riverbanks) and most common in rural areas among farming communities. Patients may have an inocula tion eschar and may develop a maculopapular rash, lymphadenopathy, and dyspnea. Severe cases progress to pneumonia, meningoencepha litis, myocarditis, DIC, and renal failure. Mortality rates range from 1% to 70% and vary by location, increasing age, myocarditis, delirium, pneumonitis, or signs of hemorrhage. If recognized in a timely fashion, rickettsial disease is very respon sive to tetracycline-based treatment. Doxycycline (100 mg twice daily for 1–14 days) is the treatment of choice for both adults and children. Combination therapy with doxycycline and azithromycin reduces complications and death in patients with severe scrub typhus. Purpura Fulminans (See also Chaps. 160 and 315) 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 congestive 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, less often, Aeromonas hydrophila or other gram-negative organisms, can be associated with ecthyma gangrenosum (see Figs. 170-1 and A1-34): hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration, most frequently located on the legs and trunk. Echthyma gangrenosum is most common among patients with neutropenia, extensive burns, and hypogammaglobulinemia. Other Infections Associated with Rash Vibrio vulnificus and other

noncholera Vibrio bacteremic infections (Chap. 173) can cause focal skin lesions and overwhelming sepsis in hosts with chronic liver

disease, heavy alcohol consumption, iron storage disorders, diabe tes, renal insufficiency, hematologic disease, or malignancy or other immunocompromising conditions. More than 95% of the cases are in the subtropical Pacific and Atlantic Oceans coastal regions in the Northern Hemisphere. After ingestion of contaminated raw shellfish (typically oysters from the Gulf Coast in U.S. cases), 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 35–60%, particularly when the patient presents with hypotension and septicemia. Outcomes are improved when patients are treated with fluoroquinolones with or without cephalosporins or with tetracyclinecontaining regimens. Other infections, caused by agents such as Aeromonas, Klebsiella, and E. coli, can cause hemorrhagic bullae and death due to overwhelming sepsis in cirrhotic patients. Capnocytoph aga canimorsus can cause septic shock in asplenic or cirrhotic patients. Infection typically follows a dog bite. Serovars A–C appear more virulent, constituting 92% of human infections but only 7.6% of canine isolates. Patients present with fever, chills, myalgia, vomiting, diarrhea, dyspnea, confusion, and headache. Findings can include an exan them or erythema multiforme (see Figs. 59-9 and A1-24A), cyanotic mottling or peripheral cyanosis, petechiae, and ecchymosis. About one-third of patients with sepsis develop septic shock, and 11–30% of patients with this fulminant form die of overwhelming sepsis and DIC. Survivors may require amputation because of gangrene. Erythroderma TSS (Chaps. 152 and 153) is usually associated with erythroderma. The patient presents with fever, malaise, myalgias, nausea, vomiting, diarrhea, and confusion. There is a sunburn-type rash that may be subtle and patchy but is usually diffuse and is found on the face, trunk, and extremities. Erythroderma, 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. Early renal failure may precede hypotension and distinguishes this syndrome from other sep tic 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 through a careful history. Coloniza tion 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 injec tion of black-tar heroin. The diagnosis of TSS is defined by the clini cal criteria of fever, rash, hypotension, and multiorgan involvement, although fever is typically absent when TSS is caused by C. sordellii. 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. Clindamycin improves outcomes when included in the treatment regimen. The use of IV immunoglobulin is associated with improved survival in some studies, in conjunction with clindamycin therapy. Viral Hemorrhagic Fevers Viral hemorrhagic fevers (Chaps. 215 and 216) are zoonotic illnesses caused by viruses that reside in either animal reservoirs or arthropod vectors. These diseases occur world wide 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; and Crimean-Congo hemorrhagic fever, which has an extensive geographic distribution), Filoviridae (e.g., Ebola and Marburg virus

infections in Africa), and Flaviviridae (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 vec tors for most viral fevers are found in rural areas; dengue and yellow fever are important exceptions. After a prodrome of fever, myalgias, and malaise, patients develop evidence of vascular damage, petechiae,

and local hemorrhage. Shock, multifocal hemorrhaging, and neuro logic signs (e.g., seizures or coma) predict a poor prognosis. Dengue (Chap. 215) is the most common arboviral disease worldwide. More than 100–400 million cases occur each year, ~25% of which are symptomatic with at least 12,000–20,000 deaths. Patients have a triad of symptoms: hemorrhagic manifestations, evidence of plasma leak age, and platelet counts of <100,000/μL. Mortality rates are 10–20%. If dengue shock syndrome develops, which is associated with severe hepatitis and neurologic involvement, mortality rates can reach 40%. Ebola infection has been associated with outbreaks with high mortality rates. From 1976 to 2022, 35 outbreaks were reported with an average case fatality rate of approximately 50%. Symptoms can appear 2–21 days after exposure, but most patients become ill within 9 days. The patient first presents with fatigue, fever, headache, and muscle pains, and the illness can progress to multiorgan failure and hemorrhaging. Careful volume-replacement therapy to maintain blood pressure and intravascular volume is key to survival in these infections.

Other viral illnesses with rash, such as measles, can be associated with significant mortality rates, especially in patients who develop organ complications such as pneumonia, pancreatitis or encephalitis. Measles continues to be responsible for more than 100,000 deaths per year worldwide, and to cause outbreaks in populations with low vac cination rates. ■ ■SEPSIS WITH A SOFT TISSUE/MUSCLE

PRIMARY FOCUS See also Chap. 134. 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 surgical incision and may also be associated with recent varicella, childbirth, or muscle strain. Diabetes mellitus, IV drug use, chronic liver or renal disease, and malignancy are associated risk factors. The most common causes of necrotizing fasciitis are group A streptococci alone (Chap. 153) and a mixed facultative and anaerobic flora (Chap. 134). The incidence of group A streptococcal necrotizing fasciitis has been increasing for the past quarter-century; surveillance in the United States links 13% of the cases to active IV drug use or homelessness. Physical findings are initially minimal except for soft tissue edema and mild erythema compared with the severity of pain and the degree of fever. 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 thrombosis of the small blood vessels and destruction of the peripheral nerves—an ominous sign. The mortality rate is 11–34% overall and increases when in association with TSS. With surgery, outcomes are significantly better. Necrotizing fasciitis may also be due to Clostridium perfringens (Chap. 159); in this condition, the patient is extremely toxic and the mortality rate is high. Within 48 h, rapid tissue invasion and systemic tox icity associated with hemolysis and death ensue. The distinction between this entity and clostridial myonecrosis is made by muscle biopsy. CHAPTER 127 Approach to the Acutely Ill Infected Febrile Patient Clostridial

Myonecrosis (See also Chap. 159) Myonecrosis is often associated with trauma or surgery but can develop spontane ously. 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 examina tion, 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 preterminally. 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 trunk 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. 143) Bacterial meningi tis is one of the most common infectious disease emergencies involv ing the central nervous system. Although hosts with cell-mediated immune deficiency (including transplant recipients, diabetic patients, elderly patients, and cancer patients receiving certain chemotherapeu tic agents) are at particular risk for Listeria monocytogenes meningitis, most cases in adults are due to S. pneumoniae (30–60%) and N. men ingitidis (10–35%). The classic presentation of fever, meningismus, and altered mental status is seen in only one-third to one-half of patients and is more common in adults over 60 years of age, although the elderly can also 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 associ ated with coma, seizures, hypotension, a purpuric rash, a pneumococ cal etiology, respiratory distress, a CSF glucose level of <0.6 mmol/L (<10 mg/dL), a CSF protein level of >2.5 g/L, and peripheral leukope nia or thrombocytopenia. Rapid initiation of treatment is essential; the odds of an unfavorable outcome may increase by 30% for each hour that treatment is delayed. Dexamethasone is an adjunctive treatment for meningitis in adults, especially for infections caused by S. pneu moniae, but is not recommended for Listeria meningitis. It must be given before or with the first dose of antibiotics; otherwise, it is unlikely to improve outcomes. PART 5 Infectious Diseases Suppurative Intracranial Infections (See also Chap. 145) Sup purative intracranial infections present along with sepsis and hemo dynamic instability. Rapid recognition of the toxic patient with central neurologic signs is crucial to improvement of the prognosis of these entities. Patients with diabetes or hematologic disease may be at increased risk for these infections. 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 infec tion; 70% of cases are due to staphylococci (including MRSA), and the remainder are due primarily to aerobic or

anaerobic streptococci. Fungi have been common in some series. A unilateral or retro-orbital 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, ophthalmo plegia, and papilledema. The mortality rate is as high as 30% in older studies with frequent neurologic sequelae but recent reports indicate improved survival as high as 90%. 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. Broad-spectrum antibiotics and early surgical intervention at the primary site of infection may improve outcomes. Anticoagulation or steroids are of uncertain benefit. Brain Abscess (See also Chap. 145) Brain abscess often occurs without systemic signs. Almost half of patients are afebrile, and pre sentations 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, or after surgery or

trauma. The infection progresses over several days from cerebritis to an abscess with a mature capsule. More than one-fourth to one-half of infections are polymicrobial, with an etiology consisting of aerobic bac teria (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 (<20%) 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; 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. Patients who receive medical therapy alone, compared with those receiving combined medical and surgical interventions, have higher mortality and a greater chance of neurologic sequelae. Cerebral Malaria (See also Chap. 231) This entity should be urgently considered for inhabitants of, or recent travelers to, areas endemic for malaria. Any patient with a change in mental status or repeated seizure in the setting of fulminant malaria has cerebral malaria. Fulminant malaria is caused by Plasmodium falciparum and is associated with temperatures of >40°C (>104°F), hypotension, jaundice, acute respiratory distress syndrome, and bleeding. Patients present with a febrile illness and lethargy or other neurologic signs, 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 examina tion, 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% mortal ity rate. Intravenous artesunate is associated with better outcomes. Children with neurologic deficit at hospital discharge, seizure recur rence during treatment, and/or ischemic neural injury on MRI are at particular risk for neurologic and mental health sequelae. Intracranial and Spinal Epidural Abscesses (See also

Chap. 453) 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 abscess and meningitis have been

linked to epidural or paraspinal glu cocorticoid injections. 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. ICEAs typically present as fever, mental status changes, and neck pain, while SEAs often present as fever, local ized spinal tenderness, and back pain. ICEAs are typically polymicro bial, 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, for infection at a higher vertebral-body level, for impaired neurologic status on presentation, and for dorsal rather than ventral abscess location. 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, pneu monia, pyelonephritis, or cholangitis) can result in bacteremia and sepsis. 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 epiglot titis, in which edema suddenly compromises the airway). TSS has been associated with focal infections such as septic arthritis, peritonitis, sinusitis, and wound infection. Lemierre’s syndrome is jugular septic thrombophlebitis primarily caused by Fusobacterium necrophorum, but it can be caused by other Fusobacterium spp., anaerobic streptococci and other bacteria. Lemierre’s syndrome is associated with metastatic infectious emboli (primarily to the lung but sometimes to the liver or

other organs) and sepsis, with mortality rates of >15%. Fusobacterium bloodstream infections have been associated with occult gastrointesti nal or genitourinary malignancy. Rhinocerebral Mucormycosis (See also Chap. 224) Individ uals with diabetes or immunocompromising conditions such as solid organ transplants or hematologic malignancies 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, surgical intervention, and antifungal therapy, the process continues on an inexorable invasive course, with mortality rates of 50–85% or greater. Uncontrolled diabetes and increasing age are nega tive prognostic factors. Acute Bacterial Endocarditis (See also Chap. 133) This entity presents with a much more aggressive course than subacute endocarditis. Bacteria such as S. aureus, S. pneumoniae, L. monocy togenes, 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. Mortality rates range from 10% to 40%. The host may have comorbid conditions such as underlying malignancy, diabetes mellitus, IV drug use, or alcoholism. Rheumatic valvular disease remains the most prevalent risk factor in Africa but is much less common in the United States. The patient presents with fever, fatigue, and malaise <2 weeks after onset of infection. On physi cal 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. Myo cardial abscesses can form, eroding through the septum or into the conduction system and causing life-threatening arrhythmias or highdegree conduction block. Large friable vegetations can result in major arterial emboli, metastatic infection, or tissue infarction including stroke. 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. Inhalational Anthrax (See also Chap. S4) 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, short ness 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 documented in 38% of these patients. Survival was more likely when antibiotics were given during the prodromal period and when multidrug regimens with at least two bacteriocidal antibiotic agents were used. In the absence of urgent intervention with antimicrobial agents and supportive care, inhala tional anthrax progresses rapidly to hypotension, cyanosis, and death. Viral Respiratory Tract Illness Viral respiratory tract illnesses can cause severe disease; several new syndromes have been described in the past decade. For patients who present with a respiratory illness and a relevant exposure and travel history, these viral illnesses must be considered and appropriate infection control measures instituted in addition to supportive care. Avian and Swine Influenza (See also Chap. 206) 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 symp toms; this illness can progress rapidly to bilateral pneumonia, acute respiratory distress syndrome, multiorgan failure, and death. Younger

age appears to be associated with a lower risk of complications. Early antiviral treatment with neuraminidase inhibitors should be initiated along with aggressive supportive measures. Unlike avian influenza, whose human-to-human transmission has so far been rare and has not been sustained, influenza caused by a novel swine-associated A(H1N1) virus emerged in 2009 and caused more than 60 million cases and 12,000 deaths in 1 year. Patients most at risk of severe disease were children <5 years of age, elderly persons, patients with underlying chronic conditions, and pregnant women. Obesity also has been identi fied as a risk factor for severe illness. The virus continues to circulate as a seasonal influenza virus, along with A(H1N1) strains. Although influenza cases dropped during the peak of the COVID-19 pandemic, they are again increasing and cause 3–5 million cases of severe illness and 300,000–650,000 deaths each year.

SARS, COVID-19, and MERS (See Chaps. 204 and 205) Novel betacoronaviruses have now been identified as the cause of severe acute respiratory syndrome (SARS, caused by SARS-CoV-1), Middle East respiratory syndrome (MERS, caused by MERS-CoV), and COVID-19 (caused by SARS-CoV-2). Although the three viruses have many simi larities, they differ in degree of contagion and case fatality rates. SARS and MERS “super-spreaders” are very symptomatic and typically criti cally ill, hospitalized patients. This is in contrast to COVID-19 where patients with highly transmissible virus are often asymptomatic or have mild disease. SARS emerged in 2002 in China and was diagnosed in several countries, primarily in Asia. Possible animal reservoirs include bats and civets. SARS-CoV-1 is characterized by efficient human trans mission but relatively low mortality. The potential SARS-CoV-1 pan demic was controlled through identification and isolation of infected patients. There have been no reported cases since 2004. CHAPTER 127 MERS likely has a bat reservoir and was first recognized in 2012 in Saudi Arabia. Human cases have been associated with direct and indi rect contact with dromedary camels. Unlike SARS and COVID-19, MERS exhibits inefficient human transmission but carries a high mortality rate. As of 2023, >2600 cases had been

confirmed, most in the Arabian Peninsula, with 35% mortality. MERS ranges from asymptomatic infec tion to acute respiratory distress syndrome, multiorgan failure, and death. Elderly men with comorbidities appear to be at highest risk for poor outcomes. Despite little documented human-to-human transmis sion in the community, nosocomial infection must be prevented by adherence to strict infection control practices. MERS is currently a low-level public health threat and is likely to remain so unless the virus mutates and its transmissibility increases. Approach to the Acutely Ill Infected Febrile Patient COVID-19 caused by SARS-CoV-2 resulted in a pandemic of his toric proportion. Originally linked to cases in China, SARS-CoV-2 spread internationally at a rapid pace. As of December 2023, cases approached 773 million worldwide with almost 7 million confirmed deaths; the United States has reported more than 103 million cases and over 1.1 million deaths. Actual infection may exceed reported cases by 8−10 fold. The primary mode of transmission of COVID-19 is through direct person-to-person contact via respiratory droplets; transmission by the airborne route or by contact with contaminated surfaces is much less common. Greatest risk of infection is associated with close and prolonged contact such as in household or congregate settings. Rates of secondary infection among household contacts are high: >50% in studies early in the pandemic. Although ~80% of patients with symptomatic COVID-19 infection have mild disease such as cough, sore throat, fever, gastrointestinal symptoms, and taste and smell alterations, ~5% of patients develop respiratory failure, shock, and multiorgan system failure. Patients typi cally have been symptomatic for 5−7 days before progression to severe pneumonia and hypoxemia. Shock, often in the setting of cardiac injury/myocarditis, arrhythmias or cardiomyopathy, and thromboem bolic complications such as pulmonary emboli or stroke, can occur. Other manifestations include acute kidney or liver injury. Laboratory findings include lymphopenia, elevated lactate dehydrogenase, and often evidence of a cytokine-release type syndrome with elevated C-reactive protein, d-dimer, ferritin, and proinflammatory cytokines such as interleukin 6 (IL-6). Chest radiographs and CT imaging reveal

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