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Infectious Disease Emergencies

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The severity of an infectious disease is largely determined by how the host responds to the virulence factors of the invading pathogen. Occasionally, this interaction (especially in immunocompromised patients) results in severe sepsis, septic shock, or its complications, which accounts for the majority of deaths attributable to infectious diseases in the developed world. Alternatively, local complications determine host survival (Table 1). The host–pathogen interaction and general principles of management of life-threatening infections are highlighted in Fig. 1.

In certain clinical situations (eg, severe sepsis, meningitis), rapid initiation of appropriate antibiotic therapy is a critical determinant of survival. In other diseases, ''source control'' (eg, debridement of infected tissue in necrotizing fasciitis) is urgently required. This article reviews principles of recognition and management of a selection of commonly encountered infectious disease emergencies, including sepsis, necrotizing soft tissue infections, acute meningitis, and the emerging issue of severe *Clostridium difficile* colitis. Less common but potentially deadly environmentally acquired or zoonotic pathogens are discussed, as are special patient populations, including the febrile returning traveler and the asplenic patient.

Sepsis

Sepsis, severe sepsis, and septic shock as defined by the consensus panel of the American College of Chest Physicians and the Society of Critical Care Medicine are outlined in Table 2 [1]. Classification of the spectrum of sepsis in a patient can be done with initial focused evaluation using the patient's vital signs and a minimal set of laboratory examinations with attention

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Table 1
Potential terminal events of an infectious process

Infectious process	Terminal event
Systemic disease with (eg, gram-negative bacteremia) or without bacteremia (eg, toxic shock syndrome, severe *C difficile* colitis)	Severe sepsis, septic shock, and its complications: acute respiratory distress syndrome, disseminated intravascular coagulation, multisystem organ dysfunction syndrome
Local effects	
Severe encephalitis or brain abscess	Brain herniation
Endocarditis	Severe congestive heart failure from valvular dysfunction or arrhythmia from conduction system involvement
Local toxin effects	Myocarditis and cardiogenic shock from diphtheria or respiratory failure from tetanus
TB cavitary disease or pulmonary aspergilloma	Asphyxiation from severe pulmonary hemorrhage
Severe epiglottis or diphtheritic membranes	Asphyxiation and upper airway obstruction
Typhoid ileitis	Peritonitis, shock, and hemorrhage from perforation

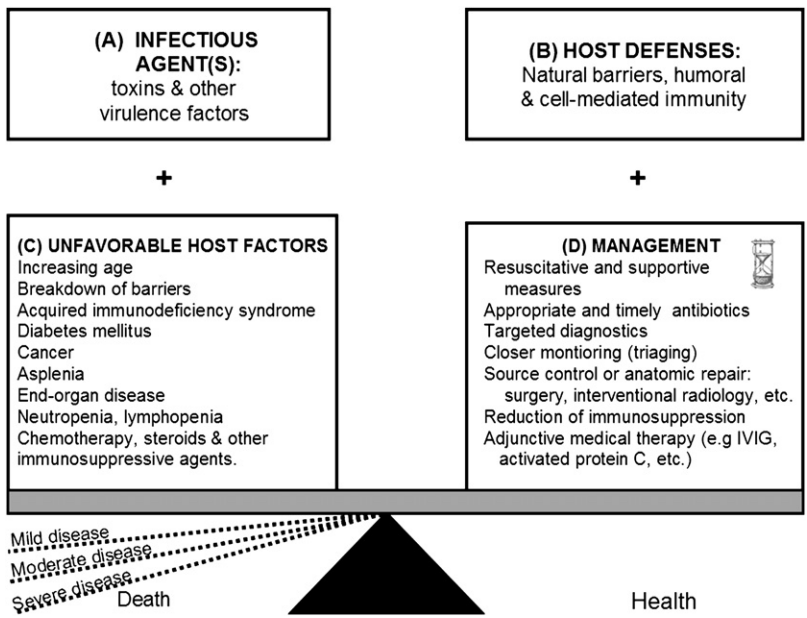

Fig. 1. Diagramatic scheme showing interaction between (*A*) infectious agent (*B*) host defenses. In some instances, the virulence of the infecting agent coupled with (*C*) unfavorable host factors can overwhelm host defenses leading to severe disease. (*D*) General principles of disease management of infectious disease should be applied to restore health. IVIG, intravenous immunoglobulin.

Table 2
A summary of information needed during initial evaluation to classify severity of infection

	Clinical findings	
Vital signs	Temperature: >38.4°C (100.4°F) or <36°C (96.8°F)	Systolic blood pressure < 90 mm Hg or MAP <70 mm Hg for at least 1 h despite adequate volume resuscitation, or the use of vasopressors to achieve the same goals
	Heart rate: >90 beats/min	
	Respiratory rate: >20 breaths/min or Pa_{CO2} of <32 mm Hg	
Abnormal labs	WBC: >12,000/mm^3 or <4000/mm^3 or >10% immature neutrophils	

Sepsis: documented or suspected infection with two or more vital signs or laboratory criteria. Severe sepsis: sepsis with evidence of organ dysfunction. Septic shock: sepsis with persistent hypotension despite one hour of fluid resuscitation or use of vasopressors.

for signs of end-organ dysfunction (eg, mental status changes, and decreased urine output). As patients progress from sepsis to severe sepsis and septic shock, their prognosis worsens, and the need for urgent intervention and a higher level of care (eg, transfer to intensive care unit) increases. Patients who meet these criteria are a major challenge; a great variety of infectious agents may be responsible, and noninfectious etiologies (eg, pulmonary embolism, acute myocardial infarction, thrombotic thrombocytopenic purpura, and high-grade lymphoma) may mimic sepsis. In cases in which the cause is not immediately obvious, the clinical history needs to include comorbidities, travel and exposure history, previous microbial colonization or infection, immunosuppression, and recent hospitalization. Standard tests include a complete blood count, metabolic profile, chest radiography, electrocardiography, blood cultures (before antibiotics if possible), and an arterial blood gas in critical patients. Additional testing (eg, lumbar puncture, CT of the abdomen, and serologies for various infectious agents) is often necessary as directed by the clinical history and examination.

Adjunctive measures are a crucial aspect in the management of patients who have severe sepsis. Aggressive fluid resuscitation and vasopressors (eg, dopamine or norepinephrine) are generally indicated if the patient has refractory hypotension. Drotrecogen alpha (activated) has been demonstrated to reduce the risk of death of patients in who have severe sepsis [2]. This drug should be avoided in patients who have single-organ dysfunction or who are at high risk for catastrophic bleeding (eg, recent neurosurgery, thrombocytopenia). Achieving euglycemia with blood glucose levels less than 150 mg/dL (8.3 mmol/L) also improves outcome. Source control (ie, removal of the focus of infection) with the aid of surgery, interventional radiology, and other subspecialties should be an early priority.

A rational approach to empiric antimicrobial therapy forms a cornerstone in the management of these life-threatening infections. It is well established that delayed or microbiologically inadequate antibiotic therapy (ie,

treatment with antibiotics to which the pathogen was later shown to be resistant) is associated with a worse outcome [3,4]. The choice of empiric antibiotics is complex, and a variety of factors, including drug allergy, drug–drug interactions, potential side effects, and ability to penetrate a particular site of infection, need to be considered. For community-acquired infections, resistant gram-negative rods (eg, *Pseudomonas aeruginosa*) generally do not have to be covered. Because of the increasing prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections extending beyond obvious skin and soft tissue infections, vancomycin is reasonable pending further culture information [5]. If an intra-abdominal source is suspected, anaerobic coverage is required. For severe health care–associated or hospital-acquired infections, antimicrobial resistance is common, and empiric treatment has to be tailored according to institutional antibiotic resistance patterns, colonization history, likely site of infection, and previously used antimicrobials. Fig. 2 provides an overview of antibacterial spectrum of activity of commonly used drugs for critically ill patients who have hospital-acquired infections. In general, empiric treatment should cover

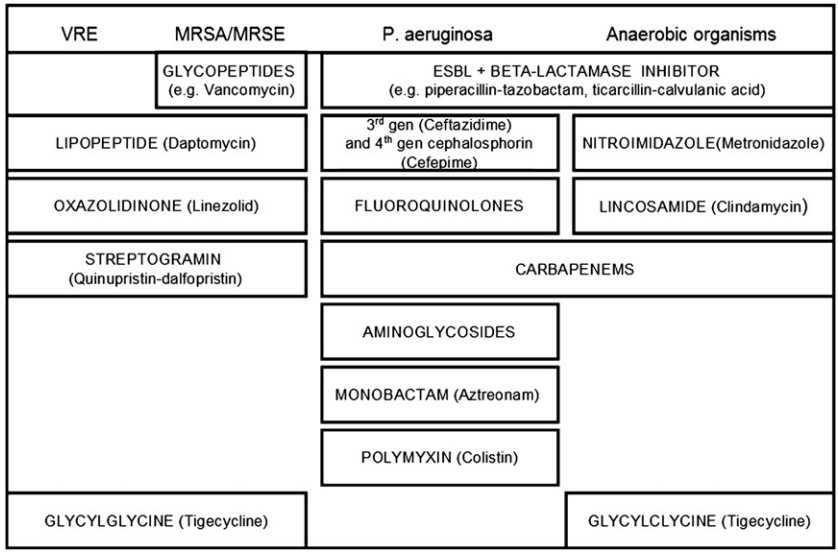

Fig. 2. Antibacterial class and spectrum of activity against common bacterial pathogens causing health care–associated infections. In general, empiric treatment of critically ill patients who have health care–associated infections requires treatment covering MRSA and *Pseudomonas aeruginosa*. Local institutional antibiotic resistant patterns, suspected site of infection, and patient history alter empiric antibiotic selection. Daptomycin is ineffective for pneumonia because it is inactivated by pulmonary surfactants. Aminoglycosides are rarely used alone except for urinary tract infections. The carbapenem ertapenem does not have reliable activity against *P aeruginosa*. Tigecycline has activity against most gram-negative organisms except *P aeruginosa*. ESBL, extended-spectrum beta lactams; VRE, vancomycin-resistant enterococcus; MRSA, methicillin-resistant *S aureus*; MRSE, methicillin-resistant *S epidermidis*.

MRSA and include a drug with activity against *P aeruginosa*. Coverage for vancomycin-resistant enterococcus may be warranted in patients who have a history of infection or colonization with this organism and severe sepsis.

The use of combination therapy for gram-negative infections is controversial; recent meta-analyses have not demonstrated a benefit, and no high-quality prospective study has been conducted using current antimicrobials in the population encountered in the modern hospital [6]. In addition, in patients who have fever and neutropenia, monotherapy with an extended spectrum beta lactam (eg, a carbapenem, antipseudomonal penicillin/beta-lactamase inhibitor, or third- or fourth-generation cephalosporin) is equivalent to or superior (ie, less toxicity) than combination therapy with two gram-negative agents (ie, addition of fluoroquinolone or aminoglycoside to beta-lactam) [7]. By increasing the ''density'' of antimicrobial use, gram-negative combination therapy promotes the development of antibiotic-resistant organisms and superinfection. In addition, increased risk of nephrotoxicity has been a consistent finding when aminoglycosides are used as one agent in combination therapy [8]. The most important issue is to determine that the spectrum of empiric coverage includes the gram-negative rods most commonly isolated in similar patients in the treating hospital; this relies on knowledge of local antimicrobial sensitivities. In some hospitals, this can generally be accomplished with one gram-negative agent. Once a pathogen has been identified, therapy should be narrowed. If combination therapy for gram-negative infection was initiated, one agent can usually be stopped when the patient improves.

Candida spp. are the fourth most common hospital blood stream isolate, and delay in initiation of appropriate therapy has been associated with increased mortality [9]. Thus, in patients who have severe sepsis and who are at high risk for candidemia (eg, a patient who has had recent abdominal surgery or who has a central venous catheter who becomes septic on broad-spectrum antibiotics), empiric treatment for *Candida spp*. with an azole (eg, fluconazole) or echinocandin (eg, anidulafungin, caspofungin, or micafungin) is appropriate. Patients who have extensive prior treatment with an azole (eg, fluconazole) should be empirically treated with echinocandins because of the risk of fluconazole-resistant candida species. Because of their toxicity, polyenes (ie, amphotericin products) are generally not used in this situation.

Special patient population—the asplenic patient

In the patient who does not have a spleen, certain organisms (eg, *Streptococcus pneumonia*, *Hemophilus influena*, *Neisseria meningitides*, or *Babesia microti*) may cause rapidly overwhelming infection with high mortality rates. In addition to patients who have congenital asplenia or who have had surgical removal of the spleen, so-called ''functional asplenia'' with similar risk may result from diseases such as sickle cell anemia or thalassemia. At the first sign of infection, prompt clinical evaluation, including blood cultures

and initiation of antibiotics with activity against encapsulated organisms (eg, ceftriaxone), is indicated pending culture results. Asplenic patients who are bitten by a dog or cat should also receive amoxicillin/clavulinic acid or another antibiotic (eg, ceftriaxone) with activity against *Capnocytophaga canimorsus*, which may cause purpura fulminans in this patient population. Vaccination against *S pneumonia* and *H influenza* type B and *N meningitides* (with the meningococcal vaccine, diphtheria conjugate) is indicated in patients who have asplenia or expected asplenia [10].

Skin and soft tissue infections

Skin and soft tissue infections are common indications for hospital admission. Cellulitis, which is infection of the superficial and subcutaneous layers of the skin, may require close observation and intravenous antibiotics, but in many patients can be treated as outpatients. Infections involving deeper structures (ie, fascia or muscle) may be immediately life threatening. From the point of view of the treating physician, the most important decision is differentiating deeper necrotizing infections requiring urgent surgical intervention from more superficial cellulitis [11]. Clinical risk factors for deeper or necrotizing soft tissue infections include trauma or abdominal surgery, diabetes mellitus, alcoholism, and renal disease. The presence of purple or red bullous lesions, pain on palpation over contiguous but superficially unaffected areas, indistinct margins, crepitus, loss of sensation distal to the affected area, and rapid progression suggest a deeper infection. Systemic toxicity (eg, renal failure, hypotension, and acidosis) can also be considered a ''warning sign'' for a deeper or necrotizing infection, but it is often a late finding. Other laboratory parameters that may help discriminate between superficial and necrotizing soft tissue infections include C-reactive protein greater than 150 mg/dL, white blood cell count greater than 15,000 cells/μl, hemoglobin less than 13.5 g/dL, and sodium less than 135 mmol/L [12]. Plain films may demonstrate gas in the soft tissues, and MRI or CT may reveal abscess or evidence of enhancement, edema, or thickening in the fascia. The lack of gas in the soft tissue does not exclude a diagnosis of a necrotizing infection. The absence of abnormal findings in the fascia on MRI makes necrotizing fasciitis less likely; its presence, however, may occur with simple cellulitis. Rapid progression of the extent of the involved area or clinical deterioration in uncertain cases suggests the need for surgical exploration. Another option in ambiguous cases is biopsy or surgical exploration to determine if the fascia is involved because observation of the deeper soft tissue is the only definitive method to make the diagnosis.

Management of deeper necrotizing infections of the skin and soft tissue requires a combined medical and surgical approach, and repeated and sometimes extensive surgical debridement is often necessary. These infections may be monomicrobial or polymicrobial, and this usually cannot be determined when the decision for initial antibiotic therapy is made. Thus, initial

therapy should include coverage of the most common pathogens (eg, beta hemolytic *streptococci*, *S aureus*, *E coli*, and *Clostridium perfringens*). Combination therapy with a beta-lactam/beta-lactamase inhibitor (eg, ampicillin-sulbactam or piperacillin-tazobactam) combined with clindamycin (to decrease toxin production) is recommended. Clindamycin may be stopped if toxin-producing bacteria (eg, beta hemolytic *streptococci* or *S aureus*) are not isolated. Patients who are allergic to penicillin may be treated with an aminoglycoside or fluoroquinolone in combination with clindamycin [13]. Community-associated MRSA has been described as a causative agent in necrotizing fasciitis (typically with more purulence and a more indolent course), and, given the increasing frequency of this pathogen in skin and soft tissue infections in general, many experts recommend the addition of vancomycin for unstable patients until culture data are available [14,15]. Intravenous immune globulin has been used in patients who have severe group A strep infections, but the efficacy of this treatment is unproven.

Special patient populations/pathogens

Although immunosuppressed patients are at increased risk of necrotizing soft tissue infections, the principles of diagnosis and management of skin and soft tissue infection outlined previously are not significantly different in most immunosuppressed patients. Some heavily immunosuppressed patients (eg, neutropenic patients) may develop cutaneous manifestations of systemic infections (eg, ecthyma gangrenosum), and empiric treatment should include coverage of *P aeruginosa*.

Skin and soft tissue infections in immunocompromised individuals warrant consideration of *Vibrio vulnificus*. *V vulnificus*, like other vibrios, is commonly found in warm estuarial and marine environments. Mortality as high as 50% in immunocompromised patients (including patients who have cirrhosis or hemochromatosis or patients who abuse alcohol) has been reported [16]. *V vulnificus* infection should be suspected in patients who give a history of ingestion of raw seafood or wound infection after exposure to seawater who later develop sepsis with associated hemorrhagic bullous skin lesions progressing to necrosis. *V vulnificus* grows without difficulty in standard blood culture media or on nonselective media (such as blood agar) routinely used for wound cultures. Preferred treatments include ceftazidime 2 g IV every 8 hours, ceftriaxone 1 g IV every 24 hours, or cefotaxime 2 g IV every 8 hours. Many experts combine any of these agents with doxycycline 100 mg IV or orally twice a day. Fluroquinolones are alternatives to cephalosphorins in cases of allergy [17].

Acute meningitis

Acute meningitis is a potentially life-threatening infection in which symptoms develop over hours to a few days. Rapid diagnosis, determination of

etiology, and institution of therapy is essential to decrease mortality and morbidity. Typical signs and symptoms of acute bacterial meningitis may include severe headache, photophobia, fever, and stiff neck and may progress to delirium and seizure. Skin, conjunctiva, and mucous membranes should be examined closely for the petechial or ecchymotic lesions associated with *N menigitidis*. Pneumococcus may cause purpura fulminans, disseminated intravascular coagulation, widespread purpura, and gangrene of the extremities. In patients who have suggestive symptoms, lumbar puncture is required to make the diagnosis and identify the infectious cause.

Patients who have immunocompromised state, papilledema, change in mental status, focal neurological deficit, or a history of central nervous system disease are at greater risk for mass lesion, which may increase the risk of herniation at the time of lumbar puncture. Patients who do not have such risk factors should undergo urgent lumbar puncture followed by institution of antimicrobial therapy. Patients who have such risk factors should have a head CT before lumbar puncture is performed, but antimicrobial therapy should not be delayed [18].

Virtually all patients who have bacterial meningitis have cerebrospinal fluid (CSF) leukocytosis (ie, 100–10,000 cells/mm^3) with an elevated protein concentration and reduced glucose. If the patient has not recently received antibiotic therapy, cultures will be positive in about 75% of patients, and Gram stain of CSF will be positive in 60% to 90% of patients [18]. For patients who have negative Gram stains who have received previous antimicrobial therapy, latex agglutination tests for *S pneumonia*, *N meningitides*, and *H influenza* may be helpful in determining etiology. In patients who have suspected *N meningitides*, droplet precautions should be instituted until treatment has been administered for 48 hours. Close household or school contacts of a proven case of *N meningitides* should receive chemoprophylaxis with rifampin 600 mg twice a day for 2 days or a single 500-mg dose of ciprofloxacin. Most health care workers, unless they had close contact with the respiratory secretions of the source patient, do not require chemoprophylaxis.

Various laboratory or clinical parameters (eg, procalcitonin levels, c-reactive protein, and CSF formula findings) have been studied to differentiate aseptic meningitis due to ''routine'' viral pathogens from bacterial meningitis with negative Gram stains [19,20]. Although these methods require further validation and greater clinical availability, some institutions have ready availability of polymerase chain reaction (PCR) for enterovirus from the CSF. If results can be obtained rapidly, patients may be discharged and avoid unnecessary antibiotic therapy. Clinicians admit and observe many patients who have negative Gram stain pending the availability of culture results. In uncertain cases (particularly if antibiotic therapy was given before lumbar puncture or if the CSF formula or clinical picture is highly suggestive of bacterial meningitis), a full course of 10 to 14 days of therapy is administered.

In patients who have a negative Gram stain or who cannot immediately undergo lumbar puncture, empiric therapy should cover *S pneumonia*,

N meningitides, and *H influenza*; a third-generation cephalosporin (eg, ceftriaxone 2 g IV every 12 hours) is combined with vancomycin (15–20 mg/kg IV every 12 hours). The need for vancomycin is based on the increasing incidence of penicillin-resistant pneumococcus. Alternative agents for allergic patients include carbapenems and fluroquinolones. For patients at risk for *Listeria monocytogenes* (eg, immunosuppressed patients, patients > 50 years old, and patients who have malignancy), ampicillin (2 g IV every 4 hours) should be added. Patients who have had recent neurosurgical or other medical procedures involving structures contiguous to the central nervous system should be treated with a meropenem or cefepime in addition to vancomycin to treat hospital-acquired gram-negative organisms. Patients who have negative Gram stain and mental status changes or focal neurologic signs should be treated with acyclovir (10 mg/kg IV every 8 hours) for possible Herpes Simplex virus (HSV) meningoencephalitis. Temporal lobe hemorrhage, lymphocytic pleocytosis, and normal glucose are suggestive of HSV meningoencephalitis. A PCR for HSV DNA on the CSF is the diagnostic test of choice, and if negative, acyclovir can be usually be discontinued. After a pathogen has been identified, therapy can be narrowed. Aqueous penicillin G 24 million units daily is sufficient to treat penicillin-sensitive *S pneumonia*. The use of adjunctive corticosteroids to decrease morbidity and mortality has long been controversial; however, a recent randomized trial indicated a reduction in morbidity and mortality in adults who had pneumococcal meningitis treated with dexamethasone 10 mg IV every 6 hours for 4 days. The first dose must be given before or concurrent with the first dose of antimicrobials, and if *S pneumonia* is not isolated, the dexamethasone should be stopped [21].

Special patient populations/pathogens

Immunosuppression alters the differential diagnosis and presentation of meningitis or meningoencephalitis. In addition to the routine community-aquired pathogens discussed previously, additional viruses (eg, *Cytomegalovirus*, human Herpes virus 6), fungi (eg, *Cryptococcus neoformans*, endemic fungi), and bacteria (eg, *Nocardia spp*.) need to be considered. Immunosuppressed patients are much more likely to develop central nervous system disease if infected with West Nile virus. If no etiology is readily apparent on Gram stain of CSF, a cryptococcal antigen should be sent on CSF, and empiric treatment for *Listeria monocytogenes* is indicated. Infectious disease consultation is strongly recommended for immunosuppressed patients who have meningitis or menigoencephalitis.

Two neurologic illnesses worth discussing are rabies and botulism. Major animal reservoirs of the rabies virus are bats, raccoons, skunks, and foxes, with bats being the most common source in the United States [22]. After an average incubation period of 1 to 3 months, prodromal flu-like symptoms progress rapidly to hallucinations and delirium or ascending flaccid

paralysis. The virus may be detected from the saliva, CSF, serum, or central nervous system tissue using reverse transcriptase PCR. Nuchal skin samples including at least 10 hair follicles/6 mm size can be sent to the CDC for direct fluorescent antibody testing. Once patients exhibit hydrophobia, paralysis, or signs of encephalitis, treatment is mostly supportive. A single case survived after drug-induced coma and treatment with ribavirin and amantidine [23]. This investigational protocol is available by contacting Dr. Rodney Willoughby at Children's Hospital of Wisconsin (414-266-2000).

Botulism results from neurotoxin produced by *Clostridium botulinum* and may be acquired from food (typically home canned) or an infected wound. Clinical symptoms generally include symmetric cranial neuropathies and descending paralysis without fever or significant sensory abnormalities [24]. Toxin assays may be conducted on food and clinical specimens by the CDC. Treatment consists of supportive measures and early ($<$24 hours after symptoms if possible) administration of specific antitoxin available from the CDC (404 639-2206). Wounds should be debrided. Although no evidence exists of its efficacy, some clinicians treat with aqueous penicillin G 20 million units daily.

C difficile enteritis

For many years, *C difficile* was generally considered a ''nuisance pathogen'' with relatively low morbidity and mortality [25]. In the past decade, hospitals throughout North America have reported severe outbreaks of *C difficile* colitis with increased numbers of cases, poor reponse to therapy, and severe disease with much higher rates of colectomy and death [25–27]. These outbreaks are due to a hypertoxin-producing strain that has acquired resistance to fluoroquinolones; this class of antibiotics has been implicated as a risk factor for acquiring *C difficile* colitis in the hospital setting [28]. Proton pump inhibitor use seems to be a risk factor in the inpatient and outpatient settings [29,30]. Severe cases, including deaths, have been reported in patients who have not had significant recent antibiotic use or health care environment exposure [31].

For the hospitalist, a high index of suspicion and awareness of local institutional *C difficile* rates are essential. Clinical clues suggestive of *C difficile* colitis as a cause of diarrhea in the antibiotic-treated patient include rapid increase in white blood cell count, recent episode of *C difficile* colitis, and thickened colon observed on CT of the abdomen. Although no randomized trial has been conducted, some studies have suggested poor response to metronidazole [25], and patients who have evidence of severe disease (eg, white blood cell count $>$ 20,000 cell/μL, sepsis) should be treated with oral vancomycin (125–500 mg qid). Patients who have ileus may require gentle enemas with vancomycin, and the addition of intravenous metronidazole (500 mg every 6–8 hours), which has enterohepatic circulation, may be helpful. In severely ill patients, early surgical consultation is recommended.

Fever in the returning traveler

Fever in the returning traveler may be caused by ''routine pathogens'' (eg, community-acquired respiratory viruses, bacterial pneumonia, and Epstein-Barr virus) or more ''exotic'' pathogens that are less familiar to most clinicians in the developed world. An exhaustive review of this topic is beyond the scope of this article, and the differential diagnosis in an individual traveler depends on region of travel, specific exposures, and adherence to prescribed prophylactic regimens and pretravel vaccination. Physicians should concentrate initial diagnostic efforts on ruling out the most common potentially deadly infections: malaria, typhoid fever, and dengue. In one series of 6957 febrile travelers seeking care, malaria was found in 21%, dengue in 6%, and typhoid fever in 2% [32]. Because clinical syndromes associated with these three infections overlap, evaluation of febrile travelers (assuming exposure to areas where these diseases are endemic) should include blood smears for malaria, blood cultures for typhoid fever, and serologies for dengue. Treatment for malaria depends on the identified species and risk for resistance in the geographic area in which it is acquired. Possible regimens for *Plasmodium falciparum* (the most dangerous species) include quinine sulfate 10 mg/kg of the salt every 8 hours for 3 to 7 days combined with doxycycline 100 mg twice daily for 7 days. Typhoid fever is usually treated with 500 to 750 mg ciprofloxacin orally twice a day for 7 to 14 days; strains acquired in Asia may be resistant, and ceftriaxone 2 g IV daily or azithromycin 1 g orally followed by 500 mg daily are alternative treatments pending culture and sensitivity results. No specific treatment for dengue fever is available.

Zoonotic/tickborn pathogens with sepsis-like presentations

Some less common environmentally acquired or zoonotic pathogens may cause fulminant septic-like clinical syndromes with a significant morbidity and mortality if appropriate treatment is not instituted early. Although certain clinical findings (eg, rash, cytopenias, and conjunctival suffusion) may be helpful, any patient who has an undifferentiated septic presentation without a clear etiology should be queried on animal and environmental exposures. Exposures to question include ticks (eg, rocky mountain spotted fever, ehrlichiosis), lakes/ponds (eg, leptospirosis), rodents (eg, plague, rat bite fever), and farm or wild animals (eg, Q fever, tularemia). If the exposure and clinical picture are suggestive, empiric treatment based on likely pathogens (often with doxycycline) may be indicated. Season is relevant because most rickettsial diseases are much more common in the warmer months.

Leptospirosis

Leptospirosis may be acquired in most parts of the United States, with the highest rates observed in Hawaii. Animals excrete leptospires into

standing water, and humans are infected though contact with this water [33]. Most cases are mild and resolve without treatment; severe leptospirosis is a multisystem disease with renal and hepatic dysfunction (ie, Weil's syndrome) being most prominent. Striking features may include a highly elevated bilirubin with only mild transaminitis and conjunctival suffusion [34]. Diagnosis relies on serology, but seroconversion may occur late, requiring repeat serologies. Thus, in suspected cases, empiric treatment with penicillin or doxycycline is indicated.

Q fever

Coxiella burnetti is a small, gram-negative rod acquired from exposure to farm animals and rarely household pets or ticks. The organism is present in highest numbers in the placenta, so attending the birth of infected animals is a major risk factor [35]. Most patients develop a self-limited influenza-like illness, but multisystem organ failure or endocarditis may occur [36]. The organism cannot be grown with routine media, and diagnosis relies on serologic testing. Doxycycline is first-line therapy; fluoroquinolones or macrolides are alternative treatments.

Plague

Plague remains endemic in the western United States, and most cases occur in the Southwest. *Yersinia pestis* is transmitted by fleas to rodent populations, and humans in contact with fleas or infected rodent carcasses may become infected. After a brief incubation period (up to a week), symptoms most commonly include bubos (tender swollen lymph nodes), but 10% to 25% of patients develop undifferentiated sepsis without bubos [37]. Diagnosis is most commonly made by culture of blood, sputum, or aspiration of a bubo; serologic tests are available. Streptomycin has long been the mainstay of therapy; alternatives include gentamicin and doxycycline. Respiratory isolation should be continued until at least 48 hours of antimicrobials have been administered and sputum cultures are shown to be negative.

Tularemia

Francisella tularensis is a zoonoses that is prevalent throughout the Northern hemisphere. Humans may be infected by an insect vector or by direct contact with an infected animal. After an up to 21-day (but generally shorter) incubation period, the most common clinical manifestation is ulceroglandular tularemia, which is a discrete ulcer with regional lymphadenopathy. Undifferentiated septic presentations (typhoidal or respiratory tularemia) may occur, with the exposure history being the only clue to diagnosis [38]. The organism is difficult to grow, and diagnosis generally relies on serology. Treatment has generally been with streptomycin 10 mg/kg IM twice a day for 10 days; doxycycline or gentamicin are alternatives.

Other rickettsial diseases and erhlichiosis

The diseases in this category of greatest concern in North America include Rocky Mountain spotted fever (RMSF), murine typhus, human monocytic ehrlichiosis (HME), and human granulocytic erhlichiosis (HGE). The combination of fever, headache, and rash should prompt questioning for exposure to these diseases. With the exception of murine typhus, which is transmitted by fleas, all of the previously mentioned diseases are transmitted by ticks. RMSF, HGE, and HME are most common in a band stretching from Virginia to Oklahoma. Murine typhus is most commonly seen in Texas. The spectrum of clinical manifestations ranges from a nonspecific febrile illness to multisystem organ failure; the latter is more common with RMSF. The absence of rash does not exclude the diagnosis, and transaminitis or thrombocytopenia is common. Diagnosis and decision to treat is generally based on clinical suspicion and exposure history, although circulating morulae are frequent in the blood smears of patients who have HGE. Diagnosis is generally confirmed with serology. Treatment, generally effective if instituted early, is with doxycycline.

Hantavirus

Hantavirus species were first described to cause disease in North America in the early 1990s. Human infection occurs by contact with infected rodents. Hantavirus pulmonary syndrome, the clinical syndrome observed in North America, is characterized by a flu-like illness followed by noncardiogenic pulmonary edema and shock. Hantavirus pulmonary syndrome has a mortality rate of 50%. Diagnosis is by means of serology, and ribavirin has been used as therapy with mixed results [39].

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