

# Infectious Disease Emergencies

## Frontline Clinical Pearls

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### KEYWORDS

- Antibiotic resistance • *Staphylococcus aureus* • Necrotizing fasciitis • Meningitis
- Sepsis

### KEY POINTS

- General internists are often the first practitioners to evaluate and manage hospitalized patients who have developed a severe, life-threatening infection.
- Early recognition of infectious disease emergencies is essential to guide appropriate initial therapy and avert avoidable morbidity and mortality.
- Many diseases have certain hallmarks which, if recognized, may dictate specific life-saving intervention.
- In an era of antibiotic resistance, the primary care practitioner must have a high index of suspicion for resistant pathogens and be familiar with appropriate broad and organism-specific therapies.
- The armamentarium of therapies in infectious disease emergencies includes not only antimicrobial drugs, but also such diverse modalities as surgical intervention and immunologic agents.

### INTRODUCTION

Infectious diseases in the mild to moderate form represent a bulk of office visits for internists and general practitioners. Often, when one of their patients develops a serious life-threatening infection, they are the first ones to manage the patients in the hospital. The hallmark of infectious disease emergencies is that with early and appropriate diagnosis and management, most of them are not just treatable, but curable. It is the first 48 hours of initial management that determines the further course and prognosis. Even when infectious disease specialists are available for consultation, the immediate management is rendered by the admitting physician. It is with this in mind that the editor of this issue requested our team to write the first article as a generalists' view of infectious disease emergencies. We chose to start each organ system

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with relevant clinical vignettes. Our goal is to provide a case-based learning tool for the generalist aimed at providing help in rationalizing differential diagnosis followed by presumptive antimicrobial therapy and diagnostic workup. Each discussion offers a few frontline clinical pearls.

## HEAD AND NECK INFECTIONS

### *Meningitis*

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An 18-year-old previously healthy college freshman presents with about 24 hours of fever, nausea, vomiting, headache, and decreased ability to concentrate. He is also complaining of severe myalgias and a rash. On physical exam, he is febrile, tachycardic, tachypneic, and hypotensive. He has positive Brudzinski and Kernig signs but no focal neurologic signs. He has a petechial rash, which is worsening. Laboratory data show a leukocytosis accompanied by thrombocytopenia, as well as a coagulopathy. A lumbar puncture is done emergently by the emergency department (ED) physician and cerebrospinal fluid (CSF) is sent for a cell count, glucose, protein level, Gram stain, culture, and sensitivity. The ED calls you to admit the patient.

While awaiting the results on the CSF, you are trying to decide on the best presumptive antibiotic therapy for this patient. You decide the best course of action is the following:

- A. Ceftriaxone 1 g intravenous (IV) daily
- B. Ceftriaxone 2 g IV daily
- C. Zosyn 3.375 IV every 6 hours
- D. Vancomycin 1 g IV every 12 hours
- E. Ceftriaxone 2 g IV every 12 hours plus vancomycin 15 mg/kg IV every 12 hours

The patient will be going to the intensive care unit (ICU) and the ED nurse would like to know how to prevent transmission of his infection in the hospital setting. The patient has been heard coughing.

You order the following status:

- A. Contact precautions
- B. Airborne precautions with a negative-pressure room
- C. Droplet precautions
- D. Standard hygiene precautions with good hand-washing practices

The patient is now in the ICU and is on aggressive volume repletion and has already received the antibiotics you had ordered. You take a further look at his laboratory data and realize he is hypoglycemic, hyponatremic, and mildly hyperkalemic. The ICU team is having difficulties maintaining his blood pressure and have had to start him on vasopressors.

You decide to order the following laboratory studies:

- A. A disseminated intravascular coagulation (DIC) panel
- B. A cortisol level
- C. A peripheral smear
- D. A cosyntropin stimulation test
- E. All of the above

### **Discussion**

Meningitis caused by *Neisseria meningitidis* tends to strike young, previously healthy individuals, and can be devastating, progressing to death over a few hours. *N meningitidis* is

the most common cause of bacterial meningitis in children and young adults in the United States, with an overall mortality rate of 14%.<sup>1</sup> It has replaced *Haemophilus influenzae* as the second most common cause of community-acquired adult bacterial meningitis.

The typical triad of fever, neck stiffness, and altered mental status is seen less commonly than with *Streptococcus pneumoniae* meningitis but those findings are more common when a petechial rash is present. The myalgia associated with *N meningitidis* infection is more severe than that seen with influenza virus infection and can be an alerting symptom as to the possibility of meningococemia. Other signs and symptoms of sepsis and shock, such as leg pain, cold hands and feet, and pale or mottled skin, should be sought out, as they correlate with severity of disease.

Physical examination should include special attention to vascular instability, such as hypotension and tachycardia. Meningeal irritation should be explored with Brudzinski and Kernig testing. A thorough examination for a petechial rash should be done, including areas of pressure on the body where it is most commonly found, such as belt lines and elastic straps regions.

The severity of the petechial rash correlates with the severity of DIC and thrombocytopenia in these patients. Progression of the rash from a petechial rash to ecchymoses, to painful indurated areas with erythematous borders can be prevented with early antibiotic therapy. The areas can form bullae and vesicles with ensuing gangrenous necrosis called purpura fulminans.

Diagnosis is made with culture and Gram stain from a sterile site. CSF, blood in patients with meningitis and meningococemia, or skin biopsy can all yield a diagnosis.

The yield of these studies will depend on the scope of meningococcal disease, whether it is meningitis with or without meningococemia.

Lumbar puncture should be performed and typically shows low glucose, less than 45 mg/dL, protein higher than 500 mg/dL and a white cell count higher than 1000 with neutrophilic predominance. Latex agglutination testing on the CSF can be useful but has limitations, as the sensitivity for serogroup B, which is the most common serogroup in the United States, is low.

Thrombocytopenia and coagulopathy should prompt an evaluation for DIC, and in the presence of DIC, poor response to treatment with shock should alert to the possibility of adrenal infarction leading to adrenal insufficiency (the Waterhouse-Friderichsen syndrome).

Presumptive treatment for *N meningitidis* meningitis is a third-generation cephalosporin, such as cefotaxime, or high-dose ceftriaxone at 2 mg IV every 12 hours to achieve ideal CSF levels. Vancomycin is not effective but is rather used for *S pneumoniae* meningitis at hospitals with high resistance rates to ceftriaxone. It is added to ceftriaxone for initial therapy of meningitis while a microbiological diagnosis is being sought. Antibiotic administration should not be delayed until a lumbar puncture is done, as *N meningitidis* infection can be lethal in a matter of hours.

Droplet precautions should be instituted because the organism is a respiratory pathogen and spread is most likely by the aerosol route, especially in patients who are actively coughing. The organism is larger than other organisms, such as *Mycobacterium tuberculosis*, and therefore airborne precautions with a negative-pressure room are not needed.

Persistent shock with thrombocytopenia and a coagulopathy should trigger a search for DIC with a DIC panel, a peripheral smear looking for fragmented red blood cells secondary to DIC, as well as a workup for adrenal insufficiency with a cortisol level and a cosyntropin stimulation test.

Morbidity and mortality rates have changed little since the 1960s because endotoxin-induced vascular damage has been difficult to treat. In addition, because

of its lower incidence, practitioners often do not have enough exposure to the disease to be able to diagnose it quickly enough.

#### Clinical Pearls

1. Consider *N meningitidis* meningitis in a young healthy patient with a sepsis syndrome, meningitis symptoms, and a rash.
2. Treat as soon as the diagnosis is considered with a third-generation cephalosporin, such as high-dose ceftriaxone 2 g IV every 12 hours.
3. Patients should be placed on droplet precautions immediately to prevent respiratory spread in the hospital.
4. Look for the Waterhouse-Friderichsen syndrome in patients who have persistent shock and features of DIC.

### **Encephalitis**

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A 40-year-old previously healthy man is brought in to the ED by emergency medical services (EMS), as his family was concerned over a 3-day history of fevers and an altered mental status. It is winter and he has not had any insect or animal exposures. His family has not noticed any rashes. He has not had any recent travel or sick contacts.

In the ED, the patient is confused, febrile, and tachycardic but has a normal blood pressure and oxygen saturation. He does not have signs of meningeal irritation or a rash and any focal neurologic signs. At the end of the physical examination, the patient experiences tonic clonic activity on the left side of his body followed by generalized tonic clonic activity bilaterally with loss of consciousness.

His laboratory studies show leukocytosis and a normal creatinine. The patient appears postictal and is going to be wheeled away for a magnetic resonance image (MRI) scan of the head.

Based on the patient's presentation your most likely diagnosis is

- A. Septic bacterial meningitis
- B. Aseptic viral meningitis
- C. West Nile virus encephalitis
- D. Eastern equine encephalitis
- E. Herpes simplex virus encephalitis

You recognize that the patient needs a lumbar puncture and an MRI of the head but you would like to start presumptive treatment for the patient's condition. The most important therapeutic intervention in this case would be the initiation of:

- A. Ceftriaxone 2 g IV every 12 hours
- B. Ampicillin IV
- C. Vancomycin 1 g IV every 12 hours
- D. Acyclovir 10 mg/kg IV every 8 hours

The patient has been started on antimicrobial therapy and gets a lumbar puncture, which shows 200 white blood cells (WBCs) with lymphocytic pleocytosis with mildly elevated protein of 100 mg/dL and normal CSF glucose. His MRI shows necrosis in the right temporal lobe and the neurologist was able to perform an electroencephalogram (EEG) and read it at once with the comment that there were PLEDs (periodic lateralizing epileptiform discharges).

The best diagnostic test you would like to make sure was done is

- A. Herpes simplex viral culture from the CSF
- B. Paired antibody test on the CSF and serum for West Nile virus

- C. Herpes simplex virus polymerase chain reaction (PCR) from the CSF
- D. Herpes simplex CSF antibody
- E. Paired antibody test on the CSF and serum for St Louis encephalitis virus

### **Discussion**

Herpes simplex virus type 1 (HSV-1) is the most common cause of fatal sporadic encephalitis worldwide. Herpes simplex virus type 2 (HSV-2) encephalitis is usually not seen in adults but is seen in neonates. Disease can occur in any season as opposed to West Nile virus, eastern equine encephalitis virus, and St Louis encephalitis virus, which tend to occur in summer and fall and require an insect/animal exposure.

The virus can cause infection following an acute episode of HSV-1, during an episode of HSV-1 reactivation with invasion into the central nervous system (CNS), or by reactivation of latent HSV-1 into the CNS without apparent skin lesions or rash.

Clinical symptoms include fever, headache, altered mental status, focal symptoms, and focal seizures with or without secondary generalization. Mental status changes and abnormal brain activity, such as focal deficits and seizures, are seen in herpetic encephalitis and are absent in meningitis. Signs of meningeal irritation may or may not be present on examination, and a herpetic rash is not seen when the virus is latent and directly reactivates into the CNS.

CSF laboratory abnormalities include a high WBC count but usually less than 250, as opposed to meningitis in which the WBC count is often in the thousands. There is lymphocytic pleocytosis as opposed to neutrophil predominance in septic meningitis. Protein levels may be elevated but usually are less than 150 mg/dL, whereas protein levels are higher than that threshold in septic meningitis. Glucose levels in the CSF are usually normal in herpes encephalitis, whereas they are often low in meningitis.

Abnormal MRI findings in the temporal region are suggestive of herpes encephalitis, as are EEG findings, such as PLEDS, which indicate focality in the lateral lobe regions<sup>2</sup>

The standard diagnostic test for herpes encephalitis in adults is herpes simplex PCR testing from the CSF. It has a sensitivity of 98% and a specificity of 94%. CSF PCR for HSV-2 is more useful in neonates, in whom it is more likely to cause herpes encephalitis.

CSF viral culture for herpes has a sensitivity of less than 10% and has been abandoned for diagnosing herpes encephalitis. CSF antibody testing for herpes simplex yields better results than HSV CSF cultures with a sensitivity of 8% and specificity of 90%.

Brain biopsy had been the gold standard but has the drawback of being invasive. There are often delays in obtaining results from the tissue and there is a possibility of a false-negative result owing to errors in sampling and culturing. It has been replaced by PCR testing and is reserved for patients who are deteriorating and a clear diagnosis has not been made.

Patients who are untreated have significant morbidity and mortality. Mortality approaches 70% without treatment and is reduced to 20% to 30% with treatment. Early therapy with acyclovir 10 mg/kg IV every 8 hours reduces mortality and morbidity such as cognitive deficits.

### **Clinical Pearls**

1. Consider herpes encephalitis in patients with fever, headache, and altered mental status.
2. Herpes encephalitis has a propensity to localize to the temporal lobes, causing seizures and temporal lobe abnormalities on EEG, such as PLEDS.
3. Temporal lobe abnormalities on MRI, such as necrosis, are suggestive of herpes encephalitis.

4. The diagnostic test of choice is HSV PCR from the CSF.
5. Early treatment with IV acyclovir should be instituted as soon as possible and reduces morbidity and mortality.

### **Brain Abscess**

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A 55-year-old male with a past medical history of poorly controlled diabetes is brought into the ED by EMS. His family called EMS, as he had tonic clonic activity on his right side with subsequent generalization and loss of consciousness. He was postictal when EMS arrived. You meet the family and learn that he has had extensive dental disease and had extensive dental work in the past 2 to 3 weeks.

He had a left frontal headache, which was not responding to acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). They had also noticed that he was growing increasingly inattentive in the past few days and his judgment was impaired. The day of admission, he was getting drowsier before he had seizure activity.

On physical examination, the patient is febrile and postictal and he has papilledema.

The next diagnostic step is

- A. You obtain consent from the family and proceed to do a lumbar puncture
- B. You send the patient for an MRI of the brain
- C. You obtain an EEG at once
- D. You start the patient on aspirin for stroke prevention

The patient has had diagnostic imaging and laboratory work is back showing a leukocytosis and pre-renal azotemia. He has received some medications through EMS and is now awake. You proceed to examine him and he does have difficulty focusing his attention. He also has extensive dental caries and periodontal disease with evidence of abscesses, as well as a right-sided hemiparesis. He does not have neck stiffness. Grasp, suck, and snout reflexes are present.

You find out that he received decadron 10 mg IV with an order for 4 mg IV every 6 hours thereafter. The MRI is showing a large left frontal abscess with substantial surrounding edema and mass effect. You decide to call neurosurgery to evaluate the patient for potential aspiration of the abscess to identify the causative organism. Meanwhile, you are contemplating starting antibiotic therapy. The best option at this point for what you suspect to be an odontogenic source of the brain abscess is

- A. IV metronidazole with the addition of IV ceftriaxone or cefotaxime
- B. IV erythromycin
- C. IV doxycycline
- D. IV cefazolin

### **Discussion**

Brain abscess can occur by direct spread or through the hematogenous route. Direct spread tends to cause solitary abscesses, whereas hematogenous spread usually results in multiple abscesses.

Otogenic infections tend to spread to the temporal lobe and cerebellum.

Sinus and odontogenic infections tend to spread to the frontal lobes.

Headache is the most common symptom and localizes to the area of the abscess. Symptoms are also representative of the part of cerebral cortex involved. Frontal abscesses are most common and can present with drowsiness, impaired judgment and attention, seizures, and if the abscess is large enough, contralateral hemiparesis.

In the setting of unilateral symptoms (headache) or signs (hemiparesis or cranial palsy), or evidence of elevated intracranial pressure, such as papilledema, a lumbar puncture (LP) is contraindicated because of the risk of herniation. MRI is the study

of choice to identify brain abscesses and should be performed before an LP if there is risk for herniation.

Microorganisms involved in causing brain abscesses from odontogenic sources include aerobic and anaerobic streptococci and *Haemophilus* species and anaerobes *Bacteroides*, *Prevotella*, and *Fusobacterium* species.

Penicillin G covers most oral microorganisms, including both aerobic and anaerobic streptococci. Metronidazole has excellent penetration into brain abscesses and has excellent bactericidal activity against anaerobes. The combination of IV ceftriaxone or cefotaxime and IV metronidazole<sup>3</sup> is the preferred empiric treatment for a brain abscess from an odontogenic source. Tetracycline, erythromycin, and cefazolin do not cross the blood brain barrier effectively and should not be used for treatment of brain abscesses.

IV glucocorticoids should be added if there is significant mass effect on imaging, as seen in our patient.

Neurosurgical consultation should be pursued with the hope of aspirating the abscess to guide antimicrobial therapy and decreasing the size of the abscess.

#### Clinical Pearls

1. Brain abscesses can occur by direct spread or through hematogenous spread.
2. Direct spread results in a solitary abscess, whereas hematogenous spread tends to result in multiple abscesses.
3. LP should not be performed if focal signs, symptoms, or papilledema are present because of the risk of herniation.
4. MRI is the modality of choice to detect brain abscesses.
5. IV glucocorticoids should be given to patients with evidence of mass effect from a brain abscess.
6. Odontogenic brain abscesses are best treated with a combination of IV ceftriaxone and IV metronidazole.

### **Sinusitis**

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A 30-year-old man with type 1 diabetes presents to his primary care physician. He is complaining of polyuria, polydipsia, and polyphagia and has had poor blood sugar control in the past few days. His blood sugar was in the 200 to 300 mg/dL range originally but today is reading in the critical range (above 500) on his machine. In the past 24 to 48 hours he has had complaints of chills, facial swelling, headache, and purulent nasal discharge.

On physical examination the patient is febrile and appears uncomfortable, toxic, and has facial swelling and sinus pain on palpation. Quick nasal examination shows nasal ulceration with a black eschar. His blood glucose in the office is critically high.

You call 911 and have the patient transferred emergently to the ED for treatment.

You call the ED attending and ask him to administer the following antifungal as you are worried that the patient has mucormycosis:

- A. IV amphotericin B
- B. IV fluconazole
- C. Oral ketoconazole
- D. Oral posaconazole

The patient arrives to the ED and testing shows that he has a high anion gap metabolic acidosis. Antifungal therapy is started and emergent infectious disease consultation and ear, nose, and throat (ENT) consultation for debridement are obtained.

### **Discussion**

Life-threatening rhinosinusitis and pulmonary infections are the most common presentations of mucormycoses. Infection occurs through inhalation of spores and inability to clear them. *Mucor* has a ketone reductase, which allows it to thrive in an acidic environment. As a consequence, a patient with diabetes and acidosis is at risk for mucormycosis.

Signs and symptoms of rhinosinusitis include fever, nasal ulceration or necrosis, periorbital or facial swelling, and headache.

Diagnosis is made by identification of organisms through histopathology, which is confirmed by culture. Endoscopic evaluation by an ENT should be performed early to look for necrosis/ulceration and to obtain tissue for histopathology.

IV amphotericin B is the first-line antifungal agent, whereas posaconazole is used as step-down therapy or in patients who do not respond or cannot tolerate amphotericin B.<sup>4</sup>

Correction of hyperglycemia and metabolic acidosis is critical, as is early surgical consultation for aggressive surgical debridement.

#### **Clinical Pearls**

1. Patients with diabetes and acidosis are at risk for fungal rhinosinusitis attributable to *mucor*.
2. *Mucor* has a ketone reductase, which allows it to thrive in an acidic environment.
3. IV amphotericin B is first-line treatment.
4. Posaconazole is used as step-down therapy or in amphotericin-intolerant nonresponding patients.
5. Early surgical consultation is needed for aggressive debridement and to help make the diagnosis through histopathology and culture.

### **Septic Thrombophlebitis**

A 20-year-old previously healthy male presents to the ED with a 7-day history of fevers, sore throat, and right-sided neck pain. He has also started to have coughing and feels short of breath. He had not seen a physician for his symptoms. In the ED, he is febrile and has an erythematous pharynx with exudates. He has tenderness and swelling along the right jaw over the sternocleidomastoid muscle and has scattered rhonchi on examination.

Blood cultures are drawn and a chest radiograph demonstrates multiple nodules consistent with septic emboli. Before sending the patient for a computed tomography (CT) scan of the neck and chest, you would like to give him empiric antibiotics for what you think is Lemierre syndrome (suppurative thrombophlebitis of the jugular vein following pharyngitis).

All of the following are good first-line choices for this infection except

- A. An IV carbapenem
- B. IV ampicillin-sulbactam
- C. IV piperacillin-tazobactam
- D. IV ticarcillin-clavulanate
- E. IV vancomycin

### **Discussion**

Lemierre syndrome is a condition frequently associated with a previous pharyngeal infection. Patients tend to be young and healthy before their pharyngitis.<sup>5</sup> It can also be seen in the setting of an IV catheter coursing through the jugular vein.

Patients typically present with fevers, rigors, and pharyngeal erythema or exudates. Tenderness, erythema, and induration along the course of the vein can be present on examination.



In patients with an oral cause of Lemierre syndrome, the most common pathogens are anaerobic *Fusobacterium* species. Other causative organisms include *Eikenella corrodens*, *Porphyromonas asaccharolytica*, streptococci including *Streptococcus pyogenes*, and *Bacteroides*.

In patients with a catheter-related Lemierre syndrome, skin flora and nosocomial pathogens cause the disease.

Diagnosis can be made through blood cultures or by culture of purulent material. CT scanning of the neck may demonstrate filling defects in the internal jugular vein. CT scanning of the chest may show septic pulmonary emboli.

*Fusobacterium necrophorum* produces beta lactamases, so a beta lactamase-resistant antibiotic should be used when the nidus of infection is oral to begin with.

Appropriate choices include an IV carbapenem, IV ampicillin-sulbactam, IV piperacillin-tazobactam, and IV ticarcillin-clavulanate.

When the infection is caused by an intravascular catheter, IV vancomycin should be used for good skin flora coverage and the catheter should be removed.

Surgical intervention is needed if the patient does not respond to antibiotics.

Anticoagulation should be considered if the thrombus is extending.

Clinical Pearls

1. Lemierre syndrome represents suppurative jugular vein thrombosis.
2. It can be caused by an oral infection or an intravascular catheter.
3. A beta lactamase-resistant antibiotic or carbapenem is needed if the infection arises from the oral region.
4. IV vancomycin for good skin flora coverage is needed if an intravascular catheter is the nidus of the infection.
5. Surgery is indicated in case of lack of response to antibiotics.
6. Intravascular catheter removal is necessary to remove the nidus of infection.
7. Anticoagulation should be considered if the thrombus is expanding.

### **Upper Airway Obstruction**

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An 18-year-old male presents to the ED complaining of sore throat with odynophagia, difficulties clearing secretions, and fevers. He is also complaining of hoarseness. The patient is febrile and appears toxic. He has labored breathing and on quick examination has erythema in the oropharynx with tenderness in the neck, as well as pooled secretions. He has intercostal retractions and stridor. The patient is turning cyanotic and is emergently intubated by the ED physician. The ED physician does notice significant erythema in the oropharynx and inflammation and erythema of the epiglottitis.

You happen to be in the ED admitting another patient and the ED physician approaches you about the this patient, whom you have been taking care of in an outpatient setting.

You recognize the patient and tell the ED physician that his family does not believe in immunizations and the patient has not had *Haemophilus influenzae* serotype b (Hib) immunization and he has several younger siblings who have not had childhood immunizations either.

The ED physician would like your help in making antibiotic selection. There is a high incidence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in the area.

You ask him to administer the following antibiotics:

- A. Ceftriaxone only
- B. Cefotaxime only
- C. Clindamycin only

- D. Vancomycin only
- E. Ceftriaxone and vancomycin

### **Discussion**

Epiglottitis is inflammation of the epiglottis and surrounding structures. It can progress rapidly and cause fatal airway obstruction.

Symptoms of epiglottitis in adults include sore throat, odynophagia, fever, drooling, and hoarseness. Signs on physical examination include fever, stridor, pooled secretions, inflammation, and edema of the epiglottis, as well as varying degrees of upper airway obstruction. More severe disease is associated with cyanosis and intercostal retractions.

Laboratory findings include leukocytosis. Bacteremia can be detected in some cases.

Radiologic findings include a thumb sign (enlarged protruding epiglottis).

Visualizing the airway in a secure setting, such as the ED, the operating room, or ICU, is recommended and in patients with respiratory difficulties securing the airway is paramount.

Laboratory and radiographic studies should be deferred until airway patency is secured.<sup>6</sup>

Empiric antibiotic therapy should be directed at *Haemophilus influenzae* b, especially in patients who are not immunized, beta hemolytic streptococci, and *S aureus*, including MRSA in areas of high incidence.

Ceftriaxone or cefotaxime plus clindamycin or vancomycin depending on local resistance patterns are recommended as first-line empiric treatment.

#### **Clinical Pearls**

1. Epiglottitis is inflammation of the epiglottis and surrounding structures and can result in rapidly lethal upper airway obstruction.
2. Maintenance of an airway is the primary objective.
3. Empiric antibiotic therapy includes ceftriaxone or cefotaxime plus clindamycin or vancomycin, depending on local resistance patterns.

## **CHEST INFECTIONS**

### ***Pneumonia***

A 76-year-old woman with recurrent chronic obstructive pulmonary disease exacerbations, requiring frequent oral steroids, presents with 2 days of cough with productive sputum, shortness of breath, chills, and fatigue. A chest radiograph shows a right lower lobe infiltrate.

Which of the following is not a clinical predictor of severity?

- A. Age
- B. Sex
- C. Confusion
- D. Tachypnea
- E. Infiltrate on chest radiograph
- F. All of the above are clinical predictors of severity

The patient's sputum Gram stain is positive for gram-negative bacilli. Which is the best initial antibiotic regimen?

- A. Moxifloxacin
- B. Ceftriaxone and azithromycin

- C. Piperacillin-tazobactam and ciprofloxacin
- D. Piperacillin-tazobactam and vancomycin

This patient responds rapidly to parenteral antibiotics. Further hospital management includes which of the following?

- A. Counseling on smoking cessation
- B. Repeat chest radiograph
- C. Influenza and pneumococcal vaccines
- D. Transition to oral antibiotics

### Discussion

Clinical predictors of severity can help identify patients who do not need hospital admission for treatment of pneumonia. Two common prediction calculators include the Pneumonia Severity Index (PSI) and CURB 65. The PSI is calculated based on age, sex, comorbid diseases, physical examination, and laboratory and chest x-ray findings.<sup>7</sup> CURB65 is the mnemonic for confusion, urea (BUN) higher than 20 mg/dL (7 mmol/L), respiratory rate of 30 breaths per minute or more, blood pressure higher than 90 mm Hg systolic or higher than 60 mm Hg diastolic, and age older than 65 years. It is a simpler predictor and can be used in the absence of a urea measurement in the office setting.<sup>8</sup> An infiltrate on chest imaging is a diagnostic requirement for pneumonia according to guidelines from the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS).<sup>9</sup> In addition, multilobar pneumonia is a risk factor for treatment failure.

Patients with gram-negative bacilli in the sputum should receive empiric treatment for *Pseudomonas aeruginosa* pneumonia. Treatment guidelines recommend coverage with 2 antipseudomonal antibiotics, which would include a combination of an antipseudomonal beta-lactam, antipseudomonal quinolone (ciprofloxacin or levofloxacin), and an aminoglycoside. The most common cause of community-acquired pneumonia remains *S pneumoniae*. Other common causes include *Mycoplasma pneumoniae*, *H influenzae*, *Chlamydia pneumoniae*, *Legionella*, and respiratory viruses, such as influenza. Community-acquired MRSA can cause a necrotizing pneumonia and empiric coverage should be considered in all patients who present with severe community-acquired pneumonia.<sup>9</sup>

An infiltrate on chest radiograph may take several weeks to clear. Similarly, patients may have persistent cough for several weeks following a lower respiratory tract infection. A chest radiograph should be repeated after several weeks in patients older than 50 years to document resolution of the infiltrate and screen for underlying disease or malignancy.

### Parapneumonic Effusion/Empyema

A 67-year-old man presents with cough, shortness of breath, and fever. His chest radiograph shows a left lower lobe infiltrate with left-sided pleural effusion, which layers to 1.5 cm on decubitus view.

In addition to IV antibiotics for pneumonia, what is the next best step in this patient's management?

- A. IV diuretics
- B. Echocardiogram
- C. Repeat chest radiograph in 24 to 48 hours to reassess effusion
- D. Thoracentesis
- E. Chest tube

For this patient, which of the following pleural fluid values is not indicative of empyema?

- A. pH lower than 7.20
- B. Glucose higher than 60 mg/dL
- C. Pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio higher than 0.6
- D. Nucleated white blood cells of more than 50,000 cells/ $\mu$ L
- E. Negative culture

Which of the following is not appropriate surgical management of loculated empyema?

- A. Thoracentesis
- B. Chest tube
- C. Video-assisted thoracoscopic surgery (VATS)
- D. Open thoracostomy

### **Discussion**

All parapneumonic effusions that are greater than or equal to 10 mm and free flowing must be differentiated from empyema. Uncomplicated effusions are usually sterile and resolve with treatment of pneumonia. They should be followed with serial chest radiographs. Complicated parapneumonic effusions may or may not respond to antibiotics alone. Empyema should always be drained, in addition to antibiotic therapy.<sup>10</sup>

Although the bacterial infiltration of pleural fluid causes neutrophil invasion, decrease in pleural fluid pH, and decrease in glucose through anaerobic metabolism, bacteria may not always grow on culture. Pleural effusions with pH lower than 7.20 and glucose less than 60 mg/dL are not likely to resolve on their own and need drainage. Empyemas are associated with a high number of neutrophils, which lyse and cause elevated fluid LDH.<sup>10</sup>

In addition to a prolonged course of antibiotics for sterilization of the pleural space, empyemas must be completely drained.<sup>10</sup> Although thoracentesis can be both a diagnostic and therapeutic treatment of pleural effusion, it is ineffective in removing loculated empyemas.

Drainage options for loculated effusions include chest tube placement under ultrasound or CT guidance, VATS, and open thoracostomy. Pleural fibrosis may restrict lung reexpansion and maintain a cavity from an empyema. Decortication or pleurectomy may be needed to remove the pleural peel. Decortication can be done with thoracoscopy or thoracotomy.

### **Myocarditis**

A 28-year-old man presents with 3 days of worsening dyspnea and sudden-onset sharp left-sided chest pain. On physical examination he is febrile and tachycardic. An electrocardiogram (ECG) shows diffuse P-R depression and ST elevation. An ST-segment elevation myocardial infarction (STEMI) alert is called.

What is the best initial management?

- A. Tissue plasminogen activator
- B. Cardiac catheterization
- C. Ibuprofen
- D. Methylprednisolone
- E. Colchicine

Subsequent workup reveals an elevated brain natriuretic peptide and creatinine kinase MB. An echocardiogram shows a small pericardial effusion and ejection fraction of 25%.

Which is the most common cause of his presentation?

- A. Ischemia
- B. Viral infection
- C. Bacterial infection
- D. Drug hypersensitivity
- E. Collagen vascular disease

Which of the following is the most definitive diagnostic test?

- A. Endomyocardial biopsy
- B. Radionucleotide angiography
- C. Cardiac catheterization
- D. Gallium scan
- E. Cardiovascular magnetic resonance

### **Discussion**

Myopericarditis can present with acute ST segment elevations, which are usually diffuse. Initial management is with nonsteroidal anti-inflammatories. Steroids may exacerbate an acute infectious process. Colchicine is helpful for recurrent pericardial effusions that can be associated with myocarditis.

Viral infection is the most common cause of myocarditis in developed countries.<sup>11</sup>

Endomyocardial biopsy is the gold standard for diagnosing myocarditis; however, the biopsy sample may not always include affected myocardial tissue.<sup>12</sup> Most patients will respond to supportive management and do not need a biopsy.<sup>13,14</sup> Workup for cardiomyopathy, including investigations for ischemic heart disease, collagen vascular disease, hemochromatosis, and amyloidosis, should be completed before proceeding to endomyocardial biopsy. With time, ventricular dysfunction attributable to acute myocarditis often returns to normal.<sup>14</sup>

### ***Infective Endocarditis***

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A 78-year-old man develops fever following a dental procedure. On physical examination he has a soft holosystolic murmur at the apex. His ECG is unchanged, and chest radiograph is normal.

His initial blood cultures come back positive from both samples; however, subsequent cultures on antibiotics show no growth.

Which is the next best step in diagnosis?

- A. Await speciation of blood cultures
- B. CT angiogram chest
- C. Transthoracic echocardiogram
- D. Transesophageal echocardiogram

Which complication of infective endocarditis is from an immune-mediated process?

- A. Stroke
- B. Perivalvular abscess
- C. Pulmonary embolism
- D. Osteomyelitis
- E. Glomerulonephritis

Which of the following is NOT an indication for surgery in infective endocarditis?

- A. Heart failure
- B. Stroke

- C. Perivalvular abscess
- D. A large vegetation
- E. All of the above are indications for surgery

### **Discussion**

Transthoracic echocardiogram is a noninvasive initial test of choice for investigating suspected endocarditis. Although vegetations might not be visible early in the course of the disease, a new regurgitant murmur is evidence of endocardial involvement. Totally normal valve structure and function on transthoracic echocardiogram has a very high negative predictive value for infective endocarditis.<sup>15</sup>

Transesophageal echocardiogram has much better resolution and is therefore better for imaging valves for vegetations and perivalvular abscesses. It is the test of choice for prosthetic valves.

Vascular phenomena associated with endocarditis include mycotic aneurysm, arterial emboli, septic pulmonary infarcts, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions (painless erythematous macules on palms and soles). The immunologic sequelae are glomerulonephritis, Osler nodes (violaceous painful nodules in the pulp of fingers and toes), Roth spots (retinal hemorrhagic exudates), and positive rheumatoid factor. These findings, along with fever, nondiagnostic positive blood cultures, structural heart lesions, and IV drug use, make up the minor criteria for diagnosing infective endocarditis.<sup>16,17</sup>

American College of Cardiology/American Heart Association guidelines suggest surgical management for patients with valvular dysfunction leading to heart failure, difficult-to-treat pathogens, severe regurgitant murmurs with elevated left ventricular end-diastolic or left atrial pressures, perivalvular abscess, and embolic events. Vegetation size alone is not an indication for surgery.

### **Aortitis and Mycotic Aneurysm**

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A 69-year-old man with hypertension, diabetes, and hyperlipidemia presents with a 2-week history of fever, and abdominal and back pain associated with malaise, weakness, and weight loss after an episode of gastroenteritis. He has leukocytosis (WBC = 16,000/mL) and the laboratory reports that his blood culture is growing a gram-negative rod.

Questions:

1. What are the common clinical manifestations of aortitis caused by *Salmonella* sp, and how is it diagnosed?
2. How is *Salmonella* aortitis managed?

### **Discussion**

Nontyphoidal *Salmonella* are an important cause of food-borne illnesses and gastroenteritis. In some patients, especially those with risk factors for atherosclerotic disease, salmonellae are able to invade the arterial intima causing endothelial infection. Consequently, aortitis can develop in these patients, which can then lead to mycotic aneurysms that can rupture. Patients often present with a subacute course of fever and abdominal or back pain. Mortality is high if the disease is unrecognized. CT scan with contrast enhancement is the diagnostic test of choice, but arteriography can also be considered. Blood cultures are usually positive (85% of patients) and stool cultures can also be positive (64% of patients).

Surgical intervention along with antimicrobial therapy is the treatment of choice. Medical therapy alone is insufficient and carries a high mortality rate (96%). Bactericidal antibiotics, such as ampicillin/gentamicin, fluoroquinolones, or third-generation

cephalosporins, are recommended. Long-term suppression with antibiotics has also been suggested to improve survival.<sup>18</sup>

#### Clinical Pearls

1. Aortitis secondary to *Salmonella* should be considered in patients with subacute fever and abdominal/back pain in the setting of atherosclerotic risk factors and gastroenteritis.
2. CT scan with contrast is the imaging modality of choice.
3. Surgical intervention combined with antibiotic therapy is the treatment of choice.

## INTRA-ABDOMINAL AND PELVIC INFECTIONS

### *Clostridium difficile* Colitis

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Your patient who is being treated for cellulitis develops fever, abdominal pain, and diarrhea, with tachycardia and hypotension. A dilated colon and ileus is seen on radiograph. His laboratory tests reveal an elevated WBC count of 28,000 and *Clostridium difficile* infection is suspected.

#### Questions

1. What are the common clinical manifestations of *C difficile*-associated diarrhea (CDAD)?
2. What is the treatment of choice for severe *C difficile* infection (CDI), and how is recurrent CDI treated?

#### Discussion

CDI of the colon is a common cause of antibiotic-associated diarrhea, often referred to as CDAD. CDI is often seen after recent antibiotic use, in the elderly or severely ill, in the hospitalized, and in the long-term care setting. CDI refers to a patient with diarrhea who has tested positive for the *C difficile* toxin and/or has a positive stool culture. *C difficile* colitis refers to signs of mucosal inflammation, whereas pseudomembranous colitis refers to the presence of pseudomembranes, seen on endoscopy. The term CDAD is often used to refer to all forms of *C difficile* infection that are symptomatic.

Clinical manifestations of CDI may vary, from mild symptoms, such as abdominal pain and diarrhea, to severe symptoms related to fulminant colitis with resultant fever, shock, acidosis, or ileus (which can progress to toxic megacolon or bowel perforation). Leukocytosis is often present in CDI, and a high, unexplained WBC count (higher than 15,000–20,000/mL) in hospitalized patients may be the only clue to this infection. Cytotoxin assay is the gold standard, with high sensitivity and specificity, but is costly and has a long turnaround. Enzyme immunoassay is often used for rapid screening because of its rapid turnaround (<24 hours) and high specificity, but the test has only moderate and variable sensitivity (leading to some false negatives). Clinical suspicion for CDI should play a strong role in treatment decisions.

In treating CDI, the inciting antimicrobial agent should be discontinued, if possible. Metronidazole and oral vancomycin have been the leading agents used to treat CDI, although other agents have been under development and investigation. Although there is no consensus definition for “severe” CDI, the literature has suggested that older age (>60), leukocytosis (WBC >15,000/mL), fever higher than 38.3°C, elevated creatinine, presence of pseudomembranes, or location in the ICU should all be considered. Peritoneal signs, severe ileus, or toxic megacolon should all be considered a surgical emergency requiring an urgent surgical evaluation. The 2010 Infectious Disease Society of America (IDSA) guidelines suggest that, for nonsevere *C difficile* infection, metronidazole is preferred over oral vancomycin because of similar efficacy and lower cost, whereas for severe *C difficile* infection, oral vancomycin should be used as first-line treatment.<sup>19</sup> Treatment of the first recurrence is usually with the

same initial regimen, but second or later reoccurrence should be with vancomycin, using a tapered or pulse regimen.

#### Clinical Pearls

1. Unexplained leukocytosis may be the presenting clue for *C difficile* infection.
2. Oral vancomycin should be used as the antibiotic treatment of choice for severe *C difficile* infection.
3. Treatment of reoccurrence should involve a prolonged tapered or pulse regimen.

### **Acute Cholangitis**

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Your patient presents with fever and confusion. Clinically, she has tachycardia, jaundice, and marked upper abdominal pain and tenderness. The family notes that she is scheduled for a cholecystectomy for symptomatic gallstones next week.

#### Questions

1. What are the common clinical manifestations of ascending cholangitis?
2. What are the treatment measures that should be considered, including antibiotic choice, biliary drainage, or surgery?

#### **Discussion**

Biliary stones often predispose a patient to biliary obstruction and stasis. These factors, in turn, can cause migration of bacteria into the biliary system, resulting in septicemia. The most common bacteria are of colonic origin with the most common gram-negative organisms being *Escherichia coli* (25%–50%), *Klebsiella* (15%–20%), and *Enterobacter* (5%–10%). *Enterococcus* (10%–20%) is the most common gram-positive organism, whereas anaerobic bacteria (*Bacteroides* or *Clostridium*) are usually present only when there is a mixed infection. The classic Charcot triad of fever, right upper quadrant pain, and jaundice is seen in about 50% of patients with acute cholangitis. The additional presence of neurologic changes and hypotension (Reynold pentad), portends a worse prognosis with significant morbidity and mortality (approximately 50%). Leukocytosis and a cholestatic pattern of liver function tests (high alkaline phosphatase, bilirubin, and gamma-glutamyl transpeptidase) are often seen. Ultrasound is the first study recommended to noninvasively look for common bile duct dilatation and stones; however, false negatives with ultrasound may occur (10%–20%) because of the presence of small stones or a delay in common bile duct dilation, so magnetic resonance cholangiopancreatography is another option. Endoscopic retrograde cholangiopancreatography (ERCP) can be used to confirm the diagnosis, as well as intervene therapeutically.

Treatment for cholangitis should begin with appropriate antibiotic coverage and then establishment of biliary drainage within 24 hours. Common antibiotic regimens include extended-spectrum beta-lactam-based therapy, including carbapenems, or third-generation cephalosporins with metronidazole. Alternative therapies include fluoroquinolones with metronidazole. ERCP has the benefit of visualizing the biliary system as well as being able to perform sphincterotomy, stone extraction, or stent insertion, and is the preferred treatment. Percutaneous drainage by interventional radiology may be considered when ERCP is not an option. Emergent surgery is often avoided, as the nonoperative options, ERCP and percutaneous drainage, have lower morbidity and mortality.<sup>20</sup>

#### Clinical Pearls:

1. Ultrasound should be considered as the first test, to noninvasively look for common bile duct dilatation and stones.



2. Coverage for cholangitis should involve broad-spectrum (gram-positive, gram-negative, anaerobic) coverage until culture results are available.
3. Biliary drainage within 24 hours is best accomplished by ERCP, with percutaneous drainage being an option.

### **Spontaneous Bacterial Peritonitis**

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Your patient with hepatitis C–induced cirrhosis presents with fever and abdominal pain. On examination, you note a distended abdomen with shifting dullness consistent with ascites, and generalized abdominal pain. A diagnostic paracentesis is performed.

#### Questions

1. How is spontaneous bacterial peritonitis (SBP) diagnosed?
2. What are the suggested antibiotic classes for treatment of SBP?

### **Discussion**

SBP is commonly seen in patients with cirrhosis. It should be differentiated from secondary peritonitis, in which there is usually an evident intra-abdominal source. Common clinical manifestations include fever, diffuse abdominal pain, and altered mental status in patients with known ascites. If left untreated, ileus, shock, and multi-system organ failure can develop. Patients with signs or symptoms suggestive of infection should undergo a diagnostic paracentesis. SBP is diagnosed with a positive ascitic fluid culture and an elevated fluid polymorphonuclear neutrophil (PMN) count ( $>250$  cells/mm<sup>3</sup>). Empiric treatment with antibiotics is recommended as soon as possible if the cell count is elevated, as culture results may be delayed.

The most common bacteria seen in SBP are *Escherichia coli*, *Streptococcus* species, and *Klebsiella pneumoniae*. Most antibiotic regimens use a third-generation cephalosporin (eg, cefotaxime) or a fluoroquinolone. Because of resistance issues, however, if a patient has already been on a fluoroquinolone for prophylaxis, this antibiotic class should not be used for treatment.

In patients with SBP who develop renal insufficiency, the expansion of plasma volume by IV albumin has been suggested to reduce morbidity and mortality. Additionally, the incidence of SBP in patients with cirrhosis who are hospitalized for gastrointestinal bleeding is fairly high (7%–23%); therefore, empiric treatment with antibiotics is recommended.<sup>21</sup>

#### Clinical Pearls

1. Empiric therapy for SBP is suggested in the presence of fever, abdominal pain, change in mental status, and ascitic fluid PMN higher than 250 cells/mm<sup>3</sup>.
2. Cefotaxime (or similar third-generation cephalosporin) is the treatment of choice for suspected SBP.
3. Patients with cirrhosis who have gastrointestinal bleeding should be empirically treated with antibiotics.

### **Secondary Peritonitis**

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Your patient with multiple medical problems is transferred to the hospital after developing severe, acute right lower quadrant pain. She is febrile and hypotensive with diffuse rebound abdominal tenderness. CT scan of the abdomen shows free air in the peritoneum.

#### Questions

1. What are the treatment considerations in an “acute abdomen” and sepsis syndrome?
2. What are the common antibiotic regimens for treatment of secondary peritonitis?

### Discussion

Secondary peritonitis usually refers to an infection after a serious disease or injury of the abdominal cavity. Most patients present with rapid-onset abdominal pain, gastrointestinal dysfunction (anorexia, nausea, vomiting, obstipation), and systemic inflammatory response syndrome criteria (hypothermia/hyperthermia, tachycardia, tachypnea, and leukopenia/cytosis). Most episodes of secondary peritonitis can be related to bowel (ie, appendicitis, diverticulitis, gastric ulcer, inflammatory bowel disease) perforation or genitourinary issues (ie, perinephric abscess). CT scan is the preferred imaging modality. Untreated, peritonitis often can lead to intraperitoneal abscesses and sepsis syndrome with significant morbidity and mortality. Intra-abdominal infections are predominantly (>80%) polymicrobial, as noted in **Table 1**, and empiric broad-spectrum antibiotics should be considered.

Common antibiotic regimens that may be used empirically to treat intra-abdominal infections are listed in **Table 2**. The 2010 guidelines suggest that patients are in the “high risk” group if the following factors are met: Delay in initial intervention (>24 hours), high severity of illness (Acute Physiology and Chronic Health Evaluation score >15), advanced age, comorbid organ dysfunction, low albumin or poor nutritional status, diffuse peritonitis, presence of malignancy, or inability to achieve adequate debridement or source control. Even though initiation of antibiotics is important, definitive treatment involves surgical exploration, and in selected cases, percutaneous drainage.<sup>20</sup>

#### Clinical Pearls

1. Intra-abdominal infections are polymicrobial and broad-spectrum antibiotics should be administered as soon as possible (within 8 hours, and within 1 hour if septic shock is present).
2. Early source control improves morbidity and mortality.

Table 1 Common organisms in secondary peritonitis/abdominal abscesses		
Gram Positive	Gram Negative	Anaerobes
<i>Enterococcus</i> sp	<i>Escherichia coli</i>	<i>Bacteroides</i> sp
<i>Streptococcus</i> sp	<i>Enterobacter</i> sp	<i>Clostridium</i> sp
<i>Staphylococcus aureus</i>	<i>Klebsiella</i> sp <i>Proteus</i> sp <i>Pseudomonas aeruginosa</i>	<i>Peptostreptococcus</i> sp <i>Fusobacterium</i> sp

Table 2 Empiric treatment of extrabiliary intra-abdominal infections		
	Mild-Moderate Severity	High Risk or Severity
Single agents	Ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic	Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam
Combination	Cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin in combination with metronidazole	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin in combination with metronidazole

### URINARY TRACT INFECTIONS

A 60-year-old diabetic woman presents to the ED with urinary urgency, dysuria, and flank pain. Her symptoms started 3 days ago but have intensified over the past

24 hours. She is febrile at 101°F, and her heart rate is 100, respiratory rate 18, and blood pressure 135/80. She is moderately distressed because of pain in her flank. Examination shows tachycardia and tenderness to palpation of the costovertebral angle on the right.

1. You initially suspect acute pyelonephritis. What imaging is necessary to establish this diagnosis?
  - a. Magnetic resonance imaging of the abdomen
  - b. Contrast-enhanced CT of the abdomen and pelvis
  - c. Abdominal radiograph
  - d. Abdominal ultrasound
  - e. No imaging is required
2. Emphysematous pyelonephritis is a possible complication of upper urinary tract infection. It is almost exclusively diagnosed in patients with what comorbidity?
  - a. Prior urinary tract instrumentation
  - b. Diabetes mellitus
  - c. Endocarditis
  - d. Prostatitis

Pyelonephritis is a common infection in women of all ages, with a predominance in the second and third decades of life. It most often results from ascending infection originating in the lower urinary tract. Diagnosis is largely made clinically in a patient with dysuria and flank pain. Imaging is not necessary unless to exclude obstruction or other structural abnormalities of the urinary tract.<sup>22</sup> Although most often readily treated with appropriate antibiotic therapy, it can progress to serious, life-threatening disease in various clinical scenarios. These include emphysematous and xanthogranulomatous pyelonephritis, and renal abscess.

Although treatment of uncomplicated cystitis does not require urine culture, 2010 IDSA guidelines highlight the importance of local resistance patterns in selecting therapy for cystitis and acute pyelonephritis. A 5-day regimen of nitrofurantoin (Macrobid) is recommended as first-line therapy for acute uncomplicated cystitis, with efficacy near 93%. Impaired renal function is a relative contraindication because of concern for increased toxicity and decreased efficacy. Use in patients with a glomerular filtration rate less than 60 is contraindicated. Pulmonary injury and severe peripheral neuropathy are among the major toxicities. Three days of trimethoprim-sulfamethoxazole (Bactrim) is an acceptable alternative if resistance of typical infecting organisms, such as *E coli*, is less than 20% in the area. Use of trimethoprim-sulfamethoxazole in the previous 3 months is considered a contraindication to its use for acute cystitis. To avoid development of resistance, fluoroquinolones are not recommended as first-line agents despite their efficacy. In addition, resistance of *E coli* to fluoroquinolones can exceed 20% in some areas.<sup>23</sup> Moreover, extended-spectrum beta-lactamase (ESBL)-producing *E coli* are increasingly common even in community settings. Effective oral therapy is limited, but fosfomycin appears to be a reasonable first-line choice.<sup>24</sup>

In contrast to cystitis, urine culture and sensitivity should be performed in all patients with suspected acute pyelonephritis. Further, first-line therapy in acute uncomplicated pyelonephritis is a fluoroquinolone, such as ciprofloxacin (Cipro), whether or not a patient is to be hospitalized. Initial IV therapy is recommended in patients requiring hospitalization. In every instance, if local resistance to fluoroquinolones exceeds 10%, alternative therapy should be considered, at least initially. For most patients, 1 g of ceftriaxone daily is an acceptable replacement. Once again ESBL-producing organisms are a consideration in pyelonephritis and should be treated with a carbapenem.<sup>24</sup> Treatment duration is related to choice of agent and ranges from 5 to 14 days.<sup>23</sup>

Urinary tract infections are considered complicated when associated with pregnancy, diabetes, immunosuppression, and functional or structural derangement of the genitourinary system, including presence of a urinary catheter. Infections in males are also generally considered complicated. Treatment of complicated infections requires urine culture, initial IV broad-spectrum antibiotic therapy, and 7 to 14 days of antibiotic.<sup>24</sup>

When symptoms of pyelonephritis fail to improve after 2 to 3 days of appropriate antibiotic therapy, development of one of the aforementioned complications should be considered. Imaging, such as CT or ultrasound, not required for most cases of acute pyelonephritis, should be performed. Dilation of the renal collecting system, discrete fluid collection, or gas in the renal parenchyma may be revealed, suggesting obstruction, abscess, or emphysematous pyelonephritis, respectively. Renal calculi are the most common source of obstruction and can contribute to any of these processes. Emphysematous pyelonephritis occurs almost exclusively in diabetic individuals (80%). Nephrolithiasis represents a significant predisposing factor, and women are afflicted 6 times as often as men.<sup>24,25</sup> Patients are typically quite ill and hemodynamically unstable. Mortality approaches 20% to 40%.<sup>24</sup> Xanthogranulomatous pyelonephritis is also strongly associated with renal calculi and is typically a chronic inflammatory and infectious process. Necrosis can lead to large abscess formation, affecting overall renal function.

In each of these complications, consideration for prompt intervention by interventional radiology or urology is indicated. Options include percutaneous nephrostomy and nephrectomy in severe cases. Broad-spectrum antibiotics are essential, pending cultures of urine, blood, and abscess fluid.<sup>24</sup>

#### Clinical Pearls

- Nitrofurantoin is IDSA recommended as first-line therapy for acute uncomplicated cystitis.
- Fosfomycin is reasonable oral therapy for uncomplicated cystitis caused by ESBL-producing organisms.
- Imaging is not necessary in most cases of acute uncomplicated pyelonephritis.
- Carbapenems are the mainstay of therapy in pyelonephritis caused by ESBL-producing organisms.
- Diabetes and renal calculi are common entities that confer substantial increased risk of serious complications from urinary tract infections.
- Emphysematous pyelonephritis, although rare, has substantial mortality and should be suspected in patients with gas in the renal parenchyma.
- Prompt urologic intervention for percutaneous drainage is indicated in cases of infection in the setting of obstruction.

#### SKIN AND SOFT TISSUE INFECTIONS

A 40-year-old man with diabetes presents to the ED with exquisite pain of the left forearm. He reports 2 days of increasing pain and swelling. He recalls no trauma. Examination reveals low-grade fever at 100.8°F and heart rate of 92 beats per minute. Blood pressure is 140/90 and respiratory rate is 16 breath per minute. He is in mild distress because of pain. His left arm is swollen compared with his right and is mildly erythematous at the forearm with ill-defined borders. It is very tender to palpation.

1. You suspect a soft tissue infection and are considering empiric antibiotic therapy. Were he to provide a history of salt water exposure, in addition to usual

- gram-positive, gram-negative, and anaerobic coverage, you would consider which of the following?
- Azithromycin
  - Doxycycline
  - Metronidazole
  - Vancomycin
2. You suspect necrotizing fasciitis (NF) and have ordered empiric antibiotics and blood cultures. The appropriate next step in management is
- Await Gram stain from blood cultures and tailor antibiotics appropriately
  - Order soft tissue imaging with MRI and await results to guide further therapy
  - Consult surgery for immediate evaluation and consideration of tissue exploration
  - Culture the skin overlying the erythema
3. The role of clindamycin in initial antibiotic therapy in cases of NF suspected to be caused by *Streptococcus pyogenes* or *S aureus* is related to
- Anaerobic coverage
  - Gram-negative coverage
  - Antipseudomonal coverage
  - Antitoxigenic effect in cases of suspected toxin-producing staphylococcal or streptococcal infection

NF describes a soft tissue infection involving the subcutaneous tissues from the skin to the underlying musculature. Although precise incidence is elusive, the Centers for Disease Control and Prevention report approximately 650 to 800 cases of NF caused by Group A Streptococcal (GAS) infection annually in the United States. This rate has remained stable over the past several years but likely underestimates true incidence, as many cases are not caused by GAS.<sup>26</sup> Mortality rates have fallen in recent years, but remain near 25% or greater in most series.<sup>27</sup> Mortality is far greater in cases with hemodynamic compromise, as in toxic shock syndrome. NF is often classified as Type I (polymicrobial), accounting for up to 80% of infections, or Type II (usually *S pyogenes*, *S aureus*, or a combination of the two). Some investigators describe a Type III, which denotes infection resulting from deep penetrating trauma and typically involves clostridial species.<sup>28</sup>

In any patient presenting with erythema, pain, and swelling of an extremity or of a site of recent injury, a diagnosis of NF should be considered. Several underlying diseases or conditions may predispose to necrotizing infections, including diabetes, IV drug use, peripheral vascular disease, chronic kidney disease, liver disease, and decubitus ulcers. Some inciting event or injury is present in up to 80% of cases. Exposure history is very important, as salt water, fresh water, and human and animal bites may suggest particular bacteriologic characteristics.

Examination may reveal erythema and edema with ill-defined margins. Blistering or bullae may be present and erythema may progress to bluish-gray discoloration or necrosis in a matter of 1 to 2 days. Pain is usually out of proportion to examination findings. Additionally, marked tenderness and a firm, woody feel to the subcutaneous tissues should prompt further investigation. Although imaging, including plain films, may help to identify depth of infection and gas in tissues, there is no substitute for prompt surgical exploration. If there is suspicion for NF, a small incision can be made at the bedside and a probe inserted into the wound. In the patient with NF, there will be little to no resistance of dissection down to muscle. Further, a classic “dish-water” exudate may be identified.<sup>28,29</sup> Gram stain of this fluid may help to tailor antibiotic therapy in the early stages of treatment, although blood cultures and tissue

culture obtained at surgery are superior. If initial exploration at the bedside supports a diagnosis of NF, further debridement should occur promptly in the operating room and continued until only viable tissue remains. Patients should be reexplored in the operating room within 24 hours. Although NF usually presents and progresses rapidly, it may occur more insidiously and present first as cellulitis. Clues to development of NF and therefore indications for surgical exploration and debridement in a patient being treated for cellulitis include failure to respond to antibiotics, hemodynamic compromise, and skin necrosis or subcutaneous gas.

As aforementioned, NF may be polymicrobial or monomicrobial. Clues to polymicrobial or Type I infection include involvement of a decubitus ulcer, recent bowel surgery, infection at the injection site in IV drug users, and spread from a perineal lesion. Fournier gangrene describes such an infection of the perineum, classically in males, typically arising from a genitourinary source. Ludwig angina refers to NF in the neck and mediastinum, which typically originates from oral flora. Organisms may be numerous, with an average of 5 isolates, and typically include aerobes and anaerobes. Because of their respective locations and the marked morbidity and mortality associated with local spread, these infections can be particularly severe. In all cases of suspected Type I NF, initial antibiotic therapy should include agents directed at gram-positive bacteria, anaerobes, and enteric gram negatives. Additional therapy targeting resistant gram positives and gram negatives should also be considered (**Box 1**).

Type II infection should be suspected when disease presents in the extremities in patients with some predisposing condition or recent superficial injury. Such injuries may range from scratches to insect bites to recent varicella infection. Group A streptococcus (*S pyogenes*) and *S aureus* are the most common isolates; however, in patients with saltwater exposure, especially those with underlying liver disease or a history of alcohol abuse, *Vibrio vulnificus* should be suspected. Similarly, in patients with freshwater exposure, *Aeromonas hydrophila* should be considered. Tetracyclines are shown to be effective against both of these water-borne bacteria and should be added in patients with a suggestive history. Because of the prevalence of resistant *S aureus* species, strong consideration should be given to gram-positive coverage directed at MRSA.<sup>5</sup> In addition to its activity against gram-positive bacteria, clindamycin is a mainstay of therapy in both type I and type II infection because of its antitoxigenic effects.<sup>29,30</sup> **Box 1** presents a summary of antibiotic recommendations.

There is growing literature on the role of IV immune globulin (IVIG) in the treatment of hemodynamically unstable patients with NF.<sup>28,30</sup> The mechanism of action centers around antibody neutralization of exotoxins and resultant modification of the inflammatory response seen in toxic shock syndrome. It is reasonable to consider early initiation of IVIG in patients who are hypotensive with suspected staphylococcal or streptococcal infection. Hyperbaric oxygen therapy has been suggested, based on similar antitoxigenic effects and the role of high oxygen tensions in combating anaerobic organisms. True benefit to morbidity and mortality requires further study.

#### Clinical Pearls

- Early surgical intervention is mandatory and should not be delayed.
- Clindamycin has significant benefit not only related to its antimicrobial spectrum, but also to its antitoxigenic effects.
- Water exposure should prompt consideration of *Vibrio vulnificus* (salt water) or *Aeromonas Hydrophila* (fresh water) infection and addition of doxycycline therapy.
- IVIG may be an important tenet of therapy in patients with hemodynamic compromise or organ failure.

**Box 1****Initial intravenous antibiotic selection by disease type**

## Type I Infections

Piperacillin-tazobactam<sup>a,b</sup> (Zosyn) 3.375 g every 6 hours plus

Clindamycin 600–900 mg every 6–8 hours plus

Ciprofloxacin (Cipro) 400 mg every 12 hours

## Type II infections

Clindamycin 600–900 mg every 6–8 hours plus

Vancomycin<sup>c</sup> 30 mg/kg/d divided into 2 doses or

Linezolid (Zyvox) 600 mg every 12 hours

If *Vibrio vulnificus* or *Aeromonas hydrophila* suspected, add –

Doxycycline 1 g every 12 hours

<sup>a</sup> Some authorities advocate antibiotic coverage directed against MRSA in all patients. In this case, vancomycin can replace piperacillin-tazobactam.

<sup>b</sup> Patients who are allergic to penicillin may also be treated with vancomycin in lieu of piperacillin-tazobactam.

<sup>c</sup> Some authorities advocate penicillin, nafcillin, or ceftazidime as first-line therapy, but current concerns favor initial coverage for MRSA.

Data from Refs.<sup>28–30</sup>

A 65-year-old man with history of hypertension presents within 2 hours after suffering a fall in his garden. He had been preparing stakes for tomato plants when he fell onto the sharp point of one of the stakes. He suffered a penetrating wound to the right shoulder and complains of pain in that area. At initial examination, he is afebrile and hemodynamically stable. He has a deep wound to the right deltoid area. He is given a tetanus immunization. The wound is irrigated and sutures applied. He is discharged from the ED. One day later, he returns with erythema and edema in the area of the wound and feeling weak. He is febrile to 101.4°F with a heart rate of 110 per minute and blood pressure of 110/60 mm Hg. Blisters now overlie the area and it is very tender to palpation.

- Given the deep penetrating wound and soil exposure, you consider which of the following organisms?
  - Pseudomonas aeruginosa*
  - Enterococcus*
  - Clostridium perfringens*
  - Escherichia coli*
- Infection with which of the following organisms should prompt investigation for occult gastrointestinal malignancy?
  - Pseudomonas aeruginosa*
  - Clostridium septicum*
  - Clostridium perfringens*
  - Escherichia coli*

Clostridial myonecrosis is a subset of necrotizing soft tissue infections responsible for fewer than 5% of cases. Some authorities refer to it as type III NF.<sup>27</sup> More than half of cases can be traced to some type of deep penetrating trauma or a crush injury,

whereas approximately one-third are related to surgery (usually gastrointestinal). The remainder are spontaneous.<sup>31</sup> Causal organisms include several clostridial species, including *perfringens*, *septicum*, *histolyticum*, and *novyi*. Predisposing conditions are similar to other causes of NF, although isolation of *C septicum*, particularly in patients without antecedent injury or surgery, should prompt investigation for colonic or hematologic malignancy, as these have been found in up to 80% of cases.<sup>28</sup>

Hallmarks of clostridial infection include extremely rapid progression, bullae on the skin, gas in the tissues, and early onset of hemodynamic compromise and organ failure. Hemodynamic instability is related largely to multiple toxins produced by the organism. Although classically described as gram-positive bacteria, clostridia may appear gram positive or gram negative when stained from infected tissue.<sup>30</sup>

Treatment is once again early surgical debridement and antibiotic therapy. First-line therapy is clindamycin (for antimicrobial and antitoxigenic effects) with the addition of penicillin, primarily because 5% of isolates are clindamycin resistant. IVIG and hyperbaric oxygen therapies are additional therapeutic modalities. Evidence for hyperbaric oxygen is stronger for clostridial species than some other bacteria because they are strict anaerobes.

#### Clinical Pearls

- *Clostridium* infection may be marked by extremely rapid progression of local infection (up to 2 cm/h)<sup>28</sup> and hemodynamic compromise.
- Gas in tissues is a diagnostic clue, although not exclusive to *Clostridium*.
- Clindamycin is a vital part of effective antibiotic therapy.
- Spontaneous infection with *C septicum* is associated with gastrointestinal or hematologic malignancy in 80% of cases.

A 24-year-old man presents several hours after suffering a wound to his right hand. He was in an altercation at a bar and suffered the wound when he punched another patron in the mouth. He reports moderate pain in the right hand. He is afebrile with stable vital signs. There are abrasions along the metacarpal phalangeal joints (MCPs) of his right hand and a 0.5-mm laceration over the third MCP. There is minor swelling and pain with active motion.

1. Which of the following represents appropriate initial management?
  - a. Cleanse and suture the wound.
  - b. Cleanse the wound and discharge the patient without further therapy. Tell him to return if he develops fevers or drainage from the wound.
  - c. Consult general surgery to evaluate the wound.
  - d. Begin empiric antibiotic therapy.

Human bite wounds may result from actual bites or from trauma involving one person's body part striking the teeth of another. Physical altercations are often involved. Common isolates include streptococci (present in 80% of cases), *S aureus*, *Eikenella corrodens* (10% to 29% of cases), and *Fusobacterium* species.<sup>29,32</sup> Typical infections include 5 or more isolates and include anaerobes in more than 60% of cases. Many anaerobic isolates are beta-lactamase producers.<sup>29</sup>

No matter the time interval from injury to presentation, copious irrigation and local wound disinfection should be performed on all human bite wounds. Wounds should not be sutured.<sup>32</sup> All patients should be assessed for appropriateness of tetanus toxoid administration. Prophylactic antibiotics are mandatory in even the most superficial wounds. For hand wounds, as in the patient described in the question,



consultation with a surgeon with expertise in hand injuries should be sought. Exploration to evaluate for involvement of the joint and/or tendon is often necessary in puncture wounds.<sup>29</sup> Imaging, including plain films, can help uncover fractures, gas in the tissues, and osteomyelitis.

Optimal antibiotic therapy must consider the common organisms and their particular resistance patterns. Amoxicillin/clavulanate (Augmentin) is an acceptable prophylactic agent but will not cover MRSA or some of the gram-negative rods common in infected bite wounds. Patients should be reassessed with short-term follow-up. In actively infected wounds, hospital admission and IV antibiotic therapy in addition to hand surgeon consultation are appropriate.<sup>4</sup> In these cases, broad-spectrum antibiotic therapy, often with more than one agent, is required. IDSA guidelines, currently in revision, are noncommittal but are summarized in **Box 2**.

Animal bite wounds are more common than human bites, but tend to be less severe from an infectious disease standpoint. Dogs and cats are the most common culprits and again the wounds typically involve several microbes, including aerobes and anaerobes. *Bacteroides*, propionibacteria, and fusobacteria are common anaerobes. In 40% or more cases, staphylococci and streptococci are present. *Pasteurella* species are present in 75% and 50% of cat and dog bites respectively. Mild cases can often be treated effectively with amoxicillin-clavulanate. More severe cases require IV therapy. Typical duration of therapy is 5 to 10 days but is guided by severity.<sup>29</sup>

#### Box 2

##### Suggested antibiotics for infected human and animal bite wounds requiring hospitalization

###### Human

- Cefoxitin<sup>a</sup> 1 g IV every 6–8 hours OR
- Ampicillin-sulbactam<sup>a</sup> 1.5–3.0 g IV every 6–8 hours OR
- Moxifloxacin<sup>b</sup> 400 mg IV every 24 hours

###### Animal

- Ampicillin-sulbactam OR
- Piperacillin-tazobactam 3.375 g every 6–8 hours OR
- Meropenem 1 g every 8 hours OR
- Moxifloxacin plus clindamycin

<sup>a</sup> Additional therapy targeting MRSA and/or resistant *Eikenella* may include trimethoprim-sulfamethoxazole and doxycycline.

<sup>b</sup> Additional therapy targeting MRSA and some anaerobes may include clindamycin.

Data from Nolan CM, Beaty HN. *Staphylococcus aureus* bacteremia. Current clinical patterns. Am J Med 1976;60(4):495.

#### Clinical Pearls

- Dog and cat bites commonly involve *Pasteurella* species.
- Human bites often involve *Eikenella* species, which may be resistant.
- Both bites may also include staphylococci and streptococci.
- Augmentin is often sufficient treatment for animal bites and for prophylaxis after human bites.

- Antimicrobial prophylaxis is a necessity following human bites.
- Human bites, particularly those in the hand, often require specialized surgical evaluation.
- Most human bite wounds should not be sutured early on.
- More severe infections require IV antibiotics, with careful consideration for likely resistant organisms.

## SEPSIS SYNDROMES

A 32-year-old male IV drug user presents to the ED complaining of fevers and fatigue for the past 2 weeks with rapidly worsening dyspnea over the past 4 days. On arrival, the patient is in respiratory distress, with a heart rate of 100 beats per minute, and a WBC count of 14,000/ $\mu\text{L}$ . His chest radiograph reveals widespread round opacities. What is the most likely diagnosis?

This patient meets the definition of sepsis in this scenario: systemic inflammatory response syndrome (SIRS) with a suspected microbial etiology (right-sided endocarditis in this case given his history of IV drug use) (**Box 3**).

*S aureus* is the most common cause of infective endocarditis among injection drug users<sup>33</sup> and about a third of patients with *S aureus* bacteremia have infective endocarditis.<sup>34</sup> Septic pulmonary emboli (as demonstrated here) are common, specifically in patients with tricuspid involvement.<sup>35</sup>

### ***What is the Next Step in Management?***

The mortality rate for *S aureus* bacteremia is around 20%, with MRSA carrying a higher mortality.<sup>36</sup> Therefore, MRSA must be empirically treated with vancomycin, and changed to nafcillin or oxacillin if methicillin-susceptible *S aureus* (MSSA) is grown. Parenteral therapy is the preferred route of treatment; however, oral therapy can be used to complete a full course of therapy if IV is not an option or to provide a longer course of therapy in selected patients. Dicloxacillin and cephalexin are the preferred oral alternatives for MSSA. For MRSA, the choices include trimethoprim-sulfamethoxazole, doxycycline, and linezolid (see **Table 3**).

The emergence of *S aureus* with diminished vancomycin susceptibility has been fully anticipated. Vancomycin-intermediate *S aureus* (VISA) is defined as having a minimal inhibitory concentration (MIC) of 4 to 8  $\mu\text{g/mL}$ . Vancomycin-resistant *S aureus* (VRSA) is defined as having a MIC higher than 16  $\mu\text{g/mL}$ . In these cases, an alternative antimicrobial (eg, daptomycin, linezolid) should be chosen (**Table 3**).

#### **Box 3** **SIRS**

*SIRS (2 or more)*

1. Temperature  $>38.3^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$
2. Heart rate  $>90$  beats per minute
3. Respiratory rate  $>20$  breaths per minute or  $\text{Paco}_2 <32$  mm Hg
4. WBC  $>12,000$  cells/ $\text{mm}^3$ ,  $<4000$  cell/ $\text{mm}^3$ , or  $>10\%$  band forms

*Data from Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet 2005;365(9453):63.*

<b>Table 3</b>	
<b>Treatment for <i>Staphylococcus aureus</i> bacteremia</b>	
<b>Empiric Treatment</b>	
Vancomycin (30 mg/kg per 24 h in 2 equally divided doses)	
Continue if <i>S aureus</i> is resistant to methicillin and sensitive to vancomycin	
Prove methicillin-susceptible <i>S aureus</i> , change to nafcillin or oxacillin (2 g every 4 h)	
OR	
Cefazolin (2 g every 8 h)	
<b>Alternative Agents</b>	
Daptomycin (6 mg/kg once daily)	For <i>S aureus</i> bacteremia and right-sided endocarditis, monitor weekly creatine phosphokinase levels.
Linezolid (Zyvox)	Monitor for side effects (thrombocytopenia, anemia, neuropathy). Beware of resistance.
Quinupristin-dalfopristin	Requires central venous administration due to risk of severe infusion-associated phlebitis. Monitor for side effects (hyperbilirubinemia, myalgias). Beware of resistance.
Trimethoprim-sulfamethoxazole (Bactrim)	
Clindamycin (600 mg every 8 h)	D test should be performed to ensure they are D-zone negative.
Minocycline (100 mg every 12 h)	
Levofloxacin/Levaquin (500 mg daily)	

### ***Is a Transesophageal Echocardiogram Necessary in all Patient with S aureus Bacteremia?***

Not always. Transesophageal echocardiogram (TEE) may not be necessary if the following criteria are not met: (1) prolonged bacteremia longer than 4 days, (2) presence of a permanent intracardiac device, (3) hemodialysis dependency, (4) spinal infection or nonvertebral osteomyelitis.<sup>37</sup>

#### Clinical Pearls

1. About a third of patients with *S aureus* bacteremia have infective endocarditis.
2. Recognize the emergence of VISA and VRSA strains.
3. TEE is not always necessary in *S aureus* bacteremia.

A 72-year-old man on chronic hemodialysis was admitted 1 week ago to the ICU for volume overload and acute respiratory failure requiring mechanical ventilation. Over the past 2 days, the patient has become febrile to 102°F. He is now requiring vasopressors, and has developed worsening respiratory alkalosis and an oval 1-cm ecthymic lesion with a halo of erythema on his chest. What is the most likely diagnosis?

Given that this patient is hospitalized in a critical care unit, nosocomial infection is high on the differential. Manifestations of gram-negative bacilli infections include fevers/chills, disorientation, hypotension, respiratory alkalosis, and respiratory failure in 25% of cases.<sup>38</sup>

Pathogenesis involves release of endotoxins. Ecthyma gangrenosum (seen in this patient) results from perivascular bacterial invasion with secondary ischemic necrosis, and are more common in *P aeruginosa* infections.<sup>39</sup>

Infections caused by gram-negative bacilli have decreased overall; however, emergence of multidrug resistance continues to be a rising problem.<sup>40</sup> Risk factors include

chronic comorbidities, hypoalbuminemia, organ transplantation, HIV infection, glucocorticoid use, being elderly, recent urogenital surgery, or injury during a natural disaster involving water.

Although most gram-negative infections arise from the urinary tract, the most common source in patients in the ICU is the respiratory tract.<sup>41</sup> In these patients, the common species isolated include *Enterobacter* species, *K pneumoniae*, and *P aeruginosa*. *E coli* is the most common species isolated in the community.

### ***What is the Next Step in Management?***

See **Box 4** for empiric treatment of gram-negative bacteremia in immunocompetent patients; however, antibiotic resistance must be considered, as it contributes to an increase in mortality. ESBL-producing organisms (*E coli*, *K pneumoniae*) inactivate and confer resistance to most beta-lactam agents (including penicillins, cephalosporins, and aztreonam). There has been emergence and dissemination of new ESBLs, particularly CTX-M beta lactamases and more carbapenemases.

### ***Should I Provide Double Coverage for P aeruginosa?***

Whether to use 1 or 2 drugs for *P aeruginosa* is controversial; however, a broad-spectrum antibiotic combination is recommended for patients with severe sepsis or septic shock or when the level of resistance among the most common gram-negative pathogens in a hospital is more than 20% to 25%.<sup>42</sup> Vancomycin should be added if culture results are not yet available.

Definitive antibiotic therapy should be based on culture and susceptibility results; however, if the isolate is an *Enterobacter* sp, treat with cefepime or a carbapenem even if the isolate appears to be sensitive to a third-generation cephalosporin or a beta-lactam/beta-lactamase inhibitor. This is because of the high rate of resistance that may develop during treatment.

#### Clinical Pearls

1. Although gram-negative bacilli infections have decreased, multidrug resistance continues to cause difficulties in empiric antibiotic selection.
2. Consider combination broad-spectrum antibiotics in patients with severe sepsis or septic shock, or when the level of resistance among the most common gram-negative pathogens in a hospital is more than 20% to 25% (see **Box 5**).

#### **Box 4**

##### **Empiric antibiotic choices for gram-negative sepsis**

###### Immunocompetent Patients

Antipseudomonal cephalosporin (ceftazidime 2 g every 8 hours or cefepime 2 g every 12 hours)

OR

Beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam/Zosyn 4.5 g every 6 hours, ticarcillin-clavulanate/Timentin 3.1 g every 4 hours)

OR

Carbapenem (eg, imipenem 500 mg every 6 hours, meropenem 1 g every 8 hours, doripenem 500 mg every 8 hours, or ertapenem 1 g once daily)

If patient grows a multiresistant gram-negative bacteria not susceptible to the above agents, consider Colistin (100–200 mg every 8–12 hours).

**Box 5****Combination broad-spectrum therapy for antibiotic regimens**

Amikacin (7.5 mg/kg every 12 hours) PLUS 1 of the following:

Antipseudomonal cephalosporin (eg, cefepime 2 g every 12 hours or ceftazidime 2 g every 8 hours)

OR

Antipseudomonal beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam 4.5 g every 6 hours or ticarcillin-clavulanate 3.1 g every 4 hours)

OR

Carbapenem (eg, imipenem 500 mg every 6 hours or meropenem 1 g every 8 hours, or Doripenem 500 mg every 8 hours)

A 36-year-old previously healthy woman presents to the ED complaining of severe lethargy and fevers. Per family, the patient developed a diffuse red rash followed by some sloughing of the palms and soles. She had a recent motor vehicle accident resulting in some lacerations along her arms and legs. On arrival to the ED, she requires intubation because of acute respiratory failure. Blood pressure is 90/60 mm Hg. She is found to have a profound transaminitis as well as acute renal failure.

***What is the Most Likely Diagnosis?***

Toxic shock syndrome (TSS) can be caused by either *S aureus* or group A streptococcus (GAS). Staphylococcal toxic shock must be considered in association with recent surgery, any localized staphylococcal abscess, osteomyelitis, or respiratory infection following influenza. *S aureus* strains that produce exotoxins result in 3 syndromes: food poisoning resulting from ingestion of *S aureus* enterotoxin, scalded skin syndrome (caused by exfoliative toxin), and toxic shock syndrome, caused by toxic shock syndrome toxin-1.

Severe invasive GAS infections can manifest as bacteremia, pneumonia, or necrotizing fasciitis. Toxins activate the immune system, resulting in a release of large quantities of inflammatory cytokines causing capillary leak and tissue damage, which leads to shock and multiorgan failure. Risk factors for developing TSS include minor trauma, surgical procedures, use of tampons, viral infections (varicella, influenza), and the prior use of NSAIDs.<sup>43</sup>

***How is the Diagnosis Made?***

Diagnosis of TSS is made clinically (see **Box 6**).<sup>44,45</sup>

***What is the Next Step of Management?***

Management includes hemodynamic support, aggressive surgical debridement, and empiric antibiotics (which includes clindamycin to inhibit toxin production).

- Initial empiric antibiotics should include clindamycin (900 mg IV every 8 hours) PLUS a carbapenem OR a penicillin plus beta-lactamase inhibitor combination drug (ticarcillin-clavulanate or piperacillin-tazobactam) PLUS vancomycin.
- Once microbiologic diagnosis is established, antibiotics can be tailored to include clindamycin (900 mg IV every 8 hours) PLUS vancomycin/linezolid for *S aureus* OR penicillin G for GAS.
- IVIG may be considered in severe cases.

**Box 6****Clinical criteria for the diagnosis of TSS***Clinical criteria for staphylococcal TSS:*

Fever (temperature >38.9°C)

PLUS

Hypotension

PLUS

Diffuse macular erythroderma ± desquamation

PLUS

Multisystem involvement (3 or more of the following: gastrointestinal, muscular, mucous membranes, renal hepatic, or hematologic, CNS)

*Clinical criteria for diagnosis of GAS TSS:*

Isolation of GAS from a normally sterile site

PLUS

Hypotension

PLUS

Two or more of the following: renal impairment, coagulopathy, liver involvement, adult respiratory distress syndrome, erythematous macular rash (which may desquamate) or soft tissue necrosis.

**Clinical Pearls**

1. In a patient with a local wound or other risk factors discussed previously with fever, hypotension, and skin manifestations, consider TSS.
2. Clindamycin is useful in mitigating toxin effects.
3. IVIG may have some role in severe cases.

A 24-year-old man with a history of sickle cell disease sees his primary care physician for headache and purulent nasal drainage. He is diagnosed with acute bacterial sinusitis and given a course of amoxicillin. Three days later, he presents to a local ED complaining of intractable rigors, disorientation, and a sudden rise in temperature to 102.6°F. He is found to be hypotensive on arrival. What is the most likely diagnosis?

The spleen filters blood through a series of capillaries. Mononuclear phagocytes within this system ingest circulating bacteria and process foreign material to stimulate the production of opsonizing antibody, which is imperative in clearing encapsulated organisms.

Asplenic patients (such as patients with sickle cell disease) are at increased risk for postsplenectomy sepsis (PSS). PSS is a fulminant and rapidly fatal complication of bacteremic infections caused by encapsulated organisms such as *S pneumoniae*, *N meningitidis*, and *H influenzae*. They are also at risk for parasitic infections, such as malaria and babesiosis. In a review of 349 episodes of sepsis in patients with anatomic or functional asplenia, *S pneumoniae* accounted for 57% of infections and 59% of deaths.<sup>46</sup>

***How do These Patients Typically Present?***

PSS may follow minor upper or lower respiratory tract symptoms; however, it can develop rather precipitously, presenting with complications of high-grade bacteremia with petechiae, purpura, meningitis, and hypotension.

Laboratory results reveal an elevated or markedly depressed WBC count with a marked left shift and bandemia. Earlier myeloid forms with toxic granulations and Dohle bodies can also be seen. Howell-Jolly bodies may be present, revealing evidence of asplenia. Other findings may include thrombocytopenia and DIC, along with evidence of multiorgan dysfunction. Spinal fluid may not have significant abnormalities during the early course; however, culture may be positive. Chest radiography may reveal cardiomegaly and a primary pneumonitis. Blood cultures often turn positive within hours of inoculation.

### ***Is Antigen Testing Helpful to me?***

The pneumococcal antigen test is a rapid immunochromatographic membrane assay that detects the presence of capsular polysaccharide common to all serotypes of *S pneumoniae*. The test is approved for the diagnosis of invasive pneumococcal disease using urine samples and, because most patients with pneumococcal meningitis are also bacteremic, it can also be used for the diagnosis of pneumococcal meningitis (by testing CSF or urine). Its sensitivity is 75%, whereas its specificity nears 95% compared with traditional microbiology.<sup>47</sup>

### ***What is the Next Step in Management?***

Appropriate broad-spectrum antibiotic therapy and supportive measures (including mechanical ventilation) must be rapidly instituted. Patients tend to have minimal response to fluid resuscitation, therefore inotropic agents are generally necessary (Table 4).

Splenectomy or asplenia was a risk factor for penicillin nonsusceptibility of *S pneumoniae* in a prospective international observational study of 844 patients with pneumococcal bacteremia.<sup>48,49</sup>

Even with appropriate antimicrobial treatment, pneumococcal meningitis has a mortality rate of 20% to 30%.

#### Clinical Pearls

1. Asplenic patients are at increased risk for PSS.
2. The pneumococcal antigen test in urine is a highly specific diagnostic test, and useful for the diagnosis of invasive pneumococcal disease.
3. Always consider penicillin-resistant pneumococcal infections and beta-lactamase producing *H influenzae* when choosing initial empiric therapy in patients who are postsplenectomy/asplenic.

<b>Table 4 Empiric therapy for postsplenectomy sepsis</b>	
<b>Initial Empiric Therapy</b>	<b>If Meningitis is Suspected</b>
Vancomycin 1 g IV every 12 h	Vancomycin 30–60 mg/kg IV/d in divided doses
PLUS	PLUS
Ceftriaxone (2 g IV daily) <sup>a</sup>	Ceftriaxone (2 g IV twice daily) Dexamethasone - in patients with suspected pneumococcal meningitis (15–20 min before or at the time of first dose of antibiotic administration).

Abbreviation: IV, intravenous.

<sup>a</sup> If patient has a beta-lactam allergy, may substitute levofloxacin 750 mg for ceftriaxone.

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