CHAPTER 32

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Infections in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the pathophysiology of specific infections in the ICU.
- Identify infectious complications in critically ill patients.
- Conduct appropriate diagnostic work-up for infections encountered in the ICU.
- Develop a systematic approach for managing ICU-related infections.
- Execute effective measures to prevent infectious complications in the ICU.
- Understand how to effectively work up and treat patients with sepsis.
- Choose the appropriate antimicrobial regimen for either empiric or culture-focused treatment of ICU infections.

COMMUNITY-ACQUIRED PNEUMONIA

Epidemiology

CAP is defined as pneumonia acquired outside of a hospital or long-term care facility.

Community-acquired pneumonia (CAP) is defined as pneumonia acquired outside of a hospital or long-term care facility. Estimates indicate that there are approximately 1 million hospitalizations annually in the United States for this serious illness,[1] with approximately 10% requiring ICU admission.[§] Many pathogens can cause CAP; some are related to specific epidemiologic conditions and/or risk factors. The patient's history is important when attempting to account for these potential etiologies. These include exposures (e.g., to animals and/

or their droppings), travel, time of year, presence of comorbid disease (underlying lung disease being most important), and immunosuppressive states. The emergence of drug-resistant pneumococcal isolates as well as community-associated, methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has led to differences in the ways physicians think about and manage CAP. Risk factors for β-lactam resistant *Streptococcus pneumoniae* infection include advanced age, recent β-lactam use, alcoholism, medical comorbidities, immunosuppressive illness or therapy, and exposure to children. Local antibiotic prescribing patterns may influence resistance patterns as well.

Risk factors for CAP caused by gram-negative rods include chronic steroid use, underlying pulmonary disease, and alcoholism.

Pathogenesis and Microbiology

CAP may be caused by many different pathogens, the most common of which are bacteria. The distribution of these pathogens varies with the clinical setting. *S. pneumoniae* is isolated most frequently as the etiologic cause of CAP requiring hospitalization (both ICU and non-ICU level of care). Other common causes of severe CAP treated in the ICU include *Legionella* spp., gram-negative bacilli (e.g., *Enterobacteriaceae* spp. and *Pseudomonas aeruginosa)*, and *S. aureus*.[2] Lower proportions of severe CAP (as compared with CAP not requiring ICU level of care) are caused by respiratory viruses and *Haemophilus influenzae*. The frequency of other potential etiologic agents, such as endemic fungi, will vary with the epidemiologic setting.

The three most common bacterial pathogens causing CAP are *S. pneumoniae, H. influenzae, and Moraxella catarrhalis.* In severe CAP, *S. pneumoniae* remains the most common pathogen, followed by *Legionella* spp. and gram-negative bacilli.

An increasing incidence of CAP due to CA-MRSA has been seen more recently. These strains are different from the hospital-acquired strains in both virulence and resistance patterns and can be associated with a necrotizing or cavitary pneumonia that often leads to shock and respiratory failure.[2] Most of these organisms contain the gene for Panton-Valentine leukocidin, a toxin that is associated with these clinical features.[2] CAP caused by gram-negative rods such as *Klebsiella pneumoniae* and *P. aeruginosa* is less common but may be encountered in patients with risk factors such as chronic steroid use, severe pulmonary disease, and alcoholism. These pathogens may cause a severe, necrotizing form of pneumonia requiring ICU management.

CAP caused by CA-MRSA may present as an aggressive necrotizing or cavitary pneumonia.

Clinical Features

Symptoms suggestive of pneumonia include respiratory complaints such as cough, sputum production, dyspnea, and pleuritic pain, as well as fever. Chest radiography should be performed on presentation and usually reveals pulmonary infiltrates. Lack of visible infiltrates may be secondary to dehydration, neutropenia, or early presentation. Computed tomography (CT) is more sensitive in determining the presence of pulmonary infiltrates and may be indicated if the presence of complications such as effusion, empyema, or adenopathy is suspected. Microbiologic data are used as supportive evidence for the diagnosis of CAP and may aid in the determination of appropriate treatment. Sputum Grams stain and culture have been traditionally viewed as low yield but can be quite helpful.[3] Identification of an organism along with sensitivity data can help physicians tailor antimicrobial therapy. In patients who require intubation, an endotracheal sample can be easily obtained. Inability to obtain an adequate sputum sample should not delay therapy. In addition to sputum cultures, blood cultures should be performed in patients with severe CAP. Blood cultures can reveal the infective organism even when sputum cultures are negative. Blood cultures are most helpful when drawn prior to initiation of antimicrobial therapy.

Diagnostic work-up of severe CAP should includee a sputum culture and blood cultures.

Cultures should be drawn prior to the initiation of antimicrobial therapy to increase their yield.

Severity of illness determinations can help physicians place patients in the appropriate treatment setting and may help define appropriate empiric therapy. Patients admitted with a diagnosis of CAP requiring ICU level of care will often present with respiratory failure and septic shock requiring intubation and subsequent mechanical ventilatory support. There are subsets of patients, however, who do not meet these "major" criteria and may still require treatment in an ICU. The 2007 joint IDSA/ATS consensus guidelines on the management of CAP in adults endorse the use of the CURB-65 or Pneumonia Severity Index (PSI) in conjunction with sound clinical judgment to guide site of care decisions.[§] Use of the CURB-65

criteria (confusion, uremia, respiratory rate, low blood pressure, age ≥65) will generate a severity of illness score. Patients with scores ≥2 require intensive therapy, likely in an ICU setting. The PSI consists of 20 different variables in an attempt to quantify illness severity that is then linked to an appropriate management setting (outpatient treatment, brief inpatient observation, or more traditional inpatient therapy). The benefit of the CURB-65 criteria is its ease of use; however, it is not as well validated as the PSI. The 2007 IDSA/ATS CAP guidelines outline consensus criteria to define severe CAP in an attempt to predict ICU admission needs.[§] The presence of septic shock requiring vasopressors and/or mechanical ventilation with endotracheal intubation are absolute indications for ICU admission. These are considered the major criteria in their model. Minor criteria were developed based on previous prediction models in an attempt to define those patients with an increased risk of death. The minor criteria consist of the CURB-65 criteria minus the age delineation. In addition, they also include several other indices: a PaO_2/FiO_2 ratio ≤250, the presence of multilobar infiltrates, the presence of leukopenia, and the presence of hypothermia. The threshold for ICU admission, using these criteria, is the presence of any one major criterion or at least three minor criteria.[§]

Treatment

When the patient's history suggests aspiration pneumonia, the empiric antimicrobial regimen used should cover anaerobic organisms.

The cornerstone of treatment of CAP is antimicrobials. In the ICU these medications are often used in conjunction with other treatment modalities for sepsis as well as ventilatory support for respiratory failure. In the presence of criteria of acute lung injury or acute respiratory distress syndrome (ARDS), ventilatory strategies using positive end expiratory pressure (PEEP) and low tidal volume are recommended. In critically ill patients with CAP, empiric therapy is broad and use of multiple antimicrobials is often necessary. Recommended standard empirical regimens should include coverage for the three most common bacterial pathogens, all of the atypical organisms, and most *Enterobacteriaceae* spp.[§] The patient's history will dictate whether other organisms need to be considered and, if so, what appropriate alterations to empiric therapy need to be made. It is at this point that a decision to cover for infection with MRSA or *Pseudomonas* spp. is made, as well as for other potential pathogens.

Empiric regimens for CAP should include coverage for the three most common bacterial pathogens, all of the atypical organisms, and most *Enterobacteriaceae* spp.

A β-lactam (cefotaxime or ceftriaxone) plus either azithromycin or a fluoroquinolone is the narrowest spectrum of antibiotics recommended for empiric treatment of CAP in the ICU.[§] In penicillin-allergic patients a respiratory fluoroquinolone and aztreonam is adequate initial coverage. The main alterations to these proposed regimens are when infection with MRSA or *Pseudomonas* is suspected. In the case of infection with *Pseudomonas*, an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg dose) can be used. If MRSA infection is suspected, vancomycin or linezolid should be added. Anaerobic coverage should be initiated in addition to above therapies when aspiration is suspected. Physicians should be aware of epidemiological considerations that may further alter empiric therapy and then adjust treatment as needed. Once the causative pathogen has been identified, antimicrobial therapy should be tailored (see Table 32-1). Should microbiologic testing prove to be unrevealing, empiric therapy may need to be continued for the full course.

ACUTE BACTERIAL MENINGITIS

Epidemiology

Acute bacterial meningitis (ABM) is a severe life-threatening infection involving the membranes of the central nervous system (CNS). ABM often presents in a fulminant fashion with multiple complications resulting in a high fatality rate despite the availability of potent antimicrobial therapy. The annual incidence of ABM is approximately 4–6 cases per 100,000 population in the United States.[4] Mortality rates vary and depend on the type of invading pathogen as well as the patient-specific risk factors (e.g., age and comorbid illness). Over

TABLE 32-1

COMMUNITY-ACQUIRED PNEUMONIA: ICU PATHOGENS AND THEIR TREATMENT

Common bacterial pathogens	*Streptococcus pneumoniae*	Penicillin or amoxicillin (if MIC <2) (otherwise choose agent based on susceptibility testing)
	Haemophilus influenzae	Amoxicillin or second or third-generation cephalosporin (β-lactamase producing)
Atypical organisms	*Legionella* spp.	Fluoroquinolone or azithromycin
Gram-negative bacteria	*Enterobacteriaceae* spp.	Third-generation cephalosporin or carbapenem
	Pseudomonas spp.	Antipseudomonal β-lactam plus ciprofloxacin or levofloxacin
MRSA		Vancomycin or linezolid
Anaerobes (aspiration)		Clindamycin or β-lactam/β-lactamase inhibitor
Influenza virus		Oseltamivir

time, the epidemiology of ABM has changed secondary to the introduction and widespread use of *H. influenzae* type b and *S. pneumoniae* vaccines as well as the emergence of multidrug-resistant *S. pneumoniae* as a new pathogen.

Pathogenesis and Microbiology

The pathogenesis of ABM depends on both host factors and the nature of the invading pathogens. Direct extension from adjacent structures (middle ear, paranasal sinuses, etc.) and hematogenous spread are the two routes of bacterial entry into the CNS; however, the exact mechanism of bacterial penetration through the blood–brain barrier (BBB) remains undetermined. Once the subarachnoid space has been penetrated, bacterial cell wall components stimulate the formation of various inflammatory cytokines, thereby activating the inflammatory cascade. This process further perpetuates disruption of the BBB. Inflammatory and cytokine responses have been reported to differ according to the invading organism, which may explain the variability in complication rates among various CNS pathogens.

N. meningitidis and *S. pneumoniae* are the most common causes of meningitis in adults.

In adults, *S. pneumoniae* and *Neisseria meningitidis* are the most common causes of meningitis (Table 32-2), accounting for 80% of all cases.[5] Risk factors for pneumococcal infections include otitis media, sinusitis, pneumonia, head trauma with cerebrospinal fluid (CSF) leak, immune deficiency, and asplenia. ABM caused by *S. pneumoniae* has a high fatality rate and may be associated with neurologic sequelae. The emergence of antibiotic-resistant strains of this organism limits its treatment and likely leads to higher complication and fatality rates.

N. meningitidis occurs more commonly in young adults and in college campus outbreaks. Nasopharyngeal carriage is believed to cause initiation of the meningitis with either organism.

On the other hand, *N. meningitidis* infections are more often found in children and young adults, and at times, occur in epidemics in schools and on college campuses. Individuals with complement deficiencies (C5–C8) are also known to be at far greater risk to develop neisserial infections. Following the widespread use of vaccines against *H. influenzae* capsular type b in the United States, there has been a steady decline in the incidence of meningitis

TABLE 32-2

BACTERIAL PATHOGENS CAUSING MENINGITIS IN ALL AGE GROUPS

0–3 Months	Group B streptococci
3 Months–18 years	
18–50 Years	*Streptococcus pneumonia* *Neisseria meningitidis*
>50 Years	*S. pneumonia* *Listeria monocytogenes*
Impaired immunity	*S. pneumonia* *L. monocytogenes*
Trauma/neurosurgery	*Staphylococci* Gram-negative rods

Listeria monocytogenes causes meningitis in elderly patients, neonates, and debilitated or immunosuppressed patients.

caused by this organism. *L. monocytogenes* is most commonly encountered in neonates and the elderly, as well as in debilitated patients including cancer patients, alcoholics, pregnant women, and immunosuppressed adults. Immunosuppressed adults and those who undergo neurosurgical procedures are also predisposed to develop meningitis resulting from aerobic gram-negative rods and *S. aureus*. *Staphylococcus epidermidis* infections are mostly observed in patients with cerebrospinal shunts.

Clinical Features

Fever, headache, and meningismus are typical manifestations of ABM; however, in the elderly or immunocompromised, the presentation may be subtler.

Kernig's sign is increased resistance to passive leg extension. Brudzinski's signs are associated flexion of the hips and knees with passive neck flexion.

Symptoms of ABM can be quite varied. The classic triad of fever, nuchal rigidity, and altered mental status is often not found, but most patients will have one or two of these symptoms along with additional findings, such as headache, rigors, vomiting, myalgias, and signs of cerebral dysfunction. Elderly, immunocompromised, and debilitated patients may have a less fulminant presentation in which these findings are subtler. Severe meningismus is sometimes accompanied by Kernig's sign (resistance to passive extension of the legs) and Brudzinski's sign (passive flexion of the neck causing flexion of the hips and knees). Uncommonly, patients may present with cranial nerve palsies, new-onset seizures, focal neurologic deficit, or signs of increased intracranial pressure such as severe hypertension, bradycardia, and coma. Meningococcal septicemia may also manifest with a hemorrhagic skin rash, acute adrenal insufficiency (Waterhouse–Friderichsen syndrome) caused by adrenal hemorrhage, and disseminated intravascular coagulation (DIC).

Treatment

Antibiotic therapy should be administered when clinical evaluation establishes suspicion of meningitis, and antibiotics should be given within 30 min from initial presentation.

Lumbar puncture is diagnostic of ABM in 60–90% of cases, and is associated with elevated CSF pressure and elevated CSF white blood cells.

Brain imaging with CT or MRI can exclude intracranial and parameningeal processes or complications related to meningitis.

Treatment of ABM is dependent on the timely recognition of this clinical syndrome. Patients with suspected ABM should have blood cultures drawn and undergo a lumbar puncture.† CSF sampling for protein, glucose, and Gram stain and culture should be performed. Patients suspected of having ABM should receive empiric antimicrobial therapy in combination with dexamethasone.† Delays in empiric therapy lead to increased morbidity and mortality. As such, if diagnostic tests are delayed or neuro-imaging tests are deemed necessary for further evaluation, empiric therapy should be administered as soon as possible (even if prior to the performance of diagnostic testing or CSF sampling).† Repeat CSF analysis should be performed in patients not clinically responding to appropriate antimicrobial therapy after 48 h in order to further guide treatment.

Selection of an empiric antibiotic regimen is based on the patient's age and risk factors (see Table 32-3). Large doses of bactericidal antibiotics with good CSF penetration are given to control this life-threatening infection. In adults, vancomycin plus a third-generation cephalosporin should be used.† In patients with any cellular immunodeficiency (whether disease- or drug-related), on hemodialysis, or if older than 55 years of age, ampicillin should be added to cover for *L. monocytogenes*.† Once the organism and its susceptibility is known, tailored antimicrobial therapy can be provided. Penicillin-susceptible strains of *S. pneumoniae* and *N. meningitidis* are treated with penicillin G.† *L. monocytogenes* is sensitive to ampicillin,

TABLE 32-3

CHOICES AND DOSAGES OF EMPIRIC ANTIBIOTIC THERAPY FOR BACTERIAL MENINGITIS

Adult immunocompetent	Cefotaxime or	2 g q4h
	Ceftriaxone	2 g q12h
	+Vancomycin	1 g q12h
Over 50 years or with impaired immunity	Ampicillin	2 g q4h
	+Cefotaxime or Ceftriaxone	
	+Vancomycin	
Nosocomial or postneurosurgery	Vancomycin	1 g q12h
	+Cefepime	2 g q12h
	±Aminoglycoside[a]	

[a]Gentamicin, amikacin, or tobramycin if *Pseudomonas* is suspected; patients with gram-negative meningitis who fail systemic therapy should be considered for intrathecal or intraventricular aminoglycoside therapy

and usually an aminoglycoside is added for the first several days of therapy.† Methicillin-sensitive staphylococcal infections should be treated with nafcillin or oxacillin; vancomycin has poor CSF penetration compared to nafcillin and should be reserved for resistant infections. For infections caused by highly resistant *S. pneumoniae* (minimal inhibitory concentration (MIC) >2 g/mL), treatment with vancomycin and a third-generation cephalosporin is recommended.†

In cases of suspected pneumococcal meningitis, steroids should be administered before the first dose of antibiotics.

The need for adjunctive treatment with dexamethasone in patients with ABM is somewhat controversial. Published data on this topic do not provide a clear answer concerning the utility of steroids in this clinical setting. A study published in 2002 showed that adjunctive dexamethasone use in patients with pneumococcal meningitis improved outcomes by reducing both complications and mortality.[6] As such, current recommendations include the use of steroids as a treatment modality. Dexamethasone should be used empirically when there is suspicion for or a possibility of *S. pneumoniae* infection, and continued if confirmed with results from CSF Grams stain or blood cultures.† The beneficial effect of steroids is seen only when administered prior to or with the first dose of antibiotics. On the other hand, a 2007 randomized, double-blind, placebo-controlled trial in Sub-Saharan Africa did not support the routine adjunctive use of corticosteroids in the management of patients with suspected ABM.[7] In this area, pneumococcus is the primary pathogen, and an overwhelming proportion of patients included in the trial were HIV-positive.[7] The causal relationship for these findings is unclear, but could potentially have implications for HIV-positive patients in developed countries as well. Results from a similarly conducted study performed in patients with suspected bacterial meningitis in Vietnam illustrated a beneficial effect in those patients with microbiologically proven disease.[8] In this trial no difference in outcome was seen in the comparison of all patients with suspected bacterial meningitis.[8]

Postexposure prevention of ABM is directed toward individuals exposed to patients infected with *N. meningitidis.* One dose of ciprofloxacin (500 or 750 mg) or rifampin twice a day for 2 days (10 mg/kg; not exceeding 600 mg/day) is recommended and is effective in eradicating nasopharyngeal carriage of *N. meningitidis* for close contacts. Ceftriaxone (250 mg IM) has been administered as alternative meningococcal chemoprophylaxis for pregnant women and persons intolerant of ciprofloxacin.

SEPSIS

Epidemiology

Sepsis is a syndrome resulting from a cascade of deranged inflammatory events caused by serious infection. It is associated with nonspecific systemic manifestations that often lead to multiple organ system failure.

Sepsis is a syndrome whereby a serious infection induces a cascade of deranged inflammatory events causing nonspecific systemic manifestations that often lead to multiorgan dysfunction.[9] Clearly any infection can cause such a presentation, and the severity of illness may vary considerably in the presence of these nonspecific findings; hence the heterogeneity of the sepsis syndrome. The same presentation is observed in certain diseases without any evidence of infections, such as acute pancreatitis and major trauma. This noninfectious inflammatory pattern, which mimics sepsis, has been termed the systemic inflammatory response syndrome (SIRS).

Despite better understanding of the pathophysiology of sepsis, mortality approaches 30–40%.

Despite the availability of advanced life-supportive care and the introduction of newer antimicrobial therapy, sepsis is among the leading causes of ICU admissions and continues to be the most common complication seen in critically ill ICU patients. Moreover, sepsis remains associated with a mortality rate of 30–40% and is the most common cause of death in most ICUs in the United States and Europe.[10]

Pathogenesis and Microbiology

A more detailed discussion of the pathogenesis of sepsis is covered in Chap. 23. In brief, an infectious stimulus or one of its byproducts triggers the release of proinflammatory cytokine mediators (tumor necrosis factor-alpha, interleukin-1, interleukin-8), which

An infectious stimulus triggers the release of proinflammatory cytokines, such as tumor necrosis factor, interleukin-1, and interleukin-8.

initiates a systemic inflammatory response. Initial hypotheses regarding sepsis suggested that unimpeded proinflammatory responses contributed to the clinical features of this syndrome. Current evidence supports the hypothesis that sepsis results from derangements in the host immune response, i.e., an imbalance between proinflammatory and antiinflammatory cytokines (interleukin [IL]-1 receptor antagonist, IL-4, IL-10, tumor necrosis factor receptor antagonist).[9] In such an uncontrolled inflammatory milieu, other mechanisms such as redistribution of regional blood flow, reduction in oxygen supply, oxidant injury, and alterations in intermediary metabolism contribute to tissue ischemia and injury, resulting in organ dysfunction. The difference between sepsis and SIRS lies only in the precipitating stimulus; in SIRS, the initial insult is thought to be noninfectious.

The most common sites of infection associated with sepsis are the lung, abdominopelvic region, and urinary tract.

Any serious infection can lead to sepsis, and no single organism predominates. The spectrum of pathogens involved varies according to the host and the affected organ. The most common site of infection giving rise to severe sepsis is the lung (e.g., pneumonia), followed by the abdominal or pelvic region (e.g., cholecystitis), then the urinary tract (e.g., pyelonephritis). Staphylococcal infections and infections with enteric gram-negative organisms are frequently associated with nosocomial sepsis. Immunocompromised patients may develop sepsis from viruses and fungal pathogens, as well as from bacteria. The history, physical examination, and initial work-up often establish a suspected source of infection, although a proportion of patients will have no identifiable source of infection.

Clinical Features

Positive blood cultures are seen in 30% of patients and about 20–30% have no identifiable source of infection.

Sepsis can be confirmed by right heart catheterization. The usual findings include elevated cardiac output, low systemic vascular resistance, and low to normal pulmonary capillary wedge pressure.

Sepsis represents a continuum of clinical presentations (see Table 32-4). Systemic manifestations from infections define sepsis and the presence of organ dysfunction, or tissue hypoperfusion defines severe sepsis. The term septic shock is used when hypotension or hypoperfusion is refractory to fluid resuscitation. Sepsis is a clinical diagnosis in patients with suspected infection who present with fever or hypothermia, tachypnea, tachycardia, leukocytosis, or leukopenia. The diagnosis is confirmed by abnormalities in central hemodynamics. An elevated cardiac output, low systemic vascular resistance, and low to normal pulmonary artery occlusion pressure (wedge pressure) are characteristic of sepsis. During the early stages of sepsis, clinical features may be more specific and may vary according to the host and the affected organ; for example, hypoxemia and dyspnea would suggest pneumonia as the cause of sepsis. In elderly and immunocompromised patients or with the progression to severe sepsis, the site of infection tends to be less evident because of poor host response or multiple organ dysfunction. For instance, hypoxemia and dyspnea may reflect diaphragmatic dysfunction or ARDS in a patient who has abdominal sepsis.

A clinical picture suggesting sepsis should always prompt a diagnostic work-up that is directed toward identification of the source of infection and subsequent isolation of the responsible pathogen. A sepsis work-up is incomplete if it does not include a white blood cell count with a peripheral smear, chemistry profile, blood cultures, urine cultures, and a chest X-ray. Additional testing is usually guided by the history and physical examination. For example, a sputum Gram stain and culture are obtained when the clinical scenario is consistent with pneumonia. It is generally recommended to sample any fluid collection that

TABLE 32-4

CLINICAL FEATURES OF SEPSIS

CLINICAL PRESENTATION	LABORATORY
Fever or hypothermia	Leukocytosis or granulocytopenia
Tachypnea	Thrombocytopenia
Tachycardia with or without hypotension[a]	Respiratory alkalosis/hypoxemia
Oliguria	Hyperglycemia
Confusion or obtundation	Lactic acidosis

[a]Hypotension is usually defined as systolic blood pressure <90 mmHg or a drop of >40 mmHg from baseline. The term septic shock is used in the presence of sepsis-related hypotension refractory to fluid resuscitation

TABLE 32-5

UNUSUAL CAUSES OF SEPSIS OR SEPSIS-LIKE SYNDROME

Bacterial infections
Mycobacterial: tuberculosis, *Mycobacterium avium* complex
Rickettsial: Rocky Mountain spotted fever, ehrlichiosis
Nonbacterial infections
Viral: dengue, enteroviruses, hepatitis A or B, influenza, cytomegalovirus, herpes zoster viruses
Malaria
Fungal: *Candida*, *Aspergillus*
Noninfectious
Drug-related: anaphylaxis, neuroleptic malignant syndrome
Drug intoxication: cocaine, organophosphate
Drug withdrawal: alcohol
Anaphylaxis
Systemic vasculitis: polyarteritis nodosa, systemic lupus erythematosus
Acute pancreatitis
Acute hepatic failure
Heatstroke
Rhabdomyolysis

is found on diagnostic imaging because it may be the source of infection. Moreover, to optimize the microbiologic yield, all cultures should be obtained before administering antibiotics. Assessment of risk factors and comorbidities helps in the diagnostic work-up and the selection of antimicrobial therapy; however, if the primary site of infection is not readily identifiable, a systematic search for infection should cover the respiratory, gastrointestinal, biliary, and genitourinary tracts, along with the central nervous and cardiovascular systems.

With a high clinical suspicion for sepsis, conduct a diagnostic work-up directed at locating an infectious source and a specific pathogen.

Patients already in the hospital or in the ICU are vulnerable to developing secondary sepsis from either failure of their therapy or superimposed nosocomial infections. Specific nosocomial infections, which add significantly to the morbidity and mortality of patients, are discussed in more detail in this chapter. Often it becomes difficult to isolate the offending organism and ascertain whether the systemic inflammatory process is infectious or noninfectious in patients with prolonged hospitalization. These patients are typically colonized with numerous pathogenic organisms, particularly those receiving multiple antibiotics or systemic corticosteroids, making it more difficult for clinicians to identify an organism as pathogenic or as just a colonizer. Nonbacterial infectious pathogens such as fungi are less common causes of sepsis in most ICUs, but this may vary depending on geographic location and host susceptibility. These pathogens, along with the noninfectious causes of sepsis-like syndrome, should be considered in patients whose illness has no clear etiology (see Table 32-5).

Fluid collections found on imaging studies should be sampled before administration of antibiotics, if possible, to ensure the highest yield.

Sepsis is commonly encountered in hospitalized, debilitated patients, and those at risk to develop nosocomial infections.

Management

The strategy to manage sepsis and septic shock consists of two main approaches: (1) initial resuscitation and infection control, and (2) maintaining hemodynamics and adjunctive support. The first phase of sepsis management is relatively well defined and vital to having an improved outcome, whereas optimal supportive therapies remain to a certain extent debatable. Recent international guidelines for the management of severe sepsis and septic shock have been published, and an abridged summary of their recommendations is found in Tables 32-6 and 32-7.[‡]

Management of sepsis should focus on aggressive initial resuscitation and early institution of antimicrobial therapy and drainage of any abscesses.

Infection control involves the use of antimicrobials, drainage, or debridement (surgical or nonsurgical) of abscesses or necrotizing tissue when present, and surgery to repair any perforated viscous. Findings from the history, physical examination, and initial diagnostic work-up usually lead to a presumptive diagnosis and guide the initial choice of empiric antimicrobial therapy (Table 32-8). Any uncertainty about the cause of sepsis, site of infection, or type of pathogen justifies the use of aggressive broad-spectrum antibiotics, especially in the current era when resistant pathogens are a more common entity. As would

TABLE 32-6

MANAGEMENT OF SEPSIS: GOALS OF RESUSCITATION AND CONTROLLING INFECTION

GOALS	METHODS
Initial resuscitation	Maintain CVP 8–12 mmHg Maintain MAP ≥64 mmHg Maintain UOP ≥0.5 mL/kg/h
Diagnosis: identification of source of infection and its control	Obtain cultures prior to antimicrobial administration (two or more blood cultures and cultures of other sites as clinically indicated) Identify source of infection Apply source control methods as indicated (e.g., abscess drainage, tissue debridement, iv catheter removal)
Antibiotic therapy	Initiate antibiotic therapy early and initially use broad-spectrum antibiotics with likely activity and penetration based on presumed source Perform regular reassessment to optimize efficacy, prevent resistance, and avoid toxicity of antimicrobials Stop antibiotics if cause of sepsis deemed noninfectious

CVP, central versus pressure; MAP, mean arterial pressure; UOP, Urine output

Assessment of risk factors and comorbid conditions aid the diagnostic work-up and subsequent antimicrobial choice.

Despite the development of many investigational therapies, exceptional bedside care and optimal hemodynamic support remain vital for management of sepsis.

Low-dose steroid therapy should be avoided for the *routine* management of patients with sepsis. It is unclear if systemic steroids are beneficial for a subgroup of patients with refractory shock.

be suspected, an increase in mortality is observed in patients who receive delayed or inappropriate antimicrobial therapy. The ideal scenario is to start antibiotics very early in sepsis (immediately after obtaining all cultures) and then identify the cause of the infection and mechanically address the issue if necessary (drainage, surgery, etc). Unfortunately, not all patients present early in the course of their disease, and many progress to septic shock and require extensive supportive therapies despite adequate antimicrobial coverage. While vasopressor therapy, mechanical ventilation, and renal replacement interventions have a clear role in the management of severe sepsis, other interventions are still at question. The recent international guidelines suggest the use of corticosteroids in patients with refractory shock, treat hyperglycemia with intravenous insulin therapy, and possibly use colloids for resuscitation.[‡] However, findings from recent large multicenter trials demonstrated no consistent measurable benefit of these interventions on sepsis mortality[11,12] and that using pentastarch (a colloid) should even be avoided. Therefore, until clinical investigations demonstrate an effective approach to optimize adjunctive therapies and modulate the host inflammatory response, meticulous bedside care assuring optimal hemodynamic interventions to prevent secondary organ injury and complications offers the best hope for patient survival.

TABLE 32-7

MANAGEMENT OF SEPSIS: USE OF ADJUNCTIVE THERAPIES

THERAPY	RECOMMENDATIONS
Fluid replacement	Use crystalloids or colloids for fluid resuscitation Target CVP 8–12 mmHg Use fluid challenge technique with close monitoring
Vasopressor use	Target goal MAP ≥65 mmHg Use norepinephrine and dopamine as initial vasopressors of choice
Steroid use	Consider i.v. hydrocortisone therapy in adults with septic shock unresponsive to adequate fluid resuscitation and vasopressors
Recombinant human activated protein C	Consider use only in adult patients with sepsis-induced organ dysfunction and clinically determined high risk of death (APACHE II score ≥25) when no contraindications present

TABLE 32-8

EMPIRIC ANTIBIOTIC SELECTION FOR SEPSIS

Life-threatening sepsis	Aminoglycoside (gentamicin, tobramycin or amikacin) plus one of the following Cefepime Piperacillin-tazobactam Carbapenems Suspected MRSA: add vancomycin
Intraabdominal or pelvic infections	Piperacillin-tazobactam, ampicillin-sulbactam, imipenem or cefepime + metronidazole
Billiary tract sepsis	Third-generation cephalosporin (cefotaxime or ceftriaxone)
Urosepsis	Third-generation cephalosporin (cefotaxime or ceftriaxone) or Ciprofloxacin
Neutropenia	Cefepime Imipenem Piperacillin/tazobactam + aminoglycoside

NOSOCOMIAL INFECTIONS

Nosocomial Pneumonia

Epidemiology

Nosocomial (or hospital-acquired) pneumonia (HAP) is defined as a pneumonia that occurs in patients who have been hospitalized for more than 48 h. Ventilator-associated pneumonia (VAP) is a subset of HAP that occurs more than 48 h following endotracheal intubation. Health care associated pneumonia (HCAP) is pneumonia that occurs in patients with recent extensive health care contact (e.g., receipt of intravenous therapies, wound care, and/or hemodialysis clinic attendance within prior 30 days, residence in a nursing home or long-term care facility, or hospitalization within prior 90 days). These are common nosocomial infections carrying with them significant morbidity and mortality. The incidence of nosocomial pneumonia increases according to the patient's underlying severity of illness and is a common problem in the ICU, especially in mechanically ventilated patients. In addition, pneumonia is associated with the greatest mortality of any nosocomial infection: the attributable mortality is high and can range up to 24–50% in mechanically ventilated patients.[13]

Nosocomial pneumonia is associated with the highest mortality of all nosocomial infections in the ICU.

Time of onset of pneumonia is an important epidemiologic variable. Early-onset HAP and VAP occur within 4 days of hospitalization and carry a better prognosis due to increased likelihood of antibiotic-sensitive bacteria as causal organisms. In contrast, late-onset HAP and VAP are defined as occurring 5 days or more into a patient's hospitalization. As such, these tend to be associated with multidrug resistant (MDR) pathogens and carry an increased morbidity and mortality.[§§] Patients with early-onset HAP or VAP who have been recently hospitalized provide an exception and are at greater risk for infection with MDR pathogens; these patients should be approached in the same way as those with late-onset HAP and VAP.[§§]

Pathogenesis and Microbiology

The pathophysiology of nosocomial pneumonia is complex and varies among different hospital patient populations. Although risk factors can help identify patients with nosocomial pneumonia, management of such infections remains extremely challenging because of emerging resistant organisms, lack of a gold standard for diagnosis of pneumonia, and associated morbidities.

Risk factors for nosocomial pneumonia include severity of illness, comorbid conditions, malnutrition, advanced age, mechanical ventilation, and heavy sedation.

Risk factors for nosocomial pneumonia are either related to host factors or extrinsic factors. Host factors include severity of illness, associated comorbidities, malnutrition, and advanced age.[13] Extrinsic factors are related to interventions that interfere with the integrity of the host defense mechanisms such as nasogastric tubes, mechanical ventilation via endotracheal or nasotracheal intubation, and the use of heavy sedation or neuromuscular blockade. Most extrinsic risk factors impair swallowing and leave the upper airway unprotected from aspiration. Bacteria invade the lower respiratory tract via aspiration, inhalation of

TABLE 32-9

PREEXISTING CONDITIONS ASSOCIATED WITH PHARYNGEAL COLONIZATION BY GRAM-NEGATIVE BACTERIA

Prolonged hospitalization	Coma
Antibiotic exposure	Pulmonary disease
Major surgery	Renal disease
Diabetes mellitus	Neutropenia

contaminated aerosols, or hematogenous spread. Overt or covert aspiration (at times referred to as microaspiration) of oropharyngeal or gastric flora is thought to be the most common route of organism delivery to the lower respiratory tract. In critically ill patients, the oropharynx becomes colonized with gram-negative organisms a few days after admission to the hospital, especially if the patients have been exposed to antimicrobial therapy. Once an inoculum of pathogenic organisms reaches the lower respiratory tract, medical disease processes that reduce host immunity and violation of the host anatomic barriers make the ideal milieu for pneumonia to flourish.[13]

Since aspiration is a common route of pathogen entry into the lower respiratory tract and since critically ill patients have an altered oropharyngeal and gastrointestinal flora, one can understand the differences in responsible pathogens between nosocomial pneumonia and CAP. Nosocomial pneumonia may be caused by a wide variety of bacterial pathogens but has been most commonly associated with enteric gram-negative bacilli (see Table 32-9). Pneumonias caused by resistant gram-positive pathogens such as *S. aureus,* particularly the methicillin-resistant strains, are becoming more widespread in ICUs.[14] Prevalence of specific pathogens causing nosocomial pneumonia varies among ICUs because of variability in ICU microflora.

MDR bacteria have emerged as more frequent causes of nosocomial pneumonia, and the frequency of these infections varies in different ICUs.[14] Risk factors for pneumonia with MDR pathogens include recent antimicrobial therapy, prolonged hospitalization, specific ICU flora, and immunosuppressive disease or therapy.[14] They are more likely etiologic organisms in late-onset HAP and VAP. Knowledge of the local ICU microflora (*P. aeruginosa, Klebsiella* spp*., Enterobacter* spp*., Serratia* spp., *Acinetobacter* spp., and MRSA) with their local resistance patterns should guide the initial empiric treatment when these infections are suspected.

Clinical Features

Microbiologic evaluation via sputum or tracheal aspirate is nonspecific for diagnosing nosocomial pneumonia because a positive culture may reflect colonization.

The criteria for diagnosing pneumonia include clinical, radiographic, and laboratory evidence of infection. Classical signs and symptoms of pneumonia can be present and can include cough with new onset of purulent sputum or change in the character of sputum. Fever, tachypnea, dyspnea, tachycardia, hypoxemia, leukocytosis, crackles, or dullness to percussion are often present. In addition, one may find new or progressive infiltrates on chest radiographs and organisms isolated from sputum or blood cultures. Unfortunately, clinical evaluation is frequently limited in complicated and critically ill patients with a resultant decrease in the positive predictive value of many clinical findings normally associated with the diagnosis of pneumonia (see Table 32-10). Isolation of organisms from blood or pleural fluid cultures in the right setting is highly specific for pneumonia, but the prevalence of bacteremia in patients with nosocomial pneumonia is relatively low. On the other hand, the microbiology of sputum and tracheal aspirate is nonspecific for the diagnosis of nosocomial pneumonia because the majority of hospitalized patients are colonized with a number of potentially pathogenic organisms.

TABLE 32-10

RADIOGRAPHIC MIMICS OF PNEUMONIA

Atelectasis (most common)	Pulmonary infarct
Aspiration	Asymmetric pulmonary edema
Pleural effusions	Pulmonary hemorrhage
Acute respiratory distress syndrome	Bronchiolitis obliterans organizing pneumonia
Pulmonary contusion	

Many intensivists favor using invasive diagnostic techniques (fiberoptic bronchoscopy [FOB] to obtain bronchoalveolar lavage [BAL] fluid or protected specimen brushing [PSB]) because they are believed to be more accurate than clinical diagnosis. Published guidelines for the management of HAP suggest incorporating both the clinical and microbiologic data to guide the decision-making process regarding initiating and discontinuing antibiotic therapy.[§§] In this algorithm, physicians should obtain lower respiratory tract sample for microscopy and culture and initiate appropriate empirical antibiotic therapy when HAP, VAP, or HCAP is clinically suspected. Clinical response should be continually assessed in the days following therapy. If there is no evidence of clinical improvement 48–72 h following initiation of therapy and cultures are negative, a physician should search for other pathogens, complications, or sites of infection. If cultures are positive in the setting of a lack of clinical improvement at this time, antibiotics should be adjusted or other diagnoses and/or sites of infections sought. On the other hand, if clinical improvement occurs within that time period and cultures are positive, de-escalation of therapy should be performed based on culture data. If cultures are negative at 48–72 h and the patient is clinically improving, physicians should consider stopping antibiotics.

Tracheal aspirate Gram stains are often used to initiate empiric antibiotic therapy, and results from semiquantitative or quantitative cultures along with serial clinical evaluations after 2–3 days of empiric treatment guide the decision to maintain, change, or discontinue the initial empiric coverage.

Invasive testing is the accepted standard for the diagnosis of pneumonia in immunocompromised patients; BAL and PSB have a superior yield and a higher accuracy compared to noninvasive techniques in immunocompromised patients due to a higher prevalence of nonbacterial pathogens in these patients. Yield from the cultures is significantly reduced if the patient is already on antibiotic therapy; therefore, all cultures should be obtained before initiation of therapy, regardless of the diagnostic technique used to obtain respiratory secretion samples.

Poor bronchoscopic technique, early pneumonia, and use of antibiotics may reduce the sensitivity and specificity of bronchoscopic sampling.

Treatment and Prevention

It is obvious that accurate diagnosis is critical for optimal antimicrobial therapy. Hospital microflora, timing of the onset of the nosocomial pneumonia, types of risk factors, and severity of the patient's illness guide initial empiric antibiotic therapy (see Table 32-11). Supportive therapy, including ventilatory, hemodynamic, and nutritional support, together with the appropriate antimicrobial coverage are the cornerstones of successful treatment of nosocomial pneumonia. Inadequate initial antibiotic regimens, even if changed later in the course of the illness, are consistently found to be a significant risk factor for poor outcome in patients with nosocomial pneumonia.[§§]

Inappropriate antibiotic choice is a significant risk factor for mortality in nosocomial pneumonia.

The key decision in empiric treatment lies in the decision to cover for MDR pathogens based on the patient's clinical risk factors and the susceptibility patterns of one's ICU's flora. Initial therapy for patients diagnosed with early-onset HAP or VAP and without any risk factors for infection with MDR pathogens should include coverage for *S. pneumoniae*, *H. influenzae,* methicillin-sensitive *Staphylococcus aureus aureus* (MSSA), and antibiotic-sensitive

TABLE 32-11

ETIOLOGIC ORGANISMS OF NOSOCOMIAL PNEUMONIA AND INDICATED EMPIRIC THERAPY

CLINICAL SCENARIO	POTENTIAL PATHOGENS	EMPIRIC THERAPY
Early-onset HAP or VAP and no risk factors for MDR pathogens	*S. pneumoniae* *H. influenzae* MSSA Antibiotic-sensitive GNR *E. coli* *Klebsiella pneumoniae* Enterobacter spp. *Proteus* spp. *Serratia marcescens*	Ceftriaxone or levofloxacin, moxifloxacin, ciprofloxacin or ampicillin-sulbactam or ertapenem
Late-onset HAP or VAP or HCAP with risk factors for MDR pathogens	Etiologic pathogens causing early-onset disease plus *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL) Acinetobacter MRSA	Antipseudomonal cephalosporin or antipseudomonal carbapenem or β-lactam/β-lactamase inhibitor plus antipseudomonal fluoroquinolone or aminoglycoside plus linezolid or vancomycin

enteric gram-negative bacilli (see Table 32-11).[§§] Antibiotics recommended for empiric therapy in this clinical situation include ceftriaxone, a respiratory fluoroquinolone, ampicillin-sulbactam, or ertapenem. Late-onset disease carries an increased risk of infection with MDR pathogens such as *P. aeruginosa,* ESBL *K. pneumoniae, Acinetobacter* spp., and MRSA. These patients who are at risk for pneumonia caused by MDR pathogens should be initially treated with broad-spectrum combination therapy until further culture data are known.[§§] The 2005 ATS/IDSA guidelines suggest the use of an antipseudomonal cephalosporin or a carbapenem or β-lactam/β-lactamase inhibitor plus an antipseudomonal fluoroquinolone or aminoglycoside plus linezolid or vancomycin as initial empiric therapy in late-onset HAP and VAP (Table 32-11).[§§] Choice of specific agents should be based on the presence of risk factors for MDR pathogens, as well as the local microbiology and antibiogram. Combination therapy is recommended, at least initially, to provide a broad-spectrum empiric regimen that is likely to provide at least one active drug against the MDR etiologic agent. Broad-spectrum empiric antimicrobial therapy should eventually be tailored to each individual patient based on clinical and microbiologic data. The optimal duration of therapy is not known; however, it has been shown that in patients with VAP, appropriate antimicrobial treatment for 8 days is as clinically effective as treatment for 15 days. In addition, shorter duration of treatment may reduce a patient's future risk for infection with increasingly resistant pathogens.[15] Unfortunately, even with the correct choice of antibiotics, overall mortality from nosocomial pneumonia remains substantial (25–50%)[13]; hence, prevention of such infection will have the greatest impact on the outcome of hospitalized patients.

Effective strategies for reducing the incidence of nosocomial pneumonia include strict infection control policies, reduction of the duration of mechanical ventilation, appropriate positioning of hospitalized patients, and limitation/early removal of invasive devices. Utilization of contact precautions for selected transmittable organisms (MRSA, group A Streptococci, *N. meningitidis,* penicillin-resistant *S. pneumoniae,* multiresistant gram-negative bacilli, *Mycobacterium tuberculosis,* and respiratory viruses) is the most important maneuver shown to be effective in reducing incidence of nosocomial pneumonia.

Semiupright position and contact precautions are the most effective maneuvers to prevent nosocomial pneumonia.

Intubation and subsequent mechanical ventilation markedly increase the risk for nosocomial pneumonia. It is recommended that intubation be avoided, possibly with the use of noninvasive positive pressure ventilation.[§§] Attempts at limiting the duration of mechanical ventilation should be made by the use of aggressive weaning protocols when applicable. Causality between acute sinusitis and nosocomial pneumonia has been suggested and, as such, the use of oral endotracheal and orogastric tubes, rather than nasotracheal and nasogastric tubes, can reduce the incidence of nosocomial sinusitis and possibly nosocomial pneumonia.[§§]Aspiration is thought to be the major mechanism leading to nosocomial pneumonia. The supine position facilitates aspiration and, thus, patients should be positioned in a semirecumbent position to help decrease its occurrence.[16] Enteral feeding is also associated with higher rates of aspiration and, thus, nosocomial pneumonia.[§§] The alternative, parenteral feeding, has associated potential risks such as line infections, and the risks/benefits of these two options must be weighed appropriately. It is uncertain whether the use of a specific ulcer prevention strategy (sucralfate vs. H2-blockers) has an impact on the development of nosocomial pneumonia; most of the evidence shows no significant differences between the two strategies.[17] Indiscriminate use of selective decontamination of the oropharynx and the digestive tract with topical antibiotics has not been found to be effective. In intubated patients, special endotracheal tubes have been introduced and shown to be effective in reducing VAP.

Intravascular Catheter-Related Infection

Epidemiology

Intravascular catheter-related infection is a serious complication of intravascular access. In current health care settings, intravascular devices are used frequently for administration of fluids and medications or for hemodynamic monitoring. These devices are most useful in the ICU setting, but they carry risk with their use. This inherent risk varies with the type of

catheter being used as well as the hospital epidemiology, anatomic catheter location, and duration of placement.[e]

Central venous catheters account for more than 90% of all catheter-related bacteremias; bacteremias secondary to peripheral venous catheter infections are rare. Before describing the pathogenesis and management of catheter-related infections, it is important to know the terminology used in this setting. First, the catheter is said to be colonized when a certain number of organisms grow from the culture of a removed catheter tip. Although colonization is thought to be a prerequisite for development of a line infection, it does not present with local or systemic signs of infection. Second, catheter-related infections may present as: (1) an exit site infection (local [<2 cm from catheter exit site] cellulitis and abscess formation), (2) a tunnel infection (local signs of inflammation or infection >2 cm from catheter exit site along tract of tunneled catheter), or (3) as a catheter-related bacteremia. Catheter-related bacteremia is correlated with significant colonization, even in the absence of local infection, and is defined as bacteremia originating from the catheter site; therefore, this diagnosis is based on isolation of the same organism from the catheter and the blood. Third, a blood culture is said to be contaminated because of improper sterilization technique while obtaining the blood sample and does not represent colonization or infection.

Central venous catheters cause 90% of catheter-related bacteremias.

Diagnosis of catheter-related bacteremia is based on the isolation of the same organism from the catheter and the blood.

Pathogenesis and Microbiology

Catheter-related infections are highly associated with colonization of the catheter, usually arising from skin colonization of the patient.[18] This is why attempts are made to avoid cannulation of the femoral veins as the inguinal region may be difficult to sterilize. Less commonly, the catheter tip is seeded hematogenously from a distant source following a transient bacteremia. Within 24–48 h of catheter insertion, a fibrin sheath forms around the intravascular surface of the catheter. During bacteremia, this fibrin sheath serves as a nidus for attachment and growth of organisms. Fibrin sheath formation and adherence of bacteria to catheters is related to the smoothness and thrombogenicity of the catheter, which varies among the different types of catheters. Contamination of the hub from inappropriate handling or blood draws and infection of the dermal tunnel from migration of organisms along the subcutaneous tunnel are common causes of catheter-related infections. Lastly, catheter-related infections can rarely be caused by contaminated infusates.

The most common cause of catheter-related bacteremia is dermal tunnel infection due to migration of organisms from contaminated or endogenous skin flora.

Skin colonization at the insertion site is strongly associated with catheter-related bacteremias.

Coagulase-negative staphylococci (*S. epidermidis*) and *S. aureus* bind easily to the surface of catheters and the fibrin sheath, and by far, are the most common causes of line infections.[e] The third most common organisms to cause catheter infections are *Enterococcus* spp. followed by Candida (*C. albicans*). Catheter-related infections caused by Candida spp. are more often seen in patients on multiple antimicrobials and receiving total parenteral nutrition.[e] Individuals who are on antimicrobials may also be more at risk to develop catheter-related infections with other organisms such as gram-negative enterics, (*Klebsiella* spp or *E. coli*), *Stenotrophomonas maltophilia, Flavobacterium* species, *Corynebacterium* species, or *Malassezia furfur.*

Clinical Features

The presentation of a catheter-related bacteremia is quite varied. Fever and leukocytosis with or without other signs of sepsis are common scenarios in ICUs. Complicated line infections often involve bacteremias with obvious sepsis, evidence of septic emboli, and even infected venous thrombi at the site of the catheter. As such, physicians should have a low threshold to search for the presence of catheter-related infections. Inspection of catheter sites should be part of the daily evaluation of hospitalized patients; paradoxically, an inflamed and erythematous site may be sterile, but a normal-appearing site may be significantly colonized. It should be remembered that signs of local inflammation at the insertion site are neither sensitive nor specific to detect catheter-related bacteremias or colonization. Clinical suspicion should be coupled with laboratory criteria to formally diagnose a catheter-related infection. Positive blood cultures in patients without an easily identifiable source of infection should raise the suspicion for a catheter-related bacteremia. Traditionally, blood cultures are

Inspection of the catheter site is important, but local inflammation at the insertion site is not very specific for colonization of the catheter.

obtained percutaneously from a distant site as well as from the catheter, which is then removed and sent for culture.

Catheter-related bacteremia is diagnosed when the same organism is isolated from blood cultures and catheter cultures in the absence of another active source of infection.[e] A positive culture from purulent exudate at the site of insertion is also accepted as a sign of catheter-related infection. Interpretation of blood cultures obtained from the same catheter that has raised concern for infection, rather than from a distant site, is always fraught with uncertainty; blood cultures may be positive because of contamination (poor technique obtaining the blood) or colonization, even in the absence of a true bacteremia.

Two accepted methods for culturing catheters yield meaningful information. The first and most frequently used method is the semiquantitative culture method (the Maki technique) in which a segment of the catheter is rolled on a culture medium, and colony-forming units (cfu) are counted following overnight incubation.[19] Because approximately 80% of catheter-related infections are caused by dermal tunnel infections, care should be taken to culture the intradermal segment (0.5 cm below the skin to 3 cm distally), not only the tip of the catheter. Catheter-related infection, by this method, is defined as the presence of 15 or more cfu; fewer than 15 cfu on semiquantitative cultures indicate insignificant colonization and is less likely to account for bacteremia.[18] The second method, the quantitative culture method (the Brun–Buisson technique), counts the number of organisms grown from catheter segment cultures after sonification of the catheter. Positive quantitative cultures are defined as more than 10^3 organisms in the broth and are associated with bacteremia.

Both the catheter tip and intradermal segment should be cultured. For the semiquantitative method, positive cultures are defined as growth of more than 15 cfu.

In contrast to semiquantitative and quantitative techniques used to establish the diagnosis of colonization and catheter-related infections, two other methods obviate removing the catheter. These methods can be especially useful as a method of detection in patients with limited vascular access. The first method consists of obtaining simultaneous blood samples from the catheter and from a peripheral vein for paired quantitative blood cultures. The finding of 5–10 times more colonies from blood drawn through the catheter compared to the peripheral site suggests catheter-related bacteremia and has been found to be most accurate in determining infections associated with tunneled catheters.[20] The second method relies on time required for blood cultures (also drawn concurrently from the catheter and a peripheral vein) to become positive. In catheter-related bacteremia, there is a positivity time differential between the two samples; blood cultures drawn through the catheter become positive at least 2 h earlier than the peripheral blood inoculum because of the higher organism count in the former.[21]

Treatment and Prevention

Often when a line infection is suspected in a seriously ill septic patient (those with hypotension, organ dysfunction, septic thrombosis, or persistent fever and bacteremia), blood cultures are obtained, the catheter is removed and sent for semiquantitative or quantitative cultures and empiric therapy with vancomycin, to cover *Staphylococcus* spp. and *Enterococcus* spp., is started. For critically ill patients and when gram-negative organisms are suspected, additional empiric gram-negative coverage should be included (third- or fourth-generation cephalosporins, fluoroquinolones, aminoglycosides, β-lactam-β-lactamase inhibitors, or carbapenems).[e] Antifungal therapy should be initiated also in patients suspected of having fungemia.[e] When the results from blood and catheter (or site) cultures become available, treatment can then be adjusted according to the results of the cultures and sensitivities. If the site is not colonized or the patient does not respond to therapy, another source for the infection should be sought and treated accordingly.

Local colonization without bacteremia usually responds to line removal (unless there is an expanding cellulitis) and antimicrobial therapy may not be required. The specific duration of therapy for catheter-related infection is variable. These infections can be subdivided into uncomplicated and complicated infections (e.g., those with septic thrombosis, endocarditis, or osteomyelitis). Catheter-related infection with bacteremia caused by organisms other than *S. aureus* is treated for 5–7 days after line removal; uncomplicated *S. aureus* catheter-related bacteremia is usually treated for 14 days.[e] Complicated catheter-related infections require a

longer duration of therapy and treatment must be individually tailored.[e] Unfortunately, some patients continue to have evidence of sepsis despite these measures, and under such circumstances, one should consider complications such as septic emboli, septic thrombophlebitis or cardiovascular infections. Patients with the risk factors such as antimicrobial therapy for more than 14 days, parenteral nutrition, growing *Candida* from two or more sites, complicated intraabdominal surgery, and neutropenia with persistent fever (>3 days despite empiric antibiotics) are at risk for candidemia. Such patients, if stable, should be started on fluconazole 400 mg/day and, if candidemia is confirmed, treatment should be continued for 14 days after line removal and clearance of cultures.[e] Unstable patients and those already on fluconazole who do not improve should be treated with an echinocandin.[e] Due to the associated risk of endophthalmitis, an ophthalmologic exam is recommended at the end of treatment.

Once catheter-related infection is documented, the catheter should be removed except in some instances of uncomplicated *S. epidermidis* line infections.[e] In contrast, infections of surgically implanted, long-term indwelling catheters (Broviac, Hickman, or Cook catheters) are commonly left in place unless the bacteremia is associated with a tunnel infection or if they are complicated by expanding cellulitis, septic thrombophlebitis, or resistant bacteremia despite appropriate antibiotics. Should this bacteremia recur following treatment, removal of the tunneled catheter is recommended.[e]

Treatment for catheter-related bacteremia involves removal of the central venous catheter in seriously ill patients and *S. aureus* infection. Removal of a surgically implanted catheter is not always required.

The most effective method for prevention of catheter-related infections is to limit the duration of the catheter. Other prevention strategies include appropriate selection of the catheter and insertion site, aseptic precautions during insertion of the catheter, and meticulous care of the catheter site and the delivery system. Cannulating the subclavian vein is associated with the lowest incidence of infection (but has a higher risk for other noninfectious complications), whereas use of the femoral vein site carries with it a higher infectious risk. Avoiding multilumen thrombogenic catheters and using cuffed or bonded catheters with antiseptics or antimicrobials will reduce, but not eliminate, the risk of catheter-related infections. Applying chlorhexidine at the insertion site reduces cutaneous bacterial colonization and thus dermal tunnel infections. Dry gauze or permeable dressings are more effective than transparent dressings for site care in decreasing the cutaneous flora. Changing the dressing daily and using topical antimicrobials also reduce the rate of skin colonization and catheter-related infections. Avoiding frequent interruptions to the delivery system, especially with total parenteral nutrition, minimizes risks of contamination. Changing catheters routinely over a guidewire does not prevent line infections; in the presence of dermal tunnel colonization or infection, this practice does not sterilize the tunnel. In addition, some clinicians advocate removal of high-risk catheters following an episode of bacteremia to prevent seeding of the catheter. Again, and most importantly, the central catheter should be removed when no longer required.

Catheter-related infections are preventable with strict aseptic techniques, proper choice of insertion site, and meticulous local care.

Clostridium difficile Colitis

Epidemiology

Clostridium difficile commonly causes antibiotic-associated colitis in hospitalized patients. The clinical presentation of *C. difficile* infections is variable, ranging from asymptomatic carriage or a simple self-limited watery diarrhea to a severe pseudomembranous colitis resulting in sepsis, toxic megacolon, and death. It is the most common cause of enteric infection in the hospital setting and its prevalence continues to rise. *C. difficile*-associated diarrhea often occurs in elderly, debilitated patients with a history of antimicrobial use in the hospital setting.[22] Additional potential risk factors include acid suppression, NSAID use, and enteral feeding.[22]

C. difficile colitis presentation ranges from self-limited diarrhea to severe toxic megacolon.

Pathogenesis and Microbiology

C. difficile is an anaerobic gram-positive bacterium that colonizes the gastrointestinal tract in some normal healthy adults and an increased proportion of hospitalized adults as well as neonates. It is hypothesized that antibiotics alter the colonic flora, facilitating

Antibiotics, by altering intestinal flora, allow overgrowth of anaerobic bacteria, including *C. difficile.*

Pseudomembranes, which are loosely adherent yellow–white exudative mucosal plaques, are found in about 25% of patients with mild disease and 87% of patients with severe disease.

the uncontrolled growth of anaerobic bacteria, including *C. difficile.* Antibiotic-associated colitis may result from any antimicrobial agent, but most frequently follows treatment with clindamycin and cephalosporins. Spores of this organism can be found widely in the patient's surrounding environment, a presence heightened in the hospital setting.[23] Patients generally acquire infection through the fecal-oral route, but *C. difficile* can also be transmitted after exposure to patients or staff who are infected or colonized with *C. difficile.*

Pathogenic strains of *C. difficile* elaborate two protein exotoxins, toxin A and toxin B, which can both cause colonic damage in humans. Strains that do not produce these toxins are not pathogenic. The presence of toxin A, in animal models, is associated with an inflammatory diarrhea and inflammatory cell infiltration of bowel wall mucosa. These toxins, when present, can also cause damage to the colonic mucosa, leading to ulcer formation. The expulsion of serum proteins and inflammatory cells from the mucosal defect can lead to the formation of pseudomembranes on the colonic mucosal surface. On direct inspection, pseudomembranous colitis is visualized as raised yellow plaques with associated edema and hyperemia of the bowel wall.

Recently, there have been reports of a more virulent strain of *C. difficile*. This toxin-gene variant strain has been associated with outbreaks of *C. difficile*-associated diarrhea in the U.S. health care facilities. There has been a change in this strain's toxin production, allowing significantly higher levels of toxin A and resulting in higher incidences of complications and death.[24] It has been postulated that increasing fluoroquinolone use in these facilities may select for infection with this aggressive strain.

Clinical Features

The clinical manifestations of *C. difficile* colitis usually include fever, leukocytosis, and watery diarrhea. Symptoms are usually temporally associated with the administration of antibiotics. More severe forms of this disease involve evidence of colitis with more severe diarrhea, as well as crampy abdominal pain. Pseudomembranous colitis is associated with these symptoms as well as the presence of pseudomembranes on sigmoidoscopic examination. Toxic megacolon is a severe complication that often results in acute peritonitis secondary to bowel perforation and even death. Patients with this severe form of disease often have a marked leukocytosis, high fever, and metabolic acidosis. Although diarrhea is the most common manifestation of *C. difficile* colitis, it is not invariably present, especially in the most critically ill.

C. difficile infection can be diagnosed by a variety of tests. Endoscopy demonstrating pseudomembranes and mucosal injury can establish the diagnosis of *C. difficile*-induced colitis most quickly and accurately. These pseudomembranes are more likely to be present in patients with more severe disease. Radiographic findings are often nondiagnostic and nonspecific; thickening or distension of the colon is suggestive of pseudomembranous colitis. Pneumatosis coli and intrahepatic portal venous air have been described in patients with severe *C. difficile* colitis. On the other hand, the laboratory diagnosis of *C. difficile* colitis has become more accurate and is based on the demonstration of bacterial toxins in stool samples.

The tissue culture cytotoxicity test is the gold standard for the laboratory diagnosis of *C. difficile* colitis; however, most hospitals use ELISA tests for both toxins A and B.

The gold standard for laboratory diagnosis is the tissue culture cytotoxicity assay; however, most hospitals use rapid enzyme immune assays (enzyme-linked immunosorbent assay, or ELISA). The ELISA methods rely on the use of monoclonal or polyclonal antibodies against both toxins A and B. ELISA testing has a lower sensitivity and specificity than the culture cytotoxicity test; therefore, a negative test does not exclude the diagnosis, and if the index of suspicion is high, colonoscopy should be performed. Colonoscopy is more useful than sigmoidoscopy because the disease may spare the rectum and the pseudomembranes may be found proximal to the sigmoid colon.

Treatment and Prevention

Management of *C. difficile* infections depends on the severity of illness. Mild diarrheal illness often responds to discontinuation of the offending antibiotic. In contrast, critically ill

patients require treatment with either vancomycin (125 mg p.o. q.i.d) or metronidazole (500 mg p.o. or intravenously q8h). Even in these patients , efforts should be made to discontinue any unnecessary antimicrobials.

Usually, when *C. difficile* colitis is suspected, empiric therapy with metronidazole or vancomycin is administered orally, pending results of diagnostic work-up. Either vancomycin or metronidazole for 10–14 days, when given via the enteral route, appears to be equally effective in the treatment of *C. difficile* colitis, but cost issues favor the use of metronidazole with initial infection.[25] Clinical improvement is usually noted within 3 days. For severe complicated *C. difficile* colitis, however, treatment with oral vancomycin may be associated with substantially higher cure rates.[26] When severe *C. difficile* colitis is suspected clinically, radiographic imaging should be performed and, if abnormal, surgical consultation obtained. Surgical intervention may be required to prevent a fatal outcome if medical management fails.

Intravenous vancomycin is not effective in C difficile colitis, but intravenous metronidazole is often used with adequate response rates. The parenteral route is used mostly in postoperative patients or those with an ileus, but with progression to toxic megacolon, vancomycin enemas are also administered together with intravenous metronidazole.

Infection control policies are imperative in prevention and control of *C. difficile* infection. These include contact isolation of infected patients, strict hand-washing techniques, and antibiotic restriction. Contact precautions should be used in patients with suspected or proven *C. difficile* infection, as it can be shed into the environment by these patients. Proper handwashing with soap and water is more effective than that with alcohol-based products as the bacterial spores are resistant to killing with alcohol. Due to the definite association between administration of antibiotics and both colonization and disease caused by *C. difficile,* limitation of unnecessary antibiotic use can serve to decrease rates of infection. Discontinuation of antibiotics, when possible, can help in the treatment of this infectious entity, although this is often not possible. At this time, treatment of asymptomatic carriers is not routinely recommended as an effort to decrease transmission of *C. difficile*.

Nosocomial Urinary Tract Infections

Epidemiology

Risk factors for nosocomial urinary tract infections include the presence of an indwelling catheter, female sex, diabetes mellitus, and poor catheter care.

Infections involving the urinary tract are commonly encountered in the ICU. These infections may involve the bladder, ureters, kidneys and, in men, the prostate. The most significant risk factor for these infections is the presence of an indwelling catheter. It is intuitive that the duration of catheterization influences the incidence of nosocomial urinary tract infections. Other risk factors for urinary tract infections include female sex, diabetes mellitus, and poor catheter care.[27]

Pathogenesis and Microbiology

Pathogens most commonly associated with nosocomial UTIs are enteric gram-negative rods. The presence of the catheter allows for organisms less commonly associated with urinary tract infections, such as staphylococci and yeast, to become pathogenic.

A catheter placed into the bladder serves as a path for bacteria and yeast to follow. The catheter surface may act as a site for bacterial adherence that allows the bacteria to move along the surface of the catheter and subsequently enter the bladder to cause infection. Urinary tract infections can be caused by a wide spectrum of organisms. The most frequently encountered organisms remain the gram-negative enteric bacteria (GNR). However, because of the exposure to antibiotics and direct entrance to the bladder by the catheter, other organisms such as nonenteric GNR, staphylococci, streptococci, enterococci, and yeast can become pathogens.

Clinical Features

Urinary tract infections can vary from a simple cystitis to more complicated infections such as pyelonephritis, pyelonephritis with bacteremia, and urosepsis. Cystitis can be missed because the patient may not be able to verbalize any symptoms. Pyelonephritis may present

with leukocytosis and fever. When bacteremia is associated with the UTI, full-blown severe sepsis can develop.

Since an indwelling catheter can be colonized by many bacteria, growing an organism from the urine does not mean there is an infection. The cornerstone to diagnosis of these infections includes not only the culture but also urinalysis with microscopy. A quantitative WBC on urine microscopy of greater than 10 WBC/mL often predicts an infection. Growth of cultured organisms greater than 10^5 cfu/mL is widely accepted as consistent with infection.

Findings on urinalysis with microscopy indicative of infection include quantitative WBC>10 WBC/mL and subsequent organism growth of $>10^5$ cfu/mL.

The urine specimen itself is easily obtained when a urinary catheter is in place. The specimen taken for urinalysis and culture should not be taken from the collection bag, but from the catheter itself.

Treatment and Prevention

Empiric therapy for nosocomial UTI will depend on individual patient and pathogens common to individual hospitals and ICUs. Patients with prior infections and use of antimicrobials are susceptible to infection with resistant organisms. If the urine Gram stain reveals GNR treatment can be initiated with a third-generation cephalosporin or a fluoroquinolone. If infection with *P. aeruginosa* is suspected, ceftazidime, cefepime, or ciprofloxacin can be utilized. Ampicillin or vancomycin can be used to treat Enterococcal infections. Treatment can then be tailored according to obtained culture data and sensitivities. When choosing an antimicrobial, one should also take into account the urine drug concentrations. For example, medications such as moxifloxacin, voriconazole, and the echinocandins do not get into the urinary tract in sufficient levels to be effective.

Urinary tract infections associated with indwelling catheters are considered complicated and, as such, require a longer duration of therapy as compared with treatment of simple cystitis. Complicated UTIs generally require treatment with antibiotics for 10–14 days depending on the severity of infection and the patient's clinical response.

Prevention of nosocomial UTI relies on avoiding unnecessary catheterization and timely removal of catheter when it is no longer needed.

Nosocomial UTIs are most often associated with the presence of urinary catheters and, as such, avoiding unnecessary catheterization and timely removal of the catheter are the mainstays of prevention. Short-term catheterization is acceptable in the ICU as most critically ill patients require accurate urine output measurement, but the catheter should be removed as soon as the patient's clinical status permits. Proper catheter care and management also aids in decreasing the incidence of catheter-associated UTI. This includes proper placement (using sterile technique), proper anchoring to limit traction on the urethra, and soap and water cleansing during bathing as maintenance care. Other postulated prevention methods including antimicrobial irrigation of the bladder, the use of antimicrobial-coated catheters, and/or the administration of prophylactic antibiotics have not been shown to be substantially beneficial in patients with indwelling bladder catheters.

SUMMARY

Infections are encountered routinely in the ICU. Nosocomial pneumonias along with intravascular catheter-related infections are the most common infections and account for most of the mortality associated with ICU infections. An understanding of the mechanisms involved in the development of infection in patients admitted to the ICU aids in the appropriate management of these patients and the subsequent prevention of devastating complications. More importantly, meticulous examination of each patient, assessment of risk factors, and knowledge of the types of organisms specific to the clinical scenario allow early and appropriate empiric therapy. Early institution of appropriate antimicrobials is important for the prevention of sepsis and its fatal sequelae. On the other hand, antibiotic therapy must be tempered by judicious use based on clinical information and on the severity of the patient's condition, thereby blunting the perpetuation of antibiotic resistance.

REVIEW QUESTIONS

1. **Which of the following is the most appropriate management plan for a 45-year-old man with hypotension, fever of 39.5°C, headache, nuchal rigidity, and somnolence?**
   - **A.** Computed tomography (CT) scan of the head
   - **B.** Lumbar puncture with Gram stain of the cerebrospinal fluid
   - **C.** Initiation of antibiotic therapy with ceftriaxone and vancomycin, concomitant lumbar puncture, and admission to the ICU
   - **D.** Admission to the ICU followed by performing lumbar puncture and starting dopamine

2. **A 65-year-old man with steroid-dependent chronic obstructive pulmonary disease and coronary artery disease is postcoronary artery bypass graft day 4. The patient has failed multiple attempts at weaning and continues to be on mechanical ventilatory support. The patient received cefazolin prophylaxis for 2 days postoperatively and treated with cefotaxime for a urinary tract infection. Over the next 24 h, he developed a fever of 39°C, progressive hypoxemia requiring increased oxygen supplementation, and progressive right lower lobe infiltrates on chest radiograph. Which management plan is best?**
   - **A.** Obtain blood and sputum cultures, continue cefotaxime, and wait for the culture and sensitivities before changing antibiotic therapy
   - **B.** Repeat urinalysis, remove the indwelling bladder catheter, and continue current antibiotic regimen
   - **C.** Start additional antibiotic therapy to include coverage of gram-negative organisms, including Pseudomonas species, and persistent gram-positive organisms, including MRSA, after obtaining sputum, blood, and urine cultures
   - **D.** Perform fiberoptic bronchoscopy with segmental right lower lobe lavage, obtain blood culture, continue cefotaxime, and wait for culture and sensitivity
   - **E.** Remove all central lines, send catheters for quantitative culture, and start vancomycin

3. **A 55-year-old man with a long history of alcoholism was admitted with hypotension, hypothermia, leukocytosis, left lower lobe consolidation, and right middle lobe consolidation on radiograph after being found stuporous in an alley behind a local cafe. The patient was admitted to the ICU for bilobar pneumonia where he was intubated because of poor gas exchange and progressive infiltrates on chest X-ray. At that point, he was started on clindamycin for suspected aspiration pneumonia. On day 5 in the ICU, he started having fever up to 39°C and profuse diarrhea, and on day 6, he became lethargic, hypotensive, and was noted to have bloody diarrhea. The appropriate management for this patient includes:**
   - **A.** Treat with immodium (an antidiarrheal) and dietary fiber supplementation
   - **B.** Obtain blood, sputum, urine cultures, and stool specimen for *Clostridium difficile* toxin assay and initiate empiric treatment with oral metronidazole and intravenous vancomycin for the remainder of the antibiotic course
   - **C.** Stop clindamycin and start broad coverage antibiotics to treat nosocomial-acquired pneumonia
   - **D.** Obtain CT scan of head and lumbar puncture, continue clindamycin if cerebrospinal fluid is negative for meningitis, and obtain transthoracic echocardiography to look for endocarditis

4. **A 40-year-old woman with gastroparesis receiving chronic outpatient TPN via a right upper extremity PICC line develops fever. Fever persists and she reports to the emergency department for evaluation. Shortly after arrival, she becomes tachycardic and hypotensive requiring ICU admission. The appropriate management plan for this patient is**
   - **A.** Initiation of antifungal therapy with fluconazole
   - **B.** Initiation of broad-spectrum antibiotic therapy as well as antifungal therapy and concomitant blood cultures, chest X-ray, and urinalysis with micro and culture to determine source of infection
   - **C.** Removal of PICC line
   - **D.** Admission to ICU and initiation of vasopressors

5. **A 45-year-old man presents with a chief complaint of dyspnea. He also describes productive cough and fever present for several days. He notes a recent hospitalization for an upper GI bleed. Radiographic imaging performed in the ED reveals a right middle and lower lobe infiltrate. Physical exam reveals an unkempt man with poor dentition, progressive respiratory distress, and rhonchi in the right lower lung field. His ETOH level on presentation is 200. He soon becomes increasingly hypoxic and hypotensive, and requires intubation for respiratory failure. Which of the following antibiotic combinations is most appropriate to give to this patient?**
   - **A.** Ceftriaxone and azithromycin
   - **B.** Clindamycin
   - **C.** Ceftriaxone, azithromycin, and clindamycin
   - **D.** Vancomycin and piperacillin-tazobactam

ANSWERS

1. The answer is C. Acute bacterial meningitis (ABM) is a fulminant fatal process, especially if recognition of the disease and institution of therapy are delayed. Often, there is concern about potential brain herniation if a lumbar puncture is performed in patients who have mental status changes and unsuspected brain masses; therefore, most clinicians obtain a CT scan before doing the lumbar puncture. However, CT scan of the brain is never considered a valid reason to delay antimicrobial treatment in patients suspected to have ABM. Lumbar puncture with fluid analysis is necessary in this scenario, but treatment with appropriate antibiotics should be instituted as soon as the diagnosis is suspected and after obtaining blood cultures. It may be true that this patient needs ICU care, but that should not delay the work up and treatment of ABM.

2. The answer is C. This patient has developed a ventilator-associated pneumonia that has led to clinical deterioration in the setting of antibiotic therapy for a urinary tract infection. Although the patient may have an inadequately treated urinary tract infection, he has worsening respiratory status and a chest radiographic finding suggesting a nosocomial ventilator-acquired pneumonia. The patient's new infection is likely due to a resistant organism; therefore, to continue his daily antibiotic regimen with cefotaxime while waiting for culture and sensitivity is inappropriate. Although some clinicians advocate the use of fiberoptic bronchoscopy to obtain quantitative bronchoalveolar lavage on protected specimen brush cultures, it is an accepted practice to obtain sputum and blood cultures while waiting for culture and sensitivity results and change to antimicrobial treatment to include treatment for MRSA and *Pseudomonas*.
3. The answer is B. The patient developed signs of sepsis and deteriorated, despite improvement of his pneumonia. His sepsis work-up should include *C. difficile* toxin assay because of the diarrhea. Other sources of infection may be his urinary tract, central indwelling catheter, spontaneous bacterial peritonitis, or meningitis. Endocarditis should be suspected if he has a new cardiac murmur or persistent bacteremia. The change in mental status in this patient is likely related to sepsis, and although CT scan of the brain and lumbar puncture may be required, other antibiotics should be added to clindamycin to treat his new sepsis. Indiscriminate use of antidiarrheals without first ruling out infection in a patient with fevers may lead to severe complications, including toxic megacolon. Intravenous fluids with potassium supplementation would be appropriate in this patient with profuse diarrhea. Flexible sigmoidoscopy may be helpful in diagnosing pseudomembranous colitis. In this patient with aspiration pneumonia, empiric metronidazole and stool analysis for *C. difficile* toxin are most appropriate.
4. The answer is B. At this early stage of presentation, the source of this patient's sepsis syndrome is unclear although catheter-related infection is likely. As such, a complete diagnostic work-up is warranted to search for the source of infection. Given her hemodynamic instability, broad-spectrum coverage should be initiated. Given her TPN dependence, she is at risk for associated fungemia and use of antifungals should be considered. Fluconazole alone would not be adequate as she should receive empiric coverage for bacterial pathogens. While she may require ICU admission and vasopressor agents, and possibly even PICC line removal, but most important should be empiric treatment for her sepsis syndrome and diagnostic work-up.
5. The answer is D. This man is presenting with pneumonia. His illness is severe enough to have led to respiratory failure. The presence of gingival disease and alcohol use raise the question of possible aspiration and, with it, possible anaerobic infection. Given this patient's recent hospitalization, he is at risk for infection with hospital-acquired pathogens. Clindamycin alone, while covering possible anaerobic infection, would not treat for a nosocomial infection. Vancomycin and piperacillin-tazobactam will cover anaerobes as well as common potential causative organisms of nosocomial pneumonia (including MRSA and *Pseudomonas*) and is the indicated treatment in this clinically unstable patient. Attempts should then be made to make a microbiologic diagnosis with blood and sputum cultures to tailor therapy.

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