Patients who have cancer have a greater tendency to acquire infections than the general population. The critically ill cancer patient is at a high risk for infections and its resulting complications. Multiple factors are responsible for this heightened risk of infection. In addition to complex cancer treatments, disruption of physical barriers including mucosal and integumentary systems, neutropenia, cellular and humoral immune dysfunction, splenectomy, presence of indwelling vascular catheters, and local tumor effects contribute to the increased risk of infection. In this population, organisms with low virulence potential are capable of causing significant morbidity and mortality.1–3 Organisms that cause infections in critically ill patients who have cancer span the entire gamut including bacteria, viruses, fungi, and protozoa.

Sepsis remains a common reason for hospital admission, accounting for approximately 750,000 admissions per year in the United States with a rising incidence.1,4 Patients who have cancer have a 30% higher risk for death from sepsis, which accounts for approximately 10% of all cancer deaths.2,4,5 Infection is a major cause of prolonged hospitalization and organ dysfunction in patients who have cancer. The National Institutes of Health estimated the direct medical costs for cancer in 2008 to be $93.2 billion.6 It is estimated that the annual hospital costs for patients who have cancer with severe sepsis alone is in excess of $3 billion.5 A total of
1,479,350 new cancer cases and 562,340 deaths from cancer are projected to occur in the United States in 2009.7

EPIDEMIOLOGY

Patients who have cancer are ten times more likely to acquire sepsis than patients who do not have cancer and account for 2.3% to 25% of severe sepsis and septic shock cases.2,4,5,8,9 Hematologic cancers (66.4 per 1000) are more likely to develop severe sepsis as compared with solid tumors (7.6 per 1000) and have a higher mortality rate.5,9 The length of stay and hospital costs for patients who have cancer and severe sepsis was nearly three times that of patients who have cancer but not severe sepsis.

Racial and gender disparities in the incidence of sepsis among patients who have cancer have been noted. Non-white patients who have cancer have consistently higher rates of sepsis. The etiology remains uncertain but factors, such as disparity in access to care and differences in receiving aggressive care, have been suggested. The incidence of sepsis is higher in men relative to women. The source of sepsis is often related to the anatomic site of the primary tumor. It is more common to encounter respiratory infections in patients who have lung cancer and genitourinary infections in patients who have prostate cancer.2

CELLULAR HOST DEFENSE DYSFUNCTION

Innate Immunity

The first line of cellular defense of the host is the innate (or natural) immune system, which is in part comprised of phagocytic cells including neutrophils, monocytes, dendritic cells, and tissue macrophages. These cells defend the host from microbial invasion in a nonspecific manner through recognition of pathogen-associated molecular patterns including unique lipopolysaccharides and peptidoglycans, lipoteichoic acids, and mannans. Defense mechanisms include phagocytosis, release of oxidative and nonoxidative mediators, complement activation, and release of cytokines to signal other elements of the immune system. Neutrophils represent the largest proportion of phagocytes, are the primary cell to arrive at the site of infection and have the greatest degree of oxidative burst.

Defects to neutrophils may be either quantitative or qualitative.10–12 Chemotherapeutic agents, such as melphalan, busulfan, methotrexate, carboplatin, cisplatin, paclitaxel, doxorubicin, cyclophosphamide and etoposide lead to neutropenia by direct bone marrow suppression.13 Radiation therapy, glucocorticoids, and hyperglycemia can impair neutrophil function and delay neutrophil recovery.14–16 The three factors that are important in determining the risk of infection associated with neutropenia are the rate of neutrophil decline, degree of neutropenia (absolute neutrophil count [ANC]) and duration of neutropenia.17–20

Adaptive Immunity

The adaptive (or acquired) immune system represents a more specialized and targeted component that can be further divided into two separate mechanisms: (1) humoral (B lymphocytes, immunoglobulins and complement system); and (2) cell mediated (T lymphocytes and antigen presenting cells). Additionally, these responses maintain an immunologic memory that is not seen with the innate immune system.21

B cells produce immunoglobulins that bind to extracellular foreign antigens including bacterial, viral, and certain fungal pathogens. Immunoglobulins target organisms for phagocytosis by opsonization, activate the complement system, and block pathogen binding to mucosal or target cells.22 Patients who have B-cell defects,
including chronic lymphocytic leukemia (CLL), multiple myeloma, Waldenström macroglobulinemia, and allogeneic hematopoietic stem-cell transplantation (HSCT) recipients are susceptible to overwhelming infections with encapsulated organisms, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*.23–26 Additionally, chemotherapy and radiation can increase the risk for infection.27 The monoclonal antibody rituximab, used to treat B-cell malignancies, can predispose to infections from encapsulated bacteria and herpes virus up to several months after treatment.28 Alemtuzumab, a monoclonal antibody used for second line treatment of B-cell CLL and T-cell lymphoma, increases the risk for infection from *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*), fungi and cytomegalovirus (CMV).29,30

T-cell receptors, in contrast to immunoglobulins, are displayed on the surface of T cells and enable destruction of intracellular pathogens including viruses, bacteria, fungi, and mycobacteria by recognition of single peptide-major histocompatibility complexes.31 T cells activate phagocytes, regulate B-cell immunoglobulin production and T-cell mediated cytotoxicity. Malignancies, such as CLL, T-cell leukemia/lymphoma, hairy cell leukemia, Hodgkin’s disease and thymoma, and HSCT are associated with impaired T-cell function.23,32–34 Chemotherapeutic agents, such as fludarabine, cladribine, cyclophosphamide, methotrexate, and corticosteroids can lead to lymphopenia and lymphocyte dysfunction.35 Patients who have CLL and are treated with fludarabine are at additional risk for various pathogens, including *Listeria monocytogenes*, *P jirovecii*, CMV, herpes simplex virus (HSV), varicella zoster virus (VZV), and mycobacteria.35–37 In addition, cyclosporine and tacrolimus, commonly used as immunosuppressants following HSCT, impair T-helper cell function by blocking production of cytokines and other cell-signaling mechanisms. Newer agents, such as temozolomide, cause CD4+ lymphopenia and increase the risk for infections, such as *Pneumocystis* and *Aspergillus* pneumonia.38,39 Table 1 lists common pathogens based on the associated immune defect and by organ system involvement.

**NEUTROPENIC FEVER**

Fever in patients who are neutropenic is an oncologic emergency that necessitates the prompt administration of appropriate antibiotics. Mortality is high when the administration of antibiotics is delayed.40 Despite improvements in long-term survival, infections remain a common complication of cancer therapy and accounts for the majority of chemotherapy-associated deaths.41

**Definition**

Fever in patients who are neutropenic is defined as a single oral temperature of greater than or equal to 38.3°C (101°F) or a temperature of greater than or equal to 38.0°C (100.4°F) for more than 1 hour. Neutropenia is defined as a neutrophil count of less than 500 cells/mm³ or a count of less than 1000 cells/mm³ with a predicted imminent decrease to less than 500 cells/mm³.42

**Initial Evaluation**

The 2002 Infectious Disease Society of America guidelines stipulate that evaluation of fever in patients who are neutropenic should include a comprehensive history and physical examination with attention for subtle signs and symptoms.42 Indicators of inflammation may be minimal or absent in patients who are severely neutropenic, especially if accompanied by anemia.40 Therefore, careful search for sites of infection should include examination of the periodontium, pharynx, perineum and anal
<table>
<thead>
<tr>
<th>Organ Systems</th>
<th>Granulocytopenia</th>
<th>B-cell and Humoral Defects</th>
<th>T-cell Defects</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>Bacterial</td>
<td>Staphylococcus aureus</td>
<td><em>Legionella pneumophila</em></td>
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<td>Staphylococcus pneumoniae</td>
<td><em>Nocardia asteroides</em></td>
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<td>Streptococcus pyogenes</td>
<td><em>Rhodococcus equi</em></td>
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<td>Klebsiella spp</td>
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<td><em>Pseudomonas</em> spp</td>
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<td>Influenza</td>
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<td>VZV</td>
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<td><em>Pneumocystis jiroveci</em></td>
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<td><em>Cryptococcus neoformans</em></td>
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<td><em>Histoplasma capsulatum</em></td>
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<td><em>Strongyloides stercoralis</em></td>
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<td>Fungal</td>
<td><em>Aspergillus</em> spp</td>
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<td>Parasites</td>
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<td><em>Pseudomonas</em> spp</td>
<td><em>Salmonella</em> spp</td>
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<td><em>Klebsiella</em> spp</td>
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<td><em>Clostridium</em> spp</td>
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<td>HSV</td>
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<td>Fungal</td>
<td><em>Candida</em> spp</td>
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<td>Central Nervous System</td>
<td>Bacterial</td>
<td>Staphylococcus aureus</td>
<td>Streptococcus pneumoniae</td>
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<td>Streptococcus pneumoniae</td>
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<td>Pseudomonas aeruginosa</td>
<td>Neisseria meningitidis</td>
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<tr>
<td>Fungal</td>
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<td>Aspergillus fumigatus</td>
<td>Candida spp</td>
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<tr>
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<td>Mucoraceae</td>
<td>Cryptococcus neoformans</td>
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<td>Parasites</td>
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<tr>
<td>Genitourinary</td>
<td>Bacterial</td>
<td>Escherichia coli</td>
<td>Pseudomonas aeruginosa</td>
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<td></td>
<td>Viral</td>
<td>CMV</td>
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<tr>
<td></td>
<td>Fungal</td>
<td>Candida spp</td>
<td>Toxoplasma gondii</td>
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region, eye, bone marrow aspiration site, vascular catheter access sites, and perionychium.

Complete blood counts, blood urea nitrogen, creatinine, hepatic panel, and chest radiograph should be obtained in all patients. High-resolution CT (HRCT) will reveal evidence of pneumonia in more than one half of febrile neutropenic patients who have normal findings on chest radiographs. Complete blood counts, blood urea nitrogen, creatinine, hepatic panel, and chest radiograph should be obtained in all patients. High-resolution CT (HRCT) will reveal evidence of pneumonia in more than one half of febrile neutropenic patients who have normal findings on chest radiographs. For all patients who have intravascular catheters, a minimum of one set of blood samples should be obtained for culture from each lumen and from a peripheral vein. If a catheter entry site is inflamed or draining, the fluid exuded should be examined by Gram staining and culture for bacteria and fungi. Cultures of urine samples are indicated if signs and symptoms of urinary tract infection (UTI) exist, a urinary catheter is in place, or the findings of urinalysis are abnormal. In a series of febrile neutropenic patients with cancer who had UTIs, only 11% of the subjects who had an ANC of less than 100 cells/mm³ had pyuria. Cultures of the stool and cerebrospinal fluid (CSF) should be considered as guided by symptoms and physical examination. Aspiration or biopsy of skin lesions suspected of being infected should be performed for cytologic testing, Gram staining, and culture. Levels of C-reactive protein, interleukin (IL)-6, IL-8, and procalcitonin may be affected by bacteremia in febrile neutropenic patients, but the association is not sufficiently consistent to recommend for routine clinical practice.

**Risk Assessment**

Determining the clinical risk of patients with neutropenic fever is essential to help identify those suitable for outpatient antibiotic therapy and stratify individuals who may benefit from empiric antifungal therapy. Two assessment systems have been developed to risk stratify patients. According to the Multinational Association of Supportive Care in Cancer (MASCC) system various factors (absence of hypotension, absence of dehydration, burden of illness, age <60 years) that were associated with a better outcome were assigned an integer weight to develop a risk-index score. A risk-index score greater than or equal to 21 identified low risk patients with a less than 5% risk of complications, but if the risk score is less than or equal to 21 the risk of complications and death is significantly higher. The risk of developing bacteremia and poor outcome after treatment is even greater if the MASCC risk index is less than 15.

**Spectrum of Infection**

Bacterial infections are the most common causes of infection and at least one half of patients with neutropenic fever with counts less than 100 cells/mm³ have bacteremia. The organisms causing bacteremia are listed in Table 2. Fungi are common causes of secondary infections among patients who received broad-spectrum antibiotics. The primary sites of infection are the gastrointestinal (GI) tract, vascular access devices, and lung.

**Bacterial infections**

The spectrum of bacterial infections occurring in neutropenic fever has changed over the past three decades. In the 1970s and 1980s enteric Gram-negative bacilli, such as *Escherichia coli*, *Pseudomonas*, and *Enterobacter* species predominated being the etiologic agents in 60% to 70% of cases, whereas Gram-positive organisms, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcal* species accounted for 20% to 30% of infections. In the 1990s, Gram-positive infections began to outnumber Gram-negative infections. The reasons for the shift could be attributable to routine use of central venous catheters (CVC), use of quinolone prophylaxis, and
increased use of proton pump inhibitors. Anaerobic bacteremia occurs in less than 5% of patients who have febrile neutropenia and has not changed over the past 30 years.\textsuperscript{48} Patients who have intra-abdominal infections, neutropenic colitis, perirectal abscesses or periodontal disease are at risk for anaerobic bacteremia.

The emergence of resistant nosocomial isolates has also had an impact on infections in patients who are neutropenic. Particularly, methicillin-resistant \textit{S aureus} (MRSA) and vancomycin-resistant \textit{Enterococci} continued to increase in frequency in the 1990s.\textsuperscript{48} This increase has made a significant impact in the choice of therapeutic antimicrobials. Another group of organisms that has been increasingly found as a cause of bacteremia in patients who have cancer and HSCT is \textit{Streptococcus viridans}. The source of infection is the oropharynx in the setting of mucositis and it could manifest as toxic shock syndrome.\textsuperscript{50}

\textbf{Fungal infections}

Infections caused by fungal organisms continue to have a significant impact on mortality in patients who have cancer. The most common risk factors for fungal infections include prior use of steroids and antibiotics, advanced age, tissue damage, intensity of chemotherapy, and presence of an indwelling central catheter.\textsuperscript{51} \textit{Candida} species remain the most common cause of fungal infection in patients who are neutropenic followed by \textit{Aspergillus} species. Candidemia is most frequently caused by \textit{Candida albicans} followed by \textit{C glabrata}, \textit{C tropicalis} and \textit{C parapsilosis}. The clinical presentation is broad, ranging from catheter-related infections, single-organ candidiasis to disseminated candidiasis.\textsuperscript{51}

\textit{Aspergillosis} is seen in 30% of protracted, severe neutropenia cases and affects the lungs and sinuses.\textsuperscript{52} \textit{Aspergillus fumigatus} is the most common species that causes invasive disease. These infections are common in HSCT recipients, patients older than 18 years of age, positive CMV serology, and delayed engraftment.\textsuperscript{53} Evidence on chest CT scan of a halo or air crescent sign is felt to be highly indicative of \textit{Aspergillus} infection.\textsuperscript{54}
Management

Empiric antibiotic therapy should be administered promptly to all patients who are neutropenic at the onset of fever. In the selection of initial antibiotic regimen, one should consider the type, frequency of occurrence, and antibiotic susceptibility of bacterial isolates recovered from other patients at the same hospital. Fig. 1 provides a simplified algorithm for empiric antibiotic therapy.

Several studies have shown no striking differences between monotherapy and multidrug combinations for empiric coverage of uncomplicated neutropenic fever. Monotherapy with ceftazidime should be avoided because of resistance through extended spectrum β-lactamases and type 1 β-lactamases. Quinolones or aminoglycosides as monotherapy are not recommended as the initial antibiotic choice.

The single most important determinant of successful discontinuation of antibiotics is the ANC. If the neutrophil count is greater than or equal to 500 cells/mm³, and if patients are afebrile for greater than or equal to 48 hours, and if no infection is identified after 3 days of treatment, antibiotics may be stopped. On the other hand, if a specific etiology is found, the appropriate antibiotics are continued for a minimum of 7 days. If the ANC remains less than or equal to 500 cells/mm³, and if patients are afebrile for greater than or equal to 48 hours, the proper antibiotic course is guided by the initial risk assessment of patients and is less well defined.

There is usually no indication for the empiric use of antiviral drugs in the treatment of patients who have febrile neutropenia unless there is clinical or laboratory evidence of viral disease. The routine use of granulocyte transfusion is not usually advocated. Use of colony-stimulating factors can shorten the duration of neutropenia but does not reduce duration of fever, use of antimicrobials, or decrease in infection-related

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**Empiric Antibiotic Therapy of Febrile Neutropenia in the High Risk Patient**

<table>
<thead>
<tr>
<th>Neutrophil count &lt;500 cells/mm³ and fever (≥38°C)</th>
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<tbody>
<tr>
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<tr>
<td>Monotherapy in uncomplicated cases, with cefepime or a carbapenem*</td>
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<tr>
<td>OR</td>
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<tr>
<td>Dual therapy is indicated in complicated cases or suspicion of resistance, with an antipseudomonal cephalosporin, antipseudomonal extended spectrum β-lactams or carbapenem PLUS aminoglycoside or quinolone*</td>
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<tr>
<td>↓</td>
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<tr>
<td>Fever continues despite 3 days of antibiotics and no clear source, add empiric vancomycin</td>
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<td>↓</td>
</tr>
<tr>
<td>Fever continues despite 5–7 days of antibiotics and resolution of neutropenia is not imminent, add empiric antifungal therapy with amphotericin B or voriconazole.**</td>
</tr>
</tbody>
</table>

Fig. 1. Simplified algorithm to guide initiation and modifications in antimicrobial coverage for hospitalized patients with neutropenic fever. *Vancomycin should be added to initial coverage in cases with severe mucositis, prior use of quinolone prophylaxis, clinically suspected catheter-related blood stream infections (CRBSI), known colonization with penicillin, and cephalosporin-resistant pneumococci or MRSA, hypotension, or evidence of cardiovascular impairment. **Fluconazole represents an alternative to amphotericin B in patients who have renal insufficiency and in institutions where there are fewer non-albicans *Candida* infections.
mortality rates. Additionally, colony-stimulating factors can lead to splenomegaly and potentially increase the risk for splenic rupture.\textsuperscript{57}

**RESPIRATORY INFECTIONS**

Pneumonia is a common complication seen in patients who have cancer, particularly in those who have neutropenia. Pulmonary infiltrates are seen in 15% to 25% of patients who have profound neutropenia after intensive chemotherapy and are associated with a particularly high risk of mortality.\textsuperscript{58} Chemotherapy and immune defects of underlying hematologic disorders increases the risk for infections.\textsuperscript{10} Between 25% and 50% of infiltrates are not caused by infection and may be caused by pulmonary edema, drug toxicity, cancer progression, or radiotherapy.\textsuperscript{59}

**Incidence**

In a case series of 104 subjects who had cancer with pulmonary infiltrates, 49% had bacterial infection, 26% had a viral infection, 21% had a fungal infection, and 4% had \textit{P jirovecii} infection.\textsuperscript{60} The commonly identified pathogens were \textit{Pseudomonas aeruginosa}, \textit{S aureus}, \textit{Aspergillus} species, CMV and HSV. In a study involving subjects who had leukemia, Gram-negative bacteria caused 70% of infections, polymicrobial infections in 12% of cases, and a fungal etiology was identified in 12%.\textsuperscript{61}

**Bacterial infection**

Bacterial pathogens are the most common cause of respiratory infections complicating cancer chemotherapy. Gram-positive pathogens include \textit{S aureus}, \textit{Streptococcus pyogenes}, \textit{S pneumoniae}, and \textit{Enterococcus faecalis}, whereas \textit{E coli}, \textit{P aeruginosa}, and \textit{Klebsiella} spp are the most common Gram-negative pathogens.

The underlying malignancy and associated immune defects increases the risk for specific types of infections. \textit{S aureus} pneumonia is common in patients who receive prophylactic antibiotics against Gram-negative bacteria, elderly, diabetics, alcohol abuse, and during influenza epidemics. \textit{S viridans} pneumonia is common in patients who have leukemia and who have mucositis after high-dose cytarabine therapy.\textsuperscript{62} \textit{S pneumoniae} and \textit{H influenza} are commonly seen in multiple myeloma and CLL, where defects in the immunoglobulin function are observed. \textit{P aeruginosa} and \textit{K pneumoniae} are seen in patients who have neutropenia or leukemia. Diagnosis of bacterial pneumonia is confirmed by performing quantitative cultures of lower respiratory secretions (endotracheal aspirates, bronchoalveolar lavage [BAL], or protected specimen brush samples) to define the presence of pneumonia and the etiologic pathogen. Antibiotic selection should be dictated by the local/institutional microbiology and resistance patterns.

\textit{Legionella} species are recognized as opportunistic pathogens causing severe pneumonia in immunosuppressed hosts. \textit{L pneumophila} serogroup 1 appears to be more virulent than other serogroups; however, non-pneumophila \textit{Legionella} species are common in hospital potable water systems and can be a cause of infection in hospitalized, immunosuppressed hosts. Most of the affected patients had impairment of cellular immunity, such as lymphopenia, or immune dysfunction caused by systemic use of steroids or antineoplastic agents. The vast majority of the patients in one series had hematologic malignancies.\textsuperscript{63} Diagnosis is confirmed by performing legionella direct fluorescent antibody (DFA) on bronchoscopy specimens in patients who had suspected pulmonary infection, whereas urinary legionella antigen detects predominantly \textit{L pneumophila} serogroup 1. Treatment is with a quinolone or azithromycin for 21 days.

\textit{Stenotrophomonas maltophilia} is commonly seen in patients who have lung cancer, patients on prolonged mechanical ventilation, patients who have neutropenia, those who received broad-spectrum antibiotics, or have leukemia.\textsuperscript{64} Infection is not
accompanied by an inflammatory process and usually follows colonization of the respiratory tract. Lobar consolidation without pleural effusion is common. Factors associated with high mortality are bacteremia, refractory neutropenia, and delay in appropriate antibiotic treatment. Despite appropriate treatment, more than 50% of patients die of progressive infection or hemorrhage. Trimethoprim-sulfamethoxazole (TMP/SMX) is the treatment of choice. The newer fluoroquinolone, moxifloxacin, is superior to ciprofloxacin because it inhibits many ciprofloxacin resistant strains. Other agents, such as tigecycline, ceftazidime, cefepime, ticarcillin/clavulanate, and piperacillin/tazobactam, have variable activity. Combination therapy allows for synergism, however, its role is unclear and the efficacy needs further evaluation.

_Nocardia_ are aerobic, branching Gram-positive bacilli that are also weakly acid-fast that frequently cause necrotizing pneumonia and cavitation in patients who are immunosuppressed. Infection with _Nocardia_ species is associated with high mortality. Diagnosis is established by examination of the sputum or pleural fluid, BAL or percutaneous lung aspiration with Gram staining and modified acid-fast staining. TMP/SMX is the first line treatment and is usually given parenterally. The duration of treatment is 1 year or more in patients who are immunosuppressed. Other therapeutic options include amikacin, carbapenems, third generation cephalosporins, and linezolid.

Disseminated tuberculosis (TB) is seen in patients who are immunocompromised, particularly leukemia, and is associated with a high mortality rate. The diagnosis of TB involves detection of mycobacteria in biologic samples. Drug-susceptible TB treatment involves standardized 6 months of anti-TB drug regimens. _Mycobacterium avium_ infections are common in children who have leukemia during periods of lymphocytopenia. _Rhodococcus equi_ infection should be considered together with _M tuberculosis_ and _Nocardia_ infections in the differential diagnosis of cavitary or nodular pneumonia in patients who are immunocompromised.

Ventilator associated pneumonia (VAP) is difficult to diagnose in patients who have cancer, who often present with neutropenia and refractory thrombocytopenia. The use of fiberoptic bronchoscopy and the need for bronchial brushing may induce severe bronchial hemorrhage. A blinded plugged telescoping catheter was a reasonably accurate technique for the diagnosis of VAP in patients who have cancer, though less sensitive when compared with fiberoptic protected specimen brush technique.

**Viral infections**

Common viruses causing respiratory infection include influenza, parainfluenza, respiratory syncytial virus (RSV), CMV, and HSV. RSV accounts for 30% to 49% of all respiratory viruses in patients who are immunocompromised and have hematologic malignancies. In cancer patients, RSV usually presents as an upper respiratory tract illness that can progress to fatal pneumonia in approximately 60% of cases. Patients who have profound myelosuppression, persistent lymphocytopenia, corticosteroid use, and high Acute Physiology and Chronic Health Evaluation (APACHE) scores have the highest risk for progressing to pneumonia and death. In these patients, pneumonia has a mortality rate of 60% to 80%. This rate has decreased considerably, possibly because of earlier diagnosis and more aggressive therapy. Reverse transcriptase polymerase chain reaction (PCR) is more sensitive than antigen testing by DFA. Antigen testing might be helpful for patients who shed the virus at high levels. Aerosolized ribavirin is the treatment of choice and should be administered to high-risk patients who have leukemia. Therapy with the monoclonal antibody, palivizumab (Synagis - MedImmune, LLC, Gaithersburg, MD) has been used as an adjunct to aerosolized ribavirin and has been well tolerated.
CMV infection and pneumonia is most common in patients who have lymphoma or leukemia. The risk of infection is increased by the use of agents, such as cytarabine and fludarabine; treatment with T-cell suppressors, such as steroids and methotrexate; and use of T-cell depleting drugs, such as rituximab and alemtuzumab. The diagnosis of CMV pneumonia involves detection of virus in lung tissue by use of immunohistochemical staining, histopathological assessment, or culture. The diagnostic yield by cytology or immunohistochemical staining from BAL samples is low. However, the yield with viral-shell vial culture and conventional culture of BAL samples is high. The conventional culture is the gold standard for the diagnosis but takes 6 weeks to obtain final results, whereas the rapid viral culture by shell vial method takes 48 hours and has a sensitivity of 68% to 100%. The treatment of choice is ganciclovir or foscarnet.

Reactivation of latent HSV is common in patients who have neutropenia that occurs during induction chemotherapy and in patients who have lymphoma, acute leukemia, as well as during the conditioning phase of HSCT. HSV-1 pneumonitis may follow oral or genital HSV either through contiguous spread from the oropharynx or hematogenous dissemination. Although rare, it should be considered in neutropenic hematologic patients undergoing chemotherapy when they are not responding to antibacterial or antifungal treatment. The radiographic findings show bilateral infiltrates, which are nonspecific. Definitive diagnosis of HSV pneumonia is difficult and is established by culture of BAL fluid or blood or detection of virus in the lung tissue. Treatment is with intravenous (IV) acyclovir.

Infections caused by other viruses, such as influenza and parainfluenza, are also seen. The single most important predictor of mortality in influenza pneumonia is absolute lymphopenia. A specific reverse-transcriptase PCR that detects RNA from influenza A and B and parainfluenza viruses from nasal-wash samples are very sensitive for rapid diagnosis. Infection with enterovirus and adenovirus has also been reported in patients who have lymphoma and leukemia with lower respiratory infections. Human metapneumovirus infection has been reported in 2.7% of respiratory disease in patients who have hematological cancer. Routine diagnostic testing remains a challenge, as the virus requires special cell lines and a long incubation period for growth. There are anecdotal reports on the successful use of ribavirin, but more studies are needed to determine efficacy in randomized trials.

Fungal infections
Aspergillosis is usually acquired by inhalation of *Aspergillus* conidia and the most common manifestation is pneumonia. Invasive pulmonary aspergillosis can occur in patients who are neutropenic and is commonly fatal with mortality as high as 60%. Chest CT usually shows small, round, and dense peripheral lesions that increase in size over time. A halo sign is the first reliable sign of infection during neutropenia and has a high specificity and low sensitivity. On the other hand, nodular cavitated lesions are more frequent in patients who are not neutropenic. *Aspergillus* that is seen on sputum samples might represent colonization and not necessarily indicate infection. Contamination can occur during bronchoscopic sampling or during handling of the samples in the laboratory. Microbiological cultures of *Aspergillus* from BAL are positive in fewer than a third of patients. The gold standard is detection of hyphae by histopathologic or cytopathologic examination of a biopsy sample of lung tissue, either by video-assisted thoracoscopic surgery or transbronchial biopsy. PCR is highly sensitive and specific, and was negative in 1.4% of samples from subjects with histologically confirmed aspergillosis. However, consensus guidelines do not recommend PCR testing in BAL samples or blood samples, but recommend *Aspergillus* antigen detection in such samples. The role of serum galactomannan in the early
detection of pulmonary aspergillosis is unclear. Early diagnosis is difficult; however, early recognition and prompt antifungal treatment is key to improved survival. The drug of choice is liposomal amphotericin B 3 mg/kg/d. Clinical response in patients who have confirmed aspergillosis is the same between two preparations of amphotericin B. Voriconazole was found to be more efficacious with fewer side effects when compared with amphotericin B deoxycholate. Posaconazole can be used in refractory cases and is associated with a partial response. Caspofungin led to a partial or complete response as salvage treatment in up to 45% of patients' refractory to other antifungal agents. Despite the theoretical advantages of increasing neutrophils, colony-stimulating factors are ineffective and clinical deterioration might occur during neutrophil recovery.

*Fusarium* species, a fungus distributed in soil and plants, most commonly affects lungs and skin. Pulmonary manifestations are similar to *Aspergillus*. Treatment is with voriconazole, itraconazole, or amphotericin B. Overall mortality rate is 50% to 80%. Zygomycosis can be difficult to diagnose because blood cultures are negative and bronchial washings rarely yield hyphal forms. High-dose liposomal amphotericin B and radical surgical debridement are the treatment of choice.

*P jirovecii* pneumonia (PCP) is less common among patients who have cancer, including those who have undergone HSCT when compared with patients who have AIDS. The incidence among patients who had hematologic malignancies was higher than the incidence among patients who had solid tumors, with the majority of episodes of PCP occurring in either leukemia (49%) or lymphoma (45%). Corticosteroids are a major risk factor for PCP, particularly among patients who have solid tumors. Other predisposing factors include intensity of chemotherapy and low CD 4 count. CMV coinfection is common in patients who have PCP. Previous studies have indicated that typical radiographic features of PCP are bilateral interstitial infiltrates, whereas pleural effusions and pneumothorax are rarely observed. The diagnostic yield of BAL cytology is high. TMP/SMX is the standard treatment but might be suboptimal in hematological malignancies. The most common combination therapy was TMP/SMX plus pentamidine and there was a trend toward combination antimicrobial therapy being more commonly used in sicker patients who required mechanical ventilation than in patients who did not. Caspofungin, an echinocandin is active against the cystic form of *P jirovecii* in animal models. In combination with TMP/SMX caspofungin was used in a very small number of subjects. As a result, the role of echinocandins in patients who have cancer and PCP remains uncertain. Optimum duration of treatment is unclear, with 2 weeks being sufficient for most patients who have cancer and treatment with 3 weeks showing better outcome. Prophylaxis with TMP/SMX should be considered in patients who have lymphoblastic leukemia, patients on prednisone greater than or equal to 20 mg for more than 1 month, and in patients who have low CD4 counts.

**Parasitic Infection**

*Strongyloides stercoralis* is an intestinal nematode that causes fatal opportunistic infections in immunocompromised hosts, particularly after steroid therapy. Hyperinfections and widespread dissemination of larvae may lead to hemorrhagic pneumonitis (because of larva-induced mucosal injury during larval migration in the hyperinfection syndrome), enteritis, and Gram-negative bacteremia. Diagnosis is made by demonstrating the organisms in stool specimens or by cytology in a sputum specimen. Mortality from disseminated strongyloidiasis approaches 80% and the treatment of choice is oral thiabendazole.
GASTROINTESTINAL INFECTIONS

Normally the GI tract acts as a barrier to the external environment. Disruption of the GI mucosa leads to translocation of enteric pathogens. Risk factors for infection in patients who have cancer include mechanical disruption, such as mucositis, chemotherapy, radiotherapy, immune dysfunction, altered microbial flora, surgery, altered motility, and antimicrobial exposure. GI infections commonly seen in critically ill patients who have cancer include typhlitis, *Clostridium difficile* associated diarrhea (CDAD), and hepatosplenic candidiasis.

**Typhlitis**

Typhlitis (also reported as neutropenic enterocolitis, necrotizing enterocolitis, neutropenic enteropathy or ileocecal syndrome), occurs most commonly after intensive chemotherapy for acute leukemia, but has also been reported in patients who have untreated hematologic malignancies, neutropenia from other causes, following HSCT and in those receiving immunosuppressive therapy for solid tumors.\textsuperscript{108,109} The incidence rate varies from 0.8% to 25% with mortality rates of 50% or higher.\textsuperscript{110} The precise pathogenesis is poorly understood but chemotherapy, neutropenia, and immune dysfunction likely lead to mucosal edema, ulceration, necrosis, and focal hemorrhage in the terminal ileum, cecum, and right colon.\textsuperscript{108,109} Chemotherapeutic agents, such as cytosine arabinoside (ara-C) and etoposide (VP-16), have been most commonly implicated; however, agents, including vinorelbine, docetaxel, paclitaxel, carboplatin, gemcitabine, 5-fluorouracil, vincristine, doxorubicin, methotrexate, and cyclophosphamide have also been associated.\textsuperscript{108,111} Likely pathogens include *Pseudomonas* spp, *E coli*, *Klebsiella* spp, *Clostridium septicum*, *C difficile* and *Candida* spp and CMV.\textsuperscript{3,108,109,112} Recurrent bacteremia frequently occurs.\textsuperscript{109}

Patients who have typhlitis present with fever, right lower quadrant pain with or without rebound tenderness, diarrhea, abdominal distension or less commonly nausea and vomiting, or a palpable mass in the right lower quadrant.\textsuperscript{108,109} CT scan or ultrasound are the preferred modalities and demonstrate bowel wall thickening or pneumatosis.\textsuperscript{108,113,114} Fever, abdominal pain, and bowel wall thickening greater than 4 mm is consistent with the diagnosis of typhlitis. In patients who have bowel wall thickness greater than 10 mm, mortality is as high as 60%.\textsuperscript{110,114,115}

Initial management of typhlitis includes strict bowel rest, nasogastric decompression, intravenous fluids, consideration for total parenteral nutrition, broad-spectrum antimicrobial therapy (empirically or based on blood culture results), and surgical consultation. Antimicrobial therapy must provide coverage of enteric Gram-negatives with an extended-spectrum β-lactam/β-lactamase combination, carbapenem, or third or fourth generation cephalosporin plus metronidazole. Metronidazole should be added when *C difficile* is suspected.\textsuperscript{108} Empiric antifungal coverage for *Candida* should also be considered.\textsuperscript{112} Indications for surgical intervention include acute perforation, toxic megacolon, bowel necrosis, persistent GI bleeding or clinical deterioration. Surgery should be delayed if possible until neutrophil recovery occurs. Although no randomized trials of colony-stimulating factors have been conducted in this condition, their use has been recommended in patients at high risk for complications and poor outcomes associated with neutropenia.\textsuperscript{110,116}

**Clostridium Difficile Associated Diarrhea**

CDAD is a toxin mediated disease that occurs most commonly in the elderly hospitalized patient receiving either antibiotics or chemotherapy and its prevalence is rising.\textsuperscript{117,118} In 2005, the identification of the highly virulent strain (BI/NAP1/027) was
found to be responsible for the rise in infection rates in North America. It is characterized by fluoroquinolone resistance and is associated with increased toxin production causing a higher mortality rate than other strains.\textsuperscript{117,118} Clinically significant strains produce two exotoxins (toxin A and B). Antibiotic exposure to ampicillin, cephalosporins, clindamycin, or fluoroquinolones, bowel surgery, or chemotherapy can disrupt the normal bowel flora and predispose for \textit{C difficile} colonization.\textsuperscript{117–119} Additionally, prolonged hospitalization of more than 4 weeks can increase the rate of acquisition.\textsuperscript{119} Patients can present with mild to severe diarrhea, fever, leukocytosis, and abdominal pain. Severe cases will manifest pseudomembranes in the colon, toxic megacolon (which may present without diarrhea), perforation, sepsis, shock, and death.

All hospitalized patients who have cancer who develop diarrhea should be suspected of having CDAD, especially those who have neutropenia.\textsuperscript{119} Testing for \textit{C difficile}-associated glutamate dehydrogenase antigen allows for screening of stool samples, however, a positive result requires toxin testing to confirm the diagnosis.\textsuperscript{120} Enzyme immunoassay kits can detect toxin A, toxin B or both and can provide results in 2 to 4 hours, but are less sensitive and kits that do not detect toxin B may miss a small number of strains that only produce this toxin.\textsuperscript{121} Detection of the \textit{C difficile} toxin B in stool samples by cell-culture cytotoxin assay is specific but takes up to 48 hours to yield a result. CT findings include bowel wall thickening greater than 8 mm, wall nodularity and pancolitis.\textsuperscript{114} Endoscopy should be performed to identify pseudomembranes in patients where rapid diagnosis is required, if the stool tests are not specific enough, if there is ileus without diarrhea, or if other diagnoses are being considered.\textsuperscript{121} Sigmoidoscopy may miss a small number of cases if colonoscopy is not performed. Lower-GI endoscopy should be avoided in the setting of neutropenia.

Treatment of CDAD begins with discontinuation of the offending agent, however, this may not be feasible in patients who are critically ill and results of testing may not be readily available. Because the final diagnosis may be delayed, empiric administration is generally warranted in the ICU setting. Metronidazole (either oral or intravenous) represents the initial drug of choice, whereas oral vancomycin should be used for severe disease.\textsuperscript{122} Dual therapy may be of benefit in fulminant disease.\textsuperscript{117} A 10- to 14-day course will lead to resolution in greater than 90% of cases, however 5% to 30% of patients may have relapse in 1 to 2 weeks either because of infection by the original organism or re-infection by a new strain. Vancomycin enema can be used when oral administration is not possible and treatment with metronidazole has failed or in severe cases.\textsuperscript{122} For patients who have fulminant disease or toxic megacolon without response to treatment or suspicion of perforation, subtotal colectomy with ileostomy may be required. Hemicolecotomy should be avoided as reports suggest an increased mortality, which nevertheless is as high as 35% to 80%.\textsuperscript{117,121} The use of antidiarrheals or narcotics should be avoided because of the concern of toxin retention and possible development of toxic megacolon.\textsuperscript{117,121} Newer agents, such as rifaximin, tolevamer, and difimicin are undergoing clinical investigation.

**Hepatosplenic Candidiasis**

Hepatosplenic candidiasis, also known as chronic disseminated candidiasis, typically occurs in febrile leukemic patients with neutropenia after receiving chemotherapy. Patients develop fever, right upper quadrant pain, and elevated alkaline phosphatase. Some patients may have hepatomegaly or splenomegaly.\textsuperscript{123} Blood cultures are negative in hepatosplenic candidiasis and diagnosis requires ultrasound, CT, or MRI once neutrophil counts have recovered. CT demonstrates multiple focal lesions, occasionally with peripheral enhancement, but these findings
are not pathognomonic. Other disseminated processes, such as miliary tuberculosis, invasive molds, or malignancy, can mimic this process and therefore CT guided biopsy is generally recommended to confirm the diagnosis.123,124

Initial management of hepatic candidiasis is with amphotericin B or a liposomal formulation for 1 to 2 weeks followed by fluconazole for several months. Newer antifungal agents, including caspofungin, micafungin, and voriconazole, have been used successfully in small numbers of patients. Treatment should continue for several months until there is radiographic resolution or calcification to prevent relapse.125

CENTRAL NERVOUS SYSTEM INFECTIONS

Infections of the central nervous system (CNS) can mimic tumor recurrence or metabolic derangements and clinicians must be vigilant because signs and symptoms may be subtle and nonspecific.126,127 Symptoms include mild headache, fever, personality changes, delirium, or seizures, but patients who have cancer generally do not have nuchal rigidity or focal deficits and may present only with malaise, especially in the setting of leukopenia.126,128 Patients who have leukemia, lymphoma, primary CNS tumors, solid tumors undergoing aggressive chemotherapy, and HSCT are most commonly at risk for CNS infections.126,129 The spectrum of infection includes meningitis, cerebritis, brain abscess, and meningoencephalitis.

Pathogenesis

Pathogens that cause meningitis must cross the blood brain barrier and can lead to cerebral edema, vasculitis with possible infarction, and impaired CSF absorption, all of which may progress to herniation.126,130 The most common causes of bacterial meningitis in patients who have cancer that have not had neurosurgery are L monocytogenes, S aureus, and S pneumoniae.126,129 Patients who have L monocytogenes present most commonly with fever and a minority have gastroenteritis.131 Neurosurgical patients are more likely to develop meningitis caused by S aureus, Streptococcus bovis, and coagulase-negative Staphylococcus.127,128 Occasionally infection caused by Gram-negative organisms, such as P aeruginosa, E coli, Klebsiella, Enterobacter and Proteus species, can occur.126

Patients who have neutrophil defects (quantitative or qualitative), such as acute leukemia or chemotherapy-induced neutropenia may have an acellular CSF in the setting of severe infection.132 Encapsulated bacteria, such as S pneumoniae and H influenzae, are the most common pathogens in patients who have B cell and immunoglobulin dysfunction, whereas individuals with T-cell abnormalities are predisposed to developing infections caused by viruses and intracellular bacteria, such as Listeria monocytogenes, Nocardia asteroides, and Aspergillus.

A deficiency in cell-mediated immunity or corticosteroid use predisposes to meningitis caused by Cryptococcus neoformans, which can present with fulminant infection or as focal mass lesions.127 Patients who have neutrophil dysfunction, prolonged neutropenia, those receiving high-dose corticosteroids, chemotherapy, or broad-spectrum antibiotics, or those with CMV infection are at risk for developing Aspergillus CNS infection, either by direct extension through paranasal sinuses or hematogenous spread from the lungs.3,126,127,129 Manifestations include small hemorrhagic infarctions, abscess formation, and mycotic aneurysms.126,127,133 Less common fungal pathogens include Candida and Mucoraceae (Mucorales or Zygomycetes). Candida meningitis is usually seen in patients who have received a long course of prior antibiotics and have other manifestations of candidiasis.126,129 Mucoraceae is seen in
patients who are neutropenic with poor glycemic control, hematologic malignancies, or corticosteroid treatment.\textsuperscript{129}

Encephalitis can occur alone, with meningitis, or as a result of meningitis. Signs and symptoms include fever, headache, delirium, focal deficits, and seizures that may be focal or generalized. Presentation may be difficult to distinguish from paraneoplastic syndromes with anti-Hu, or anti-Ma, or Ta antibodies.\textsuperscript{129} Pathogens that can lead to encephalitis include Epstein-Barr virus (EBV), VZV, CMV, HSV 1 and 2, and human herpesvirus (HHV) 6, the latter of which is associated with HSCT. VZV can present with an acute, necrotizing encephalitis or a multifocal stroke-like presentation, which can mimic progressive multifocal leukoencephalopathy (PML).\textsuperscript{127,129} Reactivation is generally the cause in most cases and patients receiving radiation and corticosteroids are at higher risk. West Nile virus causes meningoencephalitis in patients who have humoral immune defects, such as B-cell dyscrasias and HSCT.\textsuperscript{127}

A focal deficit should lead to suspicion of brain abscess caused by bacterial pathogens or Aspergillus, Toxoplasma gondii, Mycobacterium tuberculosis, or N asteroides.\textsuperscript{129} Nocardia can cause infection in hosts with impaired cell-mediated immunity and post-HSCT, with infection generally beginning in the lungs. Manifestations include abscess, mass-like lesions that can mimic metastases, and less commonly meningitis.\textsuperscript{126,129} Patients who have Hodgkin’s disease and allogeneic HSCT are at higher risk for \textit{T. gondii} infection.\textsuperscript{126}

Patients who have undergone craniotomy or recent manipulation of devices, such as an intraventricular shunt or Ommaya reservoir are at risk for infection from organisms, such as \textit{S aureus}, coagulase-negative Staphylococcus, \textit{S epidermidis}, \textit{Propionibacterium acnes}, or \textit{Candida}.\textsuperscript{126,129} Development of ventricular shunt or Ommaya reservoir infections usually occurs within 2 months of placement.\textsuperscript{134}

Diagnosis

Brain CT or MRI can help to evaluate for metastatic disease or other mass lesions. Platelet counts should be greater than 50,000/mm\textsuperscript{3} to perform lumbar puncture. CSF biochemical patterns are similar to the general population; however, patients who have leukopenia may not have pleocytosis. CSF pleocytosis with lymphocytes is the most common finding in patients who have cancer.\textsuperscript{132} Culture of large amounts of CSF (10–20 mL) can confirm a diagnosis if the fluid appears clear and there is a low burden of organisms.\textsuperscript{126} India ink examination can rapidly diagnose \textit{C neoformans} infection and CSF serologic testing of cryptococcal antigen is highly sensitive.\textsuperscript{127,129} Diagnosis of Aspergillus infection can be difficult and requires a high index of suspicion and recognition of the characteristic clinical presentation in at-risk patients.

Patients who develop encephalitis may have only a CSF lymphocytic pleocytosis with normal protein and glucose levels. Serologic testing and PCR can be useful to confirm a diagnosis of CMV, enteroviruses, EBV, HHV-6, HSV type 1 and 2, and VZV.\textsuperscript{127,129} In cases of suspected West Nile virus infection serologic tests, detection of antibodies, and nucleic acid in CSF are diagnostic.\textsuperscript{127} Diagnosis of infection of a ventricular shunt or Ommaya reservoir requires positive cultures from the device.\textsuperscript{134}

Management

In situations where the suspicion of meningitis is strong and symptoms are acute, treatment must start immediately as progression to death can occur rapidly. Empiric antibiotic therapy is based on the intrinsic immune defect and likely pathogens and local resistance patterns. Initial therapy includes vancomycin and ceftriaxone, whereas ceftazidime is administered for those at risk for \textit{P aeruginosa}. In patients who have T-cell defects, sulfadiazine or TMP/SMZ should be added for coverage of
N asteroides. Ampicillin should be added in suspected cases of Listeria.\textsuperscript{127,129} Dexamethasone should be administered with the first dose of antibiotics and continued for 4 days in patients suspected to have bacterial meningitis, which has been shown to reduce neurologic sequelae and mortality.\textsuperscript{135,136} Infected devices must be removed and externalized drainage used until infection has cleared.

Initial antifungal coverage generally starts with amphotericin B. In addition to systemic therapy, intrathecal amphotericin B by way of an Ommaya reservoir may be helpful in severe infections.\textsuperscript{137} In patients who have cryptococcal meningitis, treatment with flucytosine should be added for the first 2 weeks followed by either fluconazole or itraconazole for 8 to 10 weeks as maintenance therapy.\textsuperscript{138}

Intravenous acyclovir is used for treatment of EBV, HSV, or VZV encephalitis, whereas ganciclovir is used for CMV infection. In patients who have HSCT and HHV-6 infection, treatment is with foscarnet. Empiric treatment should be started in suspected cases of T gondii with sulfadiazine and pyrimethamine. Most patients demonstrate a good response within 10 to 14 days and biopsy should be sought if clinical or radiographic response is not seen with appropriate therapy.\textsuperscript{126,127,129}

CATHETER RELATED BLOOD STREAM INFECTIONS

Intravascular catheter-related infections are a major cause of morbidity and mortality in patients who have cancer and are associated with excessive hospital costs. It is estimated that catheter-related blood stream infections (CRBSI) range between 1.0 to 1.9/1,000 catheter days.\textsuperscript{139} The four commonest types of intravascular silicone catheters are tunneled catheters (eg, Hickman, Groshong and Broviac [Bard Access Systems, Inc, Salt Lake City, UT]); non-tunneled CVC; implantable ports (eg, PORT-A-CATH [Smiths Group PLC, Smiths Medical, London, England]); and peripherally inserted central catheters.

Pathogenesis

The pathogenesis of non-tunneled CVC infection is often related to the extraluminal colonization of the catheter, which originates from the skin, and less commonly from hematogenous seeding of the catheter tip, or intraluminal colonization of the hub and lumen of the CVC.\textsuperscript{140} However, in tunneled CVC or implantable devices contamination of the catheter hub and intraluminal infection are the most common routes of infection. The microorganisms most commonly associated are coagulase-negative Staphylococci, S aureus, various species of aerobic Gram-negative bacilli, and C albicans. Patients who are neutropenic and receiving chemotherapy and those with mucositis or graft-versus-host disease of the intestine may have a tendency for hematogenous seeding of the catheters with organisms originating from the GI tract. Other factors contributing to the etiology of CRBSI include parenteral nutrition solutions and lipid emulsions, which promote the growth of bacteria and fungi, such as C parapsilosis and Malassezia furfur.\textsuperscript{141}

Diagnosis

Suspicion for CRBSI should be high if patients present with fever or chills and no other source of infection can be identified other than a CVC, especially if blood cultures are positive for S epidermidis, S aureus, or Candida species. Diagnosis relies mostly on isolating the same organism from paired cultures of blood samples taken simultaneously from the CVC and a peripheral vein or the isolation of the same organism from a catheter tip culture and from peripheral blood cultures.
The techniques to diagnose CRBSI, includes quantitative and non-quantitative cultures. The differential time to positivity is a non-quantitative test of simultaneous blood cultures drawn from a CVC and peripheral vein, where the culture from the CVC becomes positive at least 2 hours before the one drawn from the peripheral vein. The other methods of testing include simultaneous quantitative catheter cultures showing fivefold the number of colonies from a blood culture shown from CVC and compared with one drawn from peripheral vein. Finally, if the CVC tip semi-quantitative culture (roll plate) reveals greater than or equal to 15 colony forming units or CVC tip quantitative culture (sonication) reveals greater than or equal to 100 CFU, then the diagnosis of CRBSI is favored.

Management

The treatment of CRBSI depends on several factors, such as the underlying severity of disease, risk factors for infection, and the type of organism. Guidelines published by the Infectious Diseases Society of America in 2001 helps in the management of CRBSI. The initial step involves determining whether the catheter is the true source of infection.

In the case of infection caused by coagulase-negative Staphylococci, the long-term CVC may be retained and therapies with systemic antibiotics like nafcillin or vancomycin (in case of methicillin resistance) for 7 to 10 days is usually sufficient. Infection with S aureus is associated with high rates of complications, such as endocarditis, septic thrombophlebitis, and osteomyelitis. If there are no other access sites, systemic antibiotics with a β-lactam or vancomycin with antibiotic lock therapy for 14 days is recommended. Antibiotic lock therapy involves instilling a highly concentrated antibiotic solution into a catheter lumen and allowing the solution to dwell for a specified time period for the purpose of sterilizing the lumen. In most cases, removal of the catheter is recommended and treatment with systemic antibiotics for 2 weeks in uncomplicated cases to 4 to 6 weeks in deep-seated infections is optimal.

Infections caused by Gram-negative rods, such as Pseudomonas, E coli, and Acinetobacter, are associated with serious complications and a high rate of treatment failure when the catheter remains in place. Removal of the catheter and administering parenteral antibiotics, such as a carbapenem, or third generation cephalosporin for 7 to 10 days is recommended, but if there are no access sites, systemic treatment with antibiotic lock therapy may be used. Catheter removal with generous debridement of infected tissue is also advisable for patients who have atypical mycobacterial infections.

Irrespective of organism type catheter removal is indicated if the infection is recurrent or there is no response to antibiotics after 2 to 3 days of therapy. Evidence of a subcutaneous tunnel or periportal infection, septic emboli, hypotension with catheter use, septic shock, or deep seated infections are indications for removal along with prompt administration of antibiotics.

In cases of catheter-related candidemia, guidelines recommend removal of the catheter and treatment with either amphotericin B or fluconazole for 14 days after the last blood culture. If C krusei is isolated then treatment with amphotericin B is required. In a retrospective study of 416 subjects who had cancer, CVC retention was associated with poor outcome and higher rates of complications including endophthalmitis, hepatosplenic candidiasis, and peripheral abscess.

Septic thrombosis is an intravascular infection commonly associated with high-grade and persistent bacteremia or fungemia. Persistently positive blood cultures after catheter removal suggests a diagnosis of septic thrombosis or endocarditis. In general, S aureus is the most common infecting organism. Less common pathogens include Candida species and Gram-negative bacilli. In all cases, the involved catheter
should be removed. Incision and drainage along with excision of the infected peripheral vein and any involved tributaries should be done, especially when there is suppuration, persistent bacteremia or fungemia, or metastatic infection. Surgical excision and repair is needed in cases of peripheral arterial involvement with pseudoaneurysm formation.\textsuperscript{150} Heparin should be used in the treatment of septic thrombosis of the great central veins and arteries and the duration of antimicrobial therapy is 4 to 6 weeks.

**GENITOURINARY INFECTIONS**

Genitourinary (GU) infections are an infrequent complication of cancer treatment. Nevertheless, patients who have cancer remain at risk because of the impairment of the immune defense mechanisms from the underlying disease, damaged urothelium, chemotherapy toxicity, impaired voiding caused by local or spinal disease, and mechanical obstruction, which promotes bacterial growth and resultant sepsis.\textsuperscript{151} Bacteria are the most common pathogens causing GU infections, such as cystitis, pyelonephritis, prostatitis, and infection of urinary diversions, reconstructions, and stents. Patients who are neutropenic and have urinary tract infections are less likely to have dysuria and pyuria and are more likely to become bacteremic.\textsuperscript{152}

**Pyelonephritis**

Pyelonephritis in patients who have cancer is most commonly caused by \textit{E coli} followed by \textit{Proteus}, \textit{Klebsiella}, and \textit{Staphylococcus saprophyticus}. It is usually an ascending infection from the urethra, rarely hematogenous, and causes significant urosepsis. Pyelonephritis in the setting of superimposed obstruction, such as hydronephrosis, may need urgent decompression with nephrostomies or stent placement in addition to IV antibiotics.\textsuperscript{151}

Patients who have cancer and are immunocompromised are particularly susceptible to fungal pyelonephritis. \textit{C albicans} is the most common pathogen followed by other \textit{Candida} and \textit{Aspergillus} species. The kidney is the most frequently involved organ in systemic candidiasis. Fungi are filtered by the glomerulus and become lodged in the distal tubules where they multiply and produce medullary and cortical abscesses. Systemic antifungal therapy is the mainstay of treatment. The mortality of renal fungal infection remains high.\textsuperscript{153}

**Infections of Urinary Diversions**

Urinary diversions are indicated after radical cystectomy for the management of bladder carcinoma. Orthotopic bladder substitution uses a loop of small intestine, most frequently the ileum, to form a neobladder. Before surgery, antimicrobial treatment is used to minimize the bacterial population. However, these patients remain at increased risk for UTI because bacterial colonization remains. In addition, incomplete emptying of the neobladder along with excessive mucus production promotes infection.\textsuperscript{154} In patients who have orthotopic neobladder, the estimated 5-year probability of urinary tract infection and urosepsis for patients who voided independently were 58\% and 18\%, respectively. Recurrent UTI was the only predictor for urosepsis.\textsuperscript{155} \textit{E coli} is the most commonly implicated microorganism in patients who have neobladder-related UTI and was responsible for 59\% of monobacterial infections. Other organisms cultured include \textit{Klebsiella}, \textit{Proteus mirabilis}, \textit{Enterococcus}, \textit{Pseudomonas}, and \textit{Citrobacter}.\textsuperscript{156}
Ureteral Stents

Ureteral stents are placed to relieve obstruction caused by extrinsic compression that are caused by advanced cancer. Many of these patients require chronic stent changes and are prone to developing infections. A retrospective review of 28 subjects who had a total of 201 stents placed, found that 18 developed UTI and 8 had urosepsis.

SKIN AND SOFT TISSUE INFECTIONS

Necrotizing Fasciitis

Necrotizing fasciitis is a rare but potentially fatal, soft-tissue infection characterized by the necrosis of the subcutaneous fat and fascia. There are two clinical types of necrotizing fasciitis, the first type is a mixed infection caused by aerobic and anaerobic infection and occurs in patients who have diabetes and after surgical procedures. The second type is usually caused by Group A Streptococcus or methicillin-resistant Staphylococci. Prompt recognition is important, as delay in diagnosis is associated with high morbidity and mortality. Erythema, pain associated with skin discoloration and bullae might be some of the presenting signs. Diagnosis is clinical and high index of suspicion is needed in at-risk patients. Treatment consists of early and aggressive surgical debridement, intravenous antibiotics, and hemodynamic support. Treatment with intravenous immunoglobulin (IVIG) might be an effective adjunct for streptococcal toxic shock syndrome, possibly because of its ability to neutralize bacterial exotoxins.

Gram-negative infections including Pseudomonas, Aeromonas veronii, and E coli, have been reported in patients, particularly young children who have acute leukemia during neutropenia. Cytotoxic agents and steroids used in chemotherapeutic regimens further increase the risk for severe infections. Moreover, skin changes are not reliable in patients who are neutropenic because the inflammatory responses are blunted and clinical signs of systemic infection are absent early in the disease course. Therefore, severe local pain may be the only early sign of infection.

Fournier’s Gangrene

Fournier’s gangrene is a fulminant, necrotizing fasciitis of the perineal, perirectal, or genital areas, which leads to gangrene caused by thrombosis of the small subcutaneous vessels. Surgical debridement is the mainstay of treatment along with intravenous antibiotics. Cases have been described where infections with Gram-negative bacilli including Pseudomonas are seen during the profound neutropenic stage after chemotherapy in leukemia patients.

SPECIAL CONSIDERATIONS

Sepsis

Clinical trials for sepsis and septic shock frequently exclude patients who have active or metastatic cancer thereby making it difficult to determine the efficacy of new therapies in this population. Nonetheless, survival of patients who have cancer has improved during the same timeframe that treatment guidelines for severe sepsis have been implemented. Current practice guidelines as outlined by the Surviving Sepsis campaign are generally applicable to patients who have cancer and provide a framework to manage patients who meet criteria for sepsis and septic shock. Once sepsis has been recognized, appropriate antimicrobial therapy, fluid resuscitation, and source control should begin immediately. Special consideration should be
made in oncologic patients when considering antibiotic selection, including suspicion for fungal pathogens in patients who have prolonged neutropenia or after HSCT.42

A targeted, structured approach to early goal directed therapy (EGDT) of patients who are septic in an emergency department has been shown to reduce ICU and 28-day mortality.164 Because it is unclear which aspect of the EGDT protocol provided an improved outcome, all aspects of the algorithm should be employed. With that in mind, many patients who have cancer are anemic as result of underlying disease or chemotherapy. Thus, the use of packed red blood cells (PRBC) for the early part of resuscitation may improve oxygen delivery and provide volume support. However, it is not clear what the optimal hemoglobin target should be in patients who have cancer and PRBC transfusion should be guided by global indices of tissue perfusion and evidence of tissue hypoxia.

Drotrecogin alfa (activated) (Drot AA) (Xigris - Eli Lilly and Company, Indianapolis, IN) was approved in 2001 for patients who are at high risk of death from severe sepsis with an APACHE II score of 25 or more, or multiorgan failure.165–167 In the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial, approximately 18% (303/1,690) of the study population had either prior or preexisting cancer; however, no specific survival benefit has been shown in this subgroup as a result of Drot AA administration.165 Drot AA can be considered as adjunctive therapy; however, the bleeding risk needs to be balanced against the potential benefits in patients who have cancer who often have concomitant thrombocytopenia and coagulopathy. If Drot AA is to be administered in the setting of thrombocytopenia, the platelet count should be maintained above 50,000/mm³ with transfusions throughout the duration of the 96-hour infusion.168 Drot AA has been used in patients who develop severe sepsis soon after HSCT; however, efficacy is limited and bleeding risks are significant.169,170 Additionally, subjects given Drot AA who underwent recent surgery (<30 days) with single-organ dysfunction had a higher mortality and more bleeding events.167

Patients who are septic and vasopressor-dependent may benefit from the administration of low-dose hydrocortisone for critical illness-related corticosteroid insufficiency (CIRCI).171 However, large trials have generally excluded patients who have advanced cancer or underlying diseases with a poor prognosis. In the multicenter CORTICUS (Corticosteroid Therapy of Septic Shock) trial172 and landmark trial by Annane and colleagues,173 the study populations that had prior or preexisting cancer represented 16.8% and 13.7%, respectively. Again no specific benefit was determined as a result of steroid therapy for CIRCI in patients who had cancer with vasopressor-dependent septic shock. Patients who have cancer may have required corticosteroids as part of their cancer therapy and therefore replacement therapy may be warranted. However, the risk of further immunosuppression, especially in neutropenic or HSCT recipients, must be evaluated.

Targeting blood glucose values between 80 to 110 mg/dL in patients who are critically ill and have an insulin infusion has become common practice in many ICU’s.174,175 However, more recent data from the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) trial suggests that maintaining a higher threshold of blood glucose values between 140 to180 mg/dL may have fewer episodes of hypoglycemia and lower mortality.176 Though the effect of this practice in patients who have active cancer was not studied, it appears to be a reasonable target in these patients who are immunosuppressed.

Supportive Care

Colony-stimulating factors have been helpful in reducing the duration of neutropenia, the number of infectious episodes, and use of antibiotics after administration of
myelosuppressive chemotherapy. Additionally, granulocyte-CSF (G-CSF) can enhance granulocyte function by increasing the production of superoxide radicals, phagocytosis, and antibody dependent cytotoxicity. Although endogenous levels of G-CSF may be elevated in febrile neutropenic patients, exogenous administration is commonly used during these episodes. The 2006 American Society of Clinical Oncology guidelines recommend use of colony-stimulating factor to reduce the risk of febrile neutropenia in high-risk patients, although there does not appear to be an influence on mortality. The high mortality (54%) in patients who are neutropenic admitted to the ICU is caused by organ failure rather than the duration of neutropenia. In critically ill patients who are neutropenic, data on the use of G-CSF or granulocyte-macrophage CSF is limited and did not shorten duration of neutropenia nor change survival as compared with historical controls.

Granulocyte transfusions have been used since the 1960s for patients who have severe neutropenia and septicemia that was not responsive to antibiotics. With the advent of colony-stimulating factors in the 1990s, granulocyte transfusions became less common. However, the use of G-CSF before donation allows for a greater yield by leukapheresis, thereby providing a larger dose of granulocytes for the recipient. This greater yield generated new enthusiasm for granulocyte transfusions in septic neutropenic patients. A recent Cochrane review concluded that there was insufficient evidence to support or refute the use of granulocyte transfusions in patients who are neutropenic with severe infections. A possible survival benefit with using doses of granulocytes greater than $1 \times 10^{10}$ was also suggested but further investigation is required.

The administration of IVIG has shown benefit as prophylaxis in multiple myeloma and CLL and for treatment of severe VZV infections. In critically ill patients who have severe sepsis or septic shock, meta-analyses show a survival benefit for patients given polyclonal IVIG when limited studies were evaluated. Because of the heterogeneity of the data analyzed a large, randomized placebo controlled trial is required to better understand the effect of this therapy in patients who have sepsis.

### Preventive Measures

Although a comprehensive approach to managing infections in this immunocompromised population is essential, prevention of nosocomial acquired infections is equally important and challenging. Simple measures including hand washing with alcohol based solutions, barrier precautions including donning of gown and gloves during patient interactions, and chlorhexidine baths can reduce the spread of resistant pathogens. The implementation of bundles can similarly diminish the rates of nosocomial infections including CRBSI and VAP. Novel interventions, such as the use of metal surfaces, invasive devices impregnated with antimicrobial agents, or subglottic aspiration of secretions, may help further reduce the spread and development of resistant infections in patients in the ICU.

### SUMMARY

Patients who have cancer are at a higher risk for infectious complications and frequently require ICU care. Although outcomes have improved, infection remains a significant cause for morbidity and mortality. Understanding the malignancy and concomitant immune dysfunction that occurs, either caused by the underlying disease or as a result of chemotherapy or radiotherapy, will help to guide the diagnostic workup. Although the infectious complications may be similar to the general
population, the etiologies and clinical presentations are different. Patients who have cancer are also at risk for infection caused by otherwise nonpathogenic organisms. A high index of suspicion is required to properly diagnose and treat unique infections in this population. Management is based on recognizing distinct pathogens that occur with higher frequency in specific conditions seen in patients who have cancer. General supportive care to critically ill patients who have cancer is similar to other populations; however, specific therapies have not been well studied and may represent future areas of research. Preventative measures including bundling of proven interventions and novel techniques may help protect critically ill patients who have cancer.

REFERENCES


171. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients:


