

INFECTIONS IN PATIENTS WITH CANCER



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Learning Objectives

1. Assess the relative morbidity risk for patients with cancer with febrile neutropenia.
2. Justify the use of prophylactic antimicrobial drug regimens administered to patients with cancer.
3. Evaluate the appropriateness of initial antimicrobial drug therapy administered to patients with febrile neutropenia.
4. Design a plan for managing bacteremia or fungemia in patients with an infected vascular access device (VAD).
5. Determine the therapeutic end point for antimicrobial drug regimens administered to febrile patients with cancer.
6. Justify recommendations for modifying antimicrobial drug therapy in patients with febrile neutropenia.
7. Justify the use of colony-stimulating factors (CSFs) for prophylactic and therapeutic indications in patients with cancer.

Introduction

In the middle of the 20th century, chemotherapy was established as an effective antineoplastic treatment. Unfortunately, the effectiveness of many chemotherapy drugs is limited by chemotherapy-induced neutropenia, resulting in an increase in potentially life-threatening infections. In the 1970s, gram-negative bacteria were the prevalent infecting microorganisms. Fifty percent to 80% of patients with febrile neutropenia who were diagnosed with *Pseudomonas aeruginosa* bacteremia died within 2–3 days of diagnosis. This high mortality rate led to administering empiric antibiotic drug therapy to patients with febrile neutropenia. Empiric administration of gentamicin and carbenicillin substantially decreased the fatality rate of

patients with *P. aeruginosa* bacteremia. As a result, this approach was quickly accepted as standard therapy.

The management of infectious complications in patients with cancer has improved significantly since the 1970s. The pattern of infecting pathogens and their antimicrobial susceptibility has evolved. Potentially fatal infections remain a persistent risk and a challenge to treat. Current estimates are that 30% of patients administered chemotherapy for nonhematologic neoplasms and 85% of patients administered induction chemotherapy for acute leukemias develop potentially life-threatening infections. Infectious complications caused death in up to 70% of patients treated for acute leukemia. A variety of effective empiric antibiotic drug regimens have been developed to treat patients with cancer with febrile neutropenia. Seventy percent to 80% of patients with febrile neutropenia respond to initial empiric antibiotic drug therapy and less than 10% of infections are fatal. This chapter provides pharmacists with an understanding of evidence that can be applied in practice settings to optimally manage infections in patients with cancer.

Impaired Host Defenses in Patients With Cancer

Impaired Neutrophil Function

Neutrophils are the primary phagocyte in the body. Neutropenia is defined as a neutrophil count of less than 500 cells/mm³ or a neutrophil count of less than 1000 cells/mm³ with a predicted decrease to less than 500 cells/mm³. The term absolute neutrophil count (ANC) is the total number of mature segmented neutrophils and less mature neutrophils identified as bands on a white blood cell (WBC) differential. An ANC is calculated by multiplying the WBC count by the percentage of segmented neutrophils and bands reported on the WBC differential. For example,

Abbreviations in this Chapter

AmB	Amphotericin B deoxycholate
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
CSF	Colony-stimulating factor
CYP	Cytochrome P450
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
IDSA	Infectious Diseases Society of America
L-AmB	Amphotericin B liposome for injection
MASCC	Multinational Association for Supportive Care in Cancer
PCP	<i>Pneumocystis jiroveci</i> pneumonia
VRE	Vancomycin-resistant enterococci
VAD	Vascular access device
VZV	Varicella zoster virus
WBC	White blood cell

the ANC of a patient with a WBC of 8000 cells/mm³ with 48% segmented neutrophils and 2% bands, is 4000 cells/mm³ (8000 X 0.5 = 4000). Neutropenia is one of the most critical risk factors leading to infections in patients with cancer. The severity of infectious complications is correlated to the grade and duration of chemotherapy and radiation-induced neutropenia. Research published in the 1970s documented that infectious morbidity increases when a patient's ANC is less than 500 cells/mm³, and the incidence of infectious morbidity rises more rapidly when a patient's ANC falls below 100 cells/mm³. According to the 2002 Infectious Diseases Society of America (IDSA) Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer, "[a]t least one-half of neutropenic patients who become febrile have an established or occult infection and at least one-fifth of patients with neutrophil counts less than 100 cells/mm³ have bacteremia." The resolution of fever and other symptoms of infection typically do not occur until a patient's neutropenia resolves.

Chemotherapy accounts for the majority of neutropenia in patients with cancer. Typically, the neutrophil nadir occurs 7–14 days after completing myelosuppressive chemotherapy. The degree and duration of neutropenia are related to the intensity of the treatment regimen. The most profound neutropenia is commonly reported in patients who have completed induction chemotherapy for acute leukemia or myeloablative chemotherapy before hematopoietic stem cell transplantation (HSCT). Standard induction chemotherapy for a patient with acute nonlymphocytic leukemia typically results in an ANC less than 100 cells/mm³, which persists for 2–3 weeks. In general, the

chemotherapy administered to patients with less aggressive neoplasms is less myelosuppressive. These patients infrequently experience an ANC less than 100 cells/mm³. If such severe chemotherapy-induced neutropenia does occur, it rarely persists beyond several days. Underlying neoplastic disease seldom causes neutropenia; however, it is occasionally reported as a complication in patients with hematologic neoplasms or neoplasms that have replaced the normal elements in bone marrow.

Impaired Cellular and Humoral Immunity

Defects in cellular and humoral immunity are associated with certain neoplasms and with many antineoplastic therapies. Impaired T-cell and B-cell function generally results in increased susceptibility to opportunistic infections. The activation of varicella zoster virus (VZV) is a well-documented complication of Hodgkin's disease attributed to disease-related defects in cellular immunity. Defects in humoral immunity, notably the decreased production of immunoglobulins, are associated with increased infections in patients with chronic lymphocytic leukemia and multiple myeloma.

Lymphopenia is a frequent complication of chemotherapy and radiation. The incidence of infections, especially opportunistic infections, is a function of the depth and duration of lymphopenia. Immunosuppressive effects of older drugs such as cyclophosphamide and corticosteroids are well documented. Corticosteroids, which are extremely effective in treating malignant lymphomas and lymphocytic leukemias, suppress numerous aspects of lymphocyte function (Table 1-1). Newer drugs, such as fludarabine, cladribine, rituximab, and alemtuzumab, are also associated with profound and persistent suppression of cellular immune responses.

Disruption of Skin and Mucosal Barriers

The first line of host defense against microbial invasion is the physical barrier provided by epidermal and mucosal tissue. Normal flora, consisting of bacteria and yeast, colonize the skin and the mucosal surfaces of the gastrointestinal tract and assist in the normal protective function of these tissues (e.g., colonization resistance). Skin and mucosal tissues are susceptible to damage from chemotherapy, radiation therapy, and invasive procedures (e.g., needle punctures, surgical incisions, and insertion of vascular access devices [VADs]).

Mucositis caused by chemotherapy and radiation therapy is a frequent source of infection in patients with cancer. Typically, the onset of treatment-induced mucositis is diagnosed within 1 week of completing treatment and gradually resolves within a week of its onset. Patients with severe mucositis may need parenteral nutrition and analgesic support. The infection risk, length of hospitalization, and mortality can increase with the severity of mucositis. Mucosal damage in the mouth has been associated with infections caused by normal flora in the oral cavity (e.g., gram-positive bacteria and herpes simplex virus [HSV]), whereas damage to mucosa in the lower gastrointestinal tract has been associated with infections

Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *Lancet* 2003;362:1828–38. Review.

Table 1-1. Corticosteroid-Induced Effects on Lymphocyte Function

Reversible lymphopenia, CD4 depletion
Decreased lymphocyte-proliferation and migration
Impaired delayed-hypersensitivity
Impaired natural killer cell cytotoxicity
Decreased lymphokine production (interleukin-2, TNF-alpha, interferon gamma, interleukin-12)
Dysregulation of T-helper cells
Impaired phagocyte effector cell function and cellular immune response

TNF = tumor necrosis factor.

Adapted with permission from Elsevier. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *Lancet* 2003;362:1828–38.

caused by resident normal flora (e.g., enteric gram-negative bacilli).

Breaks in the epidermal barrier can result in resident microflora causing local infections that become systemic. Vascular access devices are a frequent source of infection. The infection risk varies with the type of VAD surgically implanted. The incidence of bacteremias ranges from 20.9% to 36.7% for external catheters and from 5.1% to 11.2% for subcutaneous VADs. Similarly, subcutaneous devices are associated with a lower risk of exit-site or tunnel pocket infections. The mean incidence of localized infections is 7% for subcutaneous devices and 15.8% for external catheters. Skin microflora such as coagulase-negative staphylococci, *Staphylococcus aureus*, and *Candida albicans* are the most common causes of catheter-related bacteremia.

Impaired Reticuloendothelial Function

The reticuloendothelial system consists of all phagocytic cells of the body except neutrophils. The reticuloendothelial system includes the cells lining the sinusoids of the spleen. Macrophages in the spleen function to remove non-opsonized microbes. In addition, the opsonization of microbes that occurs in the spleen enhances the phagocytosis of encapsulated bacteria. Consequently, patients with cancer who are functionally asplenic after undergoing HSCT or patients who have been splenectomized because of refractory hypersplenism are at an increased risk of developing severe infections with encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*.

Pathogens Infecting Patients with Cancer

Etiology of Infections in Patients with Cancer

The multiple defects in immune function detailed in the previous section often affect patients with cancer simultaneously. As a result, immunocompromised patients commonly develop infections caused by indigenous

bacteria, fungi, and viruses. Immunocompromised patients with cancer are also at risk for developing infections caused by exposure to exogenous pathogens. Protective isolation and routine hand washing are recommended procedures to limit the exposure of immunocompromised patients with cancer to exogenous pathogens. The etiologies of infections in patients with cancer have evolved in response to antibiotic drug therapies and supportive interventions.

Pathogens Isolated From Infected Patients

Bacterial Pathogens

Bacteria originating from a patient's normal microflora are the most common cause of infection in immunocompromised patients with cancer. In the 1970s and 1980s, the majority of microbiologically documented infections in patients with febrile neutropenia were caused by enteric gram-negative bacteria. *Escherichia coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter* species represented 60%–70% of microbiologically documented infections. Gram-positive bacteria typically found on the skin (*S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and *Staphylococcus hominis*) and oral mucosa (e.g., Viridans group streptococci [*mitis* and *oralis*], *Enterococci* [*faecalis* and *faecium*]) accounted for fewer than 40% of microbiologically documented infections.

In the early 1980s, VADs became a standard of care for patients with cancer who required reliable venous access. Although the benefits of VADs are well established, the associated risk of developing infection is also well documented. The implantation of indwelling vascular access catheters has become a major contributing factor of increased infections caused by gram-positive microflora. The most common gram-positive bacteria isolated by culture are coagulase-negative staphylococci, *S. aureus*, *Enterococci* (*faecalis* and *faecium*) and *Corynebacterium* species. Long-term use of VADs and their frequent manipulation can provide an entry site for these microflora.

Quinolone prophylaxis and high-dose cytarabine also have been linked to an increased incidence of gram-positive streptococcal infections. A prospective, multicenter study of more than 500 patients with febrile neutropenia analyzed risk factors for developing infections with gram-positive cocci. Microorganisms were isolated in 32% of the patients with febrile neutropenia. Gram-positive cocci accounted for 64% (108/168) of microbiologically documented infections with staphylococcal infections the most prevalent (65% of the gram-positive isolates were staphylococcal and 35% streptococcal). Multivariate analysis identified the administration of high-dose cytarabine, gut decontamination with colimycin, administration of nonabsorbable antifungals, and diarrhea with increased risk of streptococcal infections. Relative risks for streptococcal infections were 2.9 for patients with one risk factor, 13.2 for those with two risk factors, and 20.7 for patients with three or more risk factors.

Donnelly JP, DePauw BE. Infections in the immunocompromised host: general principles. In: Mandell GL, Bennett JE, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia: Elsevier, 2005:3421–32.

Cordonnier C, Buzyn A, Leverger G, et al. Epidemiology and risk factors for gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. *Clin Infect Dis* 2003;36:149–58.

Prophylactic antibiotic drugs have influenced the etiology of bacterial infections in patients with febrile neutropenia. The ability of prophylactic administration of quinolones, cotrimoxazole, penicillin, cefazolin, and macrolides to decrease infections has been documented. A study of bone marrow transplant recipients who were administered penicillin, cefazolin, and macrolides as prophylaxis reported a 40% reduction of gram-positive infections (about 50%–10%). However, increases in the isolation of bacteria not inhibited by the prophylactic antibiotic drugs have occurred. In four studies published during the past 5 years, gram-positive microflora accounted for 44%–67% of microbiologically documented infections in 797 patients with febrile neutropenia. The reported rates of gram-positive infections were 67.1%, 66.1%, 44.4%, and 44.1%. In the two studies that reported the highest incidence of gram-positive pathogens, the majority of patients were administered prophylactic antibiotic drugs with predominately gram-negative coverage (i.e., colistin and quinolones).

In contrast to these data, in the two studies in which prophylactic antibiotic drugs were not used or administered to less than 25% of patients, enteric bacteria were isolated in 55% of patients. *Escherichia coli*, *P. aeruginosa*, and *K. pneumoniae* continue to be the most commonly isolated gram-negative pathogens in patients with febrile neutropenia.

Finally, patients with impaired humoral immunity are at increased risk of severe complications from infections caused by encapsulated bacteria such as *S. pneumoniae* and *H. influenzae*.

Fungal Pathogens

Opportunistic microorganisms cause significant morbidity and mortality in patients with cancer, especially in those who have severe defects in cellular immunity. Fungal infections account for 2%–10% of initial microbiologically confirmed infections in patients with cancer who have febrile neutropenia. The incidence of positive fungal cultures in patients with persistent febrile neutropenia approaches 30%. Furthermore, the incidence of invasive fungal infections in autopsy studies of patients with prolonged febrile neutropenia has ranged from 40% to 69%. Among fungal pathogens, the *Candida* species are the most common cause of documented infection. *Candida albicans* and *Candida parapsilosis* colonize the skin; *C. albicans*, *Candida tropicalis*, and *Candida glabrata* colonize the oral mucosa. These *Candida* species are potential pathogens that can result in local or systemic infections in immunocompromised patients with cancer. Typically, *Candida* infections are diagnosed after neutropenic episodes that exceed 7 days.

Aspergillus species are saprophytic molds widely distributed in the environment in the form of spores. Inhalation of *Aspergillus* spores can lead to colonization of the airways, especially in patients with defective cellular immunity. Patients with cancer who develop severe and prolonged immunosuppression are predisposed to develop

Aspergillus pneumonia and invasive disease. Most often *Aspergillus* infections are diagnosed after neutropenic episodes exceeding 2 weeks. Fatality rates for patients with prolonged neutropenia and documented *Aspergillus* infections range from 60% to 80%.

Viral Pathogens

Herpes viruses (HSV, VZV, and cytomegalovirus) are ubiquitous. They seldom cause severe infections in individuals who are immunocompetent. However, in patients with defective cellular immunity, the herpes viruses are pathogenic. Patients developing chemotherapy-induced mucositis are predisposed to HSV infections. The cytomegalovirus has been a major cause of mortality in patients treated with allogeneic HSCT complicated by graft-versus-host disease.

Pneumocystis jiroveci

Pneumocystis carinii was originally classified as a protozoan parasite because of antimicrobial susceptibilities. Subsequent ribosomal RNA sequencing technology revealed that it is more similar to fungi than protozoa. Several strains have been identified. In the early 1900s, *P. carinii* isolated from rats and other animals was first recognized. In 1952, Otto Jirovec published an article that documented a *P. carinii* epidemic in humans. Molecular and immunologic studies published in 2002 led to the conclusion that the *Pneumocystis* isolated from animals is distinct from the strain isolated from humans. *Pneumocystis jiroveci* was the nomenclature introduced to identify the *Pneumocystis* strain that infects humans whereas *P. carinii* refers to the strain isolated from animals. The merit of this change in nomenclature has been a point of contention. Pneumonia caused by *P. jiroveci* in humans is commonly referred to by the acronym PCP. Patients with impaired cellular immunity are predisposed to potentially fatal PCP. Research performed in patients with acute lymphocytic leukemia discovered that cotrimoxazole is effective in treating and preventing PCP.

Clinical Presentation of Infection in Patients with Cancer

Diagnosis—Signs and Symptoms

The diagnosis of infections in immunocompromised patients with cancer requires a high degree of suspicion. Common signs and symptoms of inflammation are less prominent in patients who are severely immunocompromised. Consequently, infections are less likely to cause erythema, induration, and pus formation; productive cough and infiltrates on chest radiographs may be less prominent. Pyuria may be minimal or absent. However, inflammatory responses resulting in sepsis do occur and can rapidly progress to multisystem failure. Fever

Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis 2004;39(suppl 1):S25–S31.

onset is often the first and only symptom of possible infection. The IDSA 2002 Guidelines for the use of antimicrobial drugs in neutropenic patients with cancer define fever as a single oral temperature above 101°F or a temperature above 100.4°F for at least 1 hour. Patients with febrile neutropenia should receive a thorough physical examination to identify potential infection sites. Common infection sites include the skin (especially incisions made for VAD implantation), the alimentary tract, lungs, and perianal region.

The recommended diagnostic workup for infection in patients with cancer includes bacterial, fungal, and viral cultures of the blood, urine, and any inflammation site found on the skin and mucosa. Positive cultures confirm the cause of fever in only 30%–50% of patients with febrile neutropenia. The IDSA guidelines for managing intravascular catheter-related infections suggest that blood drawn percutaneously and from the catheter can help exclude catheter-related bacteremia. These guidelines cite data reporting positive predictive values of 73% for blood cultures drawn percutaneously and of 63% for blood cultures drawn from the catheter. The respective negative predictive values are 98% and 99%, respectively. A chest radiograph or computed tomography scan can diagnose pulmonary infections. Bronchoscopy is warranted in patients with pulmonary infiltrates. Specimens obtained by bronchoalveolar lavage should be submitted for the appropriate cultures (bacteria, fungi, and virus) and smears (acid-fast bacilli, *P. jiroveci*, *Nocardia* spp.). If diarrhea or abdominal pain is present, an assay for *Clostridium difficile* toxin should be ordered.

Risk Assessment

Characterization of a patient's risk for developing severe infectious complications is useful for making antibiotic drug management decisions. The IDSA guidelines for using antimicrobial drugs in neutropenic patients with cancer categorize febrile patients as being at either low or high risk for developing infectious complications. Patients with low-risk features may be treated with oral antibiotic drugs and may possibly be treated as outpatients. Patients with high-risk features should be hospitalized for close observation and administered parenteral antibiotic drugs.

Features known to be associated with a low risk for severe infection include the following:

- ANC greater than 100 cells/mm³
- Absolute monocyte count greater than 100 cells/mm³
- Normal findings on a chest radiograph
- Duration of neutropenia less than 1 week
- Expected resolution of neutropenia in fewer than 10 days
- No infection at the site of a VAD
- Early evidence of bone marrow recovery
- No appearance of illness

Patients whose febrile illnesses do not meet the criteria for low risk are considered at high risk for infectious complications.

In 2000, the Study Section on Infections of the Multinational Association for Supportive Care in Cancer

Table 1-2. The MASCC Predictive Model for Risk of Complications in Patients With Febrile Neutropenia

Characteristic	Score
Burden of illness ^a	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematologic tumor	4
Outpatient status	3
No dehydration	3
Age younger than 60 years ^b	2

NOTE: Highest theoretical score is 26. A risk index score of ≥ 21 indicates that the patient is likely to be at low risk for complications and morbidity.

^aChoose 1 item only.

^bDoes not apply to patients 16 years of age or younger. Initial monocyte count of ≥ 100 cells/mm³, no comorbidity, and normal chest radiograph findings indicate children at low risk for significant infections.

MASCC = Multinational Association for Supportive Care in Cancer.

Adapted with permission from Elsevier. Klastersky J. Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 2004;39(suppl 1):32–7.

(MASCC) published a risk index for identifying febrile neutropenic adult patients with cancer at low risk for developing infectious complications (Table 1-2). The index was validated in a study of 1139 patients with febrile neutropenia. The range of MASCC scores was 0 to 26, with higher scores indicating lower risk for infectious complications. A score of 21 is the threshold for designating a patient at low risk. This threshold score identified patients at low risk for developing infectious complications with a positive predictive value of 91%, a specificity of 68%, and a sensitivity of 71%. In 2004, a comparison of the MASCC risk index and an alternative model revealed that the MASCC score resulted in fewer low-risk patients misclassified as being at high risk for developing infectious complications.

Empiric Antibiotic Drug Therapy—Initiation and Monitoring

The MASCC risk index for identifying febrile neutropenic adult cancer patients at low risk for developing infectious complications (Table 1-2) can help determine which patients can be effectively treated with oral antibiotic drugs. A study is currently under way to determine whether the index can be used to identify patients at low risk for infectious complications who can be effectively treated exclusively as outpatients with empiric oral antibiotic drugs. If the hospitalization of low-risk patients with febrile

Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18:3038–51.

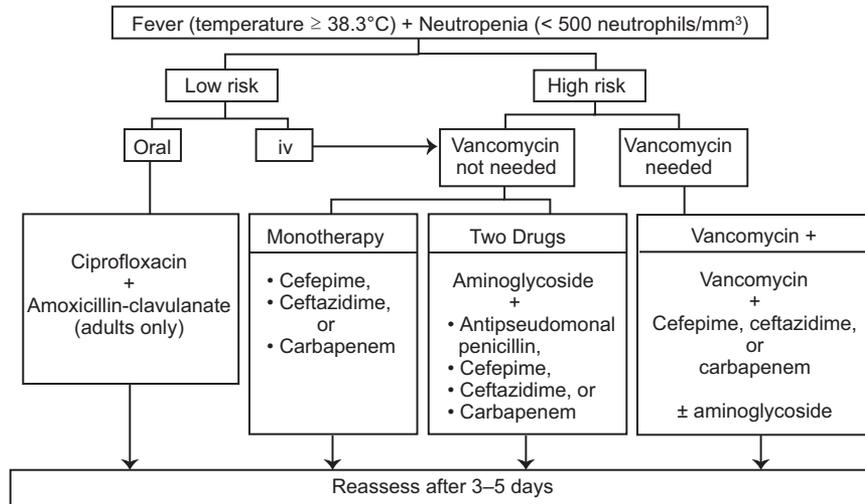


Figure 1-1. Algorithm for initial management of febrile neutropenic patients.

iv = intravenous.

Reprinted with permission from the University of Chicago Press. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730-51.

neutropenia for administration of intravenous antibiotic drugs can be avoided, a substantial cost savings can be achieved.

The infection pattern in immunocompromised patients with cancer is determined by the immune defects unique to patients' treatment regimens and underlying cancer. Bacteria are the most common pathogens identified during the initial days of febrile episodes. Chemotherapy-induced neutropenia and mucositis are the principal predisposing factors that result in normal microflora causing infection at this point. Consequently, empiric administration of broad-spectrum antibiotic drug regimens with established coverage of the most prevalent bacteria is standard practice. If patients' chemotherapy-induced neutropenia exceeds 3-7 days and does not respond to initial antibiotic drug therapy, the incidence of microbiologically documented opportunistic infections (e.g., fungi, *P. jiroveci*, and herpes viruses) increases. Patients treated with allogeneic HSCT and aggressive myelosuppressive chemotherapy for acute leukemias and lymphomas are at the greatest risk for opportunistic infections.

In 2002, the IDSA published its most recent revision of Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. These comprehensive guidelines remain the standard of care for treating febrile neutropenia. The guidelines provide four algorithms to assist clinicians with selecting and managing appropriate antimicrobial drug therapy.

Figure 1-1 addresses the initial selection of antibiotic drug therapy. Two critical assessments in guiding antibiotic therapy are a patient's risk status and need for vancomycin. Patients who are febrile who meet low-risk criteria and

without clinical findings to justify empiric vancomycin therapy (Table 1-3) can be treated safely with oral antibiotic drug combinations. The combination of amoxicillin-clavulanic acid 750 mg every 8 hours and ciprofloxacin 750 mg every 12 hours has been the most widely studied. Initial studies evaluating the effectiveness of oral regimens in hospitalized patients at low risk for infectious complications established the effectiveness of this strategy. More recently, oral regimens are being administered to carefully selected outpatients (e.g., low-risk patients who can be monitored and who can access medical care without delay). The cost-effectiveness of this approach has resulted in its acceptance for adult patients at low risk for infectious complications.

Fewer studies of initial oral antibiotic drug therapy in febrile neutropenic pediatric patients have been published because FDA labeling limits the use of quinolones in patients under age 18. Oral cefixime has been evaluated in several pediatric studies. Pediatric patients at low risk for infectious complications have been discharged from the hospital on oral cefixime after completing a minimum of 48 hours of intravenous therapy. The IDSA guidelines conclude that more data are needed to establish the efficacy of oral antibiotic drugs as initial therapy for children with febrile neutropenia.

Empiric Vancomycin

Intravenous vancomycin is recommended as initial empiric treatment for any patient if a catheter-related infection is suspected (e.g. localized inflammation), if

Vidal L, Paul M, Ben dor I, Soares-Weiser K, Leibovici L. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients: a systematic review and meta-analysis of randomized trials. *J Antimicro Chemother* 2004;54:29-37. Review.

Table 1-3. Clinical Findings that Warrant Empiric Vancomycin Therapy in Patients Regardless of Risk Status

1. Clinically suspected serious catheter-related infection,
2. Known colonization with penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*,
3. Positive blood culture for gram-positive bacteria before final identification and susceptibility testing, or
4. Hypotension or other evidence of cardiovascular impairment

Adapted with permission from the University of Chicago Press. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.

colonization with resistant gram-positive bacteria has been documented, if blood cultures are positive for gram-positive bacteria prior to final identification and sensitivity testing, or if symptoms consistent with cardiovascular complications are present (Table 1-3). Two additional factors that can increase a patient's risk of developing infections warranting vancomycin are prophylactic administration of quinolone antibiotic drugs and treatment with high-dose cytarabine. Additional evidence is needed to validate their predictive values.

Management of VAD Infections

Surgically implanted central venous catheters or subcutaneous ports contribute to the increased incidence of bacteremias caused by microflora. Data gathered from 1992 to 1999 reported that coagulase-negative staphylococci (37%), *S. aureus* (13%), *Enterococcus* (13%), *Candida* species (8%), and *E. coli* (5%) were the most common causes of bacteremia in hospitalized patients. The rise in incidence of vancomycin-resistant enterococci (VRE) during the 1990s was alarming. The National Nosocomial Infections Surveillance System reported that from 1990 to 1999 the incidence of VRE increased from 0.5% to 25.9%.

A critical determination in managing VAD-related infections is the need to remove the VAD. Guidelines for managing intravascular catheter-related infections published by the IDSA, the American College of Critical Care Medicine, and the Society for Healthcare Epidemiology of America recommend not removing a VAD unless symptoms consistent with a catheter infection accompany fever. Removal of a VAD and initiation of antibiotic drug therapy are recommended when focal findings indicate a tunnel, pocket, or exit-site infection or when endocarditis, septic thrombosis, osteomyelitis, or catheter-related fungemia is diagnosed. The suggested duration of antimicrobial drug therapy is 1–2 weeks for localized infections, 4–6 weeks for endocarditis and septic thrombosis, 6–8 weeks for osteomyelitis, and 14 days beyond resolution of signs and symptoms of fungal infections.

The guidelines state that it is appropriate to consider salvage therapy for infections associated with colonization of VADs by coagulase-negative staphylococci, *S. aureus*,

and gram-negative bacilli. Salvage therapy eradicates the infection with the infusion of systemic antibiotic drugs through the VAD and antibiotic-lock therapy. Antibiotic-lock therapy fills the lumen of the VAD with high concentrations of an antibiotic solution active against the isolated bacteria and leaves the antibiotic drug in place between intermittent infusions. Vancomycin concentrations of 1–5 mg/mL and ciprofloxacin, gentamicin, and amikacin concentrations of 1–2 mg/mL have eradicated bacteria in up to 80% of cases in published trials. The recommended duration of salvage therapy is 1–2 weeks of systemic antibiotic drug therapy and 2 weeks of antibiotic-lock therapy.

A persistent source of controversy is the safety of delaying the administration of glycopeptides until culture results document resistant gram-positive infections. A meta-analysis that evaluated data on nearly 2400 patients to address this question concluded that is safe to defer treatment with glycopeptides until infection with resistant gram-positive microorganisms is documented. These data provide additional support for the IDSA recommendation that empiric vancomycin be restricted to patients presenting with one of the variables associated with a high likelihood of a gram-positive infection (Table 1-3). Broad support exists for restricting vancomycin's use to treat infections caused by methicillin-resistant *S. aureus* to limit the development of VRE. In general, most infections caused by gram-positive bacteria do not progress rapidly. Therefore, it is not necessary to start vancomycin until culture and sensitivity results indicate it is needed. An exception to this approach has been infections caused by viridans streptococci. An increased incidence of fatal gram-positive infections caused by strains of viridans streptococci has been reported in patients not receiving vancomycin. Consequently, in settings where potentially life-threatening gram-positive infections have been documented, the empiric administration of vancomycin is warranted for patients at high risk for infectious complications. If vancomycin is included in the initial empiric therapy, it is important to monitor culture and sensitivity reports and to discontinue vancomycin if culture results are negative.

Treatment of VRE

Linezolid, quinupristin/dalfopristin, and daptomycin are effective alternatives for patients with infections caused by VRE or who cannot tolerate vancomycin (Table 1-4). All three drugs represent new chemical entities that have activity against gram-positive pathogens, including VRE. Linezolid is an oxazolidinone derivative available for intravenous and oral administration. It is a bacteriostatic drug with the exception of being bacteriocidal for penicillin-susceptible *S. pneumoniae*. One adverse effect that may limit its use in patients with cancer is thrombocytopenia, which appears to be dose and duration dependent. Thrombocytopenia has occurred in up to 10% of patients receiving linezolid for periods exceeding 2 weeks. Quinupristin/dalfopristin is a streptogramin antibiotic combination that is bacteriocidal against most susceptible

Cometta A, Kern WV, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis* 2003;37:382–9.

Table 1-4. Summary of Antimicrobial Drugs Used to Treat Vancomycin-resistant *Enterococcus*

Drug	Linezolid	Quinupristin-Dalfopristin	Daptomycin
Dosage ^a	400–600 mg every 12 hours	7.5 mg/kg every 8–12 hours	4 mg/kg every 12 hours
Route of Administration	IV or PO	IV	IV
Daily acquisition cost ^b	\$134	\$440	\$182
FDA labeling (pediatrics)	Yes	No	No
Dosage adjustments for renal impairment	No	No	Creatinine clearance ≤ 30 mL/minute increase interval to 48 hours

^aAs recommended in the Food and Drug Administration-approved package labeling.

^bEstimate based on maximum IV dosage regimen for an 80-kg patient with normal renal function. Comparable cost for vancomycin is \$10.00. FDA = Food and Drug Administration; IV = intravenous; PO = oral.

bacteria; it is bacteriostatic against enterococci. It is effective in treating *E. faecium*, but not *E. faecalis*. Consequently, quinupristin/dalfopristin is not considered appropriate for empiric therapy of suspected enterococcal infections. Its toxicity profile is notable for inflammation at the infusion site and myalgia that have been reported in up to 40% and 10% of patients, respectively. Daptomycin is a cyclic lipopeptide antibiotic drug that is bactericidal for all susceptible bacteria. It is active against both *E. faecium* and *E. faecalis*. Daptomycin is generally well tolerated, with adverse effects being reported in fewer than 10% of patients. Product labeling for linezolid includes administration to children. The safety and efficacy of quinupristin/dalfopristin and daptomycin have not been established for patients under ages 16 and 18, respectively.

Broad-Spectrum Monotherapy

It is critical that patients at high risk for infectious complications with febrile neutropenia be promptly started on intravenous antibiotic drugs that are active against the most common pathogens. The IDSA guidelines recommend that in patients at high risk for infectious complications who do not require empiric vancomycin, monotherapy with a carbapenem (imipenem-cilastatin or meropenem) or a third-generation or fourth-generation cephalosporin (ceftazidime or cefepime) is an appropriate option. In general, all of these monotherapy options provide adequate gram-negative antibacterial coverage. However, cefepime and the carbapenems are the preferred alternatives because of their superior activity against viridans streptococci, pneumococci, and *Enterobacter* species. Piperacillin-tazobactam also has been effective as empiric monotherapy in limited studies. Further evaluation of the effectiveness of piperacillin-tazobactam monotherapy in well-designed comparative trials is needed to determine whether it is a reasonable alternative to cefepime, ceftazidime, and the carbapenems.

Although the effectiveness of initiating empiric antibiotic drug therapy with a single broad-spectrum antibiotic drug has been effective, monotherapy is not standard care. A

Table 1-5. Comparative Acquisition Costs of Empiric Broad-Spectrum Antibiotic Drugs Appropriate for Empiric Monotherapy

Drug	Dosage ^a	Daily Acquisition Cost ^b
Cefepime	2 g every 8 hours	\$96
Ceftazidime	2 g every 8 hours	\$38
Imipenem-cilastatin	500 mg every 6 hours	\$104
Meropenem	1 g every 8 hours	\$93
Piperacillin-tazobactam ^c	3.375 g every 6 hours	\$56

^aAs recommended in the Food and Drug Administration-approved package labeling for the treatment of serious infections including febrile neutropenia.

^bEstimate based on a daily dose calculated for an 80-kg patient with normal renal function.

^cEffectiveness as monotherapy based on limited data.

meta-analysis of 47 randomized trials compared the effectiveness of β -lactam monotherapy and β -lactam plus an aminoglycoside combination therapy. Although there were some limitations, no difference was found between monotherapy and combination therapy for all-cause fatality. These data supported the conclusion that β -lactam monotherapy “should be regarded as the standard of care” for patients with febrile neutropenia.

Table 1-5 lists the costs of antibiotic drugs proven effective as monotherapy based on the dosage regimen in each product’s Food and Drug Administration-approved labeling. These are the dosage regimens most commonly studied in clinical trials. Whether these dosage schedules are the most cost-effective for each antibiotic drug has not been adequately studied. Data from a limited number of studies involving smaller numbers of patients suggest that lower dose regimens are equally effective. Specifically, cefepime 2 g administered every 12 hours and ceftazidime 1 g administered every 8 hours have been evaluated. The IDSA guidelines state that more outcome data are needed to determine whether the lower cost of low-dose regimens warrants their acceptance as standard treatment.

Cherif H, Bjorkholm M, Engervall P, et al. A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. *Scand J Infect Dis* 2004;36:593–600.

Klasterksy JA. Use of imipenem as empirical treatment of febrile neutropenia. *Int J Antimicrob Agents* 2003;21:393–402. Review.

Raad II, Escalante C, Hachem RY, et al. Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. *Cancer* 2003;98:1039–47.

Tamura K, Imajo K, Akiyama N, et al. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis* 2004;39(suppl 1):15–24.

Broad-Spectrum Combination Therapy

Two-drug combinations consisting of an aminoglycoside plus an extended-spectrum penicillin, cefepime, ceftazidime, or a carbapenem are alternative options for patients with febrile neutropenia at high risk for infectious complications. If vancomycin is indicated, the IDSA guidelines recommend combining vancomycin with cefepime, ceftazidime, or a carbapenem with the option of adding an aminoglycoside as a third antibiotic (Figure 1-1).

Close monitoring of a patient's response to the initial empiric therapy is vital for determining what, if any, changes in antibiotic coverage are indicated. As indicated in Figure 1-1, IDSA guidelines recommend that the initial regimen be continued for 3–5 days with the caveat that clinical deterioration and culture results may warrant earlier modification of the initial regimen. Reported median times to defervescence are 2 days for patients at low risk for infectious complications and 5–7 days for patients at high risk for infectious complications.

Figure 1-2 is the IDSA algorithm for patients who become afebrile within 3–5 days of empiric treatment. If a pathogen is isolated, susceptibility and cost data can be used to modify broad-spectrum therapy. The appropriate regimen should be administered for at least 1 week or until the patient's symptoms have resolved and repeat cultures are negative. Ideally, the patient's ANC should be greater than 500 cells/mm³. However, if a clinical response has been achieved, the IDSA guidelines suggest that stopping antibiotic drugs may be considered in a patient with an ANC less than 500 cells/mm³ if the patient has no apparent focus of infection (e.g., infection related to vascular access or mucositis) and will be closely observed. If no pathogen is isolated, patients at high risk of infectious complications are maintained on the initial intravenous antibiotic drug regimen until resolution of factors that increase the risk for infectious complications. If no pathogen is isolated, patients at low risk of infectious complications (e.g., ANC greater than 500 cells/mm³, no identified focus of infection) can be switched to an oral regimen after a minimum of 2 days of intravenous therapy. A combination of a quinolone plus amoxicillin-clavulanic acid is recommended for adult patients and cefixime for pediatric patients.

Patients whose fever persists 3–5 days after the administration of appropriate empiric antibacterial treatment and for whom no etiology has been identified require thorough reassessment of a diagnostic workup to rule out possible causes of the fever. Possible causes include an infection that is slow to respond to the initial regimen (e.g., an abscess), an infection caused by resistant bacteria, or an infection caused by nonbacterial pathogens. The IDSA guidelines propose three options for patients with persistent fever (Figure 1-3). Continuation of the initial broad-spectrum regimen is acceptable for patients who remain stable, whose anticipated duration of chemotherapy-induced neutropenia is less than 5 days, and whose diagnostic results do not support a change in broad-spectrum antibiotic drugs. If patients remain stable and vancomycin was in the initial regimen, IDSA guidelines propose discontinuing it unless supported by initial culture and sensitivity results. The second option proposes adding or changing antibiotic drugs

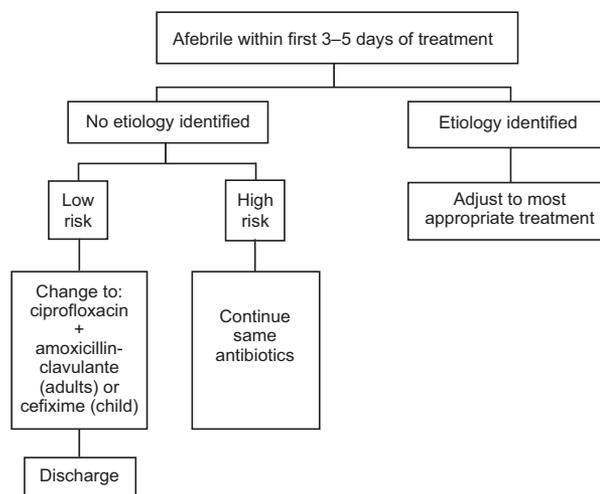


Figure 1-2. Guide for the management of patients who become afebrile in the first 3–5 days of initial antibiotic therapy.

Reprinted with permission from the University of Chicago Press. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.

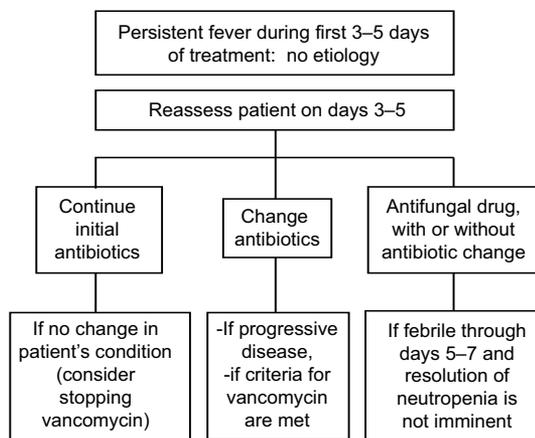


Figure 1-3. Guide to treatment of patients with persistent fever after 3–5 days of treatment.

Reprinted with permission from the University of Chicago Press. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.

if patients' infectious symptoms worsen. If the initial regimen did not include vancomycin, it should be added if previously identified factors associated with a high probability of gram-positive etiology exist. Replacing cefepime or ceftazidime with a carbapenem and adding an aminoglycoside, if not included in the initial regimen, are also feasible options. The third option is to initiate antifungal therapy. This alternative is recommended for patients whose neutropenia is expected to persist for an additional week or more. Fungal infections account for 2%–10% of initial microbiologically documented infections in patients with cancer who have febrile neutropenia.

Table 1-6. Antifungal Therapies: Dosage Regimens and Monitoring Parameters

Drug	Dosage Regimen ^a	Adverse Effects/Monitoring
Amphotericin B Deoxycholate	0.6 to 1 mg/kg/day IV; increase up to 1.5 mg/kg/day IV for documented infections	Infusion-related reactions (fever, chills, rigors, flushing, dyspnea, hypotension, hypertension, flushing, and tachycardia), nausea, vomiting, headache, renal impairment, hypokalemia, hypomagnesemia, and hyperbilirubinemia
Amphotericin B liposome for injection	3 mg/kg/day; increase up to 4.5–6 mg/kg/day for documented infections	Infusion-related reactions (fever, chills, rigors, flushing, dyspnea, hypotension, hypertension, flushing, and tachycardia), nausea, vomiting, headache, renal impairment, hypokalemia, hypomagnesemia, and hyperbilirubinemia
Itraconazole	200 mg every 12 hours IV for first 48 hours, then 200 mg/day IV; switch to oral solution as indicated ^b	Nausea, vomiting, diarrhea, rash, elevation of hepatic enzymes and bilirubin; taste disturbance after oral solution
Voriconazole	6 mg/kg IV every 12 hours for two doses, then 3–4 mg/kg IV every 12 hours; switch to 200–300 mg by mouth every 12 hours as indicated ^b	Transient alteration of light perception, visual hallucinations, transient elevation in hepatic enzymes; monitor for multiple potential drug interactions because voriconazole is metabolized by and inhibits cytochrome P450 enzymes
Caspofungin	70 mg IV on day 1, then 50 mg/day IV	Infusion-related adverse events (fever, chills, and phlebitis), and nephrotoxicity

^aCurrent standard of practice is to administer the maximum tolerated dosages of antifungal therapy to patients with documented systemic fungal infections.
^bIntravenous itraconazole and voriconazole were switched to oral formulations for patients showing clinical improvement after a minimum of 3–7 days of intravenous therapy.
 IV = intravenously.

Candida and *Aspergillus* species have been identified as the etiology of persistent fever in nearly one-third of neutropenic patients who do not respond to 1 week of empiric broad-spectrum antibacterial therapy.

Empiric Antifungal Therapy

Amphotericin B Products

The IDSA guidelines recommend that empiric antifungal therapy directed against *Candida* and *Aspergillus* species be considered for patients with febrile neutropenia who do not respond after 5 days of appropriate broad-spectrum antibiotic drugs. Amphotericin B deoxycholate (AmB) has been considered the antifungal of choice for empiric therapy. However, recent data suggest that less toxic and perhaps more effective antifungal options exist. Comparative studies of AmB and lipid formulations of amphotericin (amphotericin B liposome for injection, amphotericin B lipid complex for injection, and AmB cholesteryl sulfate complex for injection) have established that these lipid products are equally effective to AmB and cause less renal toxicity. The high cost of the lipid formulations limits their use to patients intolerant to AmB (e.g., increase in serum creatinine to 2 mg/dL, a decrease in creatinine clearance of 50%, or severe infusion-related fever, rigors, or wheezing unresponsive to appropriate premedication).

Amphotericin B liposome for injection (L-AmB) is the lipid formulation that has been most rigorously evaluated in comparative studies evaluating empiric antifungal therapy in patients with febrile neutropenia. In a comparative study of AmB and L-AmB, initial dosage regimens were 0.6 mg/kg/day intravenously and 3 mg/kg/day intravenously,

respectively. This study included guidelines for titration of doses based on a patient's clinical status. All of the recently published studies recommend that patients with documented systemic fungal infections receive the maximum tolerated dosages of antifungal therapy.

The following composite scoring system has become standard methodology for determining the efficacy of empiric antifungal therapy in patients with febrile neutropenia. The overall success of a therapy is determined by the evaluation of five outcomes: 1) resolution of fever, 2) no breakthrough fungal infection within 7 days of the end of therapy, 3) resolution of baseline fungal infection, 4) survival 7 days after therapy has been discontinued, 5) no discontinuation of therapy as a result of toxicity or lack of efficacy.

The difference in overall success rates for AmB and L-AmB was not statistically significant. The L-AmB resulted in fewer breakthrough fungal infections. Toxicity data revealed that L-AmB was better tolerated than AmB. The incidence of infusion-related adverse effects (e.g., fever and rigors) and of renal impairment was substantially lower in the group randomized to L-AmB.

Recommended doses for the L-AmB products are substantially higher than the recommended dose for AmB (e.g., 3–6 mg/kg/day and 1–1.5 mg/kg/day, respectively). Special caution is needed when processing AmB orders. Confusion regarding the 3-fold difference in dosages has resulted in patients developing severe renal toxicity after receiving AmB daily doses of 3 mg/kg. Antifungal dosage regimens are summarized in Table 1-6.

Itraconazole

Itraconazole is an extended-spectrum triazole antifungal agent that is active against *Aspergillus* species. It is

Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999;340:764–71.

available as a solution for intravenous administration and as a suspension and capsule for oral administration. Itraconazole bioavailability is significantly higher after administration of the oral suspension. Patients should be instructed to take itraconazole suspension on an empty stomach to enhance absorption. Itraconazole was proven as effective as AmB in patients with febrile neutropenia. Patients treated with itraconazole had lower rates of infusion-related reactions and nephrotoxicity. Itraconazole was administered by intravenous infusion initially, but was changed to the oral suspension in selected patients after they showed clinical improvement. A minimum of 7 days of intravenous itraconazole was required before switching to the oral solution was permitted. See Table 1-6 for dosage and monitoring recommendations.

Voriconazole

Voriconazole and caspofungin have been compared to L-AmB for efficacy as empiric antifungal therapy for patients with persistent febrile neutropenia. Voriconazole is a broad-spectrum second-generation triazole antifungal drug that is well-absorbed after oral administration. The National Institute of Allergy and Infectious Diseases Mycoses Study Group compared voriconazole and L-AmB in a study of 837 patients. Patients received antifungal therapy for up to 3 days after their ANC exceeded 250 cells/mm³, up to a maximum of 3 months. The recommended dosage regimen and monitoring parameters are provided in Table 1-6. Voriconazole was administered intravenously for a minimum of 3 days before switching to oral administration was allowed.

Comparison of the five composite measures of success revealed similar efficacy for all outcomes, except for breakthrough fungal infections within 7 days after completion of therapy. The incidence of breakthrough infections was lower in the voriconazole group. Comparison of adverse effects revealed several statistically significant differences. Voriconazole was associated with a lower rate of chills, flushing, dyspnea, and renal impairment. The most common adverse events associated with voriconazole were visual disturbances. Twenty-two percent of patients in the voriconazole group reported transient alteration of light perception compared with 1% in the L-AmB group. This effect was reported most often during the first infusion and decreased with subsequent infusions. Voriconazole also resulted in a higher incidence of visual hallucinations that was statistically significant (4.3% vs. 0.5%). Typically, the hallucinations were described as unrelated to the infusion-related changes in light perception. There was no difference between voriconazole and L-AmB in the number of patients who discontinued the assigned treatment because of toxicity. However, more patients discontinued voriconazole than L-AmB due to apparent lack of efficacy.

Because voriconazole is metabolized by cytochrome P450 (CYP) enzymes CYP2C19, CYP2C9, and CYP3A4, and it also inhibits the activity of these enzymes, the potential for significant drug interactions warrants diligence. Concurrent administration of voriconazole with rifampin, ritonavir, carbamazepine, and long-acting barbiturates is contraindicated to avoid substantial reductions in voriconazole blood concentrations. Concurrent administration of voriconazole with CYP3A4 substrates sirolimus, ergot alkaloids, cisapride, pimozide, and quinidine is contraindicated to avoid significant increases in the systemic exposure and potential for increased toxicity of these drugs. Concurrent administration of voriconazole with efavirenz and rifabutin also is contraindicated because it results in substantial decreases in voriconazole blood concentrations and substantial increases in efavirenz and rifabutin blood concentrations. In addition, voriconazole has resulted in significant increases in systemic exposure of methadone, cyclosporine, tacrolimus, and warfarin. Furthermore, *in vitro* data suggest that plasma concentrations of statins, benzodiazepines, calcium channel blockers, vinca alkaloids (CYP3A4 substrates), as well as glipizide and glyburide (CYP2C9 substrates) may be increased when administered with voriconazole. Consequently, vigilant monitoring for toxicity and consideration of dosage reduction are indicated when patients receive these drugs at the same time as voriconazole.

Caspofungin

Caspofungin is the first echinocandin antifungal agent approved for the treatment of infections caused by *Candida* species and refractory invasive aspergillosis. It was compared to L-AmB as empiric antifungal therapy in a well-designed multicenter study of 1095 patients with persistent febrile neutropenia. The composite overall success rates and durations of treatment were similar for both antifungal drugs. Caspofungin resulted in statistically significant differences in resolution of baseline fungal infections, in survival for at least 7 days after discontinuation of therapy, and in early discontinuation of therapy. Caspofungin was associated with lower rates of infusion-related adverse events and nephrotoxicity. Fewer patients discontinued caspofungin because of drug-induced adverse effects. Refer to Table 1-6 for the recommended dosage regimen and monitoring parameters.

In summary, data from well-designed, large-scale, multicenter trials evaluating empiric antifungal therapy established that itraconazole and L-AmB are as effective as, and better tolerated than, AmB. Within the past 3 years, data from two well-designed, multicenter trials established that voriconazole and caspofungin were as effective as, and better tolerated than, L-AmB. Appropriately designed trials

Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. *Ann Intern Med* 2001;135:412–22.

Walsh TJ, Pappas P, Winston DJ, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002;346:225–34.

Walsh TJ, Tepler H, Conowita GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004;351:1391–402.

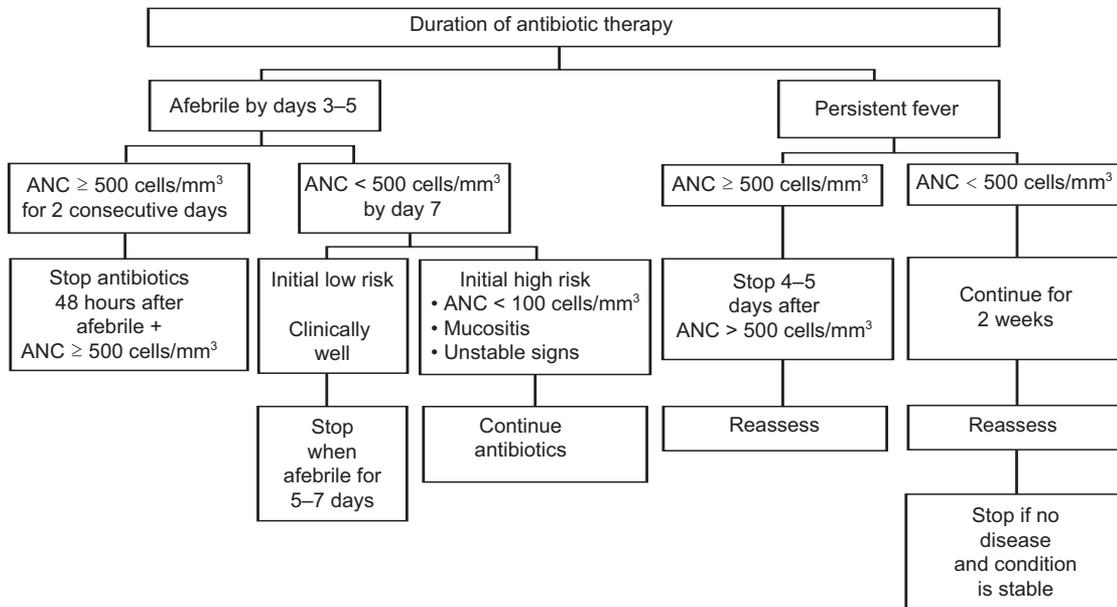


Figure 1-4. Suggested scheme for estimating the duration of antibiotic administration under various conditions.

ANC = absolute neutrophil count.

Reprinted with permission from the University of Chicago Press. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730-51.

are needed to determine the comparative cost-effectiveness of itraconazole, voriconazole, and caspofungin as empiric and primary therapy for fungal infections.

An international committee with representatives from The Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and from the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases developed standard definitions to facilitate clinical and epidemiological research addressing invasive fungal infections. The committee proposed the terms “proven,” “probable,” and “possible” to describe three levels of probability of patients having an invasive fungal infection. Patients with a probable fungal infection meet both microbiological and clinical criteria, whereas patients with a possible fungal infection meet microbiological or clinical criteria. The term preemptive antifungal therapy has been introduced to describe treating patients with febrile neutropenia with probable fungal infections in contrast to empiric antifungal therapy that defines treating patients with possible fungal infections. An assay to detect galactomannan, an antigenic polysaccharide associated with *Aspergillus*, has become useful in diagnosing invasive aspergillosis. The international committee included positive *Aspergillus* galactomannan assays in their criteria for establishing microbiological fungal infections. Specifically, two or more positive blood assays or a single positive cerebral spinal fluid or bronchoalveolar lavage fluid assay is considered diagnostic. The Food and Drug Administration approved the enzyme-linked immunosorbent assay in 2003

based on a 81% sensitivity and 89% specificity. Piperacillin-tazobactam has resulted in false-positive tests. Consequently, when interpreting positive tests in patients receiving piperacillin-tazobactam, it is recommended that the diagnosis be confirmed with other diagnostic tests.

A prompt diagnosis of fungal infections in patients with febrile neutropenia remains elusive. In three recent trials evaluating empiric antifungal therapy in 2616 patients, resolution of fever occurred in about 50% of patients. However, fewer than 10% of these patients had fungal infections confirmed microbiologically. This gap implies that defervescence may not be reliable evidence of successful antifungal therapy. Further studies need to determine whether preemptive or empiric antifungal therapy provides more cost-effective outcomes.

Duration of Antimicrobial Therapy

Figure 1-4 summarizes the IDSA guidelines for determining the duration of empiric antimicrobial drug therapy. A patient’s ANC and response to the initial empiric antimicrobial drug are critical variables in determining when it is appropriate to discontinue antibiotic drugs. Patients who respond within 3–5 days of empiric therapy may have antibiotic drugs stopped when their ANCs exceed 500 cells/mm³ for 2 consecutive days and when they remain afebrile for 48 hours.

Ascioglu S, Rex JH, de Pauw B, et al; Invasive Fungal Infections Cooperative Group of the European Organization of Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002;34:7-14.

The duration of antibiotic drugs is longer for patients who become afebrile within 3–5 days of empiric therapy but whose ANC is less than 500 cells/mm³. The IDSA guidelines propose that patients at low risk for infectious complications who remain asymptomatic can have antibiotic drugs discontinued after 5–7 days. However, for patients who initially present with findings associated with a high risk for infectious complications (an ANC less than 100 cells/mm³, mucositis, or unstable vital signs), it is recommended that administration of antibiotic drugs be continued until the ANC exceeds 500 cells/mm³. In cases of profound neutropenia without signs of imminent recovery, stopping the antibiotic drugs can be considered after 14 days, provided that a patient has no confirmed focus of infection and will be carefully monitored. If antibiotic drugs are discontinued in an afebrile neutropenic patient, careful monitoring and prompt administration of intravenous antibiotic drugs are mandatory if symptoms of infection recur.

The IDSA guidelines recommend starting patients who have a persistent fever after 5 days of empiric antibiotic drugs on empiric antifungal therapy. Reevaluation for occult bacterial, fungal, viral, or mycobacterial infections is indicated. The ANC is used to determine the duration of a febrile patient's antimicrobial drug therapy. If no infection is documented and a patient remains clinically stable, stopping the antibiotic drugs can be considered after an ANC recovery to greater than 500 cells/mm³ for 4–5 days. If a patient's ANC remains below 500 cells/mm³, clinical status determines the therapy duration. If a patient's only symptom of infection is persistent fever, stopping antimicrobial drug therapy can be considered after 2 weeks. A patient who is febrile with symptoms consistent with significant infection should have his or her antimicrobial drug therapy continued until ANC recovery occurs.

The optimum duration of antifungal therapy for patients with confirmed systemic fungal infections has not been clearly established. In a well-designed trial comparing AmB and voriconazole for the treatment of patients with invasive aspergillosis, the planned therapy was 12 weeks. In this study, voriconazole resulted in superior response rates, survival, and safety. However, in recently completed well-designed trials evaluating empiric antifungal therapy, the therapy duration for patients who were eventually diagnosed with invasive fungal infections was determined by patients' response to therapy and the ANC. In the most recent of these studies, caspofungin and L-AmB were continued for a minimum of 14 days with at least 7 days of therapy following resolution of symptoms and neutropenia.

The duration of antifungal therapy for a patient who does not have a proven or probable systemic fungal infection is determined by the patient's clinical status. In recent clinical trials, empiric antifungal therapies were stopped when a patient was clinically well with an ANC exceeding 500 cells/mm³ for 2–3 days and normal imaging studies. For a patient who remains neutropenic, but is clinically well with normal imaging studies, empiric antifungal therapy can be stopped after 14 days of therapy. For a patient with

persistent febrile neutropenia, antifungal therapy is continued for the duration of neutropenia.

Treatment of *Pneumocystis jiroveci* Pneumonia

A 1973 landmark study authored by researchers from the St. Jude Children's Research Hospital described PCP in 17 pediatric patients with cancer. This research established that corticosteroid therapy and hematologic malignancies were associated with an increased risk for PCP. In the 1980s, PCP was identified as a prevalent opportunistic infection in patients with acquired immune deficiency syndrome. Before the development of effective PCP prophylaxis, the incidence of PCP in patients undergoing allogeneic HSCT ranged from 5% to 16%. The infection in patients who were negative for human immunodeficiency virus has had a more rapid onset than in patients who are positive for human immunodeficiency virus. Severe hypoxia is the classic presenting symptom in patients with PCP. Preferred diagnostic techniques are bronchoalveolar lavage with transbronchial biopsy and open-lung biopsy. An immunofluorescent assay that detects epitopes from *Pneumocystis* cysts and trophozoites has become the preferred diagnostic test.

Cotrimoxazole, the drug of choice for PCP, is given at 15–20 mg/kg/day of trimethoprim, which is administered intravenously in four divided dosages. The regimen can be switched to an oral regimen in patients whose symptoms improve after several days of intravenous therapy and who do not have any conditions that preclude oral administration. Pentamidine and atovaquone are alternative therapies for patients who do not tolerate or respond to cotrimoxazole. Pentamidine is administered by intravenous injection at 4 mg/kg/day. Atovaquone is administered orally at 750 mg 3 times/day with meals. These treatments are generally continued for 21 days.

Treatment of Viral Infections

The IDSA guidelines recommend antiviral drugs be administered only to patients with febrile neutropenia with documented viral infections. If severe infections caused by HSV and VZV are documented in patients who are immunocompromised, intravenous acyclovir is indicated. Oral acyclovir, famciclovir, and valacyclovir can be used to treat less severe infections. The recommended dosage regimens are shown in Table 1-7. Higher dosages are required for treating VZV because it is less susceptible than HSV to these drugs. Famciclovir and valacyclovir can be administered less frequently than acyclovir because these acyclovir prodrugs are more readily absorbed. The duration of treatment of HSV and VZV infections is a minimum of 7 days and often longer due to delayed resolution of symptoms in patients who are immunocompromised.

Herbrecht R, Denning DW, Patterson TE, et al; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408–15.

Systemic cytomegalovirus infections are infrequently diagnosed in patients with chemotherapy-induced neutropenia but remain a common cause of infection in patients with cancer following HSCT. Ganciclovir and foscarnet are the antiviral drugs recommended for treating systemic cytomegalovirus infections.

Prophylactic Antimicrobial Therapy

Bacterial Prophylaxis

The IDSA guidelines provide an objective overview of the benefits and risks of antimicrobial drug prophylaxis. There is ample evidence that prophylactic administration of antimicrobial drugs reduces the incidence of infections. However, the ability of prophylactic antibiotic drugs to reduce infection-related mortality has not been reliably documented. The increase in antibiotic-resistant bacteria that is associated with prophylactic administration has been a concern. Routine use of quinolone antibiotic drugs as prophylaxis in neutropenic cancer patients has resulted in quinolone-resistant gram-negative pathogens. The IDSA guidelines do not recommend routine antibacterial prophylaxis in managing patients with febrile neutropenia.

PCP Prophylaxis

The 2002 IDSA guidelines recommend that all patients at risk for PCP receive prophylaxis with cotrimoxazole. In general, the critical risk factor associated with increased risk of PCP is impaired function of T-lymphocytes. Neutropenia by itself has not been established as a significant risk factor for *P. jiroveci* infection. Patients at greatest risk for PCP include those receiving intensive chemotherapy for acute lymphoblastic leukemia and aggressive lymphomas, all recipients of allogeneic HSCT, and recipients of autologous HSCT who have underlying hematologic malignancies. The IDSA, along with the Centers for Disease Control and Prevention and the American Society of Blood and Marrow Transplantation, have published Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients. These guidelines recommend PCP prophylaxis for recipients of allogeneic HSCT and for recipients of autologous HSCT with underlying hematologic neoplasms.

The incidence of PCP increases with increased duration and dosage of corticosteroid therapy. An increased incidence of PCP has been reported with prednisone doses as low as 16 mg/day. In one study, 25% of infected patients received

corticosteroids for 2 months or less. In another study of patients with cancer who have solid tumors, 5% developed PCP after just 1 month of corticosteroid therapy, and 70% of those infections were diagnosed when corticosteroids were being tapered.

Cotrimoxazole is the drug of choice for preventing PCP. The cotrimoxazole dose initially recommended for PCP prophylaxis was trimethoprim 5 mg/kg/day and sulfamethoxazole 25 mg/kg/day. Subsequently, lower doses were studied to evaluate whether efficacy could be maintained while decreasing the incidence of adverse effects, primarily skin rashes and myelosuppression. Currently, three lower dose cotrimoxazole regimens are included in the Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients: one double-strength tablet daily (trimethoprim 160 mg/sulfamethoxazole 800 mg), one single-strength tablet daily (trimethoprim 80 mg/sulfamethoxazole 400 mg), or one double-strength tablet by mouth 3 times/week. Alternatives for patients who cannot tolerate cotrimoxazole are dapsone given 100 mg/day orally or 50 mg orally 2 times/day, or pentamidine 300 mg every 3–4 weeks by inhalation. Additional comparative studies are needed to establish the efficacy of atovaquone for PCP prophylaxis.

Prophylaxis should be administered to recipients of HSCT from the time of engraftment until 6 months post-HSCT. Patients with HSCT who have chronic graft-versus-host disease or those on chronic immunosuppressive therapy require prophylaxis beyond 6 months. Likewise, for non-HSCT patients at risk for PCP, prophylaxis should be continued until immunosuppressive therapy is discontinued.

Fungal Prophylaxis

The 2002 IDSA guidelines recommend that fluconazole be administered to all patients receiving allogeneic transplants, patients with hematologic neoplasms receiving autologous transplants, and recipients of HSCT who were recently treated with fludarabine or cladribine. The recommended regimen is fluconazole 400 mg/day beginning the day of transplantation until bone marrow recovery (e.g., 7 days of ANC exceeding 1000 cells/mm³). This recommendation is supported by data from several studies that documented a significant decrease in the incidence of superficial and, more importantly, invasive infections caused by the *Candida* species. Most often, *C. krusei* and occasionally *C. glabrata* are resistant to fluconazole. Itraconazole is also effective in preventing systemic fungal infections caused by the *Candida* species. Several trials compared fluconazole and itraconazole for

Table 1-7. Dosage Regimens for Drugs Used to Treat Common Herpes Viruses

Drug	Acyclovir	Famciclovir	Valacyclovir
Dosage ^a			
<i>Herpes simplex</i>	5 mg/kg IV every 8 hours; 400 mg PO 5 times/day	500 mg BID PO	500 mg BID PO
<i>Herpes zoster</i>	10–12 mg/kg IV every 8 hours; 800 mg PO 5 times/day	500 mg TID PO	1 g TID PO

^aAs recommended in the Food and Drug Administration-approved package labeling for patients with normal renal function; dose adjustment for patients with renal impairment is required.

BID = 2 times/day; IV = intravenously; PO = orally; TID = 3 times/day.

prophylaxis in HSCT and in acute leukemia patients and yielded conflicting results. However, the Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients recommend that itraconazole capsules not be used in HSCT recipients for three reasons: itraconazole's bioavailability after administration of capsules is unreliable; steady-state serum concentrations are not achieved until the second week of therapy; and numerous potentially significant drug interactions have been documented with itraconazole.

Viral Prophylaxis

The IDSA, the Centers for Disease Control and Prevention, and the American Society of Blood and Marrow Transplantation Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients recommend acyclovir prophylaxis for patients who are HSV-seropositive and receiving an allogeneic transplantation. The recommended regimen is acyclovir 200 mg by mouth 3 times/day or 250 mg/m² intravenously every 12 hours. Prophylaxis should continue until engraftment or until mucositis resolves. This regimen significantly reduces the reactivation rate of HSV. Well-designed, clinical trials need to determine the comparative efficacy of acyclovir, valacyclovir, and famciclovir for HSV prophylaxis. None of these antiviral drugs has reduced the reactivation of VZV.

Use of Colony-Stimulating Factors

Three colony-stimulating factors (CSFs) have been approved for use in the United States (filgrastim, pegfilgrastim [a covalent conjugate of filgrastim and monomethoxypolyethylene glycol], and sargramostim). These products shorten the duration of neutropenia following administration of myelosuppressive chemotherapy. Pegfilgrastim was approved for use in the United States in 2002 with the labeled indication "to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia." The conjugation of filgrastim with monomethoxypolyethylene glycol effectively extends the serum half-life of filgrastim from 2–7 hours to 15–80 hours for pegfilgrastim. Studies conducted in patients with breast cancer receiving myelosuppressive chemotherapy found that one subcutaneous injection of pegfilgrastim 6 mg was equivalent to daily subcutaneous injections of filgrastim 5 mcg/kg/day. The incidence of febrile neutropenia and grade 4 neutropenia was similar between treatment groups. The pegfilgrastim package labeling states that the 6-mg fixed dose should not be administered to pediatric patients weighing less than 45 kg. A study comparing filgrastim 5 mcg/kg/day and pegfilgrastim 100 mcg/kg once after myelosuppressive chemotherapy was administered to

children with sarcomas concluded that the two formulations were equally effective in shortening chemotherapy-induced neutropenia. Pegfilgrastim offers patients and clinics the advantage of avoiding multiple daily office visits for administration of subcutaneous injections of filgrastim or sargramostim.

The American Society of Clinical Oncology (ASCO) evidence-based clinical practice guidelines first published in 1994 were most recently updated in 2000. An expert panel developed 11 specific guidelines that focus on the optimal use of CSFs. This discussion summarizes five of the guidelines considered most important to pharmacists managing CSF therapy in patients with cancer. The guidelines selected for discussion address indications for use and dosage regimens.

The first involves the administration of CSFs to prevent febrile neutropenia in patients receiving myelosuppressive chemotherapy for the first time (defined primary prophylaxis). The potential benefit of primary CSF prophylaxis is related to the incidence of febrile neutropenia associated with the chemotherapy regimen. Three studies reported that primary CSF prophylaxis significantly reduced febrile neutropenia (about 50% decrease). In these studies, the incidence of febrile neutropenia was at least 40% in the groups administered a placebo. The effectiveness of primary CSF prophylaxis to significantly reduce the incidence of febrile neutropenia in patients receiving less myelosuppressive therapy has not been consistently documented. As a result, the ASCO guidelines recommend that primary CSF prophylaxis be restricted to patients receiving chemotherapy regimens that result in an incidence of febrile neutropenia reported in the control arms of these trials (40% or higher). The National Comprehensive Cancer Network has also published clinical practice guidelines addressing myeloid growth factors in cancer treatment. Its most recently published guidelines state that CSF prophylaxis is an appropriate consideration for patients receiving chemotherapy associated with an incidence of febrile neutropenia of 20% or higher. This recommendation is based on increased costs of hospitalization and recently published trials suggesting that the prophylactic administration of CSF yields clinical benefit in patients receiving chemotherapy with lower rates of febrile neutropenia. Furthermore, the guiding principle of the panel that authored these guidelines is that cost-effectiveness was secondary to clinical outcome.

The second guideline of interest addresses secondary prophylactic CSF administration. Secondary prophylaxis is the administration of a CSF as prophylaxis for febrile neutropenia only if a patient experienced febrile neutropenia after the previous chemotherapy cycle. The 2000 ASCO guidelines recommend that secondary prophylaxis is a reasonable consideration in patients receiving potentially curative chemotherapy or chemotherapy regimens for which maintaining dose-intensity is important for achieving disease-free or overall survival benefits. In patients receiving myelosuppressive chemotherapy that does not

NCCN. Clinical Practice Guidelines in Oncology: Myeloid Growth Factors in Cancer Treatment, v.2.2.2005. Available at http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf. Accessed January 31, 2006.

result in these outcomes, dose reduction rather than secondary CSF prophylaxis is recommended.

The third guideline pertinent to the topic of infections in patients with cancer addresses the use of a CSF as an adjunct treatment to antibiotic drugs in patients with febrile neutropenia. The updated ASCO guidelines analyzed data from eight prospective, randomized, controlled studies designed to determine if CSFs added to empiric antibiotic drugs in patients with febrile neutropenia improved patient outcomes. The guidelines acknowledge that CSFs shorten the duration of chemotherapy-induced neutropenia, but conclude that no consistent clinical benefit has been documented for patients with “uncomplicated febrile neutropenia.” Adding a CSF to antibiotic drugs in these studies has not consistently resulted in decreased mortality, shorter length of hospitalization, or shorter duration of antibiotic drug therapy. Uncomplicated febrile neutropenia is described as an episode that is less than 10 days in duration and without symptoms of a documented infection (e.g., pneumonia, cellulitis, hypotension, abscess, and sinusitis) or systemic fungal infection.

The 2000 ASCO guidelines acknowledge that published data do not support routine CSF administration as adjunctive therapy for patients with febrile neutropenia. A meta-analysis of eight trials that evaluated the effectiveness of CSFs as adjunctive treatment of chemotherapy-induced febrile neutropenia reached the same conclusion. Furthermore, due to the high cost of CSFs, pharmacoeconomic studies are needed to determine the economic impact of CSF therapy.

However, the 2000 ASCO guidelines state that in patients at high risk of developing infectious complications adding a CSF to antibiotic drugs is an appropriate consideration. Factors used to identify a patient at high risk of infectious complications include an ANC less than 100 cells/mm³, sepsis syndrome and associated symptoms, pneumonia, and systemic fungal infection. Since the publication of the 2000 ASCO guidelines, a prospective, multicenter, randomized trial evaluated the effectiveness of adjuvant filgrastim in patients with “high risk febrile neutropenia.” The study was conducted in patients with solid tumors who presented with febrile neutropenia and at least one of the following high-risk characteristics: an ANC less than 100 cells/mm³, administration of chemotherapy within the last 10 days, sepsis or clinically documented infections, severe comorbidity, Eastern Cooperative Performance Status of 3 or 4, prior hospitalization, or the lack of response after 3 or more days of outpatient quinolone therapy. Filgrastim was associated with improved clinical and economic outcomes, supporting the use of a CSF as an adjuvant to antibiotic drugs in patients with febrile neutropenia at high risk for infectious complications.

Data from the trials that led to Food and Drug Administration labeling for use of filgrastim and sargramostim after induction and consolidation chemotherapy for acute nonlymphocytic leukemia suggest that these CSFs are well tolerated and have similar beneficial effects on neutrophil recovery. Filgrastim and

sargramostim resulted in significantly shortened times to recovery of ANC to greater than 500 cells/mm³ (e.g., by 4–5 days). However, differences in median survival were achieved for sargramostim but not for filgrastim. Sargramostim therapy was associated with fewer deaths from pneumonia. Whether the differences in survival between a CSF and placebo in these studies resulted from differences in patient characteristics, induction chemotherapy, supportive therapies, or the CSF regimen will remain unanswered until well-designed, prospective, comparative studies are completed.

Dosage guidelines specify that filgrastim and sargramostim can be administered subcutaneously or intravenously. In clinical practice, the subcutaneous route is preferred for both drugs. The recommended doses for filgrastim and sargramostim are 5 mcg/kg/day and 250 mcg/m²/day, respectively. Higher doses of either CSF have not improved prophylactic or therapeutic outcomes. Filgrastim is available in single-use 300-mcg and 480-mcg vials, and sargramostim is available as multiple-use 250-mcg and 500-mcg vials. Rounding of doses to the appropriate vial size is suggested as a practical approach to improve the cost-effectiveness of these CSFs. The multiuse sargramostim vials have a 28-day shelf life that may provide additional cost advantages.

The final guideline describes optimal “initiation and duration” of filgrastim and sargramostim administration. When prescribed as primary or secondary prophylaxis or as an adjunct to antibiotic drugs in high-risk patients with febrile neutropenia, these drugs are scheduled to begin no sooner than 24 hours after completion of chemotherapy and to be continued until an adequate ANC is achieved. The guidelines do not specify what ANC is adequate. However, the guideline does acknowledge that continuing a CSF until a patient’s ANC exceeds 10,000 cells/mm³ is not critical. The ANC target of 10,000 cells/mm³ was included in the filgrastim package insert labeling approved by the Food and Drug Administration in 1991. Subsequent clinical experience established that it is safe to discontinue CSFs after post-nadir ANCs exceed 1000–1500 cells/mm³ for 2–3 successive days. Further research is needed to address this issue. The recommended duration of administration for pegfilgrastim is more straightforward. Pegfilgrastim is approved to be administered as a single dose following administration of myelosuppressive chemotherapy. The 6-mg dose was selected because its effects on neutrophil recovery are similar to those achieved with daily administration of filgrastim for 14 days. No data have been published to support the administration of more than a single dose of pegfilgrastim for prophylaxis of febrile neutropenia.

In conclusion, CSFs are effective in shortening periods of neutropenia and in preventing febrile neutropenia in selected cases. However, data proving CSFs decrease infection-related mortality are extremely limited. Well-designed, comparative trials are needed to more adequately establish the cost-effectiveness of CSFs in managing infections in patients with cancer.

Garcia-Carbonero R, Mayordomo JI, Tomnamira MV, et al. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. *J Natl Cancer Inst* 2001;93:31–8.

Conclusion

The continuing development of effective chemotherapy for patients with cancer has resulted in substantial improvement of patient outcomes. However, chemotherapy-related suppression of a patient's immune system results in considerable risk for infectious morbidity and mortality. Immunocompromised patients with cancer represent a heterogeneous population at risk for a diverse and evolving variety of potentially fatal infections. The publication of IDSA and ASCO evidence-based practice guidelines has advanced the management of infections in patients with cancer. Pharmacists with a working knowledge of these guidelines and a commitment to following current literature can serve a critical role in optimizing cost-effective outcomes for these patients.

Annotated Bibliography

1. Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st Century. *Cancer* 2005;103:1103–13.

The management of patients with febrile neutropenia has improved substantially over the past 30 years. This article provides pharmacists a concise review of the Infectious Diseases Society of America's (IDSA) 2002 guidelines and more recently published articles germane to the topic. In addition, it provides insight on remaining challenges dealing with improving antifungal therapy (e.g., optimal duration of empirical antifungal treatment, the need for further research to compare the effectiveness of azole and echinocandin antifungals, and diagnostic progress that may lead to preemptive antifungal therapy replacing empirical antifungal therapy).

2. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.

A panel of experts in infectious diseases and oncology wrote the IDSA's 2002 guidelines. The panel used accepted evidence-based criteria to provide clinicians comprehensive and practical recommendations on managing infections in patients with febrile neutropenic cancer. These guidelines provide useful algorithms that incorporate known patient characteristics and risk factors that are vital to selecting appropriate antimicrobial drug therapy for patients with chemotherapy-induced febrile neutropenia. The final section addresses economic issues such as reducing costs by individualizing antibiotic regimens to a patient's risk status and to considering cost when determining the dose and duration of antimicrobial regimens. These guidelines set standards for managing patients with chemotherapy-induced febrile neutropenia. Recommendations for empiric use of antifungal agents will need to be revised to address emerging data that suggest that newer antifungal drugs may be superior to amphotericin B deoxycholate (AmB).

3. Ozer H, Armitage JO, Bennett DL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. *J Clin Oncol* 2000;18:3558–85.

Published by American Society of Clinical Oncology, this document is the second and most recent revision of its comprehensive, evidence-based practice guidelines for the use of CSFs. An expert panel reviewed and analyzed data published since 1994 in the context of the 11 recommendations published in the 1996 update. The 11 recommendations address practical aspects of clinically relevant uses of the colony-stimulating factors (CSFs) in support of patients receiving care from hematology and oncology specialists. Pharmacists responsible for ensuring appropriate use of CSFs will find this reference valuable.

4. DePauw BE, Verweij PE. Infections in patients with hematologic malignancies. In: Mandell GL, Bennett JE, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia: Elsevier, 2005:34320–41.

Patients with hematologic malignancies are treated much more aggressively than patients with solid tumors. This chapter effectively contrasts differences in the severity and incidence of infectious complications between these disparate populations. The authors provide a current and thorough overview of the clinical presentations of infections in patients at high risk of infectious complications and essential diagnostic considerations that are required to initiate appropriate antimicrobial drug therapy. Bacteremia and pneumonia are the primary focus of the chapter. Algorithms for managing intravascular catheter-acquired bacteremia and for diagnosing fungal pneumonia are provided. Additional topics include diagnosing and managing infections of the oropharynx, the central nervous system, and the gastrointestinal tract.

5. Klastersky J. Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 2004;39(suppl 1):32–7.

In 2000, the Study Section on Infections of the Multinational Association for Supportive Care in Cancer (MASCC) published a risk index for identifying febrile neutropenic cancer patients at low risk of developing infectious complications. This article provides an overview of two risk assessment tools that were developed and validated to identify patients with febrile neutropenia at low risk of developing infectious complications who can be effectively treated with oral antibiotic drugs. A comparison of the two risk assessment tools demonstrated that the MASCC index results in fewer patients at low risk of developing infectious complications being categorized as at high risk of developing infectious complications. Although patients at high risk of developing infectious complications should continue to receive appropriate intravenous antibiotic drug therapy, the author proposes that patients at low risk for developing infectious complications can be safely treated with oral combination therapy when appropriate observation is provided.

6. Paul M, Borok S, Fraser A, Vidal L, Leibovici L. Empirical antibiotics against gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2005;55:436–44.

The safety of delaying administration of glycopeptides (vancomycin, teicoplanin) until culture results confirm an infection caused by resistant gram-positive bacteria has been a persistent source of controversy. This rather complex

meta-analysis of 13 studies evaluated data on nearly 2400 patients to address this controversy. Empiric glycopeptide treatment was evaluated for initial treatment in nine trials and for persistent fever in two trials. All-cause mortality was similar in seven studies (relative risk = 0.86 [0.58–1.26]). Overall failure, failure associated with treatment modifications, development of superinfections, and adverse events also were analyzed. Results support the safety of deferring treatment with glycopeptides until a resistant gram-positive bacterial infection is confirmed. This article provides valuable evidence to pharmacists attempting to decrease the indiscriminate use of vancomycin.

7. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systemic review and meta-analysis. *BMJ* 2004;328:668–72.

This meta-analysis of 47 randomized trials compared the effectiveness of β -lactam monotherapy and β -lactam plus aminoglycoside combination therapy. The data set included 7807 patients and 8803 febrile episodes. The primary outcome was all-cause fatality at the completion of and up to 30 days following therapy completion. The mean value was 6.2%. There was no significant difference in all-cause fatality (relative risk = 0.85; 95% confidence interval = 0.72–1.02). Monotherapy resulted in fewer treatment failures and adverse events. Limitations of the study were acknowledged; sensitivity analyses indicated that the shortcomings did not affect results. The major caveat is the lack of fatality data in some of the trials. The authors conclude that β -lactam monotherapy “should be regarded as the standard of care” for patients with febrile neutropenia.

8. Rodriguez M, Fishman, JA. Prevention of infection due to *Pneumocystis* spp. in human immunodeficiency virus-negative immunocompromised patients. *Clin Microbiol Rev* 2004;17:770–82.

Pneumocystis jiroveci continues to be a persistent pathogen for patients who are immunocompromised, including selected patients with cancer who are human immunodeficiency virus-negative. The authors address the relatively recent change in nomenclature that differentiates the *Pneumocystis* species that infect animals and humans. This review provides a clinically relevant discussion of the epidemiology, diagnosis, pathophysiology, and current prophylactic options for patients with cancer at risk for *P. jiroveci* pneumonia.

9. Mermel LA, Varr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001;32:1249–72.

The IDSA, the American College of Critical Care Medicine, and the Society for Healthcare Epidemiology of America jointly published these evidence-based guidelines for managing vascular access device-related infections. Strengths of the guidelines include specific recommendations for diagnosing and managing catheter-related infections. The notable weakness of the guidelines, acknowledged by the authors, is that none of the evidence to support the recommendations was generated from randomized, double-blind, clinical trials. Rather, these guidelines are based on published data generated from small nonrandomized, clinical trials. However, until data from more rigorously designed trials prove alternative approaches are superior to these guidelines, they provide a rational standard approach to diagnosing and managing catheter-related infections. This

reference provides specific recommendations on the appropriate use of antibiotic lock therapy. The use of salvage antibiotic drug therapy is incorporated into a well-designed algorithm for managing a patient with catheter-related bacteremia.

10. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Recommendations of the CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. *MMWR Recomm Rep* 2000;49(RR-10):1–128. Available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm>. Accessed January 31, 2006.

These guidelines review current data and provide evidence-based recommendations for preventing bacterial, viral, fungal, and protozoal infections among patients who underwent hematopoietic stem cell transplantation (HSCT). Recommendations for prophylaxis of opportunistic infections are specific for allogeneic, autologous, pediatric, and adult HSCT recipients. Recommendations for prevention are rated by the strength of the recommendation and the quality of the evidence supporting the recommendation. In addition to recommendations for hospital infection control, the guidelines include strategies for vaccination and HSC safety.