Chapter 145: Infections in Immunocompromised Patients

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KEY CONCEPTS

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1 An *immunocompromised host* is a patient with defects in host immune defenses that predispose to infection. Risk factors include neutropenia, immune system defects from disease or immunosuppressive drug therapy, compromise of natural host defenses, environmental contamination, and changes in normal flora of the host.

2 Immunocompromised patients are at high risk for a variety of bacterial, fungal, viral, and protozoal infections. Bacterial infections caused by gram-positive cocci (staphylococci and streptococci) occur most frequently, followed by gram-negative bacterial infections caused by Enterobacterales and *Pseudomonas aeruginosa.* Fungal infections caused by *Candida* and *Aspergillus*, as well as certain viral infections (herpes simplex virus [HSV], cytomegalovirus [CMV]), are also important causes of morbidity and mortality.

3 Risk of infection in patients with neutropenia is associated with both the severity and duration of neutropenia. Patients with severe neutropenia (absolute neutrophil count less than 500 cells/mm^3 [0.5×10^9/L]) for greater than 7 to 10 days are considered to be at high risk of infection.

4 Fever (single oral temperature of greater than or equal to 38.3°C [100.9°F], or a temperature of greater than or equal to 38°C [100.4°F] for greater than or equal to 1 hour) is the most important clinical finding in patients with neutropenia and is usually the stimulus for further diagnostic workup and initiation of antimicrobial treatment. Infection should be considered as the cause of fever until proven otherwise. Usual signs and symptoms of infection may be altered or absent in patients with neutropenia. Appropriate empiric broad-spectrum antimicrobial therapy must be rapidly instituted to prevent excessive morbidity and mortality.

5 Empiric antimicrobial regimens for neutropenic infections should be based on patients' individual risk factors, as well as institutional infection and susceptibility patterns. The significant morbidity and mortality associated with gram-negative infections require that initial empiric regimens for treatment of febrile neutropenia have good activity against *P. aeruginosa* and Enterobacterales. Parenteral regimens most commonly recommended for initial inpatient treatment include monotherapy with an antipseudomonal β-lactam, or a combination regimen consisting of an antipseudomonal β-lactam plus an aminoglycoside. Low-risk patients may be successfully treated with oral antibiotics (fluoroquinolone plus amoxicillin-clavulanate), with the treatment setting determined by the patient's clinical status.

6 Patients with neutropenia who remain febrile after 3 to 5 days of initial antimicrobial therapy should be reevaluated to determine whether treatment modifications are necessary. Common antimicrobial modifications include addition of vancomycin (if not already administered) and antifungal therapy (amphotericin B, an echinocandin, or fluconazole). Therapy should be directed at causative organisms, if identified, but broad-spectrum regimens should be maintained during neutropenia.

7 The optimal duration of therapy for febrile neutropenia is controversial. The decision to discontinue antimicrobials is based on resolution of neutropenia, defervescence, culture results, and clinical stability of the patient.

8 Prophylactic antimicrobials are administered to patients with cancer who are expected to experience prolonged neutropenia, as well as to hematopoietic cell and solid-organ transplant recipients. Prophylactic regimens may include antibacterial, antifungal, antiviral, or

antiprotozoal agents, or a combination of these, selected according to risk of infection with specific pathogens. Optimal prophylactic regimens should consider individual patient risk for infection and institutional infection and susceptibility patterns.

9 Patients undergoing hematopoietic cell transplant (HCT, previously referred to as hematopoietic stem cell transplant) are at an extremely high risk of infection because of prolonged neutropenia following intensive chemotherapy with or without irradiation, while solid-organ transplant (SOT) recipients are at high risk because of prolonged administration of immunosuppressive drugs. Fungal (*Aspergillus*) and viral (CMV) infections are particularly troublesome in these populations, and prophylactic regimens directed against these pathogens are commonly used. When documented, these infections must be treated aggressively to optimize patient outcomes. Nevertheless, mortality rates are often high despite appropriate and aggressive antimicrobial therapy.

10 Immunocompromised patients must be continuously assessed for evidence of infection and response to antimicrobial therapy. Because a large number of antimicrobials may potentially be used, the occurrence of drug-related adverse effects must also be carefully assessed. Efforts should be directed at designing cost-effective treatment strategies that promote optimal patient outcomes.

BEYOND THE BOOK

BEYOND THE BOOK

Refer to "Chapter 143: Infection in an Immunocompromised Patient: Making a Rash Decision Level II" in Pharmacotherapy Casebook: A Patient-Focused Approach, 11e (may be obtained online through AccessPharmacy). After studying the patient presentation, briefly answer Questions 1 through 5 and the Follow-up Case Questions 1 through 3 regarding patient Scarlet Hives's febrile neutropenia following hematopoietic cell transplant. The purpose of this exercise is to gain experience in applying knowledge regarding assessment of possible infection in immunocompromised patients and development of an appropriate therapeutic plan based on clinical presentation, patient characteristics, type and severity of potential infection, past treatment history, and potential causative pathogens.

INTRODUCTION

An immunocompromised host is a patient with intrinsic or acquired defects in host immune defenses that predispose to infection. Advances in modern medicine have created more immunocompromised hosts than ever before. Historically, many of these patients died of their underlying diseases. Dramatic improvements in survival have been achieved by more aggressive therapy of underlying diseases and improved supportive care. However, because such aggressive therapy often renders patients profoundly immunosuppressed for long periods, opportunistic infections remain important causes of morbidity and mortality. This chapter focuses on risk factors for infection, common pathogens and infection sites, and prevention and management of suspected or documented infections in patients with cancer (including hematopoietic cell transplant [HCT] patients) and solid-organ transplant (SOT) recipients. Chapter 148, "Human Immunodeficiency Virus," discusses infectious complications associated with human immunodeficiency virus (HIV) infection.

RISK FACTORS FOR INFECTION/EPIDEMIOLOGY

Numerous factors, such as underlying disease, immunosuppressive drug therapy, and antimicrobial administration, determine the immunocompromised host's risk of developing infection (see Table 145-1). These same factors may also influence the epidemiology of the associated infections. Multiple risk factors are present concomitantly in many patients.

TABLE 145-1

Risk Factors and Common Pathogens in Immunocompromised Patients

Risk Factor	Patient Conditions	Common Pathogens
Neutropenia	Acute leukemia Chemotherapy	Bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, streptococci, enterococci Fungi: *Candida*, *Aspergillus*, Mucorales (*Mucor*) Viruses: Herpes simplex
Impaired cell-mediated immunity	Lymphoma Immunosuppressive therapy (steroids, cyclosporine, chemotherapy, CAR-T)	Bacteria: *Listeria*, *Nocardia*, *Legionella*, Mycobacteria Fungi: *Cryptococcus neoformans*, *Candida*, *Aspergillus*, *Histoplasma capsulatum* Viruses: Cytomegalovirus, varicella-zoster, herpes simplex Protozoa: *Pneumocystis jirovecii*
Impaired humoral immunity	Multiple myeloma Chronic lymphocytic leukemia Splenectomy Immunosuppressive therapy (steroids, chemotherapy, CAR-T)	Bacteria: *S. pneumoniae*, *H. influenzae*, *N. meningitidis*
Loss of protective skin barriers	Venipuncture, bone marrow aspiration, urinary catheterization, vascular access devices, radiation, biopsies	Bacteria: *S. aureus*, *S. epidermidis*, *Bacillus* spp., *Corynebacterium jeikeium* Fungi: *Candida*
Mucous membranes	Respiratory support equipment, endoscopy, chemotherapy, radiation	Bacteria: *S. aureus*, *S. epidermidis*, streptococci, Enterobacterales, *P. aeruginosa*, *Bacteroides* spp., *Clostridioides difficile* Fungi: *Candida* Viruses: Herpes simplex
Surgery	Solid-organ transplantation	Bacteria: *S. aureus*, *S. epidermidis*, Enterobacterales, *P. aeruginosa*, *Bacteroides* spp., *C. difficile* Fungi: *Candida* Viruses: Herpes simplex
Alteration of normal microbial flora	Antimicrobial therapy Chemotherapy Hospital environment	Bacteria: Enterobacterales, *P. aeruginosa*, *Legionella*, *S. aureus*, *S. epidermidis*, *C. difficile* Fungi: *Candida*, *Aspergillus*
Blood products, donor organs	Bone marrow transplantation Solid-organ transplantation	Fungi: *Candida* Viruses: Cytomegalovirus, Epstein–Barr virus, hepatitis B, hepatitis C Protozo: *Toxoplasma gondii*

CAR-T, chimeric antigen receptor T cell.

Neutropenia

Neutropenia is defined as an abnormally reduced number of neutrophils circulating in peripheral blood. Although exact definitions of neutropenia can vary, an absolute neutrophil count (ANC) of less than 1,000 cells/mm^3 (1.0×10^9/L) indicates a reduction sufficient to predispose patients to infection.[1-3] ANC is the sum of the absolute numbers of both mature neutrophils (polymorphonuclear cells [PMNs], also called *polys* or *segs*) and immature neutrophils (*bands*). The absolute number of PMNs and bands is determined by dividing the total percentage of these cells (obtained from the white blood cell [WBC] differential) by 100 and then multiplying the quotient obtained by the total number of WBCs.

The degree or severity of neutropenia, rate of neutrophil decline, and duration of neutropenia are important risk factors for infection.[1-5] All patients with neutropenia are considered to be at risk for infection, but those with ANC less than 500 cells/mm^3 (0.5×10^9/L) are at greater risk than those with ANCs of 500 to 1,000 cells/mm^3 (0.5×10^9 to 1.0×10^9/L). Most treatment guidelines use ANC less than 500 cells/mm^3 (0.5×10^9/L) as the critical value in making therapeutic decisions regarding the management of suspected or documented infections.[1-5] Risk of infection and death are greatest among patients with less than 100 neutrophils/mm^3 (0.1×10^9/L) ("profound neutropenia").[1-6] In patients with chemotherapy-induced neutropenia, the risk of infection is also increased according to both the rapidity of ANC decline and duration of neutropenia. Patients with severe neutropenia of more than 7 to 10 days' duration are considered to be at especially high risk for serious infections.[1-4] The duration of chemotherapy-induced neutropenia varies considerably among subsets of patients with cancer according to the specific chemotherapeutic agents used and the intensity of treatment. Patients undergoing HCT may have no detectable granulocytes in peripheral blood for up to 3 to 4 weeks and are at particular risk for severe infections with a variety of pathogens.[4-8]

Bacteria and fungi commonly cause infections in patients with neutropenia. Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *P. aeruginosa*) historically were the most common causes of bacterial infection and remain frequent pathogens.[3,5,7-12] During the 1980s gram-positive cocci (*Staphylococcus aureus*, *Staphylococcus epidermidis,* and other coagulase-negative staphylococci, streptococci, and enterococci) emerged as the most common cause of acute bacterial infections among patients with neutropenia, accounting for up to 80% of all bloodstream infections.[5] This shift was likely due to widespread use of prophylaxis with fluoroquinolones, aggressive chemotherapy regimens associated with severe mucositis, and more frequent use of central venous catheters.[5,7,9,10,13] However, gram-negative infections are again increasing in incidence and now account for approximately half of all bacterial infections.[4-7,10-12] Gram-negative infections are associated with significant morbidity and mortality, in large part due to increasing antibiotic resistance.[10-12] Patients who are neutropenic for extended periods and who receive broad-spectrum antibiotics are at high risk for fungal infections, usually due to *Candida* or *Aspergillus* spp.[1-7,13] Viral infections, although not as common as bacterial and fungal infections, also may cause severe infection in patients with neutropenia.[1,4,6,7] Successful treatment of infections in patients with neutropenia is highly dependent on resolution of neutropenia.[1-6,8]

Immune System Defects

Although not as readily quantifiable, abnormalities may exist in granulocyte function as well as in cell numbers. In addition to neutropenia, defects in T-lymphocyte and macrophage function (cell-mediated immunity), B-cell function (humoral immunity), or both predispose patients to infection.[3-5,7] Cellular immune dysfunction is the result of underlying disease or immunosuppressive drug therapy or radiation; these defects result in a reduced ability of the host to defend against intracellular pathogens. Patients with malignancies and transplant patients receiving a wide variety of immunosuppressive agents, such as cyclosporine, tacrolimus, sirolimus, mycophenolate, corticosteroids, azathioprine, antineoplastic agents, and chimeric antigen receptor T cell (CAR-T) therapy, are at risk for a wide variety of infections (Table 145-1). Although some of these pathogens are associated with only asymptomatic or mild disease in normal hosts, they may cause disseminated, life-threatening infections in immunocompromised hosts.

Underlying disease also frequently causes defects in humoral immune function. Patients with multiple myeloma and chronic lymphocytic leukemia have progressive hypogammaglobulinemia that results in defective humoral immunity. Splenectomy performed as a part of the staging process for Hodgkin's disease places patients at risk for infectious complications. Disease states with humoral immune dysfunction predispose the patient to serious, life-threatening infection with encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

Destruction of Protective Barriers

Loss of protective barriers is a major factor predisposing immunocompromised patients to infection. Damage to skin and mucous membranes by surgery, venipuncture, IV and urinary catheters, radiation, and chemotherapy disrupts natural host defense systems, leaving patients at high risk for infection. Chemotherapy-induced mucositis may erode mucous membranes of the oropharynx and gastrointestinal (GI) tract and establish a portal for subsequent infection by bacteria, herpes simplex virus (HSV), and *Candida.*[1-6] Medical and surgical procedures, such as transplant surgery, indwelling IV catheter placement, bone marrow aspiration, biopsies, and endoscopy, further damage the integument and predispose patients to infection. Infections resulting from disruption of protective barriers usually are a result of skin flora, such as *S. aureus*, *S. epidermidis*, and streptococci.[3-5]

Environmental Contamination/Alteration of Microbial Flora

Infections in immunocompromised patients are caused by organisms either colonizing the host or acquired from the environment. Microorganisms may be easily transferred from patient to patient on the hands of hospital personnel unless strict infection prevention policies are followed. Contaminated equipment, such as nebulizers or ventilators, and contaminated water supplies have been responsible for outbreaks of *P. aeruginosa* and *Legionella pneumophila* infections, respectively. Foods, such as fruits and green leafy vegetables, which often are colonized with gram-negative bacteria and fungi, are sources of microbial contamination in immunocompromised hosts.[1,6]

Most infections in patients with cancer are caused by organisms colonizing body sites, such as the skin, oropharynx, and GI tract, and are therefore caused by the patient's own endogenous flora.[4-7] The GI tract is a common site from which infections in immunocompromised hosts originate. Periodontitis, pharyngitis, esophagitis, colitis, perirectal cellulitis, and bacteremias are caused predominantly by normal flora of the gut; bloodstream infections are thought to arise from microbial translocation across injured GI mucosa.[1,6,7] Normal flora may be significantly disrupted and altered; oropharyngeal flora rapidly change to primarily gram-negative bacilli in hospitalized patients. Many patients with cancer may already be colonized with gram-negative bacilli on admission as a result of frequent prior hospitalizations and clinic visits. In hospitalized patients with cancer, however, many infections are caused by colonizing organisms acquired after admission.[1]

Although hospitalization and severity of illness are important risk factors for colonization by gram-negative bacilli, administration of broad-spectrum antimicrobial agents has the greatest impact on flora of immunocompromised hosts. Use of these agents disrupts GI tract flora and predisposes patients to infection with more virulent or resistant pathogens. Antineoplastic drugs (eg, cyclophosphamide, doxorubicin, and fluorouracil) and acid-suppressive therapy (eg, H_2-receptor antagonists, proton-pump inhibitors, and antacids) also may result in changes in GI flora and possibly predispose patients to infection.[1,4,5]

ETIOLOGY OF INFECTIONS IN PATIENTS WITH NEUTROPENIA AND CANCER

2 Infection remains a significant cause of morbidity and mortality in neutropenic patients with cancer. Febrile neutropenia occurs in 10% to 50% of patients with solid tumors and 80% to 100% of those with hematological malignancies.[1,2,5] More than 50% of patients with febrile neutropenia have an established or occult infection, but causative pathogens are microbiologically documented in only 30% to 40% of cases. Infections can be documented clinically (but not microbiologically) in another 30% to 40% of patients, with the remaining 20% to 40% of patients manifesting infection only by fever.[2-5] Bloodstream infections account for approximately 10% to 25% of all febrile episodes during neutropenia.[1,4,5,9] Patients with profound neutropenia are at greatest risk for systemic infection, with at least 20% of these individuals developing bacteremia.[1-6] Areas of impaired or damaged host defenses, such as the oropharynx, lungs, skin, sinuses, and GI tract, are common sites of infection. These local infections may progress to cause systemic infection and bacteremia.[4,5,8,9]

Table 145-1 lists organisms commonly infecting immunocompromised patients. Bacteremic episodes in patients with cancer are caused by gram-positive organisms in 45% to 75% of cases, these rates being highly institution specific.[1,3,5,7,9-11,13] Important risk factors for these infections include frequent use of indwelling central and peripheral IV catheters, frequent use of broad-spectrum antibiotics with excellent gram-negative activity but often relatively poor gram-positive coverage, high rates of mucositis caused by aggressive cancer treatments, and prophylaxis with trimethoprim–sulfamethoxazole or fluoroquinolones.[1,3,5,7-11,14] Staphylococci (especially *S. epidermidis*) account for most infections, but *Bacillus* spp. and *Corynebacterium jeikeium* are also important pathogens.[1,4,5,7,13] Rates of infection due to methicillin-resistant *S. aureus* (MRSA) have increased in the hospital and community settings.[4-6,13,14,16] Viridans streptococci, which may be resistant to β-lactams, also have emerged as important pathogens,

particularly in patients with chemotherapy-induced mucositis of the oropharynx.[3-6,12] Enterococci, including vancomycin-resistant strains, also may be problematic in many institutions.[4,6,13,14,16] Bacteremia caused by vancomycin-resistant enterococci (VRE) in patients with neutropenia is associated with a mortality rate up to 30%.[3,10,13,14,16,17]

Gram-positive infections are not always immediately life-threatening and are associated with somewhat lower mortality rates overall (approximately 5%-10%) compared with gram-negative infections.[1,4,10] However, increasing rates of antibiotic resistance have made treatment of gram-positive infections in immunocompromised patients more challenging.[4,7,10,13,14] MRSA infections are associated with increased morbidity, mortality, and hospital costs compared with susceptible organisms.[10,13,18] Methicillin resistance among coagulase-negative staphylococci, which may cause 40% to 80% of infections in certain populations, is common (70%-90% of isolates).[1,4,6,7,10,13,14] Vancomycin-resistant organisms such as VRE are increasing in importance.[1,3,4,10,13,17] Thus, prevention and timely diagnosis and treatment of gram-positive infections are clearly of great importance in the management of patients with neutropenia and cancer.

Gram-negative infections remain important causes of morbidity and mortality (approximately 10%-30%) in immunocompromised patients with cancer.[5,10] However, the relative frequency of gram-negative infections caused by specific pathogens has been changing. *E. coli* and *Klebsiella* remain the most common isolates at many centers.[4,5,7] However, strains of Enterobacterales producing extended-spectrum β-lactamases (ESBLs) that hydrolyze cephalosporins, and carbapenemases that inactivate carbapenems, have emerged and are a cause for concern.[1,4,5,7,10,14] The global spread of carbapenem-resistant Enterobacterales (CRE) is especially concerning. The frequency of infections resulting from other gram-negative organisms, such as *Klebsiella-Enterobacter*, *Serratia*, and *Citrobacter*, has also been increasing.[1,4,5] Infections with these particular organisms may be difficult to treat because of the ease of β-lactamase induction and the more frequent development of resistance to multiple antibiotics.[1,4,5,7,10-12,14]

P. aeruginosa has long been an important pathogen in patients with cancer. *P. aeruginosa* infection rates are decreasing in patients with solid tumors but not in patients with hematologic malignancies.[3,7,10] Infections caused by *P. aeruginosa* are associated with significant morbidity and mortality in patients with neutropenia, with reported mortality rates of 31% to 75%.[1,5,10] The frequency of infection caused by difficult-to-treat organisms such as *Stenotrophomonas maltophilia* appears to be increasing at many centers, probably because of selective pressures of broad-spectrum antimicrobial use.[7,11] As with gram-positive organisms, antibiotic resistance among gram-negative organisms has continued to increase at alarming rates and has made appropriate antibiotic selection for treatment of febrile neutropenia more difficult.[1,5,14,16] Mortality rates of up to 40% to 70% have been reported in patients with infection caused by multidrug-resistant gram-negative pathogens.[5,14] Although the GI tract is a common site of bacterial infection, severe infections caused by anaerobic organisms are relatively infrequent. Anaerobes are found most frequently in mixed infections, such as perirectal cellulitis and mucositis-associated oropharyngeal infections.[4,7]

In addition to bacterial infections, neutropenic cancer patients are at risk for invasive fungal infections. Patients with extended periods of profound neutropenia who have been receiving broad-spectrum antibiotics, corticosteroids, or both are at the highest risk for invasive fungal infection. Up to one-third of patients with febrile neutropenia who do not respond to 1 week of broad-spectrum antibiotic therapy will have a systemic fungal infection.[1,4,11] Large autopsy studies have documented a change over time in invasive fungal infections. Whereas from 1989 to 2003 over 30% of autopsies of patients with hematologic malignancies found deep fungal infection (75% of which were undiagnosed prior to death), this number decreased to 19% from 2004 to 2008 (49% undiagnosed prior to death). These improvements may be due to improved awareness, diagnostic techniques, and treatments. One single center estimated the average prevalence of invasive fungal infections was 30% in those autopsied over a 20-year period. Causative pathogens were usually either *Aspergillus* spp., *Candida* spp., or Mucorales fungi (such as *Mucor* spp.).[16] Mortality rates in patients with invasive fungal infections are highly dependent on pathogens, sites of infection, and underlying risk factors but often exceed 30% overall.[17]

Candida albicans is a common fungal pathogen in neutropenic cancer patients, especially those with solid tumors.[1,3,4,15,19,21] However, non-*albicans* species of *Candida* including *Candida glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* are being isolated with increasing frequency and are more common than *C. albicans* infections in some studies.[15,21] Increased infections caused by pathogens such as *Trichosporon* spp., *Fusarium* spp., and *Curvularia* spp. have also been reported.[15,19,22] The shift toward more frequent infection with non-*albicans Candida* is important because of significantly decreased rates of azole susceptibility among many of these strains.[19] Because *Candida* spp. are normal flora, alteration of body host

defenses is an important risk factor for the development of these infections. Oral thrush is the most common clinical manifestation of fungal infection. Mucous membranes damaged from chemotherapy and radiation serve as areas of *Candida* surface colonization and subsequent entry into the bloodstream; disease then may disseminate throughout the body. Organs such as the liver, spleen, kidney, and lungs are commonly involved in disseminated disease.[1,4,19] Hepatosplenic candidiasis is a particularly important infection in patients with hematologic malignancies.[7,19,21] In patients with invasive candidiasis, overall attributable mortality is as high as 35% to 50%.[3,13,15,18,21]

Invasive infections caused by *Aspergillus* spp. are a serious complication of neutropenia. Mortality rates have historically approached 80% in patients with prolonged neutropenia and/or patients undergoing allogeneic HCT; however, mortality is now reported as low as 30%.[3,20,22,24] These infections are particularly prevalent and more common in patients with hematologic malignancies and in patients undergoing HCT; invasive aspergillosis may occur in up to 10% of these patients.[3,15,19,22,24,25] Infections resulting from *Aspergillus* species (including *A. fumigatus*, *A. terreus*, *A. flavus*, and *A. niger*) usually are acquired via inhalation of airborne spores. After colonizing the lungs, *Aspergillus* invades the lung parenchyma and pulmonary vessels, resulting in hemorrhage, pulmonary infarcts, and a high mortality rate. Invasive pulmonary disease is the dominant manifestation of infection in patients with neutropenia. However, *Aspergillus* also may cause other infections, including sinusitis, cutaneous infection, and disseminated disease involving multiple organs, including the CNS.[19,25] Prolonged neutropenia is the primary risk factor for invasive pulmonary aspergillosis in patients with acute leukemia; use of corticosteroids also may predispose patients to disease.[21] Invasive aspergillosis should be suspected in neutropenic cancer patients colonized with *Aspergillus* (in sputum and/or nasal cultures) who remain persistently febrile despite at least 1 week of broad-spectrum antibiotic therapy.[1,4,25] Increased infections caused by other yeasts (such as *Trichosporon*) and molds (such as Mucorales, *Fusarium*, and *Curvularia*) have also been reported.[13,15,16,19,22]

Chemotherapy-induced mucous membrane damage may predispose neutropenic cancer patients to reactivation of HSV, manifesting as gingivostomatitis or recurrent genital infections. Untreated oropharyngeal HSV infections may spread to involve the esophagus and often coexist with *Candida* infections. Clinical disease resulting from HSV occurs most often in patients with serologic evidence (eg, serum antibodies to HSV) of prior infection. Both HSV-seropositive HCT recipients and HSV-seropositive patients with leukemia receiving intensive chemotherapy are at high risk for recurrent HSV disease during periods of immunosuppression.[3,4,6]

Pneumocystis jirovecii and *Toxoplasma gondii* are the most common parasitic pathogens found in immunocompromised cancer patients. Patients with hematologic malignancies and those receiving high-dose corticosteroids as part of chemotherapy regimens are at the greatest risk of infection.[3,4,6] Routine use of trimethoprim–sulfamethoxazole prophylaxis has substantially reduced the incidence of these infections.[1,4,6]

Because the majority of infecting organisms in patients with cancer are from the host's own flora, some centers have used routine surveillance cultures in an attempt to prospectively identify causes of fever and suspected infection. In a typical surveillance culture program, cultures of the nose, mouth, axillae, and perirectal area are performed twice weekly, and culture results are correlated with the clinical status of the patient. Because these cultures are costly and have low diagnostic yield, the utility of surveillance culture programs is believed to be limited.[1,4] However, surveillance cultures are useful as research tools and in patients with prolonged profound neutropenia, and in institutions that have high rates of antimicrobial resistance or have problems with pathogens such as *P. aeruginosa* or *Aspergillus* spp. Surveillance cultures should be limited to the anterior nares for detecting colonization with MRSA, *Aspergillus*, and penicillin-resistant pneumococci and to the rectum for detecting VRE, *P. aeruginosa*, and multiple-antibiotic-resistant gram-negative bacilli (such as CRE).[1,4]

Knowledge of infection rates and local susceptibility patterns is essential for guiding optimal management of febrile neutropenia. These parameters must be monitored closely because the spectrum of infectious complications is related to multiple factors, including cancer chemotherapy regimens and antimicrobial therapy used for treatment and prophylaxis.

CLINICAL PRESENTATION

4 The most important clinical finding in the patient with neutropenia is fever. Because of the potential for significant morbidity and mortality associated with infection in these patients, fever should be considered to be the result of infection until proved otherwise.[1,2,4,5,7] At the first appearance of fever, the patient should be evaluated carefully for other signs and symptoms of infection. The use of biomarkers such as procalcitonin (PCT) has been extensively investigated for their utility in helping diagnose infections in patients with febrile neutropenia. Although elevated PCT levels

(typically ≥0.5 ng/mL [mcg/L]) have been associated with a significantly greater likelihood of bacterial infection in the febrile patient, lack of elevated PCT levels does not necessarily correspond to lack of infection and should not be used as the sole rationale for withholding or stopping initial antibiotic therapy.[22]

CLINICAL PRESENTATION: Febrile Neutropenia[1-7]

General

- Due to high risk for serious infections, frequent (at least daily) careful clinical assessments must be performed to search for possible evidence of infection
- Physical assessment should include examination of all common sites of infection, including mouth/pharynx, nose and sinuses, respiratory tract, GI tract, urinary tract, skin, soft tissues, perineum, and intravascular catheter insertion sites

Symptoms

- Usual signs and symptoms of infection may be absent or altered in patients with neutropenia owing to low numbers of leukocytes and an inability to mount an inflammatory response (eg, no infiltrate on chest x-ray film, urinary tract infection without pyuria)
- Pain may be present at the infection site(s)

Signs

- Fever in this setting is defined as a single oral temperature ≥38.3°C (100.9°F) in the absence of other causes or temperature ≥38°C (100.4°F) for 1 hour or more. Other causes of fever unrelated to infection in this patient population include reactions to blood products, chemotherapeutic agents (and other drugs, including biologics), cell lysis, and underlying malignancy
- Usual signs of infection may be absent or altered; patients with bacteremia commonly exhibit no signs of infection other than fever

Laboratory Tests

- Neutropenia (ANC ≤1,000 cells/mm^3 [1.0×10^9/L])
- Blood cultures (two or more sets, including vascular access devices) for bacteria and fungi; cultures of other suspected infection sites (infection can be documented microbiologically in only about 30% of cases, about half of which are due to bacteremia)
- Other cultures should be obtained as indicated clinically according to the presence of signs or symptoms
- Recent surveillance cultures (nasal, rectal) should be reviewed, if available
- Complete blood count and blood chemistries should be obtained frequently to monitor neutropenia, plan supportive care, guide drug dosing, and assess patient's overall status

Other Diagnostic Tests

- Chest x-ray
- Aspiration, biopsy of skin lesions
- Procalcitonin is indicative of bacterial infection when elevated, but negative test does not rule out infection
- Other diagnostic tests as indicated clinically on the basis of physical examination and other assessments

TREATMENT

Management of patients with febrile neutropenia, including both prophylaxis and treatment of infectious complications, can be extremely challenging. Although published guidelines are available, the most optimal clinical management of these patients remains unclear in many aspects.

Desired Outcomes

4 5 The goals of therapy in neutropenic cancer patients with new fever are the following: (a) protect the neutropenic patient from early death caused by undiagnosed infection; (b) prevent breakthrough bacterial, fungal, viral, and protozoal infections during periods of neutropenia; (c) effectively treat established infections; (d) reduce morbidity and allow for continued administration of optimal antineoplastic therapy; (e) avoid unnecessary use of antimicrobials that contribute to increased resistance; and (f) minimize toxicities and cost of antimicrobial therapy while increasing patient quality of life. Empirical broad-spectrum antibiotic therapy is effective at reducing early mortality.[1,2,4,9,10]

General Approach to Treatment

General guidelines for management of febrile episodes and documented infections in patients with neutropenia are shown in Figs. 145-1 and 145-2.[1] Although many controversies remain regarding optimal management of these patients, updated evidence-based guidelines from the Infectious Diseases Society of America (IDSA) for the management of febrile neutropenia were published in 2010 and, regarding outpatient management, in 2018.[1,2] Similarly, the National Comprehensive Cancer Network (NCCN) published updated clinical practice guidelines for the prevention and treatment of cancer-related infections in 2021.[4] Selected specific recommendations are discussed in the following sections of this chapter, and their associated evidence-based rankings are summarized in Table 145-2.

FIGURE 145-1

Initial management of febrile episodes in patients with neutropenia. (ANC, absolute neutrophil count [expressed as cells/mm^3]; HCT, hematopoietic cell transplantation; MASCC, Multinational Association for Supportive Care in Cancer; PO, oral.)

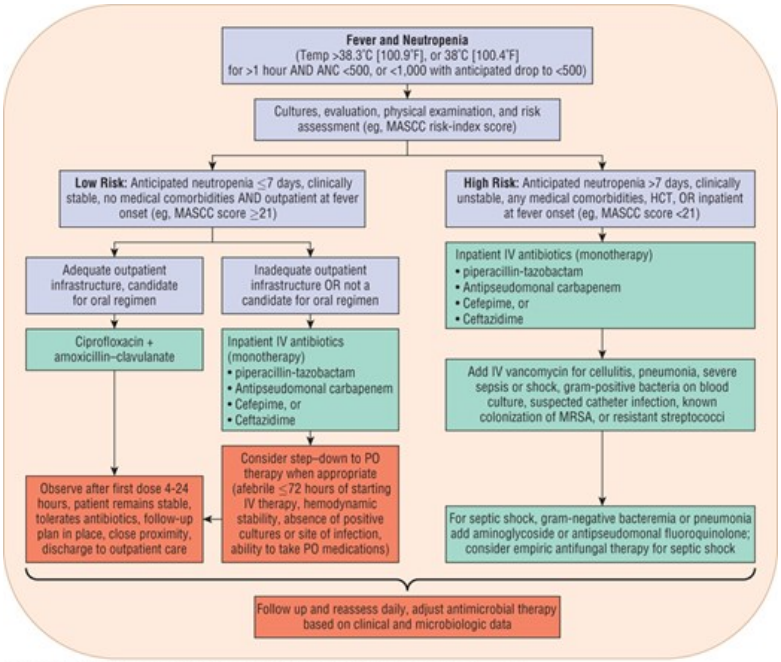


FIGURE 145-2

Subsequent management of febrile episodes in patients with neutropenia who have already received empirical antimicrobial therapy for 2 to 4 days. (ANC, absolute neutrophil count [expressed as cells/mm^3 or × 10^6/L; MDR, multidrug-resistant; PO, oral.)

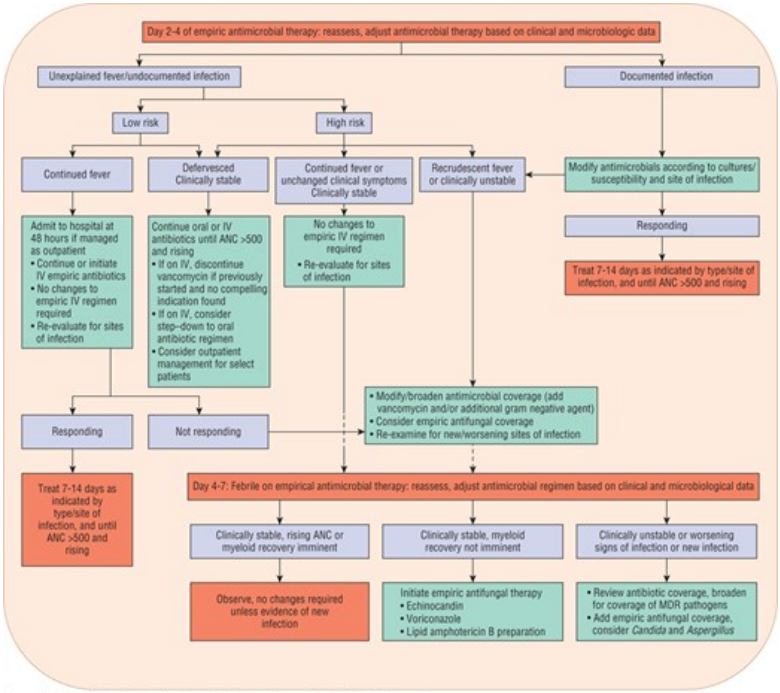


TABLE 145-2

Summary of Evidence-Based Recommendations for Management of Febrile Episodes in Patients with Neutropenia

Recommendations	Recommendation Grades[a]
The first dose of empirical antibiotic therapy should be administered within 1 hour after triage from initial presentation	Strong, low
Oral antibiotics are feasible for treatment of carefully selected patients at low risk for complications	A-1
Clinical judgment and consideration of multiple patient factors should be used when selecting candidates for outpatient management	Moderate, low
The MASCC index, Talcott's rules, and CISNE are recommended tools for identifying patients who may be candidates for outpatient management	Moderate, intermediate
Patients who are eligible for outpatient management must meet appropriate psychosocial and logistical requirements	Moderate, low
For outpatient management, first doses of antibiotics should be administered in the clinic, emergency department, or hospital	Moderate, low
Monotherapy with appropriate antibiotics is as effective as combination regimens for initial empirical treatment of febrile neutropenic episodes	A-1
Patients at high risk for serious life-threatening infections must be initially treated with IV antibiotics. Patients at low risk can be treated with either IV or oral drugs (see text for risk stratification criteria)	A-2

Oral therapy with a fluoroquinolone (ciprofloxacin or levofloxacin) plus amoxicillin-clavulanate is appropriate for initial outpatient treatment	Moderate, intermediate
Patients who become afebrile within 2-4 days of beginning initial empirical antibiotic therapy and in whom specific organisms have been identified should be treated for ≥7 days (until cultures are negative and patient has clinically recovered). Low-risk patients in whom no organism is identified can be switched to oral antibiotics if desired, whereas patients originally classified as high risk should continue on IV antibiotics	B-2
Management of Patients with Persistent Fever During First 2-4 Days of Treatment	
In patients initially receiving monotherapy or a two-drug regimen *not* including vancomycin, addition of vancomycin can be considered if any criteria for use of vancomycin are present (see the text for specific criteria)	B-3
In patients *already* receiving vancomycin as part of the initial empirical regimen, withdrawal of vancomycin should be considered after 2 days in the absence of a documented pathogen requiring continued therapy	A-2
Other initial antibiotics can be continued if the disease has not progressed, or switched to oral therapy if the patient was classified as low risk even in the presence of continued fever	A-1
Management of Patients with Fever Persisting for More Than 2-4 Days After Initial Treatment	
Reassess patient after 2 days of treatment. If still febrile by day 4, then: (a) continue the same antibiotics if clinically stable; (b) change antibiotics if any evidence of disease progression or antibiotic toxicities; or (c) add an antifungal drug if the duration of neutropenia is expected to be more than 5-7 additional days	Option a: A-1 Option b: A-3 Option c: A-3
Continuation of Antibiotics in Afebrile Patients with No Identified Infection	
Antibiotic therapy can be discontinued after 3 days of treatment if patient is afebrile for ≥48 hours and absolute neutrophil count (ANC) is ≥500 cells/mm^3 (0.5×10^9/L) for 2 consecutive days	A-2
If patient remains neutropenic, continue IV or oral antibiotics	A-2
Antibiotics should be continued in patients with profound neutropenia (ANC <100 cells/mm^3 [0.1×10^9/L]), mucous membrane lesions of mouth or GI tract, unstable vital signs, or other identified risk factors	A-2
Antibiotics can be stopped after 2 weeks in patients with prolonged neutropenia of unclear continued duration, no identified site of infection, and who can be closely observed	C-3
Alternatively, antibiotics can be discontinued after 4 days if no infection is documented and the patient shows no response to therapy	C-3
Management of Fungal Infections	
Suspected candidiasis:	
Lipid-associated amphotericin B (LAMB) or caspofungin[b]	A-1
Voriconazole	B-1
Fluconazole or itraconazole	B-1

Candidemia:	
An echinocandin[b] or LAMB	A-2
Fluconazole or voriconazole	B-3
Granulocyte Transfusions	
There are no specific indications for routine use of granulocyte transfusions	C-2
Colony-Stimulating Factors	
Colony-stimulating factors are not indicated for routine treatment of neutropenia in either febrile or afebrile patients	B-2
Prophylactic use of colony-stimulating factors should be considered for patients in whom the anticipated risk of fever and neutropenia is ≥20%	A-2
Antimicrobial Prophylaxis in Patients with Neutropenia	
Fluoroquinolone prophylaxis should be considered for high-risk patients with profound neutropenia (ANC <100 cells/mm^3 [0.1 × 10^9/L]) expected to last 7-10 days	Moderate, high
Antibacterial prophylaxis is not required in routinely recommended in low-risk patients who are expected to be neutropenic <7 days	A-3
Prophylaxis with trimethoprim–sulfamethoxazole should be administered to all patients at high risk for *Pneumocystis jirovecii* pneumonia, regardless of whether they are neutropenic	Strong, high
Prophylaxis with an oral triazole or parenteral echinocandin is recommended in high-risk patients, starting with induction chemotherapy and continued for duration of neutropenia	Moderate, intermediate
In HCT, prophylaxis with fluconazole, micafungin,[b] posaconazole, itraconazole, voriconazole, or LAMB is recommended during the period of risk of neutropenia	A-1 for fluconazole and micafungin,[b] all others B-2
In HCT recipients with graft-versus-host disease, or patients with neutropenia with hematologic malignancies, prophylaxis with posaconazole is recommended for prevention of invasive fungal infections	A-1
HSV-seropositive patients undergoing HCT or leukemia induction therapy should receive acyclovir prophylaxis during neutropenia, and for at least 30 days after HCT	Strong-high for prophylaxis, A-2 for duration
In HCT, prophylaxis with acyclovir should be administered during neutropenia and for at least 1 year afterward to prevent VZV infection or reactivation	A-2

[a]Cited evidence-based guidelines utilize different systems for grading the strengths of recommendation and quality of the associated evidence. Letter/number-based recommendations are from references 1 and 2; qualitative (descriptive) recommendations are from the other cited guidelines. Readers are advised to consult the original documents for full explanations of the grading systems and definitions used in individual guidelines.

[b]Expert opinion indicates all echinocandins are likely interchangeable and equally effective.

Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation for use, respectively; D = moderate evidence to support a recommendation against use. *Quality of evidence*: 1 = evidence from ≥1 properly randomized, controlled trial; 2 = evidence from ≥1 well-designed clinical trial without randomization, from cohort or case–control analytic studies, from multiple time series, or from dramatic results from uncontrolled experiments; 3 = evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Qualitative (descriptive) recommendations: *Strong, high*: strong recommendation based on high-quality evidence; *Strong, moderate*: strong recommendation based on moderate-quality evidence; *Strong, low*: strong recommendation based on low-quality evidence; *Moderate, high*: moderate recommendation based on high-quality evidence; *Moderate, intermediate*: moderate recommendation based on intermediate-quality evidence; *Moderate, low*: moderate recommendation based on low-quality evidence; *Weak, moderate*: weak recommendation, moderate quality evidence from RCTs with important limitations or exceptionally strong evidence from unbiased observational studies; *Weak, low*: weak recommendation, low-quality evidence for at least one critical outcome from observational studies, RCTs with serious flaws, or indirect evidence.

Data from references 1,2,4,6,22,23, and 25.

Fever in the neutropenic cancer patient is considered to be caused by infection until proved otherwise. High-dose broad-spectrum bactericidal, usually parenteral, empirical antibiotic therapy should be initiated at the onset of fever or at the first signs or symptoms of infection. Withholding antibiotic therapy until an organism is isolated results in unacceptably high mortality rates. Undiagnosed infection in immunocompromised patients can rapidly disseminate and result in death if left untreated or if treated improperly. For example, failure to initiate appropriate antibiotic therapy for *P. aeruginosa* bacteremia at the onset of fever in neutropenic cancer patients resulted in mortality rates of 15%, 48%, and 70% within 12, 24, and 48 hours, respectively.[1,4,27] Appropriate empirical antibiotic therapy is 70% to 90% effective at reducing early morbidity and mortality.[1,4,10] Therapy must be appropriate and initiated promptly, ideally within 1 hour after initial onset of fever. Antimicrobial therapy must likewise be initiated promptly in neutropenic patients with cancer who are afebrile but with other clinical signs and symptoms of possible infection.

When designing optimal empirical antibiotic regimens, clinicians must consider infection patterns and antimicrobial susceptibility trends in their respective institutions. Patient factors such as risk for infection, drug allergies, concomitant nephrotoxins, and previous antimicrobial exposure (including prophylaxis) must be considered.[1-4] Assessment of the patient's risk of infection will help determine the appropriate route and setting (eg, inpatient versus outpatient) for antibiotic administration (Fig. 145-1). Patients with neutropenia and fever can be divided into low- and high-risk groups for complications of severe infection. Risk stratification drives both type and setting of antimicrobial therapy. The Multinational Association for Supportive Care in Cancer (MASCC) risk-index score is recommended by many clinical guidelines to assess a patient's risk of complications.[1,2,4] Additional evaluation tools including Talcott groups and the Clinical Index of Stable Febrile Neutropenia (CISNE) score are also recommended.[2] These tools are provided in Table 145-3.

TABLE 145-3

Tools for Evaluating Febrile Neutropenia and Identifying Low-Risk Individuals for Outpatient Management

	Patient Characteristic	Score or Group
MASCC		
	Burden of febrile neutropenia: no or mild symptoms *OR* moderate symptoms	5 points
		3 points
	No hypotension (systolic blood pressure >90 mm Hg)	5 points
	No chronic obstructive pulmonary disease	4 points
	Solid tumor or hematologic malignancy with no previous fungal infection	4 points
	No dehydration requiring parenteral fluids	3 points
	Outpatient status	3 points
	Age <60 years	2 points
Maximum total score = 26 points; score ≥21 points indicates low risk for medical complications		
Talcott		
	Inpatients at time of fever onset	Group I
	Outpatients with acute comorbidity requiring, by itself, hospitalization	Group II
	Outpatients without comorbidity but with uncontrolled cancer	Group III
	Outpatients with cancer controlled and without comorbidity	Group IV
Groups I-III = high risk; Group IV = low risk		
CISNE		
	Eastern Cooperative Oncology Group performance status ≥2	2 points
	Stress-induced hyperglycemia	2 points
	Chronic obstructive pulmonary disease	1 point
	Chronic cardiovascular disease	1 point
	National Cancer Institute Common Toxicity Criteria mucositis of grade ≥2	1 point
	Monocytes <200/μL (0.2×10^9/L)	1 point

Maximum total score = 8 points; 0 points = low risk; 1-2 points = intermediate risk; ≥3 points = high risk. Suggested for use with patients with solid tumors who have undergone mild-to-moderate intensity chemotherapy and who appear to be clinically stable. Patients with CISNE score 0-2 would be considered candidates for

outpatient management.

Data from References 2,4.

Most experts agree that, in general, low-risk patients have an anticipated duration of neutropenia less than or equal to 7 days, are clinically stable, and have no or few comorbidities, and have no bacterial focus or systemic signs of infection other than fever. In contrast, high-risk patients are those with an anticipated duration of neutropenia greater than 7 days or profound neutropenia, are clinically unstable or have comorbid medical problems (eg, focal or systemic signs of infection, GI symptoms, nausea, vomiting, diarrhea, hypoxemia, and chronic lung disease), or have a high-risk cancer (eg, acute leukemia) and/or have undergone high intensity chemotherapy. High-risk patients (eg, MASCC less than 21, Talcott Groups I through III, CISNE ≥3) should be hospitalized for parenteral antibiotics whereas low-risk patients may be candidates for oral or outpatient antibiotics. Scoring tools such as MASCC must be used in conjunction with, not as a replacement for, careful clinical assessment of patients when selecting low-risk patients for oral outpatient management. Many additional patient factors (eg, worsening renal function, altered mental status, severe anemia, or thrombocytopenia) may increase risk of complications and potentially exclude patients from outpatient management of febrile neutropenia (see also "Oral Antibiotic Therapy for Management of Febrile Neutropenia" section below).[1,2,4,28]

The optimal antibiotic regimen for empirical therapy in febrile neutropenia remains controversial, but it is clear that no single regimen can be recommended for all patients. Because of their frequency and relative pathogenicity, *P. aeruginosa* and other gram-negative bacilli and staphylococci remain the primary targets of empirical antimicrobial therapy.[1,2,4] Although *P. aeruginosa* may be documented in fewer than 5% of bloodstream infections in the population of hospitalized patients, adequate antipseudomonal antibiotic coverage still must be included in empirical regimens because of the significant morbidity and mortality associated with this pathogen.[1,3,16] All empirical regimens must be carefully monitored and appropriately revised on the basis of documented infections, susceptibilities of bacterial isolates, development of more defined clinical signs and symptoms of infection, or a combination of these factors.

Although there are some differences among them, consensus guidelines generally recognize three different types of empirical parenteral antibiotic regimens: (a) monotherapy with an antipseudomonal β-lactam such as a cephalosporin (cefepime or ceftazidime), a carbapenem (imipenem–cilastatin or meropenem), or piperacillin–tazobactam; (b) two-drug combination therapy with an antipseudomonal β-lactam plus either an aminoglycoside or an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin); and (c) monotherapy or two-drug combination therapy as above, plus the addition of vancomycin (Fig. 145-1).[1,4] Each of these regimens has advantages and disadvantages, which are summarized in Table 145-4. There is no overwhelming evidence that any one of these regimens is superior to the others. The overall response to empirical antibiotic regimens in febrile neutropenic patients with cancer is approximately 70% to 90% regardless of whether a pathogen is isolated or which antimicrobial regimen is used.[1,3,4,10] Additionally, other alternative regimens may also be appropriate based on specific patient characteristics or susceptibilities of suspected pathogens within a specific institution.

TABLE 145-4

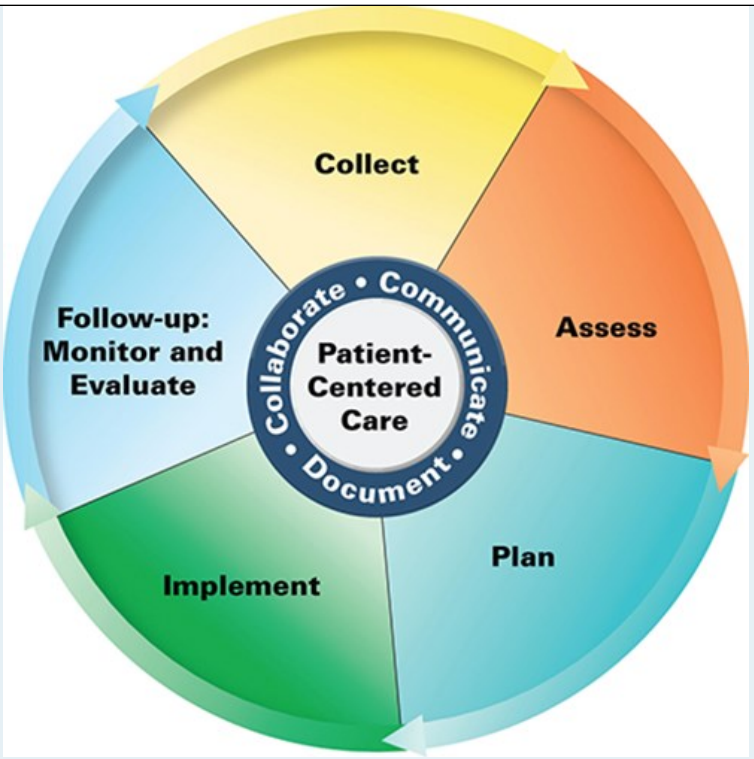
Comparative Advantages and Disadvantages of Various Antibiotic Regimens for Empiric Therapy of Febrile Neutropenic Patients with Cancer

Regimen	Potential Advantages	Potential Disadvantages
β-Lactam monotherapy (ceftazidime, cefepime, piperacillin–tazobactam, imipenem–cilastatin, or meropenem)	Efficacy comparable to combination regimens; decreased drug toxicities; ease of administration; possibly less expensive	Possibly less efficacy in profound neutropenia or prolonged neutropenia; limited gram-positive activity; no potential for additive/synergistic effects; increased selection of resistant organisms; increased colonization and superinfection rates
Antipseudomonal β-lactam plus aminoglycoside (eg, gentamicin or tobramycin + cefepime, ceftazidime, or piperacillin–tazobactam)	Traditional regimen, broad-spectrum coverage; optimal therapy of *Pseudomonas aeruginosa*; rapidly bactericidal; synergistic activity; decreased bacterial resistance; reduction of superinfections	Limited gram-positive activity; potential for nephrotoxicity; need for therapeutic monitoring of aminoglycoside concentrations
Antipseudomonal β-lactam plus fluoroquinolone (ciprofloxacin or higher-dose levofloxacin + ceftazidime, cefepime, or piperacillin–tazobactam)	Efficacy similar to other regimens when used in combination therapy; no cross-resistance with β-lactams; possibility for oral administration; may be useful in patients with renal impairment in whom aminoglycosides are undesirable	Marginal gram-positive activity; fluoroquinolones not recommended as monotherapy; resistance may develop rapidly
Empirical regimens containing vancomycin (added to antipseudomonal β-lactam ± aminoglycoside or fluoroquinolone)	Early effective therapy of gram-positive infections	No demonstrated benefit of vancomycin empirical therapy versus addition of vancomycin if needed later; increased risk of selection for vancomycin-resistant enterococci; risk of toxicities; excessive cost; need for therapeutic monitoring of vancomycin concentrations
Oral antibiotic regimens (eg, ciprofloxacin or levofloxacin + amoxicillin–clavulanate or clindamycin)	Efficacy comparable with parenteral therapy in low-risk patients; less expensive; reduced exposure of patients to nosocomial pathogens	Least studied treatment approach; less potent than parenteral antibiotics; requires compliant patient with 24-hour access to medical care should clinical instability develop

Data from references 1-5,10,27,28.

PATIENT CARE PROCESS

Patient Care Process for the Treatment of Suspected Infection in an Immunocompromised Host



Collect

- Patient characteristics (eg, age, sex, height, weight)
- Patient medical history (oncologic, surgical, vaccines, previous infections, time since transplant/engraftment/last oncologic regimen or transplant engraftment)
- Social history (eg, drug/ethanol use), travel history (eg, endemic exposures)
- Current medications (eg, antimicrobial prophylaxis/treatment, immunomodulating agents [immunosuppressive or immunostimulatory])
- Prior medications (eg, antimicrobial, oncologic, immunomodulating) and future planned medications (eg, life-saving oncologic or immunomodulating regimens)
- Objective Data

  Mean arterial blood pressure (MAP), heart rate (HR), respiratory rate (RR), O_2-saturation, altered mental status (AMS), urine output (UO), skin turgor/integrity

  Labs including white blood cells (WBC) with differential, absolute neutrophil count (ANC) and trends, serum creatinine (SCr), lactate, liver function tests (LFT), blood glucose

  Culture data (eg, bacterial, fungal, viral), microbiologic diagnostic tests (eg, procalcitonin, galactomannan, β-D-glucan, viral polymerase chain reaction tests, infectious serologies)

  Presence of central, peripheral, urinary catheters, and indwelling ports

Assess

- For febrile neutropenia: assess risk of infectious complications for possible outpatient management (see Table 145-3) including logistical barriers (eg, access to care, compliance, support)

- Hemodynamic/clinical stability and evidence of organ malperfusion (eg, MAP <65 mm Hg, HR >100 bpm, RR>22, AMS, decreased UO, renal dysfunction)
- Evidence of infection at common sites (see Clinical Presentation boxes: "Febrile Neutropenia" and "Infection in Solid Organ Transplant Patients")
- Assess risk of infection based on duration/degree of neutropenia or magnitude of immunosuppression
- Assess need for colony-stimulating factors (CSF) (see Table 145-8)
- Assess risk for infection with specific pathogens (see Table 145-1)
- Assess contraindications to specific antimicrobial therapy (eg, allergies, drug-drug/disease interactions)
- Assess previous and current culture results and susceptibilities

Plan*

- Antimicrobial regimen including specific antimicrobial(s), dose, route, frequency, and duration (see Figs. 145-1, 145-2; Tables 145-4, 145-5, and 145-7)
- Monitoring parameters including efficacy (eg, resolution of infectious symptoms, fever, ANC) and safety (eg, antimicrobial side effects, *Clostridioides difficile*, CNS toxicity)
- Patient education if treated outpatient (eg, self-monitoring, when/how to seek help, adherence)
- Referrals to other providers when appropriate (eg, infectious disease specialist)

Implement*

- Provide patient and caregiver education regarding when/how to seek advance medical attention
- Provide integrated health professionals, patient and family education (eg, expected outcomes/goals of therapy, therapeutic drug monitoring, avoidance of exposures)

Follow-up: Monitor and Evaluate*

- De-escalation of empiric antimicrobial regimens to targeted therapy (see Table 145-7)
- Resolution of infectious symptoms (see also Figs. 145-1 and 145-2)
- Presence of adverse effects specific to the antimicrobial regimen
- Presence of drug-drug interactions potentially requiring changes in drug regimens or additional therapeutic drug monitoring
- Patient adherence to outpatient antimicrobial plan
- Therapeutic drug levels to adjust antimicrobial therapy (see Table 145-6)

****Collaborate with patient, caregivers, and other healthcare professionals.***

β-Lactam Monotherapy

Monotherapy with an antipseudomonal β-lactam is recommended by IDSA 2010 and NCCN 2021 guidelines as initial parenteral therapy for management of febrile neutropenia without suspected or proven resistant organisms or complications (eg, pneumonia, hypotension, and vascular

access infection).[1,4] β-Lactam antibiotics that have been evaluated as monotherapy for management of febrile episodes in neutropenic cancer patients include antipseudomonal cephalosporins (ceftazidime and cefepime), piperacillin–tazobactam, and antipseudomonal carbapenems (imipenem–cilastatin and meropenem).[1,4] Three different meta-analyses assessing as many as 46 clinical trials involving more than 7,600 patients found no significant differences overall between monotherapy and combination therapy (β-lactam/aminoglycoside) in rates of survival, treatment response, and bacterial/fungal superinfections.[4,29] Monotherapy with antipseudomonal β-lactams is therefore recommended by treatment guidelines and routinely used for initial treatment.[1,4] Institutional susceptibility patterns and patient characteristics should drive drug selection for the management of individual patients with febrile neutropenia.[1,4]

Ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam, and cefiderocol have appropriate overall spectrum of antibacterial activity with good activity against *P. aeruginosa* and other gram-negative organisms as well as many gram-positive pathogens. Neither the 2021 NCCN nor the 2010 IDSA consensus guidelines specifically recommend these agents due to a lack of supportive clinical evidence at the time the guidelines were written.[1,4] These agents are also considered to be too broad-spectrum and expensive for routine empiric use. However, they may be considered reasonable treatment options in selected patients at high risk for, or with previous history of, infection with multidrug-resistant (MDR) pathogens or in institutions with high rates of infection with MDR pathogens in certain high-risk patients.

Use of monotherapy has several potential advantages and disadvantages (see Table 145-4). Perhaps the most common concerns are those regarding the selection of resistant strains of organisms, such as *P. aeruginosa*, *Klebsiella-Enterobacter* group, and *Serratia* spp., through expression of ESBL and type 1 β-lactamases, especially with ceftazidime.[1,4,10,14] Activity against gram-positive organisms such as coagulase-negative staphylococci, MRSA, enterococci (including VRE), penicillin-resistant *S. pneumoniae*, and some strains of viridans streptococci is poor with some single β-lactams, but cefepime and antipseudomonal carbapenems have good activity against most viridans streptococci and pneumococci.[1,4] Although ceftazidime has been widely studied and used for treatment of febrile neutropenia, newer agents may be more effective owing to ceftazidime's susceptibility to β-lactamase induction and lower activity against gram-positive organisms.[1,4,10,14,30] Ertapenem, a carbapenem, and ceftaroline, a cephalosporin active against MRSA, have excellent activity against many gram-negative organisms but should not be routinely used in the empirical treatment of febrile neutropenia due to their weak activity against *P. aeruginosa*. For the same reason, broad-spectrum tetracycline derivatives (eg, tigecycline, eravacycline, omadacycline) are not acceptable options for empiric monotherapy in most patients.

As with all empirical antibiotic regimens, patients receiving monotherapy should be monitored closely for treatment failure, secondary infections, and development of resistance. Use of monotherapy may not be appropriate in institutions with high rates of gram-positive infections or infections caused by relatively resistant gram-negative pathogens such as *P. aeruginosa* and *Klebsiella-Enterobacter*. The carbapenems are less susceptible to inducible β-lactamases and often may be used effectively in these institutions. Overall, similar efficacy has been observed with monotherapy with antipseudomonal β-lactams compared to aminoglycoside combination therapy for treatment of *P. aeruginosa* infections.[1,4,29]

Aminoglycoside Plus Antipseudomonal β-Lactam

Regimens consisting of an aminoglycoside plus an antipseudomonal β-lactam traditionally have been the most commonly used for empirical treatment of febrile neutropenia, although many such regimens may lack adequate gram-positive activity (see Table 145-4).[1,4] This relative lack of activity remains a concern because of the increasing frequency of gram-positive infections. The choice of aminoglycoside and β-lactam for inclusion in empirical regimens should be based on institutional epidemiology and antimicrobial susceptibility patterns. Similar efficacy is observed with an antipseudomonal β-lactam in combination with an aminoglycoside.[1,4,29]

Combinations of broad-spectrum β-lactams and aminoglycosides may provide improved activity (eg, synergy activity against bacteria commonly involved in neutropenic infections). The exact role of synergy in the outcome of patients with febrile neutropenia treated with empirical antibiotic therapy is somewhat controversial, particularly in light of the efficacy of single-drug regimens and nephrotoxicity associated with aminoglycosides.[29,30] Nevertheless, combinations of antibiotics appear to be beneficial in patients with persistent profound neutropenia.

Aminoglycoside toxicity may be a concern in patients receiving these regimens who are already receiving other nephrotoxic drugs, such as cisplatin and cyclosporine. Administration of aminoglycosides in large single daily doses (once-daily dosing) may be as effective, less costly, and no more toxic than conventional dosing methods. Although once-daily aminoglycoside dosing regimens appear to be safe and effective in these patients, standard dosing regimens are recommended for infections where data are not sufficient to recommend once-daily dosing (eg, endocarditis).[1,4]

Fluoroquinolones as a Component of Empirical Regimens

Because the fluoroquinolone antibiotics have broad-spectrum activity (particularly against gram-negative pathogens), rapid bactericidal activity, and favorable pharmacokinetic and toxicity profiles, these agents have been investigated as empirical therapy for febrile neutropenia. Ciprofloxacin is the preferred agent for use in this clinical setting because of its relatively better activity against *P. aeruginosa* and more extensive evidence-based support for its use.[1,4] Response rates to quinolone-containing combination regimens are comparable to those obtained with the other regimens described previously.[1,3,4] Ciprofloxacin is not recommended for monotherapy, however, because of its relatively poor activity against gram-positive pathogens, particularly streptococci, and variable response rates in clinical studies.[1,4] Although delafloxacin has a spectrum of antibacterial activity that seems favorable for febrile neutropenia, no data currently exist for this indication and its use is not recommended. Fluoroquinolones should also not be used as empirical therapy in patients who have received quinolones as infection prophylaxis because of the risk of drug resistance.[1,4] Rates of fluoroquinolone resistance are increasing, and streptococcal treatment failures are a concern.[12,14,16] Although fluoroquinolones are not generally considered first-line empirical therapy for inpatient use, they may be useful as one component of combination regimens in patients with allergies or other contraindications to first-line agents.[1,4]

Empirical Regimens Containing Vancomycin

The inclusion of vancomycin in initial empirical therapy of febrile neutropenic patients with cancer is not currently recommended by IDSA 2010 or NCCN 2021 guidelines unless the patient has specific risk factors; however, this remains an ongoing debate. This controversy continues because of the high incidence of gram-positive infections in this population, particularly MRSA. One approach is to include vancomycin in the initial empirical antibiotic regimen, thereby providing early effective treatment of possible gram-positive infections. Inclusion of vancomycin in initial empirical regimens may be appropriate because of higher rates of MRSA infections as well as aggressive chemotherapy regimens causing significant mucosal damage that increases the risk for streptococcal infections. Decreased mortality from penicillin-resistant viridans streptococcal infections has been observed when vancomycin was included in initial therapy.[1,6,30] A second approach is to withhold vancomycin from initial empirical regimens, later adding the drug if gram-positive organisms are isolated from cultures or if there is clinical deterioration. Support for both these approaches can be found in the medical literature.[1,4,30,31] Prospective studies and multiple meta-analyses have failed to document increased response rates or decreased mortality with the routine addition of vancomycin to initial empirical regimens, provided that vancomycin can be added later as needed.[1,4,30,31] In addition to increased costs of therapy, vancomycin was also associated with increased adverse effects, including nephrotoxicity.[4] Finally, concerns remain regarding selection of resistant gram-positive bacteria such as VRE with excessive vancomycin use.[1,4,26,32]

Vancomycin is recommended for inclusion in initial empirical regimens only in patients at high risk for gram-positive infection, particularly due to MRSA and coagulase-negative staphylococci (including patients with evidence of infection of central venous catheters and other indwelling lines), high risk for viridans streptococcal infection due to severe mucositis, or pneumonitis or soft tissue infection in hospitals with high rates of MRSA infections.[1,4,10,30] Rates of β-lactam resistance among viridans streptococci range up to 25%.[1,4] Empirical vancomycin use may be justified in institutions using empirical or prophylactic antibiotic regimens without good activity against streptococci (eg, ciprofloxacin) and in patients known to be colonized with MRSA or β-lactam–resistant pneumococci. In patients with preliminary culture results indicating gram-positive infection, empirical vancomycin is appropriate while the susceptibility results are pending. Lastly, empirical use of vancomycin may be recommended in patients with hypotension or other evidence of cardiovascular impairment or sepsis without an identified pathogen.[1,4] If empirical vancomycin therapy is initiated and no evidence of gram-positive infection is found after 48 to 72 hours, the drug should be discontinued.[1,4] Continuing vancomycin when not warranted results in higher costs, more toxicities, and greater risk of development of VRE.[1,4,32] Of note, augmented renal clearance occurs with some frequency (approximately 16%) in patients with febrile neutropenia and has been associated with significantly higher rates of subtherapeutic vancomycin concentrations.[33] Clinicians should be alert to the need for therapeutic drug monitoring of vancomycin in patients with febrile neutropenia and should carefully monitor patient response to therapy in those receiving vancomycin or other renally excreted antimicrobials.[27,33,34]

Other antimicrobial agents, such as quinupristin–dalfopristin, linezolid, daptomycin, telavancin, and ceftaroline, should be reserved for documented infections caused by multiresistant gram-positive pathogens that are not susceptible to, or are unresponsive to, vancomycin. The role of these drugs in the routine treatment of febrile neutropenia is undetermined, and linezolid is associated with risk of myelosuppression.[1,4]

Oral Antibiotic Therapy for Management of Febrile Neutropenia

An individual patient's risk for complications of severe infection determines appropriate antibiotic therapy and the proper setting for administration (see Table 145-4).[1-3,5] Risk stratification is based on several parameters (eg, MASCC score or other tools previously mentioned) as well as response to empirical antimicrobial therapy if IV therapy is initially given.[1] Benefits of oral therapy on an outpatient basis include increased convenience and quality of life for patients and caregivers and reduced exposure to multidrug-resistant institutional pathogens.[1,2,4] Outpatient therapy of low-risk patients is common practice in most institutions. Careful patient selection obviously is required for such management strategies. Important criteria include patient and provider comfort, a history of protocol and medication compliance, caregiver support and transportation available 24 hours per day, and close proximity (less than 1 hour or less than 30 miles [48 km]) to appropriate medical care in the event of failure to respond to outpatient antibiotic therapy.[2] If a patient qualifies for oral therapy based on clinical and other factors, the first dose of oral regimen should be given in the clinic or hospital and the patient observed for at least 4 hours to ensure tolerance and clinical stability.

Because of the excellent spectrum of activity and favorable pharmacokinetics of currently available oral antibiotics, particularly the fluoroquinolones, oral antibiotics have an important role in the management of selected patients. In patients at low risk for severe or complicated bacterial infection, empirical therapy with broad-spectrum oral antibiotic agents achieves similar patient outcomes as parenteral antibiotics, with response rates of 77% to 95%.[1,3,4,28] Patients judged to be low risk with reliable follow-up may thus be appropriate candidates for oral antibiotic therapy administered on an outpatient basis.[1-4,28] Ciprofloxacin or levofloxacin in combination with amoxicillin–clavulanate (or clindamycin for penicillin-allergic patients) for enhanced gram-positive coverage has been most commonly studied for outpatient therapy in low-risk patients and is recommended by IDSA and NCCN guidelines.[1,2,4] In general, monotherapy with ciprofloxacin should be avoided due to relatively poor gram-positive activity. Levofloxacin has been used as monotherapy for outpatient treatment of low-risk patients, due to enhanced gram-positive activity, and is formally recommended by NCCN guidelines, although the IDSA guidelines recommend only combination therapy initially. If used, only the higher-dose levofloxacin 750 mg regimen should be administered in order to provide adequate activity against organisms such as *S. aureus* and *P. aeruginosa*.[1,4] Moxifloxacin has also been endorsed as a monotherapy option by NCCN guidelines; however, the lack of *P. aeruginosa* activity warrants special consideration.[4]

In patients at low risk for severe bacterial infection who were initiated on IV antibiotics, oral antibiotics may play a role in step-down therapy. Carefully selected patients with neutropenia may be safely switched from broad-spectrum parenteral therapy to oral antibiotic regimens with response rates comparable to patients remaining on IV therapy.[1,2,4,28] Patient selection criteria generally include defervescence within 72 hours of initiation of parenteral therapy, hemodynamic stability, absence of positive cultures or a discernible site of infection, and ability to take oral medications. Many of these patients are able to complete their course of therapy at home.[1,2,4,28] Changing parenteral antimicrobials to oral regimens in carefully selected patients is an acceptable practice and allows for less expensive hospitalizations and earlier patient discharges.[2]

Antimicrobial Therapy After Initiation of Empirical Therapy

6 After initiation of empirical antimicrobial therapy (Table 145-5), judicious assessment of febrile neutropenic patients with cancer is mandatory to evaluate response, clinical status, laboratory data, and potential need for therapy adjustments. After 2 to 4 days of empirical antimicrobial therapy, the clinical status and culture results should be reevaluated to determine whether therapeutic modifications are necessary (Fig. 145-2). Modifications of antimicrobial therapy should be based on clinical and laboratory data; antibiotic therapy should be optimized based on culture results. However, during periods of neutropenia, patients generally should continue to receive broad-spectrum therapy because of risk of secondary infections or breakthrough bacteremias when antimicrobial coverage is too narrow.[1,4] The treatment duration for a documented infection should be appropriate for the particular organism and site, and should continue for at least the duration of neutropenia (until ANC greater than or equal to 500 cells/mm^3 [0.5 × 10^9/L]) or longer if clinically necessary.

TABLE 145-5

Drug Dosing Table

Drug	Brand Name	Usual Dosing Regimen	Special Population Dose	Other

Amoxicillin–clavulanate	Augmentin®	875 mg orally every 12 hours		In combination with ciprofloxacin for outpatient treatment
Ceftazidime	Fortaz®	2 g IV every 8 hours		
Ceftazidime–avibactam	Avycaz®	2.5 g IV every 8 hours, administered over 2 hours		Not studied in febrile neutropenia, but spectrum is appropriate if high rates of MDR gram-negative bacteria (esp. CRE)
Cefepime	Maxipime®	2 g IV every 12 hours		
Ceftaroline	Teflaro®	600 mg IV every 12 hours		Activity against methicillin-resistant *S. aureus*
Ceftolozane–tazobactam	Zerbaxa®	1.5 g IV every 8 hours		Not studied in febrile neutropenia, but spectrum is appropriate if high rates of MDR gram-negative bacteria
Piperacillin–tazobactam	Zosyn®	3.375-4.5 g IV every 6 hours		
Imipenem–cilastatin	Primaxin®	500 mg IV every 6 hours		
Meropenem	Merrem®	1 g IV every 8 hours		
Meropenem-vaborbactam	Vabomere®	4 g IV every 8 hours, administered over 3 hours		Not studied in febrile neutropenia, but spectrum is appropriate if high rates of MDR gram-negative bacteria (esp. CRE)
Doripenem	Doribax®	500 mg IV every 8 hours		
Tobramycin	Nebcin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours. Alternative: 5-7 mg/kg IV once daily		Traditional dosing: Guided by measured serum concentrations
Gentamicin	Garamycin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours. Alternative: 5-7 mg/kg IV once daily		Traditional dosing: Guided by measured serum concentrations
Amikacin	Amikin®	Traditional: 7.5 mg/kg IV every 12 hours. Alternative: 15-20 mg/kg IV once daily		Traditional dosing: Guided by measured serum concentrations
Ciprofloxacin	Cipro®	400 mg IV every 8 hours	Outpatient treatment: 750 mg orally	May be given orally in low-risk patients in

			every 12 hours	combination with amoxicillin–clavulanate
Levofloxacin	Levaquin®	750 mg IV once daily	Outpatient treatment: 750 mg orally once daily	May be given orally in low-risk patients
Moxifloxacin	Avelox®	400 mg IV/orally once daily	Outpatient treatment: 400 mg orally once daily	For select outpatient use, lacks *P. aeruginosa* activity
Delafloxacin	Baxdela®	300 mg IV or 450 mg orally every 12 hours		Activity includes methicillin-resistant *S. aureus* and *P. aeruginosa*; not studied in febrile neutropenia, but spectrum is appropriate
Vancomycin	Vancocin®	30-40 mg/kg/day IV in two divided doses administered every 12 hours		For methicillin-resistant *S. aureus* infection; dosing guided by serum concentrations to achieve trough of 15-20 mg/L (10-14 µmol/L)
Nafcillin	Nafcil®	1-2 g IV every 6 hours		For methicillin-susceptible *S. aureus* infection
Daptomycin	Cubicin®	Skin/soft tissue infections: 4 mg/kg IV once daily; bacteremia: 6 mg/kg IV once daily		For infection (esp. bacteremia) due to methicillin-resistant *S. aureus*, vancomycin-resistant enterococci
Linezolid	Zyvox®	600 mg IV or orally every 12 hours		For infection due to vancomycin-resistant enterococci
Ampicillin	Omnipen®, Polycillin®, Principen®	1-2 g IV every 4 hours		In combination with gentamicin for *Listeria* infection
Erythromycin	E-mycin®, Erythrocin®	1-2 g IV every 4-6 hours		For *Legionella* infection
Clotrimazole	Mycelex Troche®	10 mg orally five times daily		Administered as oral troche; dissolve in mouth
Nystatin	Nystatin Oral®	100,000 units orally every 4-6 hours		Administered as suspension; swish and swallow
Fluconazole	Diflucan®	800 mg IV or orally once, then 400-800 mg IV or orally once daily	Prophylaxis of *Candida* infection: 400 mg IV or orally once daily	
Itraconazole	Sporanox®	200-400 mg/day orally divided twice daily	Prophylaxis of *Candida* infection: 200 mg orally twice daily	Therapeutic drug monitoring recommended
Voriconazole	Vfend®	6 mg/kg IV every 12 hours	Prophylaxis in high-risk patients: 200	Therapeutic drug monitoring

		for two doses, then 4 mg/kg IV or 200 mg orally every 12 hours	mg orally twice daily	recommended
Posaconazole	Noxafil®	Suspension: 800 mg/day orally in two to four divided doses Oral DR or IV: 300 mg every 12 hours × 2 doses, then 300 mg daily	Prophylaxis in high-risk patients: 200 mg orally three times daily	DR formulation has improved bioavailability, administered with food. Suspension: administer with full meal or enteral nutritional supplements. Therapeutic drug monitoring recommended
Isavuconazonium	Cresemba®	372 mg IV/oral every 8 hours × 6 doses, then 372 mg daily		Limited clinical experience
Lipid-associated amphotericin B (LAMB)	AmBisome®, Abelcet®	3-5 mg/kg IV once daily	Prophylaxis in high-risk patients: 1 mg/kg IV once daily	
Flucytosine	Ancobon®	25 mg/kg/day orally every 6 hours		In combination with LAMB for cryptococcal meningitis. Therapeutic drug monitoring recommended
Caspofungin	Cancidas®	70 mg IV once, then 50 mg IV once daily		
Micafungin	Mycamine®	100 mg IV once daily	Prophylaxis in high-risk patients: 50 mg IV once daily	
Anidulafungin	Eraxis®	200 mg IV once, then 100 mg IV once daily		
Acyclovir	Zovirax®	5-10 mg/kg IV every 8 hours, or 800 mg orally two to five times daily	Prophylaxis of HSV or VZV: 800-1,600 mg orally twice daily; CMV prophylaxis in allogeneic HCT: 800 mg orally four times daily; HSV or VZV encephalitis: 10 mg/kg IV every 8 hours	
Valacyclovir	Valtrex®	1 g orally every 8 hours	Prophylaxis of HSV or VZV: 500 mg orally two or three times daily; CMV prophylaxis in allogeneic HCT: 2 g orally four times daily	
Ganciclovir	Cytovene®	CMV treatment or preemptive therapy: 5 mg/kg IV every 12 hours	CMV prophylaxis: 5-6 mg/kg IV daily 5 days/wk	
Valganciclovir	Valcyte®	CMV preemptive therapy: 900 mg orally every 12 hours for 2 weeks	CMV prophylaxis: 450-900 mg orally daily	

Foscarnet	Foscavir®	CMV treatment: 90 mg/kg IV every 12 hours for 2 weeks; CMV preemptive therapy: 60 mg/kg IV every 12 hours for 2 weeks	CMV prophylaxis: 60 mg/kg IV two or three times daily for 7 days, then 90-120 mg/kg IV daily	
Letermovir	Prevymis®	480 mg IV or orally once daily		For prophylaxis of CMV infection and disease in CMV-seropositive allogeneic HCT recipients, used through day 100 post-transplant
CMV hyperimmune globulin	Cytogam®	400 mg/kg IV every other day for three to five doses		Consider as adjunct to ganciclovir or foscarnet for treatment of CMV pneumonia; IVIG considered equally effective
Trimethoprim–sulfamethoxazole	Bactrim®, Cotrimoxazole®	Treatment of *P. jirovecii*: 15-20 mg/kg/day IV divided every 6 hours[b]	Prophylaxis of *P. jirovecii*: 160 mg/800 mg orally daily or three times per week	
Atovaquone	Mepron®	Treatment of *P. jirovecii*: 750 mg orally every 12 hours	Prophylaxis of *P. jirovecii*: 1,500 mg/day orally in one or two divided doses every 12 hours	
Pentamidine	Pentam®	Treatment of *P. jirovecii*: 4 mg/kg IV once daily	Prophylaxis of *P. jirovecii*: 300 mg by inhalation once monthly	
Clindamycin	Cleocin®	450-600 mg orally every 6 hours		In combination with primaquine for *P. jirovecii*, or with pyrimethamine for toxoplasmosis
Primaquine	Aralen®, Primaquine®	15 mg orally once daily		In combination with clindamycin for *P. jirovecii*
Dapsone	Dapsone®	100 mg orally once daily		In combination with trimethoprim for *P. jirovecii*
Trimethoprim	Triprim®	15-20 mg/kg/day orally divided every 6 hours		In combination with dapsone for *P. jirovecii*
Pyrimethamine	Daraprim®	50-100 mg orally once daily[c]		In combination with sulfadiazine for toxoplasmosis
Sulfadiazine	Sulfadiazine®	1 g orally every 4-6 hours		In combination with pyrimethamine for toxoplasmosis
Thiabendazole	Mintezol®	25 mg/kg orally every 12 hours (maximum 3 g/day)		For *Strongyloides* and other intestinal worm infections

In patients who become afebrile after 2 to 4 days of therapy with no infection identified, it is generally optimal to continue antibiotic therapy until neutropenia has resolved (ANC greater than or equal to 500 cells/mm^3 [0.5×10^9/L]). Some clinicians switch therapy to an oral regimen (eg, ciprofloxacin plus amoxicillin–clavulanate) after 2 days of IV therapy in low-risk patients who become afebrile and have no evidence of infection. In high-risk patients, parenteral antibiotic regimens should be continued until resolution of neutropenia.[1,4] However, in afebrile patients with prolonged neutropenia but no signs or symptoms of infection, consideration can be given to discontinuing antibiotic therapy or switching to fluoroquinolone prophylaxis (discussed in "Prophylaxis of Infections in Neutropenic Patients with Cancer" below), provided that patients can be observed carefully and have ready access to medical care.

The optimal management of patients who remain febrile in the absence of microbiologic or clinical documentation of infection remains highly controversial. Persistently febrile patients should be evaluated carefully, but modifications generally are not made to initial antimicrobial regimens within the first 2 to 4 days of therapy unless there is evidence of clinical deterioration (see Fig. 145-1).[1,3,4] It is important to note that the persistence of fever does not necessarily mean failure of a given antimicrobial regimen; up to 25% of patients with neutropenia have fever due to noninfectious causes.[7] This is particularly true if patients are otherwise clinically stable. Fever after two or more days of antibiotic therapy can be due to a number of causes, including nonbacterial infection, resistant bacterial infection or infection slow to respond to therapy, emergence of a secondary infection, inadequate drug concentrations, drug fever, infection at an avascular site (eg, catheter infection or abscess), or noninfectious causes such as tumor or administration of blood products.[1,3,4] Patients with documented infection who are receiving appropriate antimicrobial therapy (based on in vitro susceptibility tests) often remain febrile until resolution of neutropenia occurs. Therefore, the same antibiotic regimen can be continued in patients who remain febrile despite 2 to 4 days of antibiotic therapy but are otherwise clinically stable, especially if neutropenia is expected to resolve within 1 week. However, antibiotic regimens may require modification in patients experiencing toxicities (Table 145-6) as well as in patients with evidence of progressive disease, clinical instability, or documentation of an organism not covered by the initial regimen.[1,3,4] If not already part of the regimen, vancomycin should be considered as warranted by clinical and laboratory findings. However, if vancomycin was included in the initial empirical regimen and the patient is still febrile after 2 to 3 days of therapy without isolating a gram-positive pathogen, discontinuation of vancomycin should be considered to reduce the risk of toxicities or resistance.[1,4]

TABLE 145-6

Drug Monitoring of Selected Antimicrobials for Febrile Neutropenia, HCT, and SOT

Drug	Adverse Reaction	Monitoring Parameters	Comments
Antibacterial Agents			
Aminoglycosides (Tobramycin, Gentamicin, Amikacin)	Nephrotoxicity	Serum creatinine, urine output, serum concentrations	Extended-interval ("once daily") dosing potentially associated with less renal toxicity, similar efficacy to traditional dosing. Goal trough concentration <1 mcg/mL (mg/L; 2 μmol/L) during extended-interval dosing
Imipenem–cilastatin	CNS toxicities, seizures	Serum creatinine, mental status, CNS function	Increased incidence with higher dose, failure to adjust dose/interval for reduced renal function. Increased risk compared to meropenem or doripenem
Linezolid	Myelosuppression, thrombocytopenia, optic/peripheral neuropathy, serotonin	CBC, vision changes, serum lactate, heart rate,	Myelosuppression and neuropathy more common with prolonged use. Short course unlikely to affect marrow recovery in HCT. Weak MAO inhibitor, serotonin syndrome possible with other serotonergic drugs such as SSRIs and SNRIs

	syndrome	blood pressure, temperature, myoclonus	
Nafcillin	Interstitial nephritis	Serum creatinine, urine output	Reversible, requires switch to alternative β-lactam
Vancomycin	Nephrotoxicity, infusion reactions	Serum creatinine, urine output, blood pressure, heart rate, serum concentrations	Dose adjustment required for renal dysfunction. Pretreatment and slow infusion may decrease incidence of infusion reaction. Goal trough concentration 15-20 mcg/mL (mg/L; 10-14 µmol/L) for serious infections
Antifungal Agents			
Amphotericin B (lipid-associated)	Nephrotoxicity, hepatotoxicity, electrolyte disturbances, infusion reactions	Serum creatinine, electrolytes, LFTs, blood pressure, heart rate	Liposomal preparations associated with less renal toxicity, similar efficacy to standard preparation. Electrolyte disturbances occur before creatinine alterations. Pretreatment and slow infusion may decrease incidence of infusion reaction
Flucytosine	Myelosuppression, GI toxicities	CBC, GI symptoms, serum creatinine, flucytosine serum concentrations	Dose adjustment required for renal dysfunction. Goal serum concentrations are peak <100 mcg/mL (mg/L; 775 µmol/L) and trough 20-40 mcg/mL (mg/L; 155-310 µmol/L)
Posaconazole	Hepatotoxicity, rash; interactions with CYP450 3A4	LFTs, skin, posaconazole serum concentrations	Poor absorption with suspension, goals of >1 mcg/mL (mg/L; 1.4 µmol/L) for treatment and >0.7 mcg/mL (mg/L; 1 µmol/L) for prophylaxis. Parenteral formulation contains SBECD, not recommended for patients with CrCL<50 mL/min (0.83 mL/s). Multiple interactions with drugs metabolized by CYP 3A4, including immunosuppressants; close monitoring needed
Voriconazole	Mental status changes, headache, hallucinations, visual disturbances, hepatotoxicity, QTc prolongation; interactions with CYP450 2C9, 2C19, and 3A4	Mental status, visual function, LFTs, ECG, voriconazole serum concentrations	Mental status/visual changes associated with elevated troughs >5.5 mcg/mL (mg/L; 16 µmol/L); goal trough 1-5.5 mcg/mL (mg/L; 3-16 µmol/L) for treatment and prophylaxis, target trough of >2 mcg/mL (mg/L; 6 µmol/L) in disease with poor prognosis. Parenteral formulation contains SBECD, not recommended for patients with CrCL<50 mL/min (0.83 mL/s). Multiple interactions with drugs metabolized by CYP enzymes, including immunosuppressants; close monitoring needed
Antiviral Agents			

Foscarnet	Nephrotoxicity, hypocalcemia	Serum creatinine, electrolytes	IV hydration prior to administration. Dose adjustment required for renal dysfunction
Ganciclovir, valganciclovir	Myelosuppression, thrombocytopenia	CBC, serum creatinine	Dose adjustment required for renal dysfunction
Antiprotozoal/Antiparasitic Agents			
Dapsone	Hemolytic anemia, hypersensitivity (fever, jaundice, eosinophilia), peripheral neuropathy	CBC, bilirubin, LFTs, muscle strength, G6PD testing before use	Higher incidence of hemolytic anemia in G6PD-deficient patients
Pentamidine (IV)	Nephrotoxicity, leukopenia, hypotension, QTc prolongation, pancreatitis, hypo/hyperglycemia	Serum creatinine, serum blood glucose, blood urea nitrogen, CBC, blood pressure, heart rate; ECG	Adequate hydration recommended
Primaquine	Hemolytic anemia	CBC, bilirubin, G6PD testing before use	Avoid use in G6PD-deficient patients (hemolytic anemia)
Pyrimethamine	Bone marrow suppression	CBC	Folinic acid 5-10 mg/day often used for prevention of bone marrow toxicity
Trimethoprim–sulfamethoxazole	Myelosuppression, hyperkalemia, rash	Serum creatinine, electrolytes, CBC, skin	Dose adjustment required for renal dysfunction

CBC, complete blood count; ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; HCT; hematopoietic cell transplantation; LFT, liver function test; MAO, monoamine oxidase; PFT, pulmonary function test; QTc, corrected Q-T interval; SBECD, sulfobutylether-β-cyclodextrin; SOT, solid-organ transplantation; SSNRI, selective serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Therapeutic drug monitoring recommendations from Reference 30.

Initiation of Antifungal Therapy

Patients with neutropenia who remain febrile despite more than 4 to 7 days of broad-spectrum antibiotic therapy are candidates for antifungal therapy. A high percentage of febrile patients who die during prolonged neutropenia have evidence of invasive fungal infection on autopsy, even though many had no evidence of fungal disease before death.[16] Persistence of fever or development of a new fever during broad-spectrum antibiotic therapy may indicate the presence of a fungal infection, most commonly due to *Candida* or *Aspergillus* spp.[15,19,22] Blood cultures are positive in fewer

than 50% of patients with neutropenia and invasive fungal infections.[21,22] Rapid, sensitive diagnostic tests for fungi such as serum β-D-glucan, galactomannan, or fungal DNA assays are available and may be considered in higher-risk patients, however, delaying initiation of antifungal therapy pending results of these tests or isolation of fungal organisms may be associated with high morbidity and mortality. The empirical addition of antifungal therapy is thus justified in this clinical setting.[1,4] Empirical antifungal therapy should be initiated after 4 to 7 days of broad-spectrum antibiotic therapy in persistently febrile patients if the duration of continued neutropenia is expected to be greater than 1 week. Administered doses must be adequate to treat undiagnosed fungal infection and prevent fungal superinfection in high-risk patients with febrile neutropenia.[1,4,21]

Evidence-based recommendations from published guidelines for management of suspected or documented fungal infections in patients with neutropenia are summarized in Table 145-2.[21,25,34] Empirical coverage for both *Candida* spp. and *Aspergillus* should be considered because these organisms are responsible for more than 90% of fungal infections in patients with neutropenia and cancer.[6,15,19,22] *Aspergillus* is also particularly common in patients with hematologic malignancies and in patients undergoing HCT. In the setting of febrile neutropenia, lipid-associated amphotericin B (LAMB) products are almost exclusively recommended over conventional amphotericin B due to reduced toxicities despite significantly higher cost without clear improvement in efficacy.[1,4,20,21,25,34] Although the use of higher doses of LAMB has been advocated in an effort to improve efficacy, lower doses (3 mg/kg) of liposomal amphotericin B may be as efficacious as higher doses (10 mg/kg) with lower cost and fewer toxicities.[4] Although LAMB products are recommended for empiric therapy of neutropenic fever when antifungal agents are desired, they are not preferred agents in patients with presumed or documented invasive fungal infections.[4,18,21]

The azole compounds are also used in the management of febrile neutropenia.[1,4,21,25,34] The azoles have replaced LAMB as preferred antifungals for many patients with FN due to the increased cost and toxicities of LAMB.[4] However, concerns regarding the emergence of *Candida* strains with decreased azole susceptibility and unclear efficacy advantages have prevented these agents from replacing amphotericin B as the clear gold standard in patients with persistent febrile neutropenia.[20,25,34] Fluconazole has good efficacy against *C. albicans* but lacks activity against molds such as *Aspergillus*. The use of fluconazole as an alternative to amphotericin B for empirical antifungal therapy is thus perhaps most appropriate in hospitals in which infections due to *Aspergillus* or non-*albicans* strains of *Candida* are not common.[1,4,20,34] If fluconazole is used as antifungal prophylaxis in patients with cancer, it should not be included in empirical antifungal regimens. Voriconazole is the preferred agent in the treatment of documented invasive fungal infections and is recommended as a reliable option for febrile neutropenia.[1,4,34] Despite failing to meet noninferiority criteria when compared against LAMB for empiric therapy in patients with febrile neutropenia, voriconazole is a preferred agent for invasive aspergillosis (especially pulmonary) due to improved survival and less toxicity when compared to amphotericin B.[1,4,20,25,34-36] Isavuconazonium, the prodrug of isavuconazole, has activity against invasive aspergillosis and mucormycosis that is generally comparable to voriconazole and posaconazole. Isavuconazonium has shown reductions in mortality and overall treatment success similar to voriconazole in a largely neutropenic patient population with hematologic malignancies and suspected invasive fungal infections including a subgroup of proven or probable aspergillosis.[37,38] The most recent guidelines recommend isavuconazonium as an alternative to voriconazole in the treatment of invasive aspergillosis, although there are few data related to use as empiric therapy of febrile neutropenia.[4,21,34] Posaconazole has extended activity against some Mucorales and rare molds in addition to *Candida* and *Aspergillus*, but is only approved for prophylaxis of fungal infections in patients with neutropenia. The improved bioavailability of the delayed-release tablets and availability of a parenteral dosage form make posaconazole an attractive option; although clinical data are relatively limited, the most recent guidelines also recommend posaconazole as an alternative to voriconazole for presumed or documented invasive disease.[21,34] Itraconazole has similar efficacy as amphotericin B, with fewer toxicities. However, current lack of a parenteral dosage form, erratic oral absorption, numerous potential drug-drug interactions, and availability of many other antifungal options limit the use of itraconazole for empiric therapy.[21,34,35] Therapeutic drug monitoring has been recommended for some azole antifungals given potential for interpatient variability, therapeutic failure associated with subtherapeutic concentrations, and toxicities associated with supratherapeutic concentrations (Table 145-6).[4,18,21,28,31,34,39]

The echinocandin antifungals (caspofungin, micafungin, and anidulafungin) are attractive agents for treatment of febrile neutropenia because of their broad spectrum of antifungal activity and favorable adverse effect profiles. Caspofungin is as effective as, and also generally better tolerated than, liposomal amphotericin B for empirical treatment of patients with neutropenia with persistent fever.[1,4] Therefore, caspofungin is considered an appropriate alternative to LAMB and voriconazole.[1,4,20,21,25] Micafungin and anidulafungin have not been as well studied specifically in this setting; however, most experts consider them likely as effective and all echinocandins are recommended.[1,4,21,25]

Initiation of Antiviral Therapy

Patients with febrile neutropenia associated with vesicular or ulcerative skin or mucosal lesions should be evaluated carefully for infection due to HSV or varicella-zoster virus (VZV). Mucosal lesions from viral infections provide a portal of entry for bacteria and fungi during periods of immunosuppression. If viral infection is presumed or documented, patients with neutropenia should receive aggressive antiviral therapy to aid healing of primary lesions and prevent disseminated disease. Acyclovir traditionally has been used in this population. However, the newer antivirals valacyclovir and famciclovir have better oral absorption and more convenient dosing schedules. Routine use of antiviral agents in the management of patients without mucosal lesions or other evidence of viral infection generally is not recommended.[1,4] Treatment recommendations for viral infections are given in Table 145-7.

TABLE 145-7

Infectious Complications During Neutropenia, and After Hematopoietic Cell and Solid-Organ Transplantation: Syndromes of Disease and Treatment Guidelines

Pathogen	Syndromes of Disease	Recommended Treatment
Bacterial		
Gram-negative aerobic bacilli (Enterobacterales, *Pseudomonas aeruginosa*, *Haemophilus influenzae*)	Blood, urinary tract, pulmonary, abdomen	*Empiric:* Ceftazidime ± aminoglycoside,[a,b] cefepime ± aminoglycoside[a,b]; piperacillin–tazobactam; imipenem–cilastatin ± aminoglycoside[a,b]
		Definitive: According to culture and sensitivity results
Gram-positive cocci (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Enterococcus faecalis*)	Skin, blood, urinary tract, pulmonary, abdomen	*Empiric:* Nafcillin; vancomycin
		Definitive: According to culture and sensitivity results
Legionella spp.	Pulmonary	Erythromycin; azithromycin; ciprofloxacin; levofloxacin
Listeria monocytogenes	CNS	Ampicillin with gentamicin[a]; trimethoprim–sulfamethoxazole
Nocardia spp.	Skin, pulmonary, CNS	Sulfadiazine; trimethoprim–sulfamethoxazole
Fungal		
Candida spp.[c]	Blood, urinary tract, mucous membranes, skin, disseminated disease	Clotrimazole; nystatin; fluconazole; itraconazole; amphotericin B ± flucytosine; lipid-associated amphotericin B (LAMB); caspofungin; micafungin; anidulafungin
Aspergillus spp.[d]	Skin, pulmonary, CNS	Voriconazole; LAMB; caspofungin; micafungin; posaconazole; itraconazole; isavuconazole
Cryptococcus neoformans	Skin, pulmonary, CNS	LAMB + flucytosine; fluconazole
Mucorales (*Mucor*)	Rhinocerebral disease	LAMB; posaconazole
Viral		
Herpes simplex virus	Skin, CNS, mucous membranes, pulmonary	Acyclovir; foscarnet

Human herpesvirus-6	CNS, hepatic, bone marrow	Ganciclovir; foscarnet
Cytomegalovirus	Pulmonary, blood, urinary tract, GI tract	Ganciclovir; foscarnet; immunoglobulin
Varicella-zoster virus	Skin, disseminated disease	Acyclovir; foscarnet
Epstein–Barr virus	Lymphoproliferative disease	Rituximab
Papovaviruses (BK, JC)	Skin, CNS	No effective treatment
Protozoal/Parasitic		
Pneumocystis jirovecii	Pulmonary	Trimethoprim–sulfamethoxazole; atovaquone; pentamidine; dapsone + trimethoprim; clindamycin + primaquine
Toxoplasma gondii	CNS	Pyrimethamine + sulfadiazine; pyrimethamine + clindamycin
Strongyloides stercoralis	Pulmonary, CNS	Thiabendazole

[a]Choice of specific agent determined according to institutional susceptibilities to individual drugs.

[b]For penicillin-allergic adults, use aztreonam or ciprofloxacin + an aminoglycoside.

[c]Refer to the Clinical Practice Guidelines of the Infectious Diseases Society of America (*Reference 21*) for selection and dosing of antifungal agents for specific infections.

[d]Refer to the Clinical Practice Guidelines by the Infectious Diseases Society of America (*Reference 25*) for selection and dosing of antifungal agents for specific infections.

Duration of Antimicrobial Therapy

The optimal duration of antimicrobial therapy in patients with cancer and neutropenia remains controversial. Decisions regarding discontinuation of empirical antimicrobial therapy often are more difficult and complex than those regarding initiation of therapy (see Figs. 145-1). One point on which experts agree, however, is that the most important determinant of the total duration of antibiotic therapy is the patient's ANC.[1,4] If ANC is greater than or equal to 500 cells/mm^3 (0.5 × 10^9/L) for 2 consecutive days, if the patient is afebrile and clinically stable for 48 hours or more, and if no pathogen has been isolated, then antibiotics can be discontinued. Some clinicians advocate that patients with ANC less than 500 cells/mm^3 (0.5 × 10^9/L) be maintained on antibiotic therapy until resolution of neutropenia, even if they are afebrile. However, prolonged antibiotic use has been associated with superinfections resulting from resistant bacteria and fungi and increases the risk of antibiotic-related toxicities.[1,4] If low-risk patients are clinically stable with negative cultures but the ANC still is less than 500 cells/mm^3 (0.5 × 10^9/L), antibiotics may be discontinued after a total of 5 to 7 afebrile days. However, patients with profound neutropenia (ANC greater than 100 cells/mm^3 [0.1 × 10^9/L]), mucosal lesions, or unstable vital signs or other risk factors should continue to receive antibiotics until ANC has increased greater than or equal to 500 cells/mm^3 (0.5 × 10^9/L) and the patient is clinically stable.[1,4]

Patients who are persistently neutropenic and febrile, but who are stable clinically with no active site of infection, often can be successfully discontinued from antimicrobials after at least 2 weeks of therapy. However, these patients must be monitored carefully because reinstitution of antibiotics may be necessary.[1,4] An alternative approach is to place these patients on antimicrobial prophylaxis (discussed in the section "Prophylaxis

of Infections in Neutropenic Patients with Cancer" below). Patients with documented infections should receive antimicrobial therapy until the infecting organism is eradicated and signs and symptoms of infection have resolved (at least 10-14 days of therapy).

Consensus guidelines provide useful information regarding the management of febrile episodes in patients with cancer and neutropenia.[1,4] However, therapy (including initial empirical regimens, modifications, and duration of treatment) must be individualized based on specific patient parameters and response to therapy.

Colony-Stimulating Factors

Because resolution of neutropenia is arguably the most important determinant of patient outcome from both febrile episodes and documented infections, numerous studies have evaluated hematopoietic colony-stimulating factors (CSFs) (sargramostim [granulocyte-macrophage colony-stimulating factor] and filgrastim [granulocyte colony-stimulating factor]) as adjunct therapy to antimicrobial treatment of febrile neutropenic patients with cancer. A meta-analysis found that use of CSFs is associated with reduced total duration and severity of chemotherapy-related neutropenia, reduced duration of antibiotic use, fewer hospitalizations, and decreased hospital length of stay.[40] However, this meta-analysis failed to demonstrate a benefit of CSFs in relation to important outcomes such as decreased overall mortality or infection-related mortality.[40] Evidence-based guidelines from the IDSA, American Society of Clinical Oncology (ASCO), and the NCCN recommend that CSFs should not be routinely initiated in patients with uncomplicated fever and neutropenia.[1,4,41,42] However, CSFs should be considered in patients who are at high risk for infection-associated complications, or who have factors that are predictive of poor clinical outcomes.[4,41,42] These factors are summarized in Table 145-8. Patients with prolonged neutropenia and documented severe infections who are not responding to appropriate antimicrobial therapy may also benefit from treatment with CSFs.[41,42] Clinical judgment must be exercised in determining which patients may benefit from judicious use of these expensive agents.

TABLE 145-8

Recommendations for Use of Colony-Stimulating Factors in the Management of Patients with Cancer and Those Undergoing Stem Cell Transplantation

Primary prophylaxis of febrile neutropenia

1. Colony-stimulating factors (CSFs) (filgrastim, pegfilgrastim, or sargramostim) may be considered in patients who have a high risk of febrile neutropenia (>20% incidence) based on myelotoxicity of the planned chemotherapy regimen.
2. When risk of febrile neutropenia is 10%-20%, CSFs may be considered in the presence of certain patient and clinical factors predisposing to increased complications from prolonged neutropenia, including patient age >65 years; poor performance status; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; cytopenias due to bone marrow involvement by tumor; poor nutritional status; presence of open wounds or active infections; previous surgery; poor renal function; liver dysfunction, particularly when evidenced by increased bilirubin; and lack of antibiotic prophylaxis.

Secondary prophylaxis of febrile neutropenia

1. CSFs (filgrastim, pegfilgrastim, or sargramostim) recommended for patients who experienced neutropenic complications from prior cycles of chemotherapy, and in which a reduced dose may compromise disease-free or overall survival or treatment outcome.

Therapeutic use in febrile neutropenia

1. CSFs should not be routinely used for patients with neutropenia who are afebrile.
2. CSFs (filgrastim or sargramostim only) may be considered in patients with febrile neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes, including profound neutropenia (absolute neutrophil count <100 cells/mm^3 [0.1×10^9/L]); expected prolonged period of neutropenia (>10 days); patient age >65 years; uncontrolled primary disease; sepsis syndrome, or severe infection manifest by hypotension and multiorgan dysfunction; pneumonia; invasive fungal infection; other clinically documented infection; hospitalized at the time of the development of fever; or severe complications during previous episode of febrile neutropenia.

Reduction in duration of neutropenia in HCT

1. CSFs are recommended to mobilize peripheral-blood progenitor cells (PBPC) prior to chemotherapy and to reduce the duration of neutropenia after autologous PBPC transplantation.

Data from References 4,39,40.

Direct transfusion of neutrophils has also been studied for treatment of febrile neutropenia or documented infections.[5,43] Routine use of neutrophil transfusions is not generally supported by data demonstrating improved clinical outcomes. However, use may be considered in patients with profound prolonged neutropenia with severe documented infections and in whom causative organisms have not been eradicated with appropriate antimicrobial therapy in combination with CSFs.[4] At present, the use of neutrophil transfusions is not recommended for routine management of patients with febrile neutropenia.[4]

Prophylaxis of Infections in Neutropenic Patients with Cancer

Owing to the potential morbidity and mortality of infections in neutropenic cancer patients, environmental modifications and prophylactic antimicrobial regimens have been implemented to prevent these complications. The overall goal of antimicrobial prophylaxis in patients with cancer is to decrease the number and severity of systemic infections during prolonged periods of neutropenia. As with febrile neutropenia, patient risk factors for development of infection and complications should be assessed prior to initiation of prophylaxis (Table 145-9).

TABLE 145-9

Risk-Based Prophylactic Strategies for Patients with Neutropenia

Risk Group	Patient Characteristics	Prophylactic Strategies
High risk	• *Neutropenia:* Severe (absolute neutrophil count <100/mm^3 [0.1 × 10^9/L]) and/or prolonged (≥10 days) • *Malignancy/treatment:* Hematologic malignancy (acute leukemia), allogeneic HCT, GVHD with high-dose steroids (≥20 mg prednisone equivalents daily for ≥1 month), or use of alemtuzumab or purine-containing regimens	Consider bacterial prophylaxis with fluoroquinolone for duration of neutropenia. Give fungal prophylaxis with product and duration based on patient-specific factors. Give/consider viral prophylaxis with product and duration based on patient-specific factors. Consider protozoal prophylaxis with product and duration based on patient-specific factors
Moderate risk	• *Neutropenia:* Moderate duration (7-10 days) • *Malignancy/treatment:* Autologous HCT, multiple myeloma, lymphoma, chronic lymphocytic leukemia, purine analog therapy	Consider bacterial prophylaxis with fluoroquinolone for duration of neutropenia. Consider fungal prophylaxis with product and duration based on patient-specific factors. Give/consider viral prophylaxis with product and duration based on patient-specific factors. Consider protozoal prophylaxis with product and duration based on patient-specific factors
Low risk	• *Neutropenia:* Short duration (≤7 days) • *Malignancy/treatment:* Solid tumor treated with conventional chemotherapy	Antibacterial and antifungal prophylaxis not indicated. Viral prophylaxis considered during neutropenia if patient has prior HSV episode

GVHD, graft versus host disease; HCT, hematopoietic cell transplant; HSV, herpes simplex virus.

Data from References 1,4,6,27,37,42.

General Measures

Because approximately 50% of pathogens infecting neutropenic cancer patients are acquired in the hospital, reducing acquisition of infectious organisms from the environment is a basic component in controlling nosocomial infections.[1,4,6] Patients with neutropenia should be placed in reverse isolation (isolation to protect patients from contracting infections after exposure to others) with standard barrier precautions, and strict adherence to infection prevention guidelines by hospital personnel.[1,4,6] Plants and fresh or dried flowers are usually prohibited as part of standard neutropenic precautions in order to minimize risk of exposure to pathogenic bacteria. Proper handwashing and respiratory hygiene by hospital personnel are simple yet effective infection prevention measures.[44] Most patients with neutropenia do not require specific room ventilation; however, HCT recipients should be placed in a private positive-pressure room with greater than 12 air exchanges per hour and HEPA filtration.[1,4,6]

Bacterial Infections

Combinations of oral nonabsorbable antibiotics, such as gentamicin, nystatin, vancomycin, polymyxin B, and colistin, have been widely studied as a means of reducing colonization of the GI tract with virulent pathogens. Although selective intestinal decontamination with oral nonabsorbable antibiotics successfully reduces infections, these regimens are not routinely recommended for prophylaxis because of problems that include unpalatability, cost, frequent adverse effects (eg, nausea, vomiting, and diarrhea), and development of resistance.[1-6]

Prophylaxis with orally administered, systemically available antibiotics such as trimethoprim–sulfamethoxazole and fluoroquinolones is effective at reducing gram-negative infections.[1,4] Although trimethoprim–sulfamethoxazole is effective as prophylaxis against *P. jirovecii*, its lack of activity against *P. aeruginosa* is worrisome when used as prophylaxis against bacterial infection, particularly in institutions where pseudomonal infections are frequent.[1] Other concerns with trimethoprim–sulfamethoxazole prophylaxis include selection of resistant organisms, predisposition to development of oral fungal infections, and delay in bone marrow recovery resulting in prolonged neutropenic episodes.[1,4,6]

Fluoroquinolones are more effective than placebo in preventing febrile episodes and gram-negative infections in neutropenic cancer patients and, in some studies, have decreased all-cause mortality and infection-related mortality.[1,4,6,45] However, there are several potential limitations to their use. In particular, ciprofloxacin may lack adequate gram-positive activity and may not be the preferred fluoroquinolone for this reason. Although fluoroquinolone prophylaxis has been associated with colonization and infection with fluoroquinolone-resistant gram-negative organisms, these findings have not been consistent in various studies.[1,4,11,45] The risk of colonization or infection with strains resistant to the prophylactic agent is also lower with fluoroquinolones compared to trimethoprim–sulfamethoxazole.[36] However, patients experiencing breakthrough infection during fluoroquinolone prophylaxis should not be subsequently placed on a fluoroquinolone-containing empirical antibiotic regimen.[1,4] Although studies have not consistently documented increased fluoroquinolone resistance in association with prophylaxis, other potentially unfavorable outcomes such as increased risk of *Clostridioides difficile* infection should also be considered in weighing the potential benefits of fluoroquinolone prophylaxis.[1,4,11,36,45]

Although the benefits of prophylaxis with fluoroquinolones outweigh the potential risks in patients with neutropenia who are at intermediate to high risk for infection (Table 145-9), antibacterial prophylaxis in general remains somewhat controversial due to continued concerns regarding the potential for development of resistant bacteria, high cost, and lack of consistent benefits related to patient survival.[1,4,11] Therefore, antibacterial prophylaxis is not recommended routinely for all patients with neutropenia. Prophylaxis with ciprofloxacin or levofloxacin generally is indicated for intermediate- to high-risk patients expected to be profoundly neutropenic for more than 1 week as shown in Table 145-9.[1,4,6,44] Fluoroquinolone prophylaxis is not routinely recommended for patients with solid tumors.[23,27,44] High-dose levofloxacin may be preferred by some clinicians due to enhanced gram-positive activity. An oral cephalosporin (cefpodoxime) may be considered for patients intolerant of fluoroquinolones.[44] Neutrophil recovery eliminates the need for continued prophylaxis, and recovery may be facilitated by use of CSFs.[41] CSFs have also been formally recommended by ASCO and NCCN for primary prevention of FN in high-risk patients (see Table 145-8).[1,4]

Fungal Infections

Because patients with neutropenia are at risk for mucocutaneous and invasive fungal infections that are difficult to diagnose and treat, antifungal prophylaxis can be considered in intermediate- to high-risk patients at institutions where fungal infections in patients with cancer occur frequently.[1,4] The goal of antifungal prophylaxis is to prevent development of invasive fungal infections during periods of risk, thereby reducing morbidity and mortality. Similar to antibacterial prophylaxis, prophylaxis against fungal infection is specifically recommended for patients who are at risk for profound, protracted neutropenia (Table 145-9).[4,6,23,44]

Antifungal prophylaxis with an oral triazole agent (fluconazole, itraconazole, voriconazole, posaconazole, isavoconazole), parenteral echinocandin, or LAMB is recommended in select patients starting at the time of induction chemotherapy.[4,44] Fluconazole prophylaxis has been particularly well studied and reduces the incidence of both superficial and systemic fungal infections; it also significantly decreases mortality from fungal infections in patients with leukemia and HCT recipients.[4,38] However, use of fluconazole prophylaxis has contributed to the emergence of infections caused by *C. krusei* and *C. glabrata*, pathogens that frequently are resistant to fluconazole and other azole-type antifungal agents.[4,23] When compared to prophylaxis with mold-active agents, patients on fluconazole have a higher rate of aspergillosis and invasive fungal-related mortality but lower rate of adverse events leading to discontinuation.[37] The choice of a specific agent should be determined by the types of fungal isolates at individual institutions and risk for invasive mold infection compared to invasive candidiasis.[1,4,21,44,46] After initiation, antifungal prophylaxis should be continued until resolution of neutropenia or the need for institution of antifungal therapy for suspected/documented infection.[4,18,21,23,44]

Other Infections

Use of trimethoprim–sulfamethoxazole prophylaxis in patients with cancer at risk for *P. jirovecii* pneumonia has substantially reduced the incidence of this infection. Trimethoprim–sulfamethoxazole is therefore recommended for use in patients receiving higher-risk chemotherapeutic regimens (see Table 145-9).[1,4,44] Antiviral prophylaxis with acyclovir, valacyclovir, or famciclovir is recommended to reduce the risk of HSV reactivation in patients with acute leukemia undergoing intensive chemotherapy.[4,44] Prophylaxis with a nucleoside reverse transcriptase inhibitor such as entacavir or tenofovir is recommended for patients at high risk of HBV reactivation.[4,44] Finally, patients should be assessed for indications for administration of vaccines such pneumococcal, influenza, varicella, and varicella zoster in order to provide protection from vaccine-preventable infections that commonly occur in patients with neutropenia and immunosuppression.[38] Many vaccines will be most effective when administered to patients prior to beginning immunosuppressive chemotherapy regimens, while inactivated influenza vaccine may also be administered to already immunocompromised patients.[38]

When considering use of antimicrobial (antibacterial, antifungal, and antiviral) prophylaxis in patients with neutropenia and cancer, the risks and benefits of prophylaxis must be weighed against issues with development of resistance, toxicities, and other concerns.

Evaluation of Therapeutic Outcomes

10 Close monitoring of patients with febrile neutropenia, including both clinical and laboratory parameters, is essential for early detection and treatment of infectious complications. Three general therapeutic outcomes have been defined in the setting of febrile neutropenia: (a) success (survival during the febrile episode until resolution of neutropenia by judicious selection of empirical antimicrobial therapy), (b) success with modification (same as [a] but with additions/modifications to empirical therapy), and (c) failure (death during febrile neutropenia).[1] Because many of the drugs that can be used in this setting (eg, aminoglycosides and amphotericin B) have significant toxicity potential, careful attention must be paid to prevention and management of drug-related adverse effects. Evaluations of the parameters given in the Clinical Presentation are appropriate to help monitor and guide therapy. In addition, the NCCN guidelines for febrile neutropenia provide comprehensive recommendations on clinical/laboratory monitoring parameters, including schedules.[4] The reader is referred to individual chapters within this book for more detailed discussions of monitoring parameters related to specific types of infections (eg, pneumonia and urinary tract infections).

INFECTIONS IN PATIENTS UNDERGOING HCT

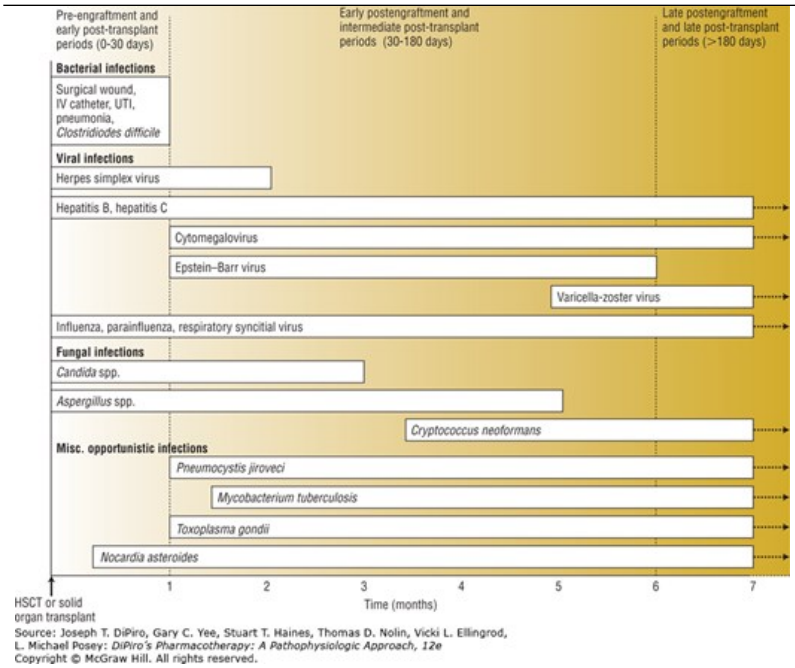
1 Infection remains a major barrier to successful HCT.[47-50] Recipients of HCT are at enhanced risk for infection because of prolonged periods of neutropenia. In addition, patients receiving allogeneic transplants (related, matched unrelated, or cord blood) receive prolonged immunosuppressive drug therapy for prevention and treatment of graft-versus-host disease (GVHD) following engraftment. Allogeneic HCT recipients are generally slower to engraft when compared to autologous HCT recipients.[4] Intensive pretransplant conditioning regimens (high-dose chemotherapy and total-body irradiation), as well as GVHD itself, often disrupt protective barriers, such as mucous membranes, skin, and the GI tract, placing patients at further risk of infection.[4,48,49] Although infectious complications are still associated with considerable morbidity and mortality, studies have documented significant reduction in mortality after HCT in association with reductions in disease caused by bacterial, fungal, and viral infections.[4] As the number of HCTs performed increases and patients live longer, the population of HCT recipients is expected to continue to grow exponentially.[42]

Etiology and Clinical Presentation of Infections

2 10 The timing with which specific types of infections typically occur following HCT is shown in Fig. 145-3, but the relative incidence and importance of specific pathogens vary greatly according to the specific type of HCT performed. Patients receiving allogeneic transplants are at greatest risk for infection after HCT and are predisposed to earlier and more severe infections with opportunistic pathogens such as *Aspergillus*. The presence of GVHD also has an impact on the incidence and timing of various infections, including invasive fungal infections.

FIGURE 145-3

Timetable for the occurrence of infections in hematopoietic cell transplantation (HCT) and solid-organ transplant patients. (UTI, urinary tract infection.)



After administration of intensive conditioning regimens to eliminate malignant cells and prevent rejection of donor cells, patients may remain profoundly neutropenic for 3 to 4 weeks. During this pre-engraftment period, patients are at risk for the same types of infectious complications that occur in other granulocytopenic patients with cancer (eg, bacterial and fungal infections) and should be managed accordingly (see Table 145-1).[4] Table 145-7 lists regimens for treatment of specific infections.

HCT recipients remain at high risk for infection after bone marrow engraftment has occurred.[4] Significant defects in neutrophil function and cell-mediated and humoral immunity, persisting for several months after transplantation, predispose patients to infectious complications. Furthermore, specific medications, regimens, and therapies utilized are associated with added risk or a prolonged risk of various infections (alemtuzumab, anti-CD20 antibodies, fludarabine, steroids, asplenia, etc.).[4] Acute and chronic GVHD following allogeneic HCT also results in prolonged periods of immunosuppression.[4,48,49] Those who experience acute GVHD had a 60% higher infection rate and higher risk of developing serious or fatal infections compared to allogeneic HCT recipients without acute GVHD.[49] Even in the absence of active GVHD, 10% to 20% of all deaths are attributable to infection after year two in allogeneic HCT recipients.[51]

HCT recipients are at significant risk for serious bacterial infections at various sites.[4,50] Bacteremia is particularly concerning following allogeneic HCT as those with GVHD have a three-fold increased risk.[48] Bacteremia has been reported in up to half of HCT recipients with gram-positive and gram-negative bacteremia occurring at similar rates.[48,50,52] However gram-negative bacteremia remains of significant clinical importance because mortality rates may reach 45% for increasingly common multidrug resistant strains.[11] *Clostridioides difficile* has become a common and important cause of gastrointestinal infections.[4,41,50]

Fungal infections, especially those caused by *Candida* and *Aspergillus* spp., are serious and often result in fatal complications. Fungi remain a serious cause of infection, particularly in allogeneic HCT recipients, for up to 1 to 2 years following transplantation and may occur in as many as 20% of patients.[4,52,54] Significant mortality is associated with invasive aspergillosis (up to 60%) and mucormycosis infections.[4] HCT recipients are also at risk for serious viral infections, particularly HSV and cytomegalovirus (CMV). HSV infections may include gingivostomatitis, esophagitis, genital lesions, and, rarely, pneumonia during the first month after transplant.[4,55] Clinical disease is more common in patients with serologic evidence of prior exposure and latent HSV infection pretransplant. Therefore, reactivation of latent disease during periods of immunosuppression is the most common etiology of HSV infection. Without prophylaxis, as many as 80% of HSV-seropositive patients experience mucocutaneous disease after intensive chemotherapy compared with less than 25% of seronegative patients.[4,55] HSV infections often coexist with *Candida* infection and mucositis secondary to chemotherapy, radiation, or both.[4,55] Painful swallowing associated with these conditions often makes it difficult for patients to take oral medications and maintain adequate nutritional intake. Because of the considerable morbidity associated with HSV reactivation after transplantation, the HSV

serologic status of patients should be determined prior to transplant.

HCT recipients are at high risk for CMV infections during the early postengraftment period. Infections range in severity from asymptomatic infection with viral shedding (urine, throat, and lungs), to life-threatening disseminated disease and interstitial pneumonia.[4,55] As with HSV, patients seropositive for CMV before transplantation are at high risk for reactivation of infection during periods of immunosuppression; up to 60% of seropositive patients develop reactivation after transplantation compared with only 3% of seronegative patients.[4,55] Other risk factors for CMV infection in HCT recipients include advanced age, human lymphocyte antigen mismatch, total-body irradiation, multiagent conditioning regimens, and presence of GVHD.[4,55] Patients without evidence of latent CMV infection (CMV-seronegative) before transplantation may develop primary CMV infection after receiving bone marrow or blood products from CMV-seropositive donors. Although the typical onset of both primary and recurrent CMV infection is 1 to 2 months after transplantation, late-onset infections may occur more than 100 days after transplantation.[4,55,56] Patients receiving allogeneic transplants are at highest risk for CMV reactivation, with progression to clinical disease in approximately 10% to 30% of patients.[4,55] The most serious clinical manifestation of CMV disease is interstitial pneumonia, which is associated with a mortality rate greater than 50% even when treated.[45] Interstitial pneumonia also may result from other infectious (*P. jirovecii*, VZV) and noninfectious causes (pulmonary damage by radiation and chemotherapy).[4,55] This clinical syndrome manifests as fever, dyspnea, hypoxia, nonproductive cough, and diffuse pulmonary infiltrates. As many as 40% of allogeneic HCT recipients will develop some form of interstitial pneumonia; it is a leading cause of infectious death in HCT recipients and a significant proportion are viral in etiology.[45]

During the late postengraftment period (beginning approximately 180 days after transplantation), infections remain a major problem in patients suffering from chronic GVHD. Infections common during the late postengraftment period include those caused by encapsulated bacteria, such as *S. pneumoniae* and *H. influenzae*, fungi, and viruses, including CMV and VZV.[4,54] Patients not undergoing allogeneic transplantation or suffering from chronic GVHD generally have few infections in this period.

Up to 60% of allogeneic patients with a history of VZV who survive up to 10 months after transplantation will develop VZV disease.[4,54,55] Infection with VZV is most common in allogeneic HCT recipients with acute or chronic GVHD.[54,55] Both primary (varicella) and recurrent disease (herpes zoster) usually present as skin lesions, most of which remain contained to local areas; however, 30% of these infections may disseminate to other cutaneous areas or body organs, causing severe morbidity or mortality.[4,45,55,57]

PREVENTION AND TREATMENT

Desired Outcomes

The goals of therapy in managing HCT recipients from the neutropenic period through the late postengraftment period are: (a) protect the patient from early death caused by undiagnosed infection; (b) employ effective prophylactic therapy to prevent common bacterial, fungal, viral, and protozoal/parasitic infections; (c) effectively and aggressively treat established infections; (d) avoid unnecessary use of antimicrobials that contribute to increased resistance; and (e) minimize toxicities and cost while increasing patient quality of life.

Prophylaxis and Management of Infections in Recipients of HCT

8 9 The overall goal of prophylaxis and treatment of infection in HCT recipients is prevention of infectious morbidity and mortality. Specific goals of antimicrobial use in HCT recipients include (a) prevention of bacterial, fungal, viral, and protozoal infections during pre-engraftment and postengraftment periods and (b) effective treatment of established infections. These goals must be achieved at the lowest possible toxicity and cost. Prophylactic therapy should be aimed specifically at pathogens known to cause a high incidence of infection within the HCT population in general and within the specific institution. In addition, prophylactic therapy should be limited to regimens proved to be effective through well-designed clinical trials.

Appropriate immunizations should be a primary consideration in the prevention of infections in HCT recipients. Immunizations against common bacterial and viral pathogens are timed to avoid periods of severe immunosuppression following HCT when the protective response to vaccination potentially would be decreased.[4,58] Recommended vaccines for immunization of HCT recipients include three doses each of diphtheria–pertussis–tetanus (or diphtheria–tetanus), inactivated polio, conjugated *H. influenzae* type b, and conjugated 13-valent pneumococcal; two doses each of

hepatitis A and HBV; and one dose of meningococcal conjugate vaccine 6 to 12 months post-transplant. One dose of the 23-valent pneumococcal vaccine should follow after 12 months. The influenza vaccine should be resumed at least 4 to 6 months after transplantation, and continued annually for life. Family members, close contacts, and healthcare providers of HCT recipients also should be vaccinated annually against influenza. The injectable inactivated influenza vaccine is preferred both before and after HCT due to severe underlying illnesses pretransplant and contraindication of the live-attenuated intranasal product post-transplant.[4,54,58] Finally, the live-attenuated measles–mumps–rubella vaccine should be administered no sooner than 24 months after HCT if the patient is considered to be immunocompetent.[44,48,54,58]

The live-attenuated varicella vaccine may be considered in patients seronegative for VZV owing to the risk of primary VZV infection, but if administered should be given no sooner than 24 months after transplant.[4,54,58] Shingrix® (recombinant zoster vaccine) is approved for immunocompetent adults and is effective at preventing herpes zoster, post-herpetic neuralgia, and herpes zoster–related complications and related hospitalizations.[49] Shingrix® is also currently recommended by the Centers for Disease Control for prevention of zoster in immunocompromised individuals and may also be considered for patients undergoing HCT.[50]

Bacterial Infections

Prophylaxis of infections in HCT recipients is similar in many ways to that used in other patients with neutropenia. Oral antibacterial prophylaxis is used commonly; considerations are the same as those discussed in the "Prophylaxis of Infections in Neutropenic Patients with Cancer" section. Although rates of bacteremia and other bacterial infections after HCT are decreased with prophylaxis, overall mortality rates have not been consistently reduced.[2,4,54,61] Therefore, routine use of prophylactic antibiotics in HCT is somewhat controversial but should be considered in patients at moderate-to-high risk of infection (Table 145-9). Fluoroquinolones are the most frequently used agents, with levofloxacin preferred over ciprofloxacin due to enhanced gram-positive activity.[4] For those intolerant to a fluoroquinolone, cefpodoxime or trimethoprim–sulfamethoxazole may be considered.[2,4] These regimens usually are started either within 72 hours of beginning the chemotherapy conditioning regimens or on the day of hematopoietic cell infusion and continued throughout the neutropenic period. Patients who become febrile while receiving prophylaxis should be managed according to general guidelines for febrile neutropenia.

Antibiotic prophylaxis against bacterial infection is also recommended in the late postengraftment period (greater than 100 days after transplantation) in certain high-risk patients, specifically allogeneic HCT recipients with chronic GVHD.[4] Antibiotics should be targeted against encapsulated bacteria, particularly *S. pneumoniae*, and should be selected based on local susceptibility patterns for these organisms; penicillin is preferred in areas with low rates of penicillin-resistant pneumococci.[4] Patients receiving trimethoprim–sulfamethoxazole for prophylaxis of other opportunistic infections may be adequately protected and do not necessarily require an additional antibiotic, though the addition of penicillin may be considered.[4] Prophylaxis should be continued as long as the chronic GVHD is being actively treated.

Viral Infections

Prophylaxis of recurrent HSV infection is recommended for all HSV-seropositive patients undergoing HCT.[2,4,55] Approximately 0% to 10% of HSV-seropositive patients receiving acyclovir experienced viral shedding, clinical symptoms of viral reactivation, or both compared with 60% to 80% of patients receiving placebo.[4,55] Many patients eventually require IV acyclovir because of the development of severe mucositis from conditioning regimens. However, oral acyclovir, valacyclovir, or famciclovir is effective and considerably less expensive in patients who can take oral medications. Valacyclovir has replaced acyclovir as first-line therapy in current guidelines. The antiviral agent usually is started at the time of the conditioning regimen and continued until bone marrow engraftment or resolution of mucositis (approximately 30 days after HCT), although longer durations of prophylaxis should be considered in allogeneic HCT recipients with GVHD or frequent HSV reactivations before transplantation.[2,4,55] In addition to preventing recurrence of HSV disease, acyclovir prophylaxis may reduce the incidence of CMV reactivation.[4,54] Patients receiving ganciclovir or foscarnet for prophylaxis or treatment of CMV infection do not need additional antiviral therapy for prevention of HSV or VZV.[4,55] Patients developing active HSV or VZV infection should be treated with high-dose acyclovir.[4,45,55-57]

Oral acyclovir or valacyclovir given for up to 12 months after transplantation also significantly reduces reactivation of VZV infections and prevents the occurrence of severe VZV disease.[2,4] Patients receiving either allogeneic or autologous HCT may therefore be considered for long-term (up to 1 year after transplantation) prophylaxis against VZV.[2,4] Immunocompromised, nonimmune patients exposed to chickenpox or shingles should receive

varicella-zoster immunoglobulin 625 units intramuscularly within 10 days (ideally as soon as possible) after close contact with persons with chickenpox or shingles for prevention of VZV-related disease.[52]

Acyclovir-resistant HSV has been reported occasionally in HCT recipients receiving acyclovir prophylaxis. Foscarnet is a drug of choice for treatment of documented infection with acyclovir-resistant HSV and should be reserved for this use.[4,45,55]

Prevention of CMV disease is a well-accepted indication for prophylaxis in HCT recipients because of the high associated infectious morbidity and mortality. If possible, CMV-seronegative patients should receive donor cells and supportive blood products from seronegative donors only; however, CMV-seropositive patients are not at significant additional risk by receiving blood or donor cells from seropositive donors.[57] Although acyclovir has relatively poor in vitro activity against CMV, a decrease in CMV infection and an improvement in overall survival were reported in HSV- and CMV-seropositive allogeneic HCT recipients receiving IV acyclovir.[4,45,55]

Ganciclovir has been well studied for prophylaxis with HCT because of its superior activity against CMV compared with acyclovir.[4,54] Oral valganciclovir has excellent pharmacokinetics, produces serum levels of ganciclovir that are at least similar to those achieved after IV administration, and is routinely used in many centers due to the convenience of oral dosing in certain patients.[4,54,55] Although administration of prophylactic valganciclovir to CMV-seropositive patients may significantly decrease the occurrence of CMV viremia, there is no clear survival benefit compared to a preemptive approach (ie, initiating IV ganciclovir or valganciclovir only after detecting a specific threshold of CMV copies from blood or bronchoalveolar fluid), and ganciclovir-related bone marrow suppression is frequently problematic.[53] Therefore, a preemptive approach is generally preferred over a ganciclovir prophylaxis strategy.[4,54,55] Preemptive therapy with ganciclovir and valganciclovir remains a current standard of therapy.[4,54,55] Detection of CMV is typically done by quantitative polymerase chain reaction (PCR)-based tests. Preemptive therapy significantly reduces the occurrence of CMV disease (including CMV pneumonia) and significantly improves survival up to 180 days after transplantation.[4] Because CMV viremia and PCR-positive bronchoalveolar lavage are highly predictive of subsequent CMV disease, preemptive ganciclovir or valganciclovir therapy should be considered for autologous HCT recipients within the first 100 days after transplantation or in allogeneic HCT recipients at any time after transplantation.[4] The doses of ganciclovir or valganciclovir for preemptive therapy are the same as those used for prophylaxis. Foscarnet can also be used for either prophylaxis or preemptive therapy of CMV disease in patients intolerant of ganciclovir or in the setting of ganciclovir resistant CMV.

CMV prophylaxis (rather than preemptive therapy) may be considered for specific allogeneic HCT recipients for the first 100 days after transplantation.[44] Letermovir is a highly active inhibitor of CMV replication approved for prophylaxis (but not treatment) of CMV infection and disease in CMV-seropositive recipients undergoing allogeneic HCT. In allogeneic HCT recipients assigned to letermovir or placebo, letermovir prophylaxis for a median of 82 days posttransplant substantially reduced CMV infections and disease within the first 6 months after transplant. Unlike ganciclovir, letermovir is not associated with bone marrow suppression and is therefore becoming an agent of choice for CMV prophylaxis in high-risk HCT recipients.[46] Clinical practice guidelines recommend that letermovir may be considered for primary prophylaxis of CMV disease in CMV-seropositive allogeneic HCT recipients.

Prophylaxis of CMV disease with either IV immunoglobulin (IVIG) or CMV hyperimmune globulin (CMVIG) has demonstrated variable and inconclusive benefits, and their use is not currently recommended.[4]

Ganciclovir and valganciclovir are the drugs of choice for treatment of active CMV infection in HCT recipients (see Table 145-6). Foscarnet also may be used for treatment or prevention of infections in HCT recipients as an alternative to ganciclovir/valganciclovir because of its relative lack of bone marrow toxicity or in cases of resistant CMV. Foscarnet-related nephrotoxicity is often problematic, however, especially in the post-transplant period when patients may be receiving other nephrotoxic agents. Cidofovir has not been well studied in HCT recipients and is also associated with nephrotoxicity, but this agent may also be considered for preemptive therapy or treatment of active disease as a third-line option.[4]

Numerous combination treatments such as interferon plus ganciclovir have been used unsuccessfully for treatment for CMV pneumonitis. However, the combination of high-dose IVIG and ganciclovir may decrease the mortality of the syndrome from 85% to 30% to 50%.[4,64] Ganciclovir plus CMVIG also is considered effective for treatment of CMV disease, although this regimen has not been studied as extensively in the HCT population in a controlled fashion. However, CMVIG was not more effective than IVIG; therefore, ganciclovir plus IVIG is considered as the treatment regimen of choice for severe or life-threatening CMV disease based on benefit-versus-risk considerations rather than definitive clinical data.[4,55,64] The potential for ganciclovir-associated bone marrow suppression prior to marrow engraftment and in patients who are just recovering from granulocytopenia remains a concern,

especially in patients with unstable renal function. CSFs are beneficial in this setting (Table 145-7), providing benefits similar to those noted in patients with neutropenia and acquired immunodeficiency syndrome receiving ganciclovir therapy for CMV retinitis.[4]

Fungal Infections

Prophylaxis with antifungal agents is efficacious and generally recommended for prevention of mucocutaneous and disseminated fungal infections in high-risk HCT recipients (Tables 140-2 and 140-9).[2,4] Patients specifically recommended for prophylaxis with fluconazole or an echinocandin include all allogeneic recipients and autologous transplant recipients with extensive mucositis.[2,4] Fluconazole remains the most commonly used agent; it is started on the day of transplantation and continued until resolution of neutropenia or, in allogeneic HCT, for at least 75 days after transplantation.[4] The variable activity of fluconazole against non-*albicans* species of *Candida* may be problematic in this population, as is lack of activity against *Aspergillus*.[4] Prophylaxis with fluconazole effectively reduced colonization, infection, and infection-related mortality due to *Candida* spp. in some HCT populations, but has not consistently reduced overall mortality or invasive infections such as aspergillosis in all types of HCT recipients.[4] Micafungin was more efficacious than fluconazole in the prevention of early-onset *Candida* infections in HCT recipients with neutropenia prior to engraftment, and also showed a trend to fewer episodes of invasive aspergillosis.[4] Posaconazole was also more effective than fluconazole in the late prevention of invasive *Aspergillus* and other fungal infections in HCT recipients with GVHD receiving additional immunosuppressive therapy.[4] In a meta-analysis, prophylaxis with agents active against *Aspergillus* were associated with a 33% reduction in mortality related to invasive fungal infections compared to fluconazole.[37] Fluconazole and micafungin are both supported by a high level of evidence for fungal prophylaxis and either are appropriate following HCT with local fungal ecology, risk factors, and cost being appropriate determinants for specific populations.[4] Most experts consider caspofungin and anidulafungin reasonable alternatives to micafungin and current guidelines do not differentiate among echinocandins.[4] Voriconazole, posaconazole, LAMB products, and to a lesser extent itraconazole may be used for prophylaxis of fungal infections in HCT recipients but do not carry the same strength of recommendation due to less favorable side-effect profiles or lack of positive comparative studies.[4] Posaconazole is the preferred agent in high-risk HCT recipients with severe GVHD due to the risk of invasive mold infections (Table 145-2).[2,4] When the risk of invasive aspergillosis infection is >6%, prophylaxis with a mold-active triazole such as posaconazole (voriconazole or isavuconazonium as alternatives) is appropriate.[2] Isavuconazonium has not been well studied for prophylaxis in HCT recipients and, although recommended as an option in some clinical guidelines, it has not been recommended in others.[2,4]

Therapeutic drug monitoring for some azole antifungals remains important (Table 145-6). Furthermore, use of azole antifungals as prophylaxis introduces the potential for pharmacokinetic (CYP450 inhibition) and pharmacodynamic (eg, QTc prolongation with most azoles and fluoroquinolones) drug-drug interactions that vary in duration and severity. Drug half-lives, potential therapeutic benefit (eg, infection-free mortality), potential harm, and future oncologic plans must be assessed when initiating, continuing, adjusting, or discontinuing a potentially interacting medication. An alternative prophylaxis regimen (echinocandin) may be preferred to an azole when the risk of a drug interaction is too great (eg, proteasome inhibitors, tyrosine kinase inhibitors, or vinca alkaloids). Consideration should be given to the mechanism of drug interaction and drug half-life before initiating therapy.[4]

Pulmonary infection with *P. jirovecii* is a relatively infrequent complication of HCT that is associated with high rates of mortality, especially in patients with GVHD.[4,50,54] Therefore, prophylaxis is recommended for a period of 3 to 6 months after autologous HCT, and for at least 6 months and while receiving immunosuppressive therapy after allogeneic HCT. Exposure to specific immunosuppressing medications (eg, >20 mg of prednisone daily for >4 weeks) also warrants prophylaxis. Prophylaxis with trimethoprim–sulfamethoxazole significantly reduces the incidence of *P. jirovecii* as well as *P. jirovecii*–related mortality so effectively that desensitization should be considered for intolerant reactions before switching to an alternative (eg, dapsone, atovaquone, or pentamidine).[4,44,54] Trimethoprim–sulfamethoxazole should also prevent *Toxoplasma gondii*, a rare but often fatal infection.[4,54]

Use of Colony-Stimulating Factors

Filgrastim, pegfilgrastim, and sargramostim have been studied in HCT recipients in an effort to speed bone marrow recovery, reduce the period of neutropenia, and decrease infectious complications. CSFs appear effective as well as safe following autologous HCT and should be utilized. Although increased rates of GVHD and mortality with use of CSFs following allogeneic HCT have been reported by retrospective studies, a meta-analysis found

no increased risk and CSFs may be given to allogeneic HCT recipients to reduce the duration of severe neutropenia.[41] The use of CSFs is now routinely recommended to mobilize blood progenitor cells and reduce the period of neutropenia in autologous transplants (Table 145-7).[33,41,42]

Evaluation of Therapeutic Outcomes

10 Close monitoring of HCT recipients, including clinical and laboratory data, is essential for early detection and treatment of infectious complications. In addition, because many of the drugs commonly used in this setting (eg, ganciclovir, amphotericin B, and trimethoprim–sulfamethoxazole) have significant toxicity potential in HCT recipients, careful attention must be paid to prevention and management of drug-related adverse effects as well as drug-drug interactions. Monitoring parameters related to specific types of infections (eg, pneumonia and urinary tract infections) should be applied as appropriate. The reader is referred to other chapters within this book for more specific information.

INFECTIONS IN SOLID-ORGAN TRANSPLANT RECIPIENTS

Solid-organ transplantation (SOT) is an established mode of treatment for end-stage diseases of the heart, lungs, kidney, liver, pancreas, and small bowel. More than 39,000 organs were transplanted in the United States in 2020, and nearly 900,000 organs have been transplanted in the United States since 1988.[55] Patient and allograft survival rates have greatly improved due to improvements in immunosuppressive drug therapy, candidate selection, and transplant surgery techniques as well as more experience in the management of complications (including infection) in these patients. Despite advances in diagnostic techniques and antimicrobial therapy, infectious complications remain important causes of morbidity and mortality after SOT.

Risk Factors

1 Many risk factors for infection are present in SOT recipients (see Table 145-1). The most important risk factor in this population is immunosuppressive drug therapy for prevention and treatment of allograft rejection. Risk of infection depends on specific immunosuppressive drug regimens as well as the intensity (numbers and doses/exposure of drugs) and duration of immunosuppression. Most opportunistic infections in transplant patients occur during the first 6 months after transplantation, when the intensity and total cumulative exposures to immunosuppressive therapy are very high.[56,57,65,66]

Immunosuppressive drugs, often in escalated doses, are used to treat episodes of graft rejection and include immunoglobulins directed against T cells (eg, antithymocyte globulin), antibodies against interleukin 2 receptors (basiliximab), T-cell–depleting antibodies (alemtuzumab), B-lymphocyte depleting antibodies (rituximab), and high-dose corticosteroids. Rejection episodes often occur during the period 2 to 4 months posttransplant when the overall cumulative dose or net state of immunosuppression is high. Therefore, patients already at risk for infection are placed at even higher risk if additional immunosuppressive therapy is needed to treat one or more episodes of graft rejection.[65,67] Immunosuppressive drug therapy must be evaluated carefully when infections occur because, in many cases, immunosuppression may have to be reduced or altered to allow patients to survive the infectious episode, at the expense of increased risk of graft rejection. Risk of increased infectious complications from immunosuppressive therapy used to treat rejection episodes is determined, at least in part, by the specific therapy used.[56,65,68]

The organ type, organ donor status, surgical technique, recipient status, and underlying illness of the recipients are also critical determinants of infection risk and possible etiologies. These considerations are extremely important within the first 3 months following SOT and may provide heightened suspicion leading to specific prophylaxis, preemptive strategies, and earlier appropriate and targeted treatment of infectious complications.[58,59,67-69]

Etiology

2 As in patients with cancer, microorganisms infecting SOT recipients are present before transplantation or are acquired from exogenous sources. Although opportunistic viral, fungal, and protozoal infections may occur commonly, bacterial infections remain the most frequent infectious complications after transplantation in all allograft recipients.[65,70,71] Liver, small bowel, and lung transplant recipients are at high risk for serious gram-negative bacterial infections as a result of the technically difficult surgical procedures and precolonization.[70,72] All transplant recipients are at risk for mucocutaneous candidiasis from species colonizing body sites. Invasive fungal infection is less common following kidney and pancreas transplantation but may occur in up to 30% to 60% of heart, lung, liver, and small bowel transplant recipients. Invasive fungal infections following lung,

liver, and small bowel transplantation are associated with mortality rates up to 60% to 80%.[73,74] *Candida* spp. is the most common of all systemic fungal infections in transplant recipients.[74-76] Abdominal surgery, especially the more complex procedures required for liver and small bowel transplantation, predispose patients to serious fungal disease, most likely as a consequence of entering an area of the body already colonized with *Candida* spp.[64] Lung and heart transplant recipients are particularly at risk for invasive aspergillosis; these infections may occur in up to 35% of patients and in lung transplant recipients may be more common than infections caused by *Candida* spp.[63,64,73,77]

Organisms present as latent tissue infections may reactivate and cause clinical disease with administration of immunosuppressive drug therapy. Disease resulting from infection reactivation has been noted with viruses (HSV, human herpesvirus-6, CMV, VZV, Epstein–Barr virus [EBV]), protozoa (*T. gondii*), and mycobacteria (*Mycobacterium tuberculosis*).[65-68] Serologic or immunologic tests are performed prior to transplantation to assess the risk for reactivation infection and identify other subclinical infections (eg, HBV, hepatitis C virus [HCV], *Legionella*). Many patients with reactivated infection have no clinical symptoms; often the only evidence of active infection is a rise in antibody titer from the pretransplant baseline, positive culture, increasing viral replication, or histologic evidence. Reactivation of latent infection may result in severe life-threatening disease in immunosuppressed hosts.[56,58,66,67]

Exogenous sources of infection in transplant patients include environmental contamination and transmission of microorganisms via transplanted organs and blood products. Environmental sources of infection are similar to those noted in other immunocompromised hosts, such as patients with cancer. Airborne pathogens, especially fungi such as *Aspergillus* and *Cryptococcus neoformans*, may cause infections in transplant patients; environmental exposure is an established risk factor for invasive mold infections among lung transplant patients.[63] Travel to areas of geographically endemic mycoses (eg, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*) or animal exposures may broaden infectious risk.[56] SOT recipients are also at high risk for nosocomial infections (MRSA, *P. aeruginosa*, *Acinetobacter*). Optimal prevention and management of nosocomial infections in transplant patients require knowledge of the current epidemiology of infections and susceptibility patterns within an institution.[56,57,60,61]

Infections transmitted via donor organs or blood products are major causes of morbidity and mortality in transplant patients and may include HSV, *T. gondii*, HBV, and HCV. The most important infections transmitted from the donor, however, are caused by CMV.[67-69] These infections may cause serious disease, predispose patients to other opportunistic infections, and contribute to acute and chronic allograft dysfunction or rejection, post-transplant lymphoproliferative disorders (particularly associated with EBV), and cardiac complications and atherosclerosis in heart transplant recipients.[67-69] In contrast to reactivation disease, transplant patients contracting primary CMV disease are at increased risk for serious life-threatening infections.[56,58,67-69] The most important source of primary CMV infection in transplant patients is the donor organ. Efforts are made to avoid transplanting organs from CMV-seropositive donors into CMV-seronegative recipients because of the potentially severe consequences. With the relative scarcity of suitable organs and the rapidity with which transplant decisions often must be made, however, this is not always possible. The consequences of transplanting an organ from a CMV-seropositive donor into an already CMV-seropositive recipient are less clear. CMV reinfection (as well as reactivation) syndromes may occur in these patients and antilymphocyte immunosuppression may increase the risk of complications.[56,59,67,69] Conversely, mammalian target of rapamycin (mTOR) inhibitors as part of a chronic immunosuppressive regimen may decrease the risk of CMV infection and related disease.[67,69] CMV serostatus, net immunosuppression, and organ type (among others factors) inform the practitioner of risk to determine an appropriate preventative strategy.[56,59,67,69] Furthermore, primary CMV disease may be transmitted from seropositive blood products. The availability of leukoreduced and CMV-seronegative blood products has decreased the risk of transmission but has not eliminated it.

Organs from donors seropositive for *T. gondii* or HSV generally are not withheld from seronegative patients as effective prophylaxis is common. Organs from known HIV-infected donors may now be used for transplantation in HIV-infected recipients (the HIV Organ Policy Equity Act) and outcomes of a limited number of transplanted patients have been favorable thus far.[70] Center-specific and HIV-specific criteria often apply, but in general those stable on antiretroviral therapy with well-controlled disease may be considered for SOT (as well as HCT) without prohibitively high risk for acceleration of HIV disease or opportunistic infections beyond what would be expected in other transplant recipients. The impact of protease inhibitors and highly active antiretroviral therapy on long-term outcome of HIV-infected patients following transplantation is believed to have improved the overall feasibility of transplanting these individuals.[70,71] Similarly, with highly effective therapies now available, organs from HCV-infected donors may be used for transplantation in HCV-infected recipients (and in some cases HCV-negative recipients).[70,72]

Timing of Infections After Transplantation

As with HCT, the overall time course for infections can be divided into three general periods after transplantation (see Fig. 145-3).[56,57] Although risk of infection with specific pathogens varies with the type of transplant, the time course of infections is similar in all transplant recipients. During the early post-transplant period (within the first month after transplantation), patients are at risk for infections already present and brought forward from the pretransplant period (eg, HBV, HCV, HIV); postoperative infections, such as surgical wound and catheter infections; infection resulting from colonized donor organs (pneumonia following lung transplant); and reactivation of HSV.[56,57,67] In the intermediate post-transplant period (1-6 months after transplant), risk is highest for viral infections, including CMV, EBV, HBV, and HCV. The combination of these "immunomodulating" viruses plus sustained immunosuppressive therapy leads to a high risk for opportunistic infections with pathogens such as *P. jirovecii*, *Aspergillus*, and *Nocardia asteroides*.[56-58] In the late post-transplant period (greater than 6 months after transplant), patients are at risk for persistent infections (particularly viral) from earlier post-transplant periods, reactivation of VZV and *Cryptococcus neoformans*, and routine infections affecting the general population.[56,57] In addition, patients who required additional immunosuppression therapy for acute or chronic rejection are at continued high risk for opportunistic infections (*Aspergillus* and *P. jirovecii*).[56,57] Although Fig. 145-3 illustrates infection patterns common to all solid-organ transplants, the relative incidence and importance of a particular pathogen vary according to the type of transplant, immunosuppression, and prophylaxis measures.

Types of Infections and Clinical Presentation

10 Transplant patients are at risk for infections occurring at a variety of sites, including skin, surgical wound, urinary tract, lungs, blood, abdomen, and CNS. However, most infections occur at or near the site of the transplanted organ. For example, heart transplant and heart-lung transplant recipients most often are infected within the lungs or thoracic cavity. Urinary tract infections remain an important cause of morbidity in renal transplant patients, especially in the early posttransplant period. Administration of prophylactic antibiotics (eg, trimethoprim–sulfamethoxazole) to these patients has reduced the incidence and severity of urinary tract infections.[4,69] Serious bacterial and fungal infections originating from the abdomen and GI tract are most common after liver transplantation and are related to variables such as length of surgery and surgical procedures performed. Risk of bacteremia, usually originating from the gut, is high in liver transplant patients. Renal transplant recipients are at the lowest risk for infections and infectious deaths, whereas patients receiving heart, lung, and liver transplants are at the highest risk for infection-related morbidity and mortality.[61,73]

In contrast to patients with febrile neutropenia, the threshold for initiating empirical antimicrobial therapy is higher in febrile transplant patients. Appropriate therapy for the large numbers of pathogens that may cause infections in transplant patients varies greatly from organism to organism (Table 145-6). Therefore, careful attempts at definitive diagnosis of suspected infections must be made. If comprehensive workup reveals no source of infection, careful observation of the febrile transplant patient (rather than empirical therapy) is common practice. Surveillance cultures and weekly quantitative amplification nucleic acid testing of CMV may be useful during the first 3 to 4 months for detecting CMV infections if the patient is not receiving prophylaxis.[56,67,69] Management and monitoring of documented infections are similar to that in other types of patients.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Infections in Solid-organ Transplant Patients

General

- Because transplant patients are at high risk for serious infections, frequent (at least daily), careful clinical assessments must be performed to search for evidence of infection
- Clinical presentation of infection is variable and depends on the type and site of infection, type of transplant, time after transplantation, immune status of the host, and dose and duration of immunosuppressive therapy
- Primary viral disease usually is more symptomatic and severe than disease caused by reactivation
- Physical assessment should include examination of all common sites of infection, including mouth/pharynx, nose and sinuses, respiratory tract, GI tract, urinary tract, skin, soft tissues, perineum, and intravascular catheter insertion sites

Symptoms

- Usual signs and symptoms of infection may be absent or altered in patients receiving intensive immunosuppressive regimens owing to an inability to mount a typical inflammatory response (eg, no infiltrate on chest x-ray film, urinary tract infection without pyuria)
- Pain may be present at infection site(s)

Signs

- Fever is the single most important clinical sign indicating the presence of infection, though it may not be present in all infected patients. Other causes of fever unrelated to infection in this patient population include reactions to blood products, drugs, embolic events, and ischemic injury
- Usual signs of infection may be absent or altered
- Signs of allograft dysfunction may be related to infection. Distinguishing fever caused by allograft rejection from that caused by infection often is difficult and frequently requires allograft biopsy

Laboratory Tests

- Blood cultures (at least two sets, including vascular access devices) for bacteria and fungi; cultures of other suspected or potential infection sites (urine, lungs, surgical wounds, and soft tissue infections)
- Other cultures should be obtained as clinically indicated according to the presence of signs or symptoms
- Complete blood count and chemistries should be obtained frequently to monitor allograft function, plan supportive care, guide drug dosing, and assess patient's overall status
- Surveillance testing for CMV and HSV may be useful during first 3 months after transplantation for early detection of infection

Other Diagnostic Tests

- Chest x-ray
- Aspiration, biopsy of skin lesions
- Other diagnostic tests as indicated clinically on the basis of physical examination and other assessments

PREVENTION AND TREATMENT

Desired Outcomes

The goals of therapy in managing SOT recipients are similar to those in HCT and include: (a) protect the patient from early death caused by undiagnosed infection, from the surgical procedure through the late postengraftment period; (b) prevent common bacterial, fungal, viral, and protozoal/parasitic infections; (c) effectively and aggressively treat established infections; (d) avoid unnecessary use of antimicrobials; and (e) minimize toxicities and cost while increasing patient quality of life and avoiding harm to the engrafted organ(s).

Prevention of Infection in Solid-Organ Transplantation

8 The goals of antimicrobial drug use in solid-organ transplant recipients are (a) prevention of infectious complications in the immediate postoperative period, (b) prevention of late infectious complications associated with prolonged periods of immunosuppression, and (c) effective treatment of established infections in order to prevent graft dysfunction and rejection and decrease patient morbidity and mortality. All of these goals must be achieved at the lowest possible toxicity and cost.

Prevention of infection in the transplant patient can be accomplished in several ways. First, risk of environmental contamination should be minimized.[56] Patients should be protected from institutional infectious outbreaks. Efforts should be made to vaccinate organ transplant candidates prior to transplantation whenever possible for vaccine preventable disease based on age and anticipated risk factors post-transplant. Live vaccines should be given more than 4 weeks in advance from the time of anticipated transplantation.[48] Transplant recipients should receive influenza vaccination annually, pneumococcal (PCV13 and/or PPSV23 separated by 8 weeks), hepatitis A and B vaccination series (if indicated, ideally started pretransplant), HPV series (if indicated), zoster series, and Tdap generally 2 months or greater following transplantation; however, their immunologic responses to these vaccines may be suboptimal due to immunosuppressive therapy.[48] Timing of reinstitution of regular vaccinations in relation to transplantation is not absolute, but live-attenuated vaccines (varicella, zoster, MMR) should be avoided early post transplantation, if not altogether, similar to recommendations for HCT.[48] An exception is made for varicella seronegative pediatric liver and kidney transplant recipients who are on low levels of immunosuppression without recent graft rejection.[48]

Because the most important source of primary CMV infection is an infected donor organ, CMV serostatus should be evaluated in all recipients and donors. Two standard strategies to manage CMV in SOT recipients have been recommended. Preemptive therapy is effective for some populations (eg, kidney transplant) but requires weekly monitoring, close follow-up and appropriate risk stratification of patients for CMV-related complications. Prophylaxis is effective and easy to administer without the need for careful discrimination of suitable patients; but, universal prophylaxis results in unnecessary exposure (toxicities) and cost to low-risk patients (CMV serostatus donor negative, recipient negative).[67,69] The best approach to preventing CMV disease remains controversial and does require risk stratification as either preemptive therapy or prophylaxis can be appropriate depending on patient specific factors (including immunosuppressive strategy). Most experts agree that CMV prophylaxis is not required in donor negative, recipient negative SOT patients. These patients may qualify for antiviral prophylaxis targeted against other herpes infections (eg, acyclovir) or preemptive therapy.[56,60,69]

CMV prophylaxis is commonly recommended in high-risk patients (ie, seronegative patients receiving seropositive organs). Oral valganciclovir and IV ganciclovir prophylaxis are effective for reducing the incidence of both primary and reactivated CMV infection in SOT.[67,69] Prophylaxis is recommended as a preferred strategy in many CMV-seropositive SOT recipients partly due to a lack of well-designed studies comparing prophylaxis to preemptive therapy in all SOT types.[67,69] Additional risk factors for CMV disease, the associated clinical impact of “indirect effects” of CMV, and logistical barriers should be considered on an individual basis when designing a strategy. For example, valganciclovir prophylaxis has been recommended for all CMV positive lung transplant recipients in part due to very high risk of CMV disease and associated severe consequences of direct and indirect effects on the graft.[56,69] The duration of CMV prophylaxis is typically 3 to 12 months depending on donor and recipient CMV serology status, immunosuppressive regimen, and type of organ transplanted.[56,67,69] Because CMV replication and disease occurs in up to one-third of donor-positive/recipient-negative SOT recipients within 3 to 6 months after stopping prophylaxis (termed postprophylaxis delayed-onset CMV disease), continued surveillance after discontinuation of prophylaxis should be considered based on patient-specific risk stratification.[56,67,69] Ganciclovir or valganciclovir prophylaxis also may significantly reduce reactivation of CMV infection in seropositive patients receiving antithymocyte globulin for treatment of acute rejection.[67,69]

Prophylactic high-dose oral acyclovir or valacyclovir effectively reduces the incidence of CMV infection and disease following renal transplantation. However, acyclovir is less active against CMV and may be less efficacious in some high-risk renal or other nonrenal transplant patients; therefore,

valganciclovir is generally preferred if prophylaxis is required.[56,67,69] Acyclovir prophylaxis may be recommended for targeting other herpes viruses when the risk of CMV is low and should not be used to treat active CMV replication.[69,74]

Preemptive IV ganciclovir or valganciclovir is an effective strategy in many SOT recipients, but requires appropriate monitoring and a reliance on patient compliance. Additionally, no established thresholds have been clearly defined as a "cut-point" for initiation of preemptive valganciclovir when monitoring quantitative CMV copies (eg, absolute value, viral load kinetics, or viral doubling time).[67,69] Neither preemptive nor prophylaxis strategies are perfect for each situation. Therefore, it is imperative that each SOT center develop a method based on patient risk, logistics, and cost and continually assess patient risk with cumulative net immunosuppression in mind when prescribing a CMV preventative strategy.[67,69] Since ganciclovir-related bone marrow suppression is not as problematic in SOT recipients as in HCT recipients and valganciclovir is relatively well tolerated, many centers in the United States opt for a prophylactic strategy while also extending either duration or preemptive monitoring when additional risk factors (eg, intensified immunosuppression) are encountered.

The additional benefit of CMVIG compared to standard CMV prophylaxis in high risk heart, lung, and small bowel transplant recipients is controversial. Cohort-level evidence suggests some possible benefit and therefore some experts will add monthly infusions in special circumstances; however, the optimal role of CMVIG has yet to be established.[56,67,69]

The use of mTOR inhibitors (sirolimus, everolimus) as part of an immunosuppressive regimen in SOT recipients may be useful in prevention of CMV disease. mTOR inhibitors exert a marked anti-CMV effect through reduction in viral replication and/or potent immunomodulating properties.[75] In a meta-analysis, patients receiving immunosuppressant regimens containing mTOR inhibitors (with or without a calcineurin inhibitor [CNI]) displayed a nearly threefold reduction in CMV infections compared to patients receiving CNI alone.[75] Although mTOR inhibitors are associated with significantly lower CMV infection rates in most SOT recipients, CMV disease with related complications is only one of many factors that must be considered when designing an immunosuppressive regimen.[67,69]

Although use of prophylactic acyclovir in HSV-seropositive patients undergoing HCT is well accepted, prophylaxis in SOT recipients remains controversial. Reactivation disease caused by HSV occurs in approximately 25% of HSV-seropositive patients who are not receiving prophylaxis.[74] Mucocutaneous disease is the most common presentation, but nonmucocutantious HSV disease also is seen occasionally and is associated with significant morbidity and high mortality (eg, HSV pneumonitis).[74] Acyclovir is therefore used at some centers because of the high incidence of clinical HSV infection after transplantation. Acyclovir prophylaxis of HSV infection may be considered in patients following a preemptive strategy for management of CMV infection, but would not be necessary in patients receiving ganciclovir or valganciclovir for CMV prophylaxis.[56,74]

Prophylactic antimicrobial agents are also of benefit to SOT recipients in certain other clinical situations. Antibiotic prophylaxis, with agents such as cefazolin started perioperatively and continued for less than 24 hours, is considered to effectively reduce wound infection rates following renal transplantation.[62,73] Although the benefits of perioperative prophylaxis have not been well studied in other types of transplantation procedures, surgical prophylaxis usually is considered mandatory for pancreas, liver, heart, lung, or small bowel transplant patients because of the high risk of perioperative bacterial infections.[62,73] High rates of infection have been reported following liver and intestinal transplant often resulting from intra-abdominal pathogens (eg, gram-negative bacteria, *Enterococcus*, *Candida*, anaerobes) depending on patient, donor, and surgical risk factors. Broader surgical prophylaxis such as a third-generation cephalosporin plus ampicillin, ampicillin/sulbactam, or piperacillin/tazobactam have been recommended for liver transplant. An even broader approach with the addition of vancomycin and fluconazole has been suggested for intestinal transplant given the high risk of multidrug resistant and polymicrobial infection.[62] Pulmonary infections are particularly common in lung and heart-lung transplant recipients. They often are caused by bacteria colonizing the airways of the diseased organs prior to transplantation. Therefore, perioperative antibiotics for lung and heart-lung procedures often are selected based on pretransplant sputum cultures and/or known colonizations of the patient (including assist devices [eg, ventricular assist device or extracorporeal membrane oxygenation circuit]).[62]

Post-transplant antibiotic prophylaxis is effective in decreasing the number of bacterial infections in renal transplant patients. Prophylactic trimethoprim–sulfamethoxazole traditionally has been used because it is inexpensive and well tolerated; other antibiotics, such as the fluoroquinolones, also have been evaluated.[56] Administration of oral low-dose trimethoprim–sulfamethoxazole (one double-strength tablet, either daily or three times/week) for 6 to 12 months for prevention of *P. jirovecii* infection following heart and lung transplantation is common, although the efficacy and optimal duration are somewhat controversial.[56] Selective bowel decontamination with nonabsorbable antibiotics in combination with a

low-bacterial diet (no fresh fruits and vegetables) may reduce oropharyngeal and GI colonization with gram-negative aerobes and *Candida* in liver transplant patients; however, conclusive evidence of benefit is lacking and this practice is not recommended routinely.[62,73] Similarly, prebiotics and probiotics cannot be currently recommended.[62]

Because immunosuppressed transplant recipients are at risk for mucocutaneous fungal infections, prophylactic oral or topical antifungal agents may be indicated in these patients. Liver, pancreas, and small bowel transplant recipients are clearly at high risk for invasive fungal infections and should receive prophylaxis with fluconazole though the optimal duration remains unclear.[62,66] Antifungal prophylaxis has also been suggested for lung and heart-lung transplant recipients due to the high incidence of invasive fungal infections in these patients (up to 35% of patients, with mortality rates up to 60%).[64] Prophylaxis targeting *Aspergillus* spp. with inhaled amphotericin B or LAMB, or systemic regimens active against *Candida* and *Aspergillus* spp. such as itraconazole, voriconazole, posaconazole, and echinocandins have all been reported; however, data from well-designed trials supporting either the general recommendation for prophylaxis or choice of specific agent are largely lacking and center-to-center variability is great.[63,65,74] Oral voriconazole or inhaled LAMB for a period of 3 to 6 months post-transplant are most often recommended for prophylaxis of invasive fungal infection in lung and heart-lung transplant recipients.[63,64] However, prophylaxis out to a year or longer is not uncommon with oral triazole agents.[63,64] Concentrations of immunosuppressant drugs should be monitored closely in transplant patients receiving azole-type antifungal agents (fluconazole, itraconazole, and voriconazole).

Transplant patients, especially heart and heart-lung recipients, without serologic evidence of prior exposure to *T. gondii* who receive organs from seropositive donors are at high risk for toxoplasmosis.[56] Many of these patients will be receiving trimethoprim–sulfamethoxazole for prophylaxis of *P. jirovecii* infection; this agent will also provide effective prophylaxis against *T. gondii* as well as *N. asteroides*. Although prophylaxis specifically for *T. gondii* is not given routinely at all centers, this therapy for a period of up to 12 months may be justified in high-risk patients because of the delays in diagnosis and serious infections associated with toxoplasmosis.[56,71]

ABBREVIATIONS

ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
CAR-T	chimeric antigen receptor T cell
CDI	*Clostridioides difficile* infection
CISNE	Clinical Index of Stable Febrile Neutropenia
CMV	cytomegalovirus
CMVIG	cytomegalovirus hyperimmune globulin
CNT	calcineurin inhibitor
CRE	carbapenem-resistant Enterobacterales
CSF	colony-stimulating factor
EBV	Epstein–Barr virus
ESBL	extended-spectrum β-lactamases
GI	gastrointestinal

GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HCT	hematopoietic cell transplantation
HSV	herpes simplex virus
IDSA	Infectious Diseases Society of America
IVIG	intravenous immunoglobulin
LAMB	lipid-associated amphotericin B
MASCC	Multinational Association for Supportive Care in Cancer
MDR	multidrug resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
NCCN	National Comprehensive Cancer Network
PCR	polymerase chain reaction
PCT	procalcitonin
PMN	polymorphonuclear leukocyte
SOT	solid-organ transplantation
VRE	vancomycin-resistant enterococci
VZV	varicella-zoster virus
WBC	white blood cell

REFERENCES

1. Freifeld AG, Bow EJ, Sepiowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Disease Society of America. *Clin Infect Dis.* 2011;52(4):e56–e93. 10.1093/cid/cir073.

2. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol.* 2018;36:1443–1453. doi: 10.1200/JCO.2017.77.6211.

3. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. *Clin Rev Oncol Hematol.* 2014;90:190–199. doi: 10.1016/j.critrevonc.2013.12.006.

4. National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), v.1.2021. July 2, 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed October 2, 2021.

5. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. *Virulence*. 2016;7:280–297. doi: 10.1080/21505594.2016.1156821.

6. Logan C, Koura D, Taplitz R. Updates in infection risk and management in acute leukemia. *Hematol.* 2020;1:135–139. doi: 10.1182/hematology.2020000098.

7. Marin M, Gudiol C, Ardanuy C, et al. Factors influencing mortality in neutropenic patients with haemotologic malignancies or solid tumours with bloodstream infection. *Clin Microbiol Infect.* 2015;21:583–590. doi: 10.1016/j.cmi.2015.01.029.

8. Cesar-Arce A, Volkow-Fernandez P, Valero-Saldana LM, et al. Infectious complications and multidrug-resistant bacteria in patients with hematopoietic stem cell transplantation in the first 12 months after transplant. *Transplant Proc.* 2017;49:1444–1448. doi: 10.1016/j.transproceed.2017.03.081.

9. Rolston KV. Neutropenic fever and sepsis: Evaluation and management. *Cancer Treat Res.* 2014;161:181–202. 10.1007/978-3-319-04220-6_6.

10. Dumford D, Skalweit MJ. Antibiotic-resistant infections and treatment challenges in the immunocompromised host. An update. *Infect Dis Clin N Am.* 2020;34:821–847. 10.1016/j.idc.2020.08.005.

11. Trecarichi EM, Tumbarello M. Antimicrobial-resistant gram-negative bacteria in febrile neutropenic patients with cancer: Current epidemiology and clinical impact. *Curr Opin Infect Dis.* 2014;27:200–210. doi: 10.1097/QCO.0000000000000038.

12. Zhang S, Wang Q, Ling Y, et al. Fluoroquinolone resistance in bacteremic and low risk febrile neutropenic patients with cancer. *BMC Cancer*. 2015;15:42–46. doi: 10.1186/s12885-015-1063-x.

13. Seagle EE, Williams SL, Chiller TM. Recent trends in epidemiology of fungal infections. *Infect Dis Clin N Am.* 2021;35:237–260. doi: 10.1016/j.idc.2021.03.001.

14. Hidron A, Edwards JR, Patel J, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol.* 2016;37:1288–1301. doi: 10.1017/ice.2016.174.

15. Nelson RE, Jones M, Lie CF, et al. The impact of healthcare-associated methicillin-resistant *Staphylococcus aureus* infections on post-discharge healthcare costs and utilization. *Infect Control Hosp Epidemiol.* 2015;36(5):534–542. 10.1017/ice.2015.22.

16. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and site of involvement of invasive fungal infections in patients with haematological malignancies: A 20-year autopsy study. *Mycoses*. 2013;56:638–645. doi: 10.1111/myc.12081.

17. Chen K, Wang Q, Pleasants RA, et al. Empiric treatment against invasive fungal diseases in febrile neutropenic patients: A systematic review and network meta-analysis. *BMC Infect Dis.* 2017;17:159–170. doi: 10.1186/s12879-017-2263-6.

18. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016:62:e1–e50. doi: 10.1093/cid/civ933.

19. Wu P-F, Liu W-L, Hsieh M-H, et al. Epidemiology and antifungal susceptibility of candidemia isolates of non-*albicans Candida* species from cancer

patients. *Emerg Microbes Infect.* 2017;6:e87. doi: 10.1038/emi.2017.74.

20. van de Peppel RJ, Visser LG, Dekkers OM, et al. The burden of invasive aspergillosis in patients with haemotological malignancy: A meta-analysis and systematic review. *J Infect.* 2018;76:550–562. doi: 10.1016/j.jinf.2018.02.012.

21. Patterson TF, Thompson GR, Deming DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63:e1–e60. doi: 10.1093/cid/ciw326.

22. Wu C-W, Wu J-Y, Chen C-K, et al. Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis. *Support Care Cancer*. 2015;23:2863–2872. doi: 10.1007/s00520-015-2650-8.

23. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol.* 2018;36:3043–3054. doi: 10.1200/JCO.18.00374.

24. Kim YJ, Jun YH, Kim YR, et al. Risk factors for mortality with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. *BMC Infect Dis.* 2014;14:161–167. doi: 10.2147/IDR.S268744.

25. Beyar-Katz O, Dickstein Y, Borok S, et al. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. *Cochrane Database Syst Rev.* 2017;6(6):CD003914. doi: 10.1002/14651858.

26. Gouliouris T, Warne B, Cartwright EJP, et al. Duration of exposure to multiple antibiotics is associated with increased risk of VRE bacteraemia: A nested case-control study. *J Antimicrob Chemother.* 2018;73:1692–1699. 10.1093/jac/dky075.

27. Hirai K, Ishii H, Shimoshikiryo T, et al. Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic vancomycin concentrations. *Ther Drug Monit.* 2016;38:706–710. doi: 10.1097/FTD.0000000000000346.

28. Ruhnke M, Cornely OA, Schmidt-Hieber M, et al. Treatment of invasive fungal diseases in cancer patients—Revised 2019 recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Mycoses*. 2020;63:653–682. 10.1111/myc.13082.

29. Blyth CC, Gilroy NM, Guy SD, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. *Intern Med J.* 2014;44(12b):1333–1349. doi: 10.1111/imj.12598.

30. Omrani AS, Almaghrabi RS. Complications of hematopoietic stem cell transplantation: Fungal infections. *Hematol Oncol Stem Cell Ther.* 2017;10:239–244. doi: 10.1016/j.hemonc.2017.05.013.

31. John J, Loo A, Mazur S, et al. Therapeutic drug monitoring of systemic antifungal agents: A pragmatic approach for adult and pediatric patients. *Expert Opin Drug Metab Toxicol.* 2019;15:881–895. 10.1080/17425255.2019.1671971.

32. Mhaskar R, Clark OA, Lyman G, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. *Cochrane Database Syst Rev.* 2014;10:CD003039. doi: 10.1002/14651858.CD003039.pub2.

33. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2015;33:3199–3212. doi: 10.1200/JCO.2015.62.3488.

34. National Comprehensive Cancer Network. Hematopoietic growth factors. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), v.4.2021; May 20, 2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed October 6, 2021.

35. Cugno C, Deola S, Filippini P, et al. Granulocyte transfusions in children and adults with hematological malignancies: Benefits and controversies. *J Transl Med.* 2015;13:362–378. doi: 10.1186/s12967-015-0724-5.

36. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev.* 2014;1:CD004386. doi: 10.1002/14651858.CD004386.pub3.

37. Ethier MC, Science M, Beyene J, et al. Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patient receiving chemotherapy or haematopoietic stem-cell transplantation: A systematic review and meta-analysis of randomized controlled trials. *Br J Cancer*. 2012;106:1626–1637. doi: 10.1038/bjc.2012.147.

38. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guidelines for vaccination of the immunocompromised host. *Clin Infect Dis.* 2014;58:e44–e100. doi: 10.1093/cid/cit816.

39. Dandoy CE, Ardura MI, Papnicalaou GA, Auletta JJ. Bacterial bloodstream infections in the allogeneic hematopoietic cell transplant patient: New considerations for a persistent nemesis. *Bone Marrow Transpl.* 2017;52:1091–1106. doi: 10.1038/bmt.2017.14.

40. Miller HK, Braun TM, Stillwell T, et al. Infectious risk after allogeneic hematopoietic cell transplantation complicated by acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2017;23:522–528. doi: 10.1016/j.bbmt.2016.12.630.

41. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in hematopoietic cell transplant recipients: Results from the organ transplant infection project, a multicenter, prospective, cohort study. *Open Forum Infect Dis.* 2017;4(2):ofx050. 10.1093/ofid/ofx050.

42. Battiwalla M, Tichelli A, Majhail NS. Long-term survivorship after hematopoietic cell transplantation: Roadmap for research and care. *Biol Blood Marrow Transplant.* 2017;23:184–192. doi: 10.1016/j.bbmt.2016.11.004.

43. Misch EA, Andes DR. Bacterial infections in the stem cell recipient and hematologic malignancy patient. *Infect Dis Clin N Am.* 2019;33:399–445. doi: 10.1016/j.idc.2019.02.011.

44. Ullmann AJ, Schmidt-Hieber M, Bertz H, et al. Infectious diseases in allogeneic haematopoietic stem cell transplantation: Prevention and prophylaxis strategy guidelines 2016. *Ann Hematol.* 2016;95:1435–1455. doi: 10.1007/s00277-016-2711-1.

45. Lin R, Liu Q. Diagnosis and treatment of viral diseases in recipients of allogeneic hematopoietic stem cell transplantation. *J Hematol Oncol.* 2013;6:94. doi: 10.1186/1756-8722-6-94.

46. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell trans-plantation. *N Engl J Med.* 2017;377:2433–2444. doi: 10.1056/NEJMoa1706640.

47. Neofytos D. Antimicrobial prophylaxis and preemptive approaches for the prevention of infections in the stem cell transplant recipient, with analogies to the hematologic malignancy patient. *Infect Dis Clin N Am.* 2019;33:361–380. doi: 10.1016/j.idc.2019.02.002.

48. Chong PP, Avery RK. A comprehensive review of immunization practices in solid organ transplant and hematopoietic stem cell transplant recipients. *Clin Ther.* 2017;39:1581–1598. doi: 10.1016/j.clinthera.2017.07.005.

49. Shingles (herpes zoster vaccination information for healthcare providers. Available at: https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html. Accessed October 3, 2021.

50. Winston DJ, Mullane KM, Cornely OA, et al. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: An international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:2116. doi: 10.1016/S0140-6736(18)30631-7.

51. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: Intercontinental prospective study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. *Clin Infect Dis.* 2017;65:1819–1828. 10.1093/cid/cix646.

52. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG: United States, 2013. *MMWR.* 2013;62(28):574–576.

53. Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: A randomized trial. *Ann Intern Med.* 2015;162:1–10. doi: 10.7326/M13-2729.

54. Britt WJ. Cytomegalovirus. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Philadelphia, PA: Elsevier, Inc.; 2020:1857–1871.e3.

55. United States Department of Health & Human Services Organ Procurement and Transportation Network. Available at: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed October 10, 2021.

56. Fishman JA. Infection in organ transplantation. *Am J Transplant.* 2017;17:856–879. doi: 10.1111/ajt.14208.

57. Guenette A, Husain S. Infectious complications following solid organ transplantation. *Crit Care Clin.* 2019;35:151–168. doi: 10.1016/j.ccc.2018.08.004.

58. Hosseini-Moghaddam SM, Shokoohi M, Singh G, et al. A multi-center case-control study of the effect of acute rejection and cytomegalovirus infection on pneumocystis pneumonia (PCP) in solid organ transplant recipients. *Clin Infect Dis.* 2018; doi: 10.1093/cid/ciy682.

59. Fischer SA, Lu K. American Society of Transplantation Infectious Disease Community of Practice. Screening of donor and recipient in solid organ transplantation. *Am J Transplant.* 2013;13:9–21. doi: 10.1111/ajt.12094.

60. Gagliotti C, Morsillo F, Moro ML, et al. Infectious in liver and lung transplant recipients: A national prospective cohort. *Eur J Clin Microbiol Infect Dis.* 2018;37:399–407. doi: 10.1007/s10096-018-3183-0.

61. Hamandi B, Husain S, Grootendorst P, Papadimitropoulos EA. Clinical and microbiological epidemiology of early and late infectious complications among solid-organ transplant recipients requiring hospitalization. *Transpl Int.* 2016;29:1029–1038. doi: 10.1111/tri.12808.

62. Anesi JA, Blumberg EA, Abbo LM. Perioperative antibiotic prophylaxis to prevent surgical site infections in solid organ transplantation. *Transplantation*. 2018;102:21–34. doi: 10.1097/TP.0000000000001848.

63. Kennedy CC, Razonable RR. Fungal infections after lung transplantation. *Clin Chest Med.* 2017;38:511–520. doi: 10.1016/j.ccm.2017.04.011.

64. Kabir V, Maertens J, Kuypers D. Fungal infections in solid organ transplantation: An update on diagnosis and treatment. *Transplant Rev.* 2019;33:77–86. 10.1016/j.trre.2018.12.001.

65. Schwartz IS, Patterson TF. The emerging threat of antifungal resistance in transplant infectious disease. *Curr Infect Dis Rep.* 2018;20:2. doi: 10.1007/s11908-018-0608-y.

66. Andes DR, Safdar N, Baddley JW, et al. The epidemiology and outcomes of invasive *Candida* infections among organ transplant recipients in the United States: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Transpl Infect Dis.* 2016;18:921–931. 10.1111/tid.12613.

67. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*. 2018;102(6):900–931. doi: 10.1097/TP.0000000000002191.

68. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019;33:e13512. 10.1111/ctr.13512.

69. Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. *Am J Transplant.* 2015;15:3024–3040. doi: 10.1111/ajt.13486.

70. Boyarsky BJ, Strauss AT, Segev DL. Transplanting organs from donors with HIV or hepatitis C: The viral frontier. *World J Surg.* 2021;45:3503–3510.

10.1007/s00268-020-05924-1.

71. Muller E, Barday Z, Mendelson M, et al. HIV-positive-to-HIV-positive kidney transplantation—Results at 3 to 5 years. *N Engl J Med.* 2015;372(7):613–620. 10.1056/NEJMoa1408896.

72. Levitsky J, Formica RN, Bloom RD, et al. The American Society of Transplantation Consensus Conference on the user of hepatitis C viremic donors in solid organ transplantation. *Am J Transplant.* 2017;17:2790–2802. 10.1111/ajt.14381.

73. Kritkos A, Manuel O. Bloodstream infections after solid-organ transplantation. *Virulence*. 2016;7(3):329–340. doi: 10.1080/21505594.2016.1139279.

74. Martin-Gandul C, Stampf S, Héquet D, et al. Preventive strategies against cytomegalovirus and incidence of α-herpesvirus infections in solid organ transplant recipients: A nationwide cohort study. *Am J Transplant.* 2017;17:1813–1822. doi: 10.1111/ajt.14192.

75. Andrassy J, Hoffmann VS, Rentsch M, et al. Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? A systematic review and meta-analysis. *Transplantation*. 2012;94:1208–1217. doi: 10.1097/TP.0b013e3182708e56.

SELF-ASSESSMENT QUESTIONS

1. What is the most important risk factor for development of severe infections in cancer patients?
   A. Alteration of normal flora by chemotherapy and antimicrobial therapy
   B. Prolonged neutropenia
   C. Severe mucositis
   D. Humoral and cellular immune system defects
2. The most common bacterial microorganism(s) causing infections in neutropenic cancer patients is/are:
   A. *Klebsiella pneumonia* and *Escherichia coli*
   B. *Pseudomonas aeruginosa*
   C. Staphylococci and streptococci
   D. *Clostridium* species
3. All of the following are appropriate antibiotic de-escalation strategies for antimicrobial coverage after a period of febrile neutropenia, except:
   A. Antibiotics can be discontinued after an appropriate duration for the isolated organism and site, provided neutropenia has resolved
   B. In low-risk patients, empiric therapy can be de-escalated to an oral regimen after 2 days of intravenous therapy provided the patient is now afebrile and has no evidence of infection
   C. In high-risk patients, empiric therapy should be de-escalated to narrow spectrum agents once an organism is isolated to prevent antibiotic resistance
   D. All of the above are appropriate antibiotic de-escalation strategies
4. Which of the following antibiotic regimens is preferred for the initial management of an episode of febrile neutropenia in a hemodynamically stable patient with a MASCC score <21?

A. Intravenous piperacillin/tazobactam

B. Intravenous cefepime plus ciprofloxacin

C. Intravenous meropenem plus vancomycin

D. Intravenous ceftaroline

5. Which of the following statements regarding initial empiric vancomycin therapy in febrile neutropenic patients with cancer is false?

A. All initial empiric regimens should contain vancomycin.

B. Patients with evidence of IV catheter infections may benefit from initial empiric therapy with vancomycin.

C. Decreased mortality from penicillin-resistant viridans streptococcal infections has been observed with initial empiric vancomycin therapy.

D. If empiric vancomycin therapy is initiated and no evidence of gram-positive infection is found after 24 to 48 hours, vancomycin should be discontinued.

6. All of the following antimicrobials are reasonable options for prophylaxis of infections in a HCT recipient expected to be profoundly neutropenic for >7 days, except:

A. Levofloxacin

B. Posaconazole

C. Acyclovir

D. Aztreonam

7. Which of the following antibiotic regimens is/are preferred for managing episodes of febrile neutropenia in low-risk patients?

A. Ciprofloxacin plus amoxicillin/clavulanate

B. Vancomycin plus levofloxacin

C. Ciprofloxacin plus clindamycin

D. Metronidazole plus moxifloxacin

8. All of the following infections would be anticipated during the immediate period (within approximately 1 month) after lung transplantation, except:

A. Surgical wound infections

B. Pneumonia

C. Cytomegalovirus (CMV) disease in a patient who was CMV-seronegative before transplantation

D. Reactivation of herpes simplex virus (HSV) infection in a patient who was HSV-seropositive before transplantation

9. Patients undergoing hematopoietic cell transplantation are at significant risk for infection in all of the following scenarios, except:

A. Primary or recurrent Varicella Zoster Virus infection in a patient with graft-versus-host disease

B. Cytomegalovirus (CMV) infection in a CMV-seronegative recipient receiving stem cell donations from a CMV-seropositive donor

C. *Candida* or *Aspergillus* infections in patients receiving allogeneic hematopoietic cell transplants

D. All of the above are scenarios in which patients are at high risk of infection

10. Compared to monotherapy, which of the following is true regarding the use of empiric dual-gram-negative coverage for high-risk febrile neutropenic patients:

A. Dual therapy is associated with a greater risk of drug-related adverse effects

B. Dual therapy is associated with a greater risk of breakthrough resistant infections

C. Dual therapy is associated with a lower risk of 30-day mortality

D. Dual therapy is associated with a lower risk of secondary fungal infections

11. Patients undergoing hematopoietic stem cell transplantation are routinely recommended to receive all of the following vaccinations within 2 years of transplant, except:

A. *Haemophilus influenzae* type B vaccine

B. Varicella vaccine

C. 23-valent pneumococcal vaccine

D. Influenza vaccine

12. Which of the following regimens would be most appropriate for prophylaxis of *Pneumocystis jirovecii* infection in a double-lung transplant recipient?

A. Trimethoprim–sulfamethoxazole two double-strength tablet orally twice daily

B. Trimethoprim–sulfamethoxazole one double-strength tablet orally once daily

C. Pentamidine 4 mg/kg intravenously once daily

D. Pentamidine 300 mg inhaled once monthly

13. Therapeutic drug monitoring is recommended during use of all of the following agents, except:

A. Voriconazole

B. Vancomycin

C. Posaconazole

D. Isavuconazonium

14. An appropriate regimen for the treatment of confirmed invasive pulmonary aspergillosis in a neutropenic cancer patient would be:

A. Fluconazole 800 mg intravenously × one dose, followed by 400 mg intravenously once daily

B. Liposomal amphotericin B 1 mg/kg intravenously once daily

C. Voriconazole 6 mg/kg intravenously twice daily × two doses, followed by 4 mg/kg intravenously twice daily

D. All of the above would be appropriate regimens for the stated patient

15. A 45-year-old female undergoes hematopoietic stem cell transplantation for advanced metastatic breast cancer and develops cytomegalovirus disease 2 months after transplantation. She is started on ganciclovir 5 mg/kg intravenously every 12 hours. The most important ganciclovir-related adverse effect that should be carefully monitored for in this patient would be:

A. Bone marrow suppression

B. Mucositis

C. Nephrotoxicity

D. Central nervous system toxicities

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Although the other listed factors are important, the duration of neutropenia is the most critical risk factor for the development of severe infections in cancer patients. See the Introduction ("Risk Factors for Infection/Epidemiology") section of the chapter for more information.

2. **C.** Although infection with many different bacterial pathogens are possible and/or relatively common, the majority of infections are caused by gram-positive bacteria including staphylococci and streptococci. See the "Etiology of Infections in Neutropenic Patients with Cancer" section of the chapter for more information.

3. **D.** All of the given options are potentially appropriate de-escalation strategies depending on laboratory results, clinical response to therapy, and continued risk factors for infection in individual patients, for example, continued neutropenia. See the Treatment ("Antimicrobial Therapy After Initiation of Empirical Therapy") section of the chapter for more information.

4. **A.** Patients with MASCC score <21 should be initially treated with broad-spectrum intravenous therapy that covers gram-negative bacteria (including *Pseudomonas aeruginosa*) as well as gram-positive bacteria. However, monotherapy is as effective as combination regimens for initial therapy and is preferred in most patients. See the Treatment ("Approach to Treatment") section of the chapter for more information.

5. **A.** Vancomycin may be included as part of the initial empiric antimicrobial regimen in carefully selected patients, but is not appropriate for all patients with neutropenic fever and should not be routinely used in all cases. See the Treatment ("Empirical Regimens Containing Vancomycin") section of the chapter for more information.

6. **D.** Prophylaxis with orally administered, systemically available antibiotics is effective at reducing gram-negative infections and is recommended for selected high-risk patients. Prophylaxis with antiviral and antifungal agents may also be appropriate in selected high-risk patients. See the Treatment ("Prophylaxis of Infections in Neutropenic Patients with Cancer") section of the chapter for more information.

7. **A.** Oral ciprofloxacin plus amoxicillin/clavulanate is the preferred antibiotic regimen for treatment of neutropenic fever in low-risk patients due to appropriate antibacterial coverage and favorable data from clinical studies. See the Treatment ("Oral Antibiotic Therapy for Management of Febrile Neutropenia") section of the chapter for more information.

8. **C.** Infections in the immediate post-transplant period typically involve infections at the site of the transplant, infections of the transplanted organ itself, or reactivation of existing infections. Cytomegalovirus-related disease typically occurs 1 to 6 months after transplantation. See the "Infections in Solid-Organ transplant Recipients" ("Timing of Infections After Transplantation") section of the chapter for more information.

9. **D.** Patients undergoing HCT are at high risk for a wide variety of infections due to prolonged periods of profound immunosuppression. These infections include reactivation of existing infections as well as diseases caused by acquisition of new bacterial, viral, and fungal pathogens. See the "Infections in Patients Undergoing HCT" ("Etiology and Clinical Presentation of Infections") section of the chapter for more information.

10. **A.** Dual, or combination, initial therapy of febrile neutropenia has not been proven to improve overall patients outcomes (eg, decreased mortality, decreased antibiotic resistance) but may result in increased rates of adverse drug effects compared to β-lactam monotherapy. See the Treatment ("Approach to Treatment") section of the chapter for more information.

11. **B.** VZV-seronegative patients undergoing HCT may be considered for receipt of the varicella vaccine to prevent primary infection. However, due to the live-virus nature of the product the varicella vaccine should generally not be administered within at least 24 months following transplantation. See the "Infections in Patients Undergoing HCT" ("Prophylaxis and Management of Infections in Recipients of HCT") section of the chapter for more information.

12. **B.** Trimethoprim–sulfamethoxazole administered once daily is the preferred regimen for prevention of *P. jirovecii* infections in transplant recipients. See the "Infections in Solid-Organ Transplant Recipients" ("Prevention of Infection in Solid-Organ Transplantation") section of the chapter for more information.

13. **D.** Therapeutic drug monitoring of isavuconazonium is not currently recommended due to lack of recommended target concentrations and unavailability of drug assays. See the Treatment ("Empirical Regimens Containing Vancomycin") and Treatment ("Initiation of Antifungal Therapy") sections of the chapter for more information.

14. **C.** Voriconazole is the preferred agent for initial therapy of invasive *Aspergillus* infections, including pulmonary aspergillosis, because of proven efficacy and fewer toxicities compared to amphotericin B products. See the Treatment ("Initiation of Antifungal Therapy") section of the chapter for more information.

15. **A.** Although considered the drug of choice for most patients with invasive CMV disease, ganciclovir's potential for myelosuppressive toxicity is an important consideration in patients who have undergone HCT. See the "Infections in Patients Undergoing HCT" ("Viral Infections") section of the chapter for more information.