76 Infectious Complications of Cancer Therapy

Nasia Safdar, Christopher J. Crnich, and Dennis G. Maki

Advances in the management of cancer, particularly the development of new chemotherapeutic agents, have greatly improved the survival and outcome of patients with hematologic malignancies and solid tumors; overall 5-year survival rates in cancer patients have improved from 39% in the 1960s to 60% in the 1990s.[1] However, infection, caused by both the underlying malignancy and cancer chemotherapy, particularly myelosuppressive chemotherapy, remains a persistent challenge.[2]

Impairment of Immunity with Cancer and Treatment of Cancer

Infection occurs commonly during treatment of cancer; 80% of patients with acute leukemia, 40% to 60% of those with lung cancer, and 50% of those with lymphoma, develop an infection at some point in the course of the illness.[3] A number of factors account for the increased risk of infection in the cancer patient: poor nutritional status, mechanical obstruction by the tumor, breach of anatomic barriers by surgery, intravascular devices (IVDs), or mucositis caused by cytotoxic chemotherapy, and defects of humoral and cell-mediated immunity that are either disease associated or follow myelosuppressive chemotherapy (Table 76.1).

Granulocytes are the most critical component of the host innate defense against infection. Granulocytopenia is defined as a neutrophil count less than 500 cells/mm^3 or less than 1,000 cells/mm^3 with expected decrease to less than 500 cells/mm^3 within 48 hours, and it is the main immune defect of cancer patients following chemotherapy.[4]

The inverse relationship between the magnitude of granulocytopenia and subsequent infection was first delineated in the 1960s by Bodey et al., in patients with acute leukemia[5]: the incidence of infection was 14% if the absolute granulocyte count fell below 500 to 1,000/mm^3 and 24% to 60% if it fell below 100/mm^3 (Figure 76.1).[5] Prolonged granulocytopenia, especially a rapid decline in circulating granulocytes, also increases the risk of deep fungal infection.[5] Absolute granulocyte counts less than 500 cells/mm^3 for more than 10 days is now viewed as the threshold for a greatly increased risk of severe infection.[6] Common pathogens causing infection in granulocytopenia include a wide array of gram-negative and gram-positive bacteria, *Candida* species, and filamentous fungi, such as *Aspergillus* and *Fusarium*.[1]

In general, with the exception of lymphoproliferative malignancies, defects of humoral immunity are not seen in most patients with cancer. However, globulin dysfunction or depletion is common in chronic lymphocytic leukemia (CLL) and nearly universal in multiple myeloma, predisposing to invasive infection with encapsulated organisms, particularly *Streptococcus pneumoniae*.[7]

Impairment of cell-mediated immunity (CMI) occurs with selected chemotherapeutic agents, such as the purine analogues,[8] and has also been described with novel therapies for cancer, such as monoclonal antibodies. Pathogens typically associated with impaired CMI include *Pneumocystis jiroveci* (formerly *carinii*), the herpesviruses, especially cytomegalovirus (CMV) and varicella-zoster virus (VZV), and atypical mycobacteria, *Candida*, and *Nocardia*.

Infections Associated with Chemotherapeutic Agents

Purine Analogues

Purine analogues, particularly fludarabine, and to a lesser extent, cladribine (2-chlorodeoxyadenosine, 2-CdA) and pentostatin (2′-deoxycoformycin, 2′-DCF), are potent chemotherapeutic agents for the treatment of lymphoproliferative malignancies, such as CLL, Waldenstrom's macroglobulinemia, non-Hodgkin's lymphoma, T-cell leukemia, Sezary syndrome, and hairy cell leukemia (HCL). This class of drugs produces profound lymphocytopenia and a marked decrease in CD4 cells that can persist for several years following the discontinuation of treatment, which, in the case of fludarabine, has been associated with a high incidence of severe opportunistic infections, as high as 50% in some series, most occurring during the first 6 weeks of therapy.[8]

Early reports on the spectrum of infections associated with purine analogues emphasized, in addition to the usual bacterial pathogens causing infection in granulocytopenic patients, an increased incidence of infections caused by pathogens associated with impaired cell-mediated immunity (CMI), particularly *Listeria monocytogenes* and *Pneumocystis jiroveci (carinii)*, occurring most often in patients who were heavily pretreated with alkylating agents and may also have received concomitant corticosteroids. Invasive infections with opportunistic pathogens, such as *Nocardia*,

TABLE 76.1. Defects in host defense mechanisms and common infections associated with malignant diseases.

Disease	*Proportion (%) of patients developing infection*	*Predominant defect*	*Common infections*
Acute leukemia, aplastic anemia	80	Granulocytopenia	Gram-positive cocci, gram-negative bacilli, *Candida*, *Aspergillus*, *Fusarium*, *Trichosporon*
Hairy cell leukemia	60	Granulocytopenia, impaired lymphocyte function, monocytopenia	Gram-negative bacilli, gram-positive cocci, mycobacteria (including nontuberculous)
Chronic lymphatic leukemia, multiple myeloma	50	Hypogammaglobulinemia	*Streptococcus pneumoniae; Haemophilus influenzae; Neisseria meningitidis*
Hodgkin's disease	75	Impaired T-lymphocyte response	*Pneumocystis*, *Cryptococcus*, mycobacteria, *Toxoplasma*, *Listeria*, *Cryptosporidum*, *Candida*, cytomegalovirus
Bone marrow transplant recipient	90	Granulocytopenia, increased activity of suppressor T lymphocytes	Gram-positive cocci, gram-negative bacilli, cytomegalovirus, *Candida*, *Aspergillus*, other herpes viruses
Breast cancer	35	Tissue necrosis	Staphylococci and gram-negative bacilli
Lung cancer	46–62	Local obstruction, tissue necrosis	Gram-positive cocci, gram-negative bacilli, anaerobic bacteria
Gynecologic malignancy	25	Local obstruction, tissue necrosis	Mixed aerobic and anaerobic enteric bacteria

Source: Adapted from Rolston and Bodey,[1] by permission of *Cancer Medicine*.

Mycobacterium tuberculosis, and atypical mycobacteria and fungi have also been reported.[9] The most frequent late infection has been herpes zoster, both localized and disseminated, with a median time to onset following treatment of 7 to 8 months.[9]

Factors that further increase the risk of infection with purine analogue therapy include organ damage, such as severe mucositis, renal or hepatic failure, prior therapy with antineoplastic agents, advanced stage of underlying cancer, advanced age and poor performance status, pretreatment pancytopenia, high doses of purine analogue therapy, and failure of the cancer to respond to purine analogue therapy.[9]

Strategies suggested to prevent opportunistic infection in patients receiving purine analogue therapy include prophylaxis against *P. jiroveci (carinii)*. No placebo-controlled trials have been conducted to address the issue; however, some authorities recommend trimethoprim-sulfamethoxazole (160/800 mg by mouth) thrice weekly for 2 months following fludarabine therapy.[8]

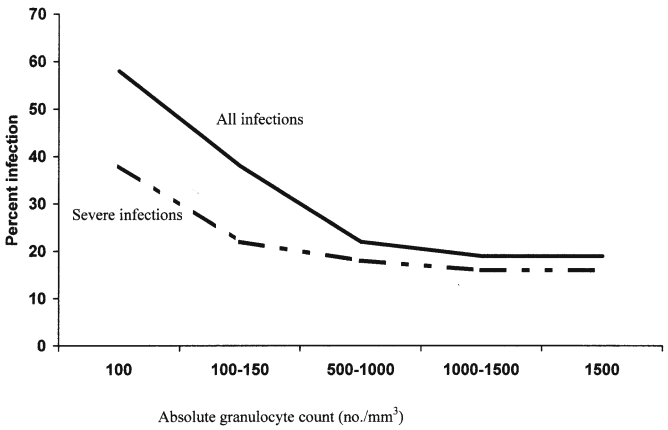


FIGURE 76.1. Relationship between granulocyte count and infection in patients with acute leukemia. The incidence of infection is inversely related to the level of circulating granulocytes. (Adapted from Bodey et al.,[5] by permission of *Annals of Internal Medicine*.)

Immunotherapy

Monoclonal antibodies are a new class of biologic anticancer agents targeted at specific receptors on tumor cells. Five monoclonal antibodies—rituximab, trastuzumab, gemtuzumab, ozagamicin, alemtuzumab, and ibritumonab tiuxetan—are in clinical trials with a variety of hematologic malignancies, especially lymphomas and solid tumors.[10] Infusion-related fever, chills, and hypotension may occur with any of the monoclonal antibodies. However, the incidence and microbiology of infections vary according to the cell line affected by the monoclonal antibody. The only commercially available monoclonal antibodies at the present time are rituximab (Rituxan), for the treatment of lymphoma and relapsed HCL, and alemtuzumab (Campath), for the treatment of CLL.

Rituximab, a chimeric monoclonal antibody, targets the B-cell antigen CD20, resulting in the depletion of peripheral B-lymphocyte counts by approximately 90% within 3 days; B-cell recovery occurs slowly, over 9 to 12 months. Mild transient reductions in granulocyte count may also be seen. Infections have been reported with the use of rituximab; however, the incidence of infections with rituximab appears to be no higher than that seen with conventional cytotoxic chemotherapy.[11]

Alemtuzumab is a chimeric monoclonal antibody that binds to the CD52 antigen. Because this antigen is present on the surface of all lymphocytes, alemtuzumab significantly depletes both B and T cells and is associated with infections caused by organisms similar to those seen with purine analogue therapy, including *P. jiroveci (carinii)* pneumonia and invasive infection caused by *Candida*, *Aspergillus*, VZV, and

TABLE 76.2. Bacterial infections in 4,452 febrile episodes in granulocytopenic cancer patients.

	1975–1977		*1986–1989*		*1994–1995*		*1999–2000*	
Infection type	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Microbiologically documented	318	(31)	344	(27)	189	(28)	207	(30)
Gram-positive	65	(21)	170	(51)	86	(46)	99	(48)
Gram-negative	201	(63)	110	(33)	54	(28)	51	(25)
Polymicrobial	42	(13)	54	(16)	49	(26)	51	(25)
Anaerobic	10	—	—	—	—	—	—	—
Unexplained fever	481	(47)	644	(53)	373	(56)	390	(57)

Source: Adapted from Rolston and Bodey,[1] by permission of *Cancer Medicine*.

CMV. All patients receiving alemtuzumab should receive trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis against *Pneumocystis carinii* pneumonia (PCP) and acyclovir for prevention of herpes simplex virus (HSV).

Myeloablative Chemotherapy and Bone Marrow Transplantation

An increasing number of cancers are now being treated with myeloablative chemotherapy, followed by autologous or allogeneic bone marrow transplantation.[12,13] The intense immunosuppression incurred by this approach, which involves high-dose cytotoxic chemotherapy and total-body irradiation, places the cancer patient at extremely high risk of infection. Typically, profound marrow suppression lasts 2 to 3 weeks until the newly infused marrow engrafts. Severe granulocytopenia and mucositis during this period, often necessitating parenteral nutrition, are major risk factors for infection. Gram-negative bacilli, fungi including *Candida* spp. and *Aspergillus*, herpesviruses, and CMV are the major pathogens causing invasive infection following bone marrow transplantation. In allogeneic bone marrow transplantation, well-conducted studies have shown that acyclovir, given prophylactically for 3 months, almost completely prevents an otherwise very high incidence of severe HSV mucosal infection.[14]

Infection in the Granulocytopenic Patient

General Considerations

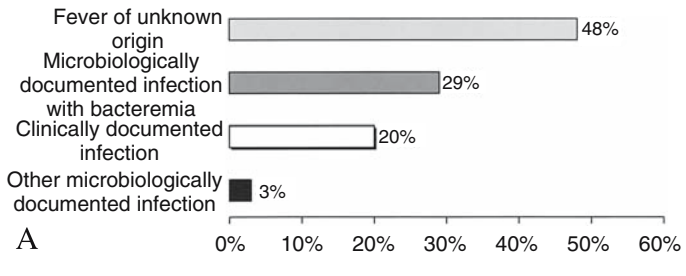
Infection remains the most frequent life-threatening complication in patients with hematologic malignancies or solid tumors. Infection is the cause of death of 50% of patients with solid tumors and lymphomas and 75% of patients with leukemia.[15,16]

Microbiology

The epidemiology and microbiology of infections in patients with granulocytopenia and malignancy has undergone a shift from predominantly gram-negative bacilli in the 1960s and 1970s, to a preponderance of gram-positive organisms in more recent years[17] (Table 76.2). Between 30% and 50% of febrile episodes in granulocytopenic patients can be confirmed microbiologically, and of these, most represent bacteremia.[6] Causes of fever in the granulocytopenic patient are shown in Figure 76.2.[18]

The emergence of gram-positive bacteria as pathogens in patients with granulocytopenia is most striking for bloodstream infections (BSIs) (see Table 76.2).[19] This dramatic shift in the ecology of invasive infection reflects greatly increased use of IVDs for long-term access, the wide use of antibiotic prophylaxis against gram-negative infections, most often with TMP-sulfa or fluoroquinolones, intense antineoplastic therapy, which produces severe mucositis, and initiation of broad-spectrum empiric antiinfective therapy at the first sign of fever in the cancer patient.

Nevertheless, gram-negative bacilli continue to be associated with major morbidity and mortality in granulocytopenic patients, and the emergence of strains highly resistant to multiple antibiotics, such as *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and *Alcaligenes xylosoxidans*, is of great concern. Resistance in all nosocomial gram-negative bacilli is increasing: data from the U.S. Centers for Disease Control and Prevention, show that nosocomial infections in intensive care unit (ICU) patients caused by gram-



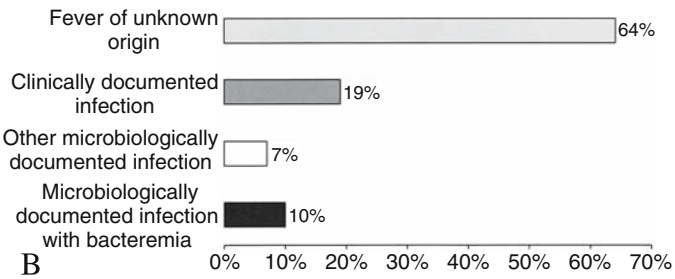


FIGURE 76.2. (A, B) Causes of fever in granulocytopenic patients with hematologic malignancies or solid tumors. Data derived from four consecutive European Organization for Research and Treatment of Cancer studies between 1991 and 2000, and from a North American Study conducted between 1992 and 1997.[212,293,294,303,304] [By permission of Marchetti O, Calandra T. Infections in the neutropenic cancer patient. In: Cohen J, Powderly WG (eds) Infectious Diseases, 2nd ed. St. Louis: Mosby, 2004:1083.]

negative bacilli resistant to third-generation cephalosporins, have risen to 32.2% of all *Enterobacter* infections and 14% of all *Klebsiella pneumoniae* infections.[20]

Moreover, new and emerging pathogens, such as *Chryseobacterium meningosepticum*, *Aeromonas* spp., *Fusobacterium nucleatum*, *Burkholderia cepacia*, *Roseomonas*, *Agrobacterium radiobacter*, and *Sphingomonas paucimobilis*, many of which are associated with significant attributable mortality, are being increasingly encountered in granulocytopenic patients.[21] The major pathogens that cause infection in granulocytopenic cancer patients are shown in Table 76.3.

Major Bacterial Pathogens in Patients with Granulocytopenia

Enterobacteriaceae

Enterobacteriaceae are the leading gram-negative pathogens implicated in bacteremia in granulocytopenic patients. Although in recent years the overall frequency of gram-negative infections has declined, the proportion of gram-negative infections caused by *Enterobacteriaceae* has remained remarkably unchanged. Data from several surveillance studies show that *Enterobacteriaceae* cause 65% to 80% of documented gram-negative infections in cancer patients, with *Escherichia coli* and *Klebsiella pneumoniae* most commonly isolated. The bloodstream is the most frequent site of infection, followed by the urinary tract and the lung.

The recent widespread emergence of resistance to beta-lactams, mediated by inducible and extended-spectrum beta-lactamases, poses a major problem.[22] Risk factors for infection caused by an extended-spectrum beta-lactamase-producing organism, include exposure to broad-spectrum cephalosporins, prolonged hospitalization, invasive devices, and immunocompromised state.[23] Although the majority of infections caused by *Enterobacteriaceae* can yet be treated with standard therapy, most often, a third-generation cephalosporin or a fluoroquinolone, a carbapenem should be used if infection with an extended-spectrum beta-lactamase-producing organism is suspected or confirmed.[24]

TABLE 76.3. The most common pathogens in granulocytopenic cancer patients.

Gram-positive aerobic bacteria
Coagulase-negative staphylococci[a]
Viridans streptococci[a]
Staphylococcus aureus[a]
Other streptococci (*Streptococcus pneumoniae*, *Streptococcus pyogenes*)[a]
Enterococcus spp.[a]
Corynebacterium jeikeium[a]
Bacillus spp.
Listeria monocytogenes
Gram-negative aerobic bacteria
Enterobacteriaceae
Escherichia coli[a]
Klebsiella spp.[a]
Enterobacter
Other (*Proteus*, *Serratia*, *Citrobacter* spp.)
Pseudomonas aeruginosa[a]
Legionella spp.
Anaerobic bacteria
Bacteroides spp.
Clostridium spp.
Fusobacterium spp.
Propionibacterium spp.
Fungi
Candida spp.
Aspergillus spp.
Other molds (*Fusarium*, *Pseudoallescheria boydii*, *Scedosporium*, Mucorales)
Viruses
Herpes simplex
Varicella-zoster
Respiratory viruses (influenza, respiratory syncytial virus)
Parasites
Strongyloides stercoralis

[a]Common causes of bacteremia.

Pseudomonas Aeruginosa

Historically, *Pseudomonas aeruginosa* has been the leading cause of life-threatening invasive infection and bacteremia in the granulocytopenic cancer patient.[25] In recent years, however, the incidence of bacteremia caused by *P. aeruginosa* has declined. A recent large retrospective cohort study of *P. aeruginosa* bacteremia in a cancer hospital, found that the incidence of BSI fell from 4.7 to 2.1 per 1,000 admissions in 1991 to 1995; however, no decline was noted in patients with acute leukemia, and *P. aeruginosa* accounted for 15% to 20% of gram-negative infections in leukemic patients.[26]

Pseudomonas aeruginosa rarely causes serious infection in the normal host but is capable of causing devastating, invasive disease if host defenses are breached by mucositis or myelosuppression from chemotherapy or the underlying malignancy, IVDs, or other invasive devices. However, the most important risk factor for life-threatening *P. aeruginosa* infection in patients with cancer is granulocytopenia.[26,27]

Pseudomonas aeruginosa causes a wide spectrum of infections in the granulocytopenic patient. Pneumonia and bacteremia are most common, but involvement of the urinary tract and skin also occurs. Skin lesions are present in approximately 20% of cancer patients with bacteremia. Ecthyma grangrenosum, the classic skin lesion historically associated with *P. aeruginosa* in patients with granulocytopenia, occurs most commonly in the axilla, groin, and perianal region[28] (Figure 76.3). Histologically, these lesions show a septic vasculitis with dense bacillary infiltration of the blood vessel walls. *P. aeruginosa* septicemia may also be associated with subcutaneous nodules, deep abscesses, cellulitis, vesicular or pustular lesions, bullae, or necrotizing fasciitis.[29]

In general, treatment of *P. aeruginosa* sepsis represents a formidable challenge, because of the intrinsic resistance of the organism to most antimicrobials, and the capacity to rapidly develop resistance during therapy. Factors associated with an unfavorable outcome include persistent neutropenia, especially an absolute granulocyte count of less than 100 cells/mm^3, septic shock, lung, skin, or soft tissue involvement, or unidentified source, renal failure, metastatic foci, rapidly or ultimately fatal underlying disease, and inappropriate antibiotic therapy.[26,27,30] Most studies have found a higher mortality rate among patients with *P. aeruginosa* bacteremia compared with other bacteremias.[26,27] It is not clear to what extent a higher mortality rate reflects the more severe underlying illnesses affecting patients susceptible to

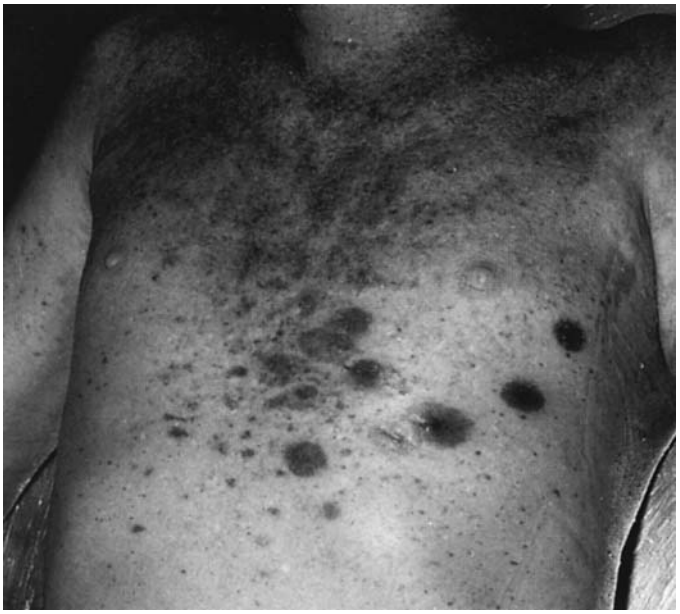


FIGURE 76.3. Classic ecthyma gangrenosum secondary to *Pseudomonas aeruginosa* infection. [By permission of Fekety R. External manifestations of systemic infections. In: Mandell GL (ed). Essential Atlas of Infectious Diseases for Primary Care. Current Medicine, vol. 1. Philadelphia: Churchill-Livingstone, 1997:45.]

Pseudomonas bacteremia as contrasted with the greater inherent virulence of the organism.

It is absolutely essential that empiric antimicrobial therapy for granulocytopenic patients with fever always include a drug or drugs active against *P. aeruginosa.* The number and choice of antibiotics in this setting are controversial, however. In a recent meta-analysis of five studies of *P. aeruginosa* bacteremia, mortality was reduced with combination therapy [relative risk (RR), 0.65; *P* less than 0.05].[31] The conventional approach to presumptive therapy in the face of granulocytopenia, or other settings in which *Pseudomonas* is a potential pathogen, is to combine treatment with an aminoglycoside or fluoroquinolone plus an extended-spectrum antipseudomonal penicillin (e.g., piperacillin-tazobactam or ticarcillin-clavulanate) or antipseudomonal cephalosporin (ceftazidime or cefepime) or a carbapenem (imipenem or meropenem). The specific choice of agents should be guided by institutional antibiotic susceptibility patterns and guidelines. Although the subject of intense debate, cohort studies and a recent meta-analysis suggest that, in patients with *P. aeruginosa* sepsis, there is a survival advantage with combination therapy as contrasted with treatment with one antimicrobial to which the infecting strain is susceptible.[31]

Staphylococcal Infections

Coagulase-negative staphylococci have emerged as major pathogens in granulocytopenic patients; two large multicenter studies in patients with hematologic malignancy or solid tumor, identified coagulase-negative staphylococci to be the most common cause of bacteremia in granulocytopenic cancer patients.[19] This increase in incidence clearly reflects an ever increasing use of long-term IVDs in this population.

Although widely regarded as organisms of low virulence, recent studies have shown that infections caused by coagulase-negative staphylococci are associated with considerable morbidity and mortality in immunocompromised patients.[32] Primary bacteremia is the major site of infection; complications, such as abscesses and septic phlebitis, have been well described.

Virtually all *Staphylococcus epidermidis* infections are health care associated and most are multiresistant, reflecting the selection pressure of widespread antibiotic use in that setting. Vancomycin remains the mainstay of therapy for coagulase-negative bacteremia.

Staphylococcus aureus is still a major pathogen causing intravascular device-related (IVDR) BSI in granulocytopenic patients and is associated with severe morbidity and mortality. Metastatic infection to distant sites, particularly endocarditis, always poses a threat. In the healthcare setting, approximately 50% of *S. aureus* isolates are resistant to methicillin (MRSA).[33] Until recently, vancomycin was the only available treatment for MRSA; however, recently, two new antimicrobials, linezolid and daptomycin, have been approved for treatment of MRSA infections. In two large randomized trials, linezolid has been shown to reduce mortality from MRSA pneumonia in ICU patients.[34] The optimal duration of therapy for *S. aureus* uncomplicated or complicated bacteremia has not been studied thus far; in most instances, a prolonged course (4–6 weeks) of parenteral antimicrobial therapy is desirable for complicated *S. aureus* bacteremia. An echocardiogram to rule out endocarditis in *S. aureus* bacteremia is highly recommended to determine whether prolonged therapy is necessary, as discussed next.

Alpha-Hemolytic (Viridans) Streptococci

Viridans streptococci have become increasingly important pathogens in cancer patients, particularly, patients with acute leukemia undergoing intensive chemotherapy and allogeneic bone marrow transplant recipients; *Streptococcus mitis*, *Streptococcus sanguis*, and *Streptococcus salivarius* are the predominant infecting species.[35–37] Viridans streptococci are now a leading cause of bacteremia in febrile, neutropenic patients. At the M.D. Anderson Cancer Center in Houston, the incidence of streptococcal bacteremia increased from 1 case per 10,000 admissions in 1972 to 47 per 10,000 in 1989.

A number of studies have examined risk factors for viridans streptococcal bacteremia in patients with cancer.[36–38] Bacteremia usually occurs in association with aggressive cytoreductive therapy for acute leukemia or allogeneic bone marrow transplantation, especially after treatment with high-dose cytosine arabinoside.[39] In a case-controlled study, the risk of viridans streptococcal bacteremia was reported to increase with profound neutropenia, prophylactic administration of trimethoprim-sulfamethoxazole or a fluoroquinolone, and use of antacids or histamine type 2 (H_2) receptor antagonists (e.g., cimetidine).[36] Another risk factor strongly implicated is the presence of mucositis[38,40,41]; in one noncomparative study of 32 patients, 78% had oral inflammation or ulceration at the onset of infection.[40] Bostrom and Weisdorf reported an association of viridans streptococcal bacteremia with an increased radiation dose to the oral cavity,[42] whereas Ringden and colleagues described an association with herpes simplex infection[43]; prophylactic acy-

clovir reduced the frequency of all bacteremias following allogeneic bone marrow transplantation.

Although the most common clinical presentation of viridans streptococcal infection in patients with cancer is primary bacteremia, in many patients, the infection is fulminant, producing septic shock and acute respiratory distress syndrome (ARDS) akin to toxic shock syndrome, resulting in a 25% to 35% mortality, despite prompt and appropriate antimicrobial therapy.[44,45]

Also of great concern is the fact that 20% to 60% of alpha-hemolytic streptococci now exhibit high-level penicillin resistance in some centers.[46,47] All these strains remain susceptible to vancomycin, although tolerance to glycopeptides has been described, and the use of antibiotic combinations, such as vancomycin plus rifampin, with or without gentamicin, may be needed to control infections caused by resistant strains.[35]

Enterococci

Enterococcal infections, distinctly uncommon in cancer patients until the mid-1970s, are now the second most common gram-positive species, after coagulase-negative staphylococci, isolated from granulocytopenic patients. Their increased frequency almost certainly derives from the very heavy use of cephalosporins over the past 25 years, drugs to which all enterococci are intrinsically resistant. The most common infections caused by enterococci are bacteremias, urinary tract infections, and postoperative surgical site infections; endocarditis is seen only rarely in patients being treated for cancer.[48] *Enterococcus faecalis* is the predominant species, accounting for 75% to 80% of enterococcal infections; however, infections caused by *Enterococcus faecium* are rapidly rising. This finding is of great concern, because 25% of all enterococcal isolates in U.S. hospitals are now resistant to vancomycin, and most of the vancomycin-resistant strains are *E. faecium*.[49] In the setting of granulocytopenia, bacteremia with vancomycin-resistant enterococci (VRE) has been associated with mortality greater than 70%.[50]

Major Infectious Syndromes in the Granulocytopenic Patient

Numerous studies have shown that infection can be clinically or microbiologically documented in only 50% of patients with granulocytopenia and fever.[51] A large multicenter study from 1985 to 1990 found, in 1,573 patients with granulocytopenic fever, that pulmonary infections were most frequent (17%), followed by BSI and fungemia; in only 5% of cases was an infection clinically and microbiologically diagnosed. The response to treatment was significantly poorer in documented infections than in unexplained fever, with the worse outcomes for pulmonary infections (crude mortality, 21%).

Perianal Infection

Perianal infections occur in 10% to 25% of patients with leukemia undergoing chemotherapy and are associated with a 15% to 35% mortality.[52] Most patients with perirectal infection have underlying hematologic malignancy, although the incidence of these infections appears to be increasing in patients with solid tumors, probably because of more intensive myelosuppressive chemotherapy. Although fever is near universal, the predominant local presenting symptom is rectal pain; fewer than half of the patients, however, have frank fluctuance or drainage. Because hypotension or septic shock occurs in 10% of patients, a high index of suspicion for this condition is essential.

The majority of anorectal infections are caused by gram-negative bacilli, particularly, *P. aeruginosa* and *E. coli*; the role of anaerobes is much less clear (Table 76.4). Computed tomography (CT) imaging should be performed to ascertain

TABLE 76.4. Major infectious disease syndromes in patients with granulocytopenia.

Syndrome	*Microbial etiology*	*Differential diagnosis*	*Diagnostic tests*
Skin and soft tissue infection			
Perirectal infection	*Pseudomonas aeruginosa* *Aeromonas* spp.		Clinical; computed tomography to determine extent of infection
Complicated cellulitis	Staphylococci, streptococci, gram-negative bacilli		Percutaneous aspirate, biopsy; computed tomography
Pulmonary infections	*P. aeruginosa*, *Klebsiella*, *Escherichia coli*, *Enterobacteriaceae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Aspergillus*, *Fusarium*, *Mucor*	Aspiration Pulmonary edema Pulmonary embolus Atelectasis Alveolar hemorrhage Acute respiratory distress syndrome Pulmonary toxicity from chemotherapy	Chest radiograph, high-resolution computed tomography, sputum stains and cultures, bronchoalveolar lavage, biopsy if platelet count permits
Granulocytopenic typhlitis	Gram-negative bacilli	*C. difficile* infection	Plain films and computed tomography of abdomen
Intravascular device-related BSI	Coagulase-negative staphylococci, *S. aureus*, enterococci	Sepsis from another source	Paired quantitative or qualitative blood cultures
Antibiotic-associated colitis	*Clostridium difficile*	Typhlitis Peritonitis	Stool toxin A and B; cytotoxin B; flexible sigmoidoscopy
Oropharyngeal-esophageal mucositis	Herpes simplex *Candida* spp.	Aphthous ulceration	Biopsy, culture for herpes simplex virus (HSV) and *Candida*

BSI, bloodstream infection.

the extent of necrotic tissue and inflammation. Combination regimens with antipseudomonal drugs should be administered, including an agent with activity against anaerobic bacteria. Surgical intervention should be considered only if the disease progresses despite adequate antimicrobial therapy. With simple cellulitis, without fluctuance or abscess, most patients will do well without surgical debridement, if granulocyte function is returning or can be anticipated to return in the immediate future. The occurrence of severe gram-negative soft tissue infection in patients with refractory profound granulocytopenia may be an indication for allogeneic granulocyte transfusion therapy to keep the infection under control until granulocyte function returns. The main predictor of improvement is recovery of granulocyte function.

Patients with fissures or hemorrhoids should undergo fissurectomy or hemorrhoidectomy when their malignancy is in remission; failure to do so will result in an increased risk of perianal infection with myelosuppression.[52]

Other Skin and Soft Tissue Infections

Skin infections in patients with cancer may also occur secondary to necrotic tumor masses, postoperative wound infection, extravasation of vesicant drugs, infected IVDs, folliculitis, infected pressure ulcers, or as a manifestation of systemic bacteremic infection. Bacterial cellulitis in granulocytopenic patients is most often caused by staphylococci or streptococci, the leading causes of cellulitis in immunocompetent patients. However, gram-negative bacilli, such as *P. aeruginosa*, which rarely cause de novo skin and soft tissue infection in normal hosts, commonly cause severe soft tissue infections in the granulocytopenic patient.

Antineoplastic therapy makes cancer patients more vulnerable to necrotizing soft tissue infections, "necrotizing fascitis," which may involve underlying muscle. These infections are usually polymicrobial, caused by gram-positive bacteria, gram-negative bacilli, and anaerobic organisms. Bacteremia occurs in up to 40% of cases.[53] In contrast to uncomplicated monomicrobial gram-negative cellulitis in the granulocytopenic patient, which can usually be managed nonsurgically, with necrotizing polymicrobial soft tissue infections, early surgical debridement is imperative to avert otherwise very high mortality.[54]

Any soft tissue inflammation occurring in patients at risk for complex cellulitis must be vigorously evaluated diagnostically, at the minimum with Gram stain and culture of percutaneous aspirates or biopsies[55]; in most cases, the Gram stain will show the infecting organisms. If a grayish hue or frank necrosis is seen or gas is present in the deep tissues on radiographic examination, surgical debridement is imperative at the outset.

Intraabdominal Infections

Focal enterocolitis (typhlitis) is a life-threatening condition occurring primarily in granulocytopenic patients.[56] Although the pathogenesis is poorly understood, mucosal injury by cytotoxic drugs in the setting of profound granulocytopenia is thought to foster microbial invasion of the bowel wall, leading to necrosis. The cecum is almost always affected but the infection may involve the entire colon. This infection is assumed to be polymicrobial; however, the presence of *Clostridium septicum*, in association with typhlitis, has been described.[57]

Typhlitis must be considered in the differential diagnosis of any profoundly granulocytopenic patient (absolute granulocyte count less than 500/μL) who presents with fever and abdominal pain, usually in the right lower quadrant. More than 60% of patients have bloody diarrhea; two-thirds develop gram-negative bacteremia. Peritoneal signs and shock suggest full-thickness necrosis with perforation of the bowel wall. Stomatitis and pharyngitis, suggesting widespread mucositis, may be present. Symptoms typically appear 10 to 14 days after cytotoxic chemotherapy, at a time when granulocytopenia is most profound and the patient is febrile.

Computed tomography is the preferred diagnostic modality; findings include presence of a fluid-filled dilated and distended cecum, diffuse cecal wall thickening, or the presence of intramural edema, air, or hemorrhage; localized perforation with free air or a soft tissue mass, suggesting abscess formation, may also be seen.[58] Other diagnoses to be excluded, include appendicitis, cholecystitis, intraabdominal abscess, pseudomembranous colitis, and Ogilvie's syndrome (colonic pseudoobstruction). In patients with uncomplicated typhlitis, that is, without peritonitis, perforation, or bleeding, nonsurgical management, with combination antimicrobial therapy, bowel rest, nasogastric suction, and IV fluids, is usually effective if there is a return of granulocyte function; in one study, 70% of affected patients survived with medical therapy alone.[59]

Surgical intervention is reserved for patients with generalized peritonitis, free perforation, persistent gastrointestinal bleeding despite correction of coagulopathy, or clinical deterioration despite medical treatment. If surgery is necessary, a two-stage right hemicolectomy is preferred, and further chemotherapy should be delayed until recovery. Resection of all necrotic tissue is essential; incomplete removal of necrotic tissue is almost always fatal.[56]

Pulmonary Infections

Pulmonary infiltrates occur in 15% to 25% of all patients with profound granulocytopenia following intensive chemotherapy.[60] In approximately two-thirds of cases, they become apparent within the first 5 days after the onset of fever. Pulmonary infections in granulocytopenic patients are associated with the highest mortality and remain a formidable challenge, diagnostically and therapeutically.[60] Noninfectious causes of pulmonary infiltrates that mimic infectious pneumonitis include aspiration, alveolitis, fluid overload, alveolar hemorrhage, malignant infiltration, and pneumonitis caused by chemotherapy or radiotherapy. Although pneumonia has become less frequent in patients with granulocytopenia because of earlier initiation of empiric antibiotic therapy with the onset of fever, gram-negative pneumonia is still common, although there has been an increased incidence of gram-positive pneumonia caused by *Streptococcus pneumoniae*, viridans streptococci, and *Staphylococcus aureus*.[61] Pneumonia caused by viridans streptococci has been encountered most commonly in patients with severe oropharyngeal mucositis following chemotherapy with high-dose ARA-C.[35] Hematogenous pneumonia occurs in 3% to 31% of patients

with bacteremia, whereas a fatal ARDS syndrome is noted with about the same incidence.

Accurate microbiologic diagnosis of pneumonia poses the greatest challenge to optimal management. In 20% to 30% of patients with gram-positive and gram-negative bacteremia, there is radiographic evidence of pneumonia, and it is usually assumed to be caused by the same organisms causing bacteremia; this is not necessarily the case, particularly with bacteremia caused by bacteria, such as enterococci, coagulase-negative staphylococci, *Bacillus* species, or *Corynebacterium jeikium*, which rarely cause pneumonia. Conventional chest radiographs show pulmonary infiltrates in less than 10% of patients who remain febrile despite antibacterial therapy, whereas CT, particularly the use of high-resolution scans, shows lung infiltrates in 50% of these patients.[62] Microbiologic diagnosis is based on blood cultures and cultures of specimens obtained by bronchoscopy or bronchoalveolar lavage. However, the role of invasive diagnostic procedures in granulocytopenic patients remains controversial; moreover, many bronchoscopists are reluctant to perform bronchoscopy, especially transbronchial biopsy, in patients with severe thrombocytopenia. During the past decade, molecular diagnostic methods have become available for the diagnosis of pneumonia caused by *S. pneumoniae*, *Aspergillus*, and *Legionella*.[63] However, the predictive value of these tests in patients with granulocytopenia and pneumonia has not been adequately characterized at this time.

The initial step in the management of a patient with a focal infiltrate early in the granulocytopenic period begins with early intensive empiric antimicrobial therapy, providing coverage for gram-positive and gram-negative pathogens. In institutions where MRSA is a common pathogen in granulocytopenic patients, the initial regimen should include vancomycin or linezolid.[34] In our institution, a fourth-generation cephalosporin (cefepime), combined with a fluoroquinolone, is most often used, but a carbapenem is also acceptable. Patients who are clinically stable and have a small infiltrate may be observed for 48 hours. If the chest radiograph is suggestive of fluid overload, a trial of diuretics may be given, but continued observation of diffuse infiltrates is not recommended, as rapid clinical deterioration tends to occur when the problem is diffuse pneumonitis.[64]

If rapid clinical improvement does not ensue, and the infiltrate has not changed, the patient may continue to be observed on therapy, and follow-up pulmonary imaging should be considered. If the infiltrate progresses on antimicrobial therapy, more aggressive diagnostic procedures are strongly recommended, preferably fiberoptic bronchoscopy with bronchoalveolar lavage (BAL).[64]

In many centers, if no improvement is noted after 5 to 7 days of antibiotics, empiric therapy with amphotericin B is started. In general, fungal infections are rarely documented before the patient has received at least 5 days of therapy.

Finally, if an infiltrate appears during antimicrobial or antifungal therapy, the approach needs to be modified in favor of an early bronchoscopy because of the high likelihood of infection caused by a fungus or a bacteria resistant to the empiric therapy, or another process altogether, such as viral pneumonitis or a noninfectious process.

In a large prospective study conducted by the Paul Ehrlich Society, supplementation of antibiotics with amphotericin B in all persistently febrile granulocytopenic patients with pulmonary lung infiltrates resulted in a favorable response rate of 78%.[65] This finding has led to the recommendation that empiric treatment with amphotericin B should be given early for all febrile granulocytopenic patients with pulmonary infiltrates, especially if there is not an early clinical response to empiric antimicrobial therapy.

Clostridium Difficile-Associated Diarrhea

Clostridium difficile is the major infectious cause of nosocomial diarrhea[66] and is associated with prolonged hospitalization and increased hospital costs.[67] The incidence of infection with this organism is increasing in hospitals worldwide as a result of the widespread use of broad-spectrum antibiotics, with reported rates ranging from 1 to 10 cases per 1,000 discharges and 17 to 60 cases per 100,000 bed-days.[68]

Patients with hematologic malignancies are at particularly high risk of developing *C. difficile*-associated diarrhea, and outbreaks have been reported.[69–71] The majority of these patients receive antimicrobial therapy; mucositis and surgical procedures also increase risk.[23] Studies have also implicated chemotherapeutic agents as independent risk factors for *C. difficile*-associated diarrhea, even in the absence of antibiotic therapy, presumably because of alteration of the normal bowel flora and extensive mucosal inflammation caused by chemotherapy, facilitating colonization by *C. difficile*.[71] A recent case-control study in hematology and oncology patients showed that antineoplastic therapy was associated with a fivefold-greater risk of developing *C. difficile* colitis [adjusted odds ratio (OR) 5.1; $P = 0.01$].[72]

Clostridium difficile infection encompasses a spectrum of conditions ranging from asymptomatic colonization to fulminant disease with toxic megacolon.[73] The usual presentation is acute watery diarrhea with lower abdominal pain and fever occurring during or shortly after beginning antimicrobial therapy. The antibiotics that most predispose to *C. difficile* infection are third- or fourth-generation cephalosporins, clindamycin, and penicillins[74]; however, virtually any antimicrobial may trigger *C. difficile* infection.

Diagnosis of *C. difficile*-associated diarrhea can be reliably made by detection of *C. difficile* toxins A and/or B by enzyme-linked immunosorbent assay (ELISA) in a stool sample.[75] If this test is negative and *C. difficile* infection is strongly suspected, then cytotoxin testing, widely regarded as the reference standard, should be performed. This test, although 94% to 100% sensitive and 99% specific, takes at least 48 to 72 hours before results are available. In severely ill patients, flexible sigmoidoscopy provides a rapid means of diagnosis, because 90% of cases of pseudomembranous colitis involve the left side of the colon; the visualization of colonic pseudomembranes is essentially pathognomonic for *C. difficile* infection (Figure 76.4). CT of the abdomen, although useful for identifying bowel wall thickness, does not differentiate between *C. difficile* and other causes of bowel wall thickening, such as ischemic colitis.[76]

The most important step in the treatment of *C. difficile* is discontinuation of the culpable antimicrobial, if possible; in approximately 25% of cases of antibiotic-associated diarrhea, this will prove sufficient to resolve the infection. However, discontinuation may not always be possible in a profoundly granulocytopenic patient who is infected or febrile. Modification of the regimen to exclude drugs with

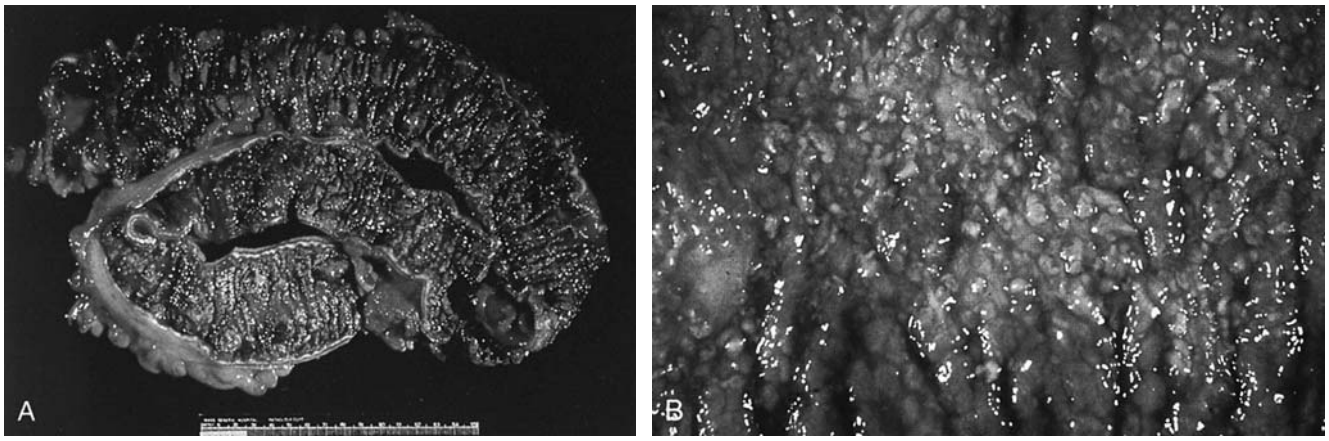


FIGURE 76.4. (A, B) Diffuse hemorrhagic colitis is seen in the resected colon. (B) Closeup reveals the diffuse mucosal irregularity and pseudomembrane formation seen with *Clostridium difficile* infection. [By permission of Stone DR, Gorbach SL (eds) Atlas of Infectious Diseases. Philadelphia: Saunders, 2000.]

unnecessary antianaerobic activity is strongly recommended if antimicrobials cannot be discontinued.

Oral metronidazole in a dose of 500 mg three times daily for 7 to 10 days is the treatment of choice for symptomatic *C. difficile* infection; vancomycin given orally should be restricted to patients who fail to respond to metronidazole or who have had relapses.[77] In critically ill patients unable to take oral medications, intravenous metronidazole should be given in conjunction with vancomycin given either by intracolonic instillation or by enema.[78] *C. difficile* colitis cannot be treated with an agent that fails to achieve high intraluminal concentrations; vancomycin given intravenously is ineffective. In most clinical situations, it is not necessary to repeat stool toxin assays in patients who are responding satisfactorily to therapy.

Clostridium difficile has now become a major nosocomial pathogen widely prevalent in healthcare institutions, and control of nosocomial transmission is also essential. A growing body of literature suggests that the inanimate environment may contribute to nosocomial transmission of *C. difficile*. Commonly used hospital disinfectants are not germicidal against *C. difficile* spores, which may persist for very prolonged periods on surfaces. A recent before–after study using sodium hypochlorite solution to disinfect a bone marrow transplant ward found that rates of *C. difficile* infection decreased from 8.3 per 1,000 patient-days to 3.4 per 1,000 patient-days; when hypochlorite disinfection was discontinued, rates rose to the baseline level.[79]

The Society for Healthcare Epidemiology of America has published a guideline for prevention and treatment of *C. difficile* infections (Table 76.5).[80] Patients with *C. difficile* should be placed in private rooms and gowns and gloves should be worn for all contacts with the patient. Hand hygiene with an antiseptic agent is essential. It is important to note that alcohol-based handrubs do *not* have activity against the spore form of *C. difficile*. Equipment, such as stethoscopes and sphygmomanometers, should be dedicated to the patient, and the environment should be terminally disinfected with an agent active against spores, such as sodium hypochlorite.

Intravascular Device-Related Bloodstream Infection

The use of IVDs has become an essential component of care to patients with cancer. Unfortunately, vascular access is associated with substantial and generally underappreciated potential for producing iatrogenic disease, particularly BSI originating from infection of the percutaneous device used for vascular access. Nearly 40% of all nosocomial bacteremias derive from vascular access in some form[81] and are associated with excess mortality,[82] increased length of hospitalization, and excess healthcare costs.[83] Different types of IVDs pose widely ranging risks of infection (Table 76.6).[84]

Figure 76.5 summarizes the microbial profile of IVD-related BSIs from 159 published prospective studies.[85] As might be expected from knowledge of the pathogenesis of these infections, skin microorganisms account for the largest proportion of IVDR BSIs.

Recent evidence-based guidelines provide the best current information on the evaluation of the ICU patient with fever or other signs of sepsis (Table 76.7).[86] Before any decision regarding initiation of antimicrobial therapy or removal of an IVD, the patient must be thoroughly examined to identify *all* plausible sites of nosocomial infection, including pneumonia, urinary tract infection, surgical site infection, or antibiotic-associated colitis, as well as line sepsis.

Despite the challenge of identifying the source of a patient's signs of sepsis,[86] several clinical, epidemiologic, and microbiologic findings point strongly toward an IVD as the source of a fever: patients with abrupt onset of signs and symptoms of sepsis without any other identifiable source should prompt suspicion of infection of an IVD; the presence of inflammation or purulence at the catheter insertion site is now uncommon in patients with IVDR BSI[87]; however, if purulence is seen, it is highly likely the patient has IVDR BSI, and this finding should prompt removal of the IVD. Finally, recovery of certain microorganisms in multiple blood cultures, such as staphylococci, *Corynebacterium* or *Bacillus* species, or *Candida* or *Malassezia* species, strongly suggests infection of the IVD.[81]

TABLE 76.5. Recommendations for prevention and treatment of *Clostridium difficile*-associated diarrhea (CDAD) in the healthcare institution.

Recommendation	*Strength of recommendation*[a]
Surveillance and diagnosis	
Surveillance for CDAD should be performed in every institution	B-III
Appropriate and prompt diagnostic testing should be performed in patients with antibiotic-associated diarrhea	A-II
Diagnostic tests for *Clostridium difficile* should be performed only on diarrheal (soft or unformed) stool specimens, unless ileus is suspected	B-III
Testing of stool specimens from asymptomatic patients for *C. difficile* (including "test of cure" after treatment)	B-II
Treatment	
If possible, discontinuation of the offending antimicrobial agent is recommended	A-I
Oral metronidazole should be considered the treatment of choice for CDAD; oral vancomycin should be administered only if there has been failure to respond to metronidazole, or if the patient cannot tolerate or is allergic to metronidazole	A-I
Treatment of asymptomatic patients with *C. difficile* colonization is not recommended	A-I
First recurrences of CDAD following treatment of initial episode should be retreated as for the initial episode	B-III
Prevention and control	
Implement policies to ensure prudent antimicrobial use	A-II
Surveillance of antimicrobial utilization in the facility should be conducted	B-III
Healthcare providers in the facility should be educated about the epidemiology of CDAD	B-III
Patients with CDAD and fecal incontinence should be in a private room; if possible, all patients with CDAD should be in private rooms	B-III
Meticulous hand hygiene with soap or an antiseptic agent is recommended after contact with patients, their body substances, or their potentially contaminated environment	B-III
Healthcare providers should wear gloves for contact with patients with CDAD	A-I
Use of disposable, single-use thermometers (rather than shared electronic thermometers) is recommended	A-II
Patient care items, such as stethoscopes and sphygmomanometers should be dedicated; if they must be shared, they should be disinfected between patients	B-III
Disinfection of the environment of a patient with CDAD should be done using sporocidal agents, such as a diluted sodium hypochlorite solution	B-II
Patients with CDAD may be removed from contact isolation when their diarrhea has resolved	B-III

[a]Data in part from the 2002 Society for Healthcare Epidemiology of America guidelines for the prevention of *Clostridium difficile*-associated diarrhea; Simor et al.,[80] *Infection Control and Hospital Epidemiology* 2002;23:696–703; from the Infectious Diseases Society of America Guidelines for weighting recommendations based on the quality of scientific evidence.[283] Category: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation for use. Quality of evidence: I, evidence from one or more properly randomized controlled trial; II, evidence from one or more well-designed observational study, multiple time-series, or dramatic results of uncontrolled experiments; III, expert opinion, descriptive studies.

It is indefensible to start antiinfective drugs for suspected or presumed infection in the critically ill patient without first obtaining blood cultures from two separate sites, at least one of which is drawn from a peripheral vein by percutaneous venipuncture. In adults, if at least 30 mL blood is cultured, 99% of detectable BSIs should be identified.[88] Similar operating characteristics are achieved in the pediatric population using a weight-based graduated volume approach to blood cultures.[89] Standard blood cultures drawn through central venous catheters (CVCs) provide excellent sensitivity for diagnosis of

TABLE 76.6. Rates of bloodstream infection (BSI) caused by various types of devices used for vascular access.

	Rates of device-related BSI			
	Per 100 catheters		*Per 1,000 catheter-days*	
Device (number of prospective studies)	*Pooled mean*	*95% CI*	*Pooled mean*	*95% CI*
Peripheral venous catheters (13)	0.16	0.08–0.23	0.60	0.31–0.88
Arterial catheters (17)	0.75	0.49–1.02	1.78	1.17–2.40
Short-term, nonmedicated central venous catheters (CVCs) (88)	4.48	4.19–4.78	2.51	2.34–2.68
Pulmonary-artery catheters (15)	1.45	1.06–1.85	5.50	4.00–7.01
Hemodialysis catheters Noncuffed (17)	7.41	6.43–8.39	2.62	2.26–2.98
Cuffed (19)	18.48	17.13–19.82	1.81	1.67–1.96
Peripherally inserted central catheters (14)	2.49	1.76–3.21	0.75	0.53–0.97
Long-term tunneled and cuffed CVCs (48)	21.25	20.13–22.38	1.53	1.44–1.62
Subcutaneous central venous ports (18)	3.91	3.22–4.59	0.13	0.11–0.15

CI, confidence interval.

Source: Data in part from Kluger and Maki,[84] based on 245 published prospective studies where every device was evaluated for infection.

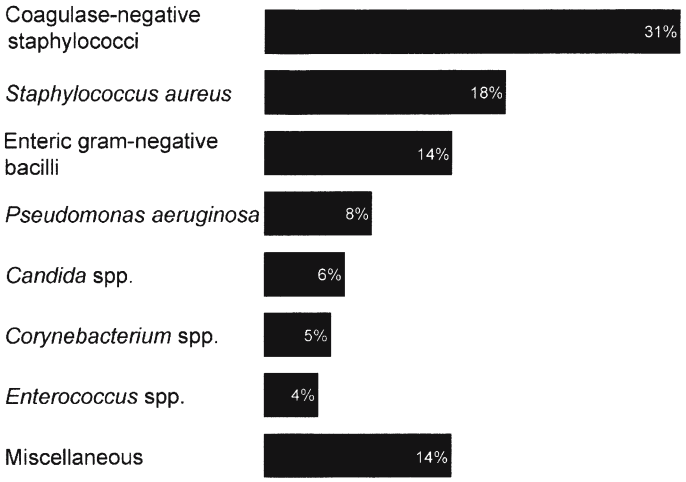


FIGURE 76.5. Microbial profile of intravascular device-related bloodstream infection based on an analysis of 159 published prospective studies. (From Maki DG, Crnich CJ,[85] by permission of *Seminars in Respiratory and Critical Care Medicine.*)

BSI but are less specific than cultures obtained from a peripheral vein.[90]

Short-term IVDs should be removed from the outset in unstable patients with suspected IVDR BSI or if IVDR BSI is documented (see Table 76.7); however, it is difficult or, more often, unnecessary to arbitrarily remove surgically implanted IVDs, such as Hickman and Broviac catheters or central venous ports. Only 15% to 45% of long-term IVDs that are removed for suspected infection are truly colonized or infected at the time of removal.[91,92] To avoid unnecessary removal of IVDs, novel methods have been developed to identify IVDR BSI without removing the device: (1) paired quantitative blood cultures drawn from the IVD and percutaneously from a peripheral vein[93]; (2) differential time-to-positivity (DTP) of paired standard blood cultures, one drawn from the IVD, the second from a peripheral vein[94]; and (3) Gram stain[95] or acridine orange staining[96] of blood samples drawn through the IVD.

Quantitative blood cultures are labor intensive and cost almost twice as much as standard blood cultures. The differential-time-to-positivity (DTP) of paired blood cultures, one drawn through the IVD and the second concomitantly from a peripheral vein, has been shown to reliably identify IVDR BSI of long-term IVDs if the blood culture drawn from the IVD turns positive 2 or more hours before the culture drawn peripherally. In studies of patients with long-term IVDs, the sensitivity and specificity of DTP are 92% and 75%, respectively.[94]

If a short-term vascular catheter is suspected of being infected because the patient has no obvious other source of infection to explain fever, there is inflammation at the insertion site, or cryptogenic staphylococcal bacteremia or candidemia has been documented, blood cultures should be obtained and the catheter should be removed and cultured (see Table 76.7). Failure to remove an infected IVD puts the patient at risk of developing septic thrombophlebitis with peripheral

TABLE 76.7. Algorithm for diagnosis and management of intravascular device (IVD)-related bloodstream infection.

- Examine the patient thoroughly to identify unrelated sources of infection.
- Carefully examine all catheter insertion sites; Gram stain and culture any expressible purulence from sites.
  - Obtain *two* 10- to 15-mL cultures:

  If standard (nonquantitative) blood cultures, draw one by *percutaneous peripheral* venipuncture and one through the suspect IVD.
  If quantitative blood culture techniques are available (e.g., the Isolator system), catheter-drawn cultures can enhance the diagnostic specificity of blood culturing in diagnosis of line sepsis. However, a peripheral percutaneous quantitative blood culture *must* be drawn *concomitantly*.
- Option regarding a peripheral IV or arterial catheter: *remove and culture catheter.*
  - Options regarding a short-term central venous catheter:

  Purulence at insertion site or no purulence, but patient *floridly septic, without obvious source*:
  Remove and culture catheter.
  Gram stain purulence.
  Reestablish access at new site.
  No purulence, patient not floridly septic:
  Leave catheter in place, pending results of blood cultures.
  or
  Remove and culture catheter, reestablish needed access at new site.
  - Options regarding surgically implanted, cuffed Hickman-type catheters.

  Remove at outset if:
  Infecting organism known to be *S. aureus*, *Bacillus* spp., JK *Diptheroid*, *Mycobacterium* species, or filamentous fungus.
  Refractory or progressive exit-site infection, despite antimicrobial therapy, especially with *Pseudomonas aeruginosa*.
  Tunnel infected.
  Evidence of septic thrombosis of cannulated central vein or septic pulmonary emboli.
  Evidence of endocarditis.
  Remove later on if:
  Any of the above become manifest.
  BSI persists 3 days or more, despite IV antimicrobial therapy through catheter.
  - Options regarding surgically implanted subcutaneous central ports (e.g., Portacath):

  Cellulitis without documented bacteremia: begin antimicrobial therapy, *withhold removing port.*
  Aspirate from port shows organisms on Gram stain or heavy growth in quantitative culture, or documented port-related bacteremia: *remove port.*
- Decision on whether to begin antimicrobial therapy, before culture results available, based on clinical assessment and/or Gram stain of exit site or the blood drawn from a long-term IVD.
- With no microbiologic data to guide antimicrobial selection in a septic patient with suspected line sepsis, consider: *IV vancomycin and ciprofloxacin, cefepime, or imipenem/meropenem.*

Source: Adapted from Maki,[213] by permission of Lippincott Williams & Wilkins.

IV catheters, septic thrombosis of a great central vein with CVCs,[97] or even endocarditis. Continued access, if necessary, can be established with a new catheter inserted in a new site. Although small studies have found some utility in catheter exchange over a guidewire in the management of CVCs suspected of being infected,[98] we believe that, in the absence of randomized studies demonstrating its safety, guidewire exchange generally should not be performed if there is strong suspicion of IVDR BSI, especially if there are signs of local infection, such as purulence or erythema at the insertion site or signs of systemic sepsis without a source (see Table 76.7). In these cases, the old catheter should be removed and cultured, and a new catheter should be inserted in a new site.

Bloodstream infection that might have originated from a long-term IVD, such as a Hickman catheter or subcutaneous port, does not automatically mandate removal of the device, unless (see Table 76.7) there has been persistent exit site infection; the tunnel is obviously infected; there is evidence of complicating endocarditis, septic thrombosis, or septic pulmonary emboli; the infecting pathogen is *S. aureus*, *Corynebacterium* JK, a *Bacillus* species, *Stenotrophomonas* spp., *Burkholderia cepacia* and all pseudomonal species, a filamentous fungus or *Malassezia* species, or a mycobacterial species; or bacteremia or candidemia persists for more than 3 days despite adequate therapy.[99] Intravascular device-related BSI caused by *S. aureus* must always prompt removal of the IVD, even if signs of bacteremia have resolved following antimicrobial therapy, because of the significant risk of infectious endocarditis (IE) or other metastatic infection if bacteremia recurs.[100,101] Similarly, we believe that patients with documented for presumed IVDR candidemia should have their catheter removed in most situations.[102–104]

In small, uncontrolled clinical trials of "antibiotic lock therapy" (ALT), usually in conjunction with systemic antibiotic therapy, cure rates of infected IVDs in excess of 90% have been reported.[105–107] Most of the IVDs reported in these studies were infected with coagulase-negative staphylococci and fermenting gram-negative bacilli; therefore, at this time ALT cannot be recommended for the management of long-term IVDs infected by *S. aureus*, *Bacillus* sp., *Corynebacterium* JK, *Stenotrophomonas* spp., *B. cepacia*, all *Pseudomonas* species, fungi, or mycobacterial species. Obviously, if IVDR BSI recurs after an attempt to salvage an IVD with ALT, the device should be removed.

Infected surgically implanted subcutaneous central ports have rarely proven to be curable with medical therapy alone, especially if it is clear that the device is infected (e.g., an aspirate from the port shows heavy growth).[108] A recent study of patients with acquired immunodeficiency syndrome (AIDS), with surgically implanted ports who developed IVDR BSI, found that ALT, combined with systemic antibiotic therapy, resulted in 70% of the ports being salvaged; however, long-term follow-up data on surveillance cultures of the ports were not reported.[109] The only other clinical study of the utilization of ALT in subcutaneous central port infections achieved salvage rates less than 50%.[110] Based on the marginal efficacy of ALT in these two studies and the historically poor cure rate achieved with systemic antibiotics alone, we believe that definitive therapy of infected subcutaneous central ports mandates removal of the infected device.

If IVDR BSI is suspected, after cultures have been obtained, the combination of IV vancomycin (for staphylococci resistant to methicillin, i.e., MRSA) with a fluoroquinolone, cefepime, or imipenem/meropenem (for multiresistant nosocomial gram-negative bacilli) (see Table 76.7), should prove effective against the bacterial pathogens most likely to be encountered (see Figure 76.5). Initial therapy can then be modified based on the ultimate microbiologic identification and susceptibilities of the infecting organisms.

How long to treat IVDR BSI will be influenced by the infecting microorganism, and by whether the patient has underlying valvular heart disease, already has evidence of endocarditis or septic thrombosis, or shows evidence of metastatic infection. If endocarditis is suspected, transesophageal echocardiography offers superior sensitivity and discrimination for detecting vegetations, as compared with transthoracic echocardiography.[101] In patients with high-grade bacteremia or fungemia, but without clinical or echocardiographic evidence of endocarditis, septic thrombosis should be suspected.[97] Central venous thrombosis can now be diagnosed by venography, ultrasonography, magnetic resonance imaging, or CT.[111]

Although there are no prospective studies to guide the optimal duration of antimicrobial therapy for IVDR BSIs, most coagulase-negative staphylococcal infections can be cured with 5 to 7 days of therapy,[112,113] whereas most infections caused by other microorganisms are adequately treated with 10 to 14 days of antimicrobial therapy.[113] These recommendations hold only as long as there are no complications related to the infection and the BSI clears within 72 hours of initiating therapy. Nosocomial enterococcal bacteremia deriving from an IVD is rarely associated with persistent endovascular infection, and unless there is clinical or echocardiographic evidence of endocarditis, treatment with IV ampicillin or vancomycin alone for 7 to 14 days should suffice.[48]

The management of *S. aureus* device-related infection deserves special mention, as there have been no prospective studies to evaluate the optimal duration of therapy for IVDR BSIs caused by this ubiquitous human pathogen. Historically, high rates of associated IE and late complications led to a universal policy of 4 to 6 weeks of antimicrobial therapy for *all* patients with *S. aureus* bacteremia. Earlier diagnosis and initiation of bactericidal therapy of nosocomial *S. aureus* BSIs in recent years have been associated with lower rates of IE and metastatic complications, prompting suggestions that short-course therapy (i.e., 14 days) is effective and safe for most patients with *S. aureus* IVDR BSI, so long as the patient defervesces within 72 hours and there is no evidence of metastatic infection.[114] In a study of transesophageal echocardiography (TEE) in 103 hospitalized patients with *S. aureus* bacteremia, 69 related to an IVD, Fowler et al. found a surprisingly high incidence of endocarditis, 23% with IVDR *S. aureus* BSI.[101] In a more recent report, these authors have reported that the routine use of TEE with IVDR *S. aureus* BSI, as a means to stratify patients into short-course or long-course therapy, is cost-effective.[115] However, at this time, there are no prospective studies to affirm this approach. Until more data are available, short-course therapy for IVDR *S. aureus* bacteremia therapy should be approached with caution, and used only when the TEE is unequivocally negative and the patient has defervesced within 72 hours of removing the IVD and starting antiinfective therapy.

All patients with an IVDR BSI must be monitored closely, for at least 6 weeks after completing therapy, especially if

they have had high-grade bacteremia or candidemia, to detect late-appearing endocarditis or other metastatic infection, such as vertebral osteomyelitis.

An updated guideline for the prevention of intravascular device-related bloodstream infections (IVDR BSIs) was published in 2002 by the CDC's Healthcare Infection Control Practices Advisory Committee.[116] The use of antimicrobial lock solutions for prevention of BSIs caused by long-term IVDs has been of particular interest in cancer patients. Seven randomized, prospective trials have examined a vancomycin-containing antibiotic lock solution for the prevention of IVDR BSI,[117] the largest of which found that use of a vancomycin or vancomycin/ciprofloxacin lock solution reduced the risk of IVDR BSI nearly 80% (*P* equal to or less than 0.005).[118] Concern about the emergence of resistance with prophylactic antibiotic-containing lock solutions has limited their acceptance to date. Three of the seven studies performed serial surveillance cultures for vancomycin-resistant enterococcus; VRE was not found in any of these studies. However, the use of prophylactic antibiotic lock solution is considered acceptable in the HICPAC Guideline if a patient with an essential long-term IVD has continued to experience recurrent IVDR BSIs despite consistent application of recommended infection control practices.[116]

Viral Infections

Patients who have inherited or acquired impairment of cell-mediated immunity are at risk of opportunistic viral infections. Not surprisingly, patients who are treated with agents with potent activity against this arm of the immune system, such as glucocorticoids, calcineurin inhibitors (i.e., cyclosporine A and tacrolimus),[119] alkylating agents (i.e., cyclophosphamide),[120] selected antimetabolites (i.e., azathioprine, methotrexate, and fludarabine),[121] and monoclonal antibodies [i.e., alemtuzumab (anti-CD52) and basiliximab and daclizumab (anti-CD25)][122] are at greatest risk. In general, reactivation of latent herpesviruses account for the majority of viral infections in this population, although community- and nosocomial-acquired infections caused by other common viral pathogens occur at an increased frequency, compared to the general population, and may be associated with increased patient morbidity and mortality.

Herpesviruses

Currently, there are eight herpesviruses that can infect humans and cause disease (Table 76.8). All members of this family demonstrate a tropism for human cells and share the ability to establish themselves in a state of latency following acute infection. Reactivation of latent infection, characterized by viral replication and shedding, tends to occur most often during periods of immunosuppression, although there is variability in the clinical manifestations of reactivated infection, depending on the virus.

TABLE 76.8. The human herpesviruses.

Alphaherpesviruses
Herpes simplex virus type 1 (HSV-1)
Herpes simplex virus type 2 (HSV-2)
Varicella-zoster virus (VZV)
Betaherpesviruses
Cytomegalovirus (CMV)
Human herpesvirus type 6 (HHV-6)
Human herpesvirus type 7 (HHV-7)
Gammaherpesviruses
Epstein–Barr virus (EBV)
Human herpesvirus type 8 (HHV-8)

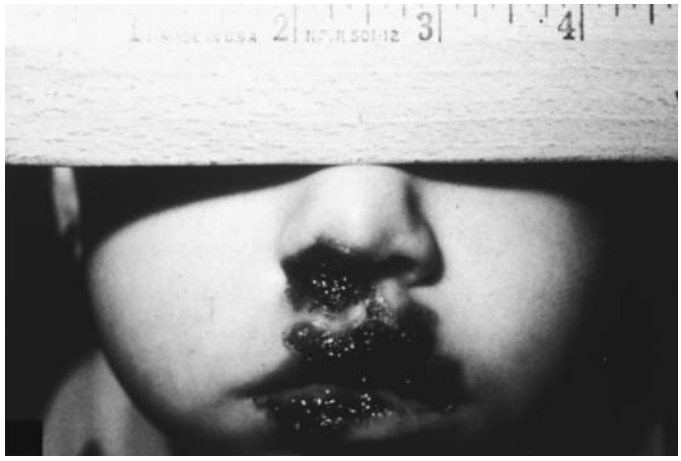


FIGURE 76.6. Herpes simplex mucositis in an immunocompromised patient. [By permission of Yogev R. Pediatric HIV infection. In: Mandell GL (ed). Essential Atlas of Infectious Diseases for Primary Care. Current Medicine, vol. 1. Philadelphia: Churchill-Livingstone, 1997:45.]

Herpes Simplex Virus Type 1 and 2

Herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) are widely distributed in the population, seroprevalence in adults approaching 95% for HSV-1 and 25% for HSV-2. Upward of 70% to 80% of seropositive stem cell transplant (SCT) patients begin to shed HSV following transplantation,[123] a finding that has led to recommendations for routine acyclovir prophylaxis in bone marrow transplantation (BMT) and patients with hematologic malignancies who are receiving chemotherapy.[124]

Herpes simplex virus infection typically manifests as localized mucocutaneous disease, most commonly involving the oral cavity, which can be necrotizing in the immunocompromised patient (Figure 76.6), less commonly the genital area. Extensive mucocutaneous disease involving the esophagus may occur in up to 10% of cancer patients with upper gastrointestinal symptoms.[123] Life-threatening disease is rare, even in this population; however, HSV pneumonia, hepatitis, encephalitis, and disseminated disease are seen, and are associated with a high mortality, despite appropriate antiviral therapy.

The diagnosis of HSV infection is usually made on clinical grounds in immunocompetent individuals; however, identification of HSV infection is complicated in cancer patients because extensive mucocutaneous disease can be caused by chemotherapeutic drugs, as well as a number of other opportunistic infections. It is thus important that the clinician strive to determine the etiology of the patient's mucocutaneous signs and symptoms.

In the case of acute mucocutaneous disease, viral culture of a swab of an unroofed vesicle or open ulcer offers the best method of confirming HSV infection, with results available

in most cases within 48 to 96 hours. Direct Giesma staining (Tzanck preparation) of fluid from an unroofed vesicle, seeking giant cells or intranuclear inclusions, cannot reliably differentiate between varicella-zoster virus (VZV) infection and HSV infection, is insensitive, and should *not* be used to rule out HSV infection. When feasible, every attempt should be made to obtain specimens for pathologic examination and viral culture or polymerase chain reaction (PCR) in patients with suspected HSV esophagitis or pneumonitis, although empiric treatment based on clinical symptoms may be necessary in patients in whom the risks of invasive tests are too high. In patients with suspected HSV encephalitis, PCR testing of cerebrospinal fluid (CSF) has shown sensitivity and specificity approaching 100%,[125] although the yield has been shown to be laboratory dependent.[126]

The treatment of HSV infections is dependent on the location and severity of infection (Table 76.9).[123] Valaciclovir and famciclovir have an oral bioavailability three to five times that of oral acyclovir, making oral therapy of serious disease a technical feasibility. Nevertheless, the use of oral therapy from the outset should be restricted to immunocompromised patients who have limited mucocutaneous disease. In the presence of extensive mucocutaneous disease, esophagitis, pneumonitis, or disseminated disease, initial therapy should begin with intravenous acyclovir, 5 to 10 mg/kg every 8 hours, to ensure adequate tissue levels, particularly in patients in whom intestinal absorption is in question. Once the patient has shown a favorable response to therapy, therapy may be completed with a highly bioavailable oral agent such as valaciclovir or famciclovir.

Varicella-Zoster Virus

Primary varicella-zoster virus (VZV) infection, in the form of chicken pox, is a ubiquitous childhood infection, most commonly associated with a diffuse vesicular rash, and is associated with secondary reactivation later in life, in the form of a painful, localized eruption, herpes zoster. Primary infection usually occurs in children under the age of 13; however, morbidity and mortality related to primary infection occurs disproportionately in susceptible adults over the age of 23.

Immunocompromised persons are at high risk of primary and reactivation disease,[127] and these patients are more likely to experience visceral dissemination, with involvement of the lungs, liver, or brain.[127] Primary VZV infection usually occurs in children with hematologic malignancy where infection is associated with pneumonia in up to 32% of untreated cases.[128] In contrast, herpes zoster is a delayed reactivated infection that occurs most commonly in adults undergoing chemotherapy and is associated with visceral involvement in up to 13% of cases.[129]

The diagnosis of varicella and herpes zoster infection is usually made on clinical grounds, with a generalized vesicular centripetal rash in lesions in varying stages of development seen in chicken pox and a unilateral dermatomal eruption with herpes zoster (Figure 76.7). Cutaneous dissemination can follow a dermatomal eruption in up to 35% of cancer patients, in contrast to only 4% in persons without cancer. Involvement of adjacent dermatomes is not unusual in immunocompetent patients and does not usually represent disseminated disease. Viral culture of lesions fails to detect the virus in 40% to 70% of cases.[130] Fluorescent antibody staining appears to be easier and far more sensitive diagnostically. Amplification of VZV DNA is of limited value in the diagnosis of cutaneous disease, but PCR of bronchoalveolar lavage and cerebrospinal fluid can be a useful adjunct in the diagnosis of VZV pneumonia or meningoencephalitis.[131,132]

Treatment of immunodeficient patients with varicella or herpes zoster is described in Table 76.9. Intravenous acyclovir, 10 mg/kg every 8 hours, is recommended for most patients; however, oral therapy with valaciclovir or famciclovir may be used in patients with mild to moderate immunosuppression who do not have evidence of disseminated or visceral disease. Resistance to acyclovir, mediated by mutation of the viral thymidine kinase, has been seen almost exclusively in patients with AIDS, but should be suspected in any patient not responding to therapy, in which case the use of foscarnet or cidofovir is recommended (see Table 76.9).[123]

The median time to onset of herpes zoster in BMT patients is 5 months[123]; as a result, preventive therapy with acyclovir or its congeners is not recommended. The use of varicella zoster-immunoglobulin (VZIG) can reduce the risk of primary infection and its attendant complications, but must be given to susceptible immunodeficient individuals within 96 hours of exposure at a dose of 125 U/10 kg (maximum dose, 625 U).[133] The use of live, attenuated varicella virus vaccine is contraindicated in immunocompromised adults at the present time, although a clinical trial of the vaccine is under way in susceptible children.[133] Household contacts of immunodeficient patients at risk should be vaccinated if they are known to be susceptible to varicella infection (i.e., children and adults with no known history of varicella).[134]

Cytomegalovirus

Cytomegalovirus (CMV) is a herpesvirus that may infect up to 50% to 70% of the population in developed countries.[123] Cytomegalovirus infection is seen mainly in patients undergoing BMT or solid organ transplantation,[135,136] although there have been increasing reports of CMV infection among

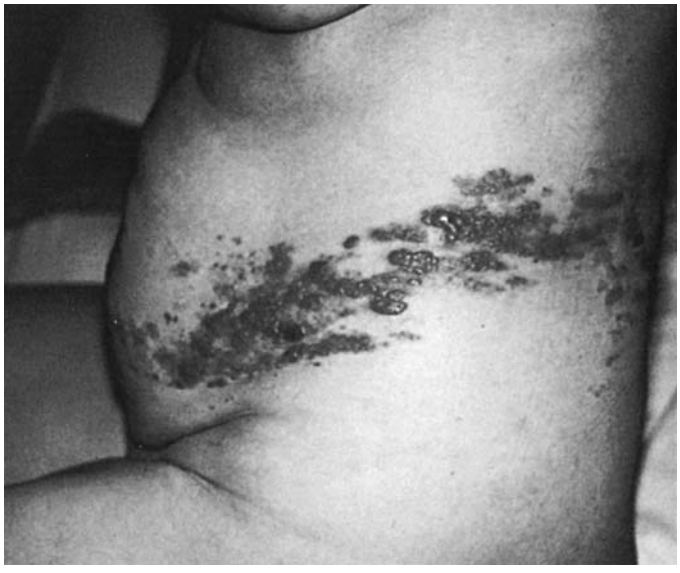


FIGURE 76.7. Herpes zoster infection in immunosuppressed adult. Note the dermatomal distribution of the eruption. [By permission of Stone DR, Gorbach SL (eds). Atlas of Infectious Diseases. Philadelphia: Saunders, 2000.]

TABLE 76.9. Treatment and prophylaxis of infections caused by viral pathogens.

Indication	*Drug*	*Route*	*Dosage*	*Duration*
HSV 1 and 2				
Prophylaxis	Acyclovir	IV	5 mg/kg q12	For the period of the most severe immunosuppression (usually 2–3 months)
		PO	200–400 mg q8 to 800 mg q12	Same
	Valacyclovir	PO	500–1,000 q12	Same
	Famciclovir	PO	500 mg q12	Same
Treatment				
Mucocutaneous disease	Acyclovir	IV	5 mg/kg q8	7–10 days
		PO	200–400 mg 5×/day	7–10 days
	Valacyclovir	PO	500–1,000 mg q12	7 days
	Famciclovir	PO	500 mg q12 or 250 mg q8	7 days
Esophageal disease	Acyclovir	IV	5 mg/kg q8	10 days
Encephalitis or pneumonia	Acyclovir	IV	10–15 mg/kg q8	14–21 days
Resistant infection	Foscarnet	IV	60 mg/kg q12 or 40 mg/kg q8	As above
	Cidofovir	IV	5 mg/kg once weekly for 2 weeks	Continue every 2 weeks until healing
VZV				
First prophylaxis (patient VZV seronegative)	VZIG immunoglobulin	IV	125 U/10 kg once	Must be given within 96 hours of exposure
Second prophylaxis (patient VZV seropositive)	Not recommended			
Treatment				
Disseminated or invasive disease	Acyclovir	IV	10 mg/kg q8	7–10 days
Localized mucocutaneous disease	Acyclovir	PO	800 mg 5×/day	7–10 days
	Valacyclovir	PO	1,000 mg q8	7–10 days
	Famciclovir	PO	500 mg q8	7–10 days
Resistant infection	Foscarnet	IV	60 mg/kg q8–q12	7–14 days or until complete healing
CMV				
Prophylaxis	Ganciclovir	IV	5 mg/kg q12 then 5 mg/kg daily	5 days From engraftment until day 100 after bone marrow transplantation (BMT)
Preemptive therapy	Ganciclovir	IV	5 mg/kg q12 then 6 mg/kg daily 5 days per week	14 days Until CMV surveillance test negative
	Foscarnet	IV	60 mg/kg q12 then 90 mg/kg daily 5 days per week	14 days Until CMV surveillance test negative
Treatment	Ganciclovir	IV	5 mg/kg q12 then 5–6 mg/kg daily	14 days 30 days or until complete recovery
Resistant infection	Foscarnet	IV	90 mg/kg q12 or 60 mg/kg q8 for 2 weeks, then 90–120 mg/kg once daily	Until complete recovery
Influenza A				
Prophylaxis	Amantidine	PO	200 mg daily	For duration of peak influenza activity in community
	Rimantidine	PO	100 mg bid	For duration of peak influenza activity in community
Treatment	Amantidine	PO	200 mg daily	4–5 days or until 24–48 hours after symptomatic improvement
	Rimantidine	PO	100 mg bid	4–5 days or until 24–48 hours after symptomatic improvement
Influenza A & B				
Prophylaxis	Oseltamivir	PO	75 qd	For duration of peak influenza activity in community
Treatment	Oseltamivir	PO	75 mg bid	5 days
	Zanamavir	inhaled	2 inhalations bid	5 days
RSV	Ribavirin	Inhaled	55 mg/h for 12 hours	7–14 days
	RSV IVIG	IV	1.5 g/kg	Once

VZV, varicella-zoster virus; CMV, cytomegalovirus; RSV, respiratory syncytial virus.

Source: Adapted in part from Reusser,[123] by permission of Mosby.

patients with leukemia, as a result of exposure to powerful immunosuppressive drugs, such as fludarabine and cytoxan.[137] Seropositive patients undergoing BMT or those who receive marrow from a seropositive donor without preventive therapy, develop infection in 60% to 70% of cases.[123] The likelihood of CMV infection is greatly increased in patients who develop graft-versus-host disease, those who receive an HLA-mismatched transplant, or those who receive antithymocyte immunoglobulin.[138,139]

Clinically, CMV infection in immunosuppressed patients can range from asymptomatic excretion to fulminant disseminated disease. Cytomegalovirus viremia often presents as unexplained fever without specific end-organ involvement but usually manifests as pneumonia or gastroenteritis. Without therapy, CMV pneumonia is fatal in up to 85% of cases.[139] Less common manifestations include esophagitis, myocarditis, hepatitis, encephalitis, and retinitis.

The diagnosis of CMV infection requires documentation of CMV in blood, tissue, or bronchoalveolar fluid specimens. Serologic, histopathologic, and direct culture methods have proven to be insensitive for diagnostic purposes, as highlighted in BMT patients where CMV cultures of blood may be negative in up to 30% of cases of proven invasive disease.[140] Newer molecular techniques, including pp65 CMV antigen detection, PCR, branched-chain DNA, and hybrid capture CMV DNA assay, have revolutionized the diagnosis of invasive CMV disease.[141] Studies of quantitative CMV antigen assays and real-time PCR have found that these tests have negative predictive values that range from 90% to 95%, with positive predictive values ranging from 50% to 84%.[141,142]

Ganciclovir should be used for the initial treatment of all suspected or established CMV disease in immunocompromised patients (see Table 76.9). Many transplant centers also use CMV immunoglobulin for the treatment of patients with CMV pneumonia; however, this recommendation is based on older studies utilizing historical controls,[143] and at least one contemporary study has failed to find additional benefit over ganciclovir therapy alone.[144] As a result, we do not recommend the adjunctive use of CMV immunoglobulin in the treatment of invasive CMV disease.

The prophylactic use of antivirals in patients at risk for developing invasive CMV disease is also another area of controversy. Many transplant centers routinely give prophylactic ganciclovir to patients who are CMV seropositive or who have received a transplant from a CMV-positive donor. Although this approach does lead to a reduction in documented episodes of invasive CMV, no study has shown a survival advantage.[123] An alternative approach, which relies on preemptive ganciclovir therapy in patients with documented CMV viremia, as determined by use of one or more of the molecular techniques already described, has been found to be associated with a survival advantage in several prospective trials.[145,146] However, studies have found that up to 86% of patients with evidence of CMV shedding, based on molecular surveillance studies, ultimately do not require therapy.[147] As a result, whether to use a prophylactic or preemptive strategy remains controversial, and the approach used will be influenced by institutional rates of CMV infection. The prevention of primary CMV infection in susceptible (antibody-negative) patients is best approached by using CMV-negative marrow and blood products.

Epstein–Barr Virus

Epstein–Barr virus (EBV) occurs in more than 90% of the population. In developed countries, primary infection occurs principally in adolescents and teenagers, and as a result primary infection is a rare phenomenon in adults with cancer. However, EBV-induced posttransplant lymphoproliferative disease (PTLD) is a threat to patients who have undergone solid organ or allogeneic BMT. The incidence of this disorder in patients with solid organ transplants varies by the degree of immunosuppression; renal transplant patients have an incidence of PTLD of 1%, whereas the incidence in small bowel transplant patients is as high as 14%.[123] In contrast, the incidence of PTLD in BMT patients appears to be lower, around 1.3%.[148] The mortality from PTLD ranges from 30% to 80%, although mortality in BMT patients approaches 90%.[149] Treatment of patients with PTLD is difficult and generally requires a reduction or, better, total cessation of immunosuppressive therapy.[150] Use of antiviral agents is generally of little benefit, although anecdotal success has been reported with infusions of donor-derived leukocytes and the use of anti-B-cell antibodies.[149]

Human Herpesvirus 6

Human herpesvirus 6 (HHV-6) causes exanthem subitum in children, and shedding of the virus may be seen in up to 60% of patients undergoing BMT.[123] Human herpesvirus 6 has been implicated as a cause of rejection, marrow suppression, encephalitis, and interstitial pneumonia in this population; however, clear evidence of a causal role has only been established clearly for encephalitis.[151] There have been no prospective trials reported to evaluate the effectiveness of antiviral therapy in infections thought to be caused by HHV-6, although both foscarnet and ganciclovir exhibit in vitro activity, and successful treatment of patients with HHV-6 encephalitis with ganciclovir and foscarnet has been reported anecdotally.[152]

Community-Acquired Viral Respiratory Pathogens

Community-acquired viral respiratory pathogens (Table 76.10) are increasingly recognized causes of infection in immunocompromised patients. In one study at the M.D. Anderson Cancer Center, a respiratory virus was isolated from 33% of adult patients presenting with a respiratory illness, 31% caused by respiratory syncytial virus (RSV), 28% by rhinoviruses or picornaviruses, 18% by influenza A or B, and 23% by parainfluenza or adenoviruses.[153] Parainfluenza, rhinoviruses, and andenovirus infections occur year round, whereas infections caused by influenza A and B and RSV peak during the winter months. Although many respiratory viral infections are community acquired, several studies have clearly demonstrated the potential for nosocomial acquisi-

TABLE 76.10. Community-acquired respiratory pathogens.

Influenza A and B
Respiratory syncytial virus A & B
Parainfluenza viruses 1, 2, & 3
Rhinoviruses
Adenoviruses
Coronaviruses

tion, most likely as a result of transmission from visitors or healthcare workers.[154,155]

Mortality associated with these infections is difficult to establish, because many patients infected by these viruses die with, rather than of, their viral infection. Nevertheless, studies examining mortality in immunocompromised patients from whom a viral respiratory pathogen has been isolated have found case-fatality rates ranging from 22% to 44%.[153] Mortality appears to be higher for patients infected with RSV; Whimby et al. found that 60% of leukemic patients who developed RSV died of complications related to their infection.[156]

Diagnostic tests for most of the major respiratory viral pathogens, such as influenza A and B, parainfluenza 1, 2, and 3, RSV, and adenovirus, are commercially available. A description of individual tests is beyond the scope of this text; however, a new rapid reverse transcriptase PCR test (Hexaplex; Prodesse, Waukesha, WI), which simultaneously tests for the presence of both influenza subtypes, the three parainfluenza subtypes, and the two RSV subtypes, has shown high diagnostic accuracy.[157]

The treatment of most respiratory viral infections is supportive; however, there are viable treatment options for influenza and RSV.[158] The neuraminidase inhibitor, oseltamivir, is active against both influenza A and B, whereas amantidine and rimantidine possess activity only against influenza A; therapeutic impact appears to be negligible if the antiviral agent cannot be started within 48 to 72 hours of onset of clinical symptoms.[158] Aerosolized ribavirin has traditionally been used in patients with RSV; however, its benefit appears to be marginal in patients with established infection. The concomitant use of RSV immunoglobulin with aerosolized ribavirin has been shown to reduce mortality in leukemic adults by 30% compared to historical controls (70% to 50%).[155] The results from an ongoing randomized trial of aerosolized ribavirin versus ribavirin plus RSV immunoglobulin are still unavailable. The use of intravenous ribavirin does not appear to be of clinical benefit and can be associated with hemolysis, limiting its utility in this population.[159]

The prevention of nosocomial transmission of community-acquired respiratory viral infections, such as influenza and RSV deserves mention, given the number of reports of institutional outbreaks.[160,161] Minimum infection control practices to prevent nosocomial respiratory viral infections include (1) timely immunization of patients and staff against influenza[162]; (2) prevention of patient contact with persons (friends, family, and healthcare staff) who have active respiratory symptoms; (3) use of rapid diagnostic tests to quickly identify symptomatic patients with potentially transmissible viral pathogens; (4) grouping patients with confirmed infection when single rooms are not available; and (5) placement of patients with suspected community-acquired respiratory viral infections in droplet isolation precautions. The use of more aggressive isolation procedures, such as contact and airborne isolation precautions, with or without the use of prophylactic antiviral agents, may require consideration with outbreaks among very high risk patients.

Fungal Pathogens

The growing problem of devastating fungal infections in cancer patients necessitates a major focus on the leading fungal pathogens in patients with malignant disease. Most fungal infections occur in patients with hematologic malignancies as a result of the intrinsic nature of the disease and the chemotherapeutic regimens that result in severe and prolonged granulocytopenia, which correlate very strongly with an increased risk of infections caused by the filamentous fungi, such as *Aspergillus* and *Fusarium*. Filamentous fungal infections are far less common in patients with lymphoma and rare in patients with solid tumors. Regardless of the type of malignancy, all patients with cancer are at increased risk of infection caused by *Candida* spp., primarily as a result of the widespread use of IVDs and the intensive chemotherapeutic regimens used in this patient population.

Candida

The risk of developing a *Candida* infection is closely associated with the type of cancer; candidiasis occurs in 9% to 25% of patients undergoing BMT, 1% to 13% of patients with granulocytopenia as a result of chemotherapy and hematologic malignancies, 1% to 2% in patients being treated for lymphoma, and 0.5% in patients undergoing treatment for solid tumors.[163] *Candida albicans* is most commonly isolated; however, many centers are experiencing a sharp rise in infections cause by non-*albicans* species, including *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis*.[164] The clinical relevance of this finding is that most non-*albicans* species are relatively resistant to azoles, including fluconazole and itraconazole, necessitating the use of alternative therapeutic agents, such as amphotericin and caspofungin.

There is a wide spectrum of diseases caused by *Candida* spp., including oropharyngeal mucosal infection, esophagitis, BSI, and hepatosplenic candidiasis. Pulmonary and neurologic involvement are rarely seen as isolated disease and most often occur in conjunction with disseminated infection.

Oropharyngeal candidiasis is characterized by the presence of typical adherent white plaques on the tongue, palate, or buccal mucosa. Staining or cultures of the adherent material usually is not necessary unless infection caused by non-*albicans* species is suspected. Treatment with clotrimazole troches is usually sufficient with limited oropharyngeal disease, although systemic therapy with fluconazole or itraconazole is mandatory in patients with severe disease or when concomitant esophagitis is suspected (Table 76.11).[165] Intravenous amphotericin or caspofungin may be necessary in patients with severe oropharyngeal disease caused by azole-resistant non-*albicans* species.

Candida esophagitis often presents with dysphagia, but retrosternal pain, nausea, vomiting, and gastrointestinal bleeding are other common complaints. Contrast radiographic studies are nonspecific and may be negative in up to 25% of cases; therefore, the diagnosis of candida esophagitis rests on detection of characteristic pseudomembranes and ulcerations by endoscopy. Examination of biopsy specimens, if obtained, confirms the diagnosis. Topical therapy with nonabsorbable antifungals is ineffective in patients with esophagitis, and systemic therapy with fluconazole, caspofungin, or IV amphotericin B is mandatory. The latter two agents are preferred in institutions with high rates of infections caused by non-*albicans* species or in patients with candida esophagitis who have received azoles in the past.

TABLE 76.11. Treatment of selected infections caused by *Candida* species.

Infection	*Drug*	*Route*	*Dosage*	*Duration*
Oropharyngeal	Clotrimazole	PO	10 mg troche 5¥/day	7–14 days
	Fluconazole	PO	100 mg daily	7–14 days
	Itraconazole	PO	200 mg daily	7–14 days
	Amphotericin B	IV	0.3 mg/kg daily	7–14 days
	Caspofungin	IV	70 mg loading dose 50 mg daily thereafter	7–14 days
Esophagitis	Fluconazole	IV/PO	200–400 mg loading dose 100–200 mg daily	14–21 days
	Amphotericin B	IV	0.3–0.7 mg/kg daily	14–21 days
	Caspofungin	IV	70 mg loading dose 50 mg daily thereafter	14–21 days
Candidemia	Amphotericin	IV	0.3–0.5 mg/kg daily	14 days after last positive culture
	Fluconazole	IV	400 mg daily	14 days after last positive culture
	Caspofungin	IV	70 mg loading dose 50 mg daily thereafter	14 days after last positive culture
Visceral candidiasis	Amphotericin	IV	0.5–0.7 mg/kg daily	Until lesions have resolved or calcified
	Fluconazole	IV	400 mg daily	Until lesions have resolved or calcified
	Caspofungin	IV	70 mg loading dose 50 mg daily thereafter	Until lesions have resolved or calcified

Source: Adapted in part from Pappas et al.,[173] by permission of *Clinical Infectious Diseases.*

Candida spp. are also an increasingly common cause of nosocomial BSI,[166] associated with case-fatality rates ranging from 30% to 60%.[167,168] Disseminated infection usually occurs as a complication of candidemia and may be associated with cutaneous lesions, retinitis or endophthalmitis, osteomyelitis, and even endocarditis. Most episodes of candidemia in nongranulocytopenic patients originate from IVDs.[169] However, controversy exists over the relative role of IVDs versus intestinal translocation in patients with granulocytopenia or who have received intensive cytotoxic chemotherapy.[170]

Studies performed two decades ago found that blood cultures are negative in more than 50% of patients with disseminated *Candida* infections confirmed at autopsy.[171] In contrast, recent studies have found that automated blood culturing systems detect up to 93% of cases of active candidemia.[172]

Recovery of *Candida* spp. from a blood culture should never be regarded as a contaminant in decisions regarding treatment. Controversies about the source of candidemia aside, a considerable body of literature suggests that retention of an IVD is associated with prolonged candidemia and excess mortality.[102–104] As a result, we believe that IVDs should be removed from most patients with proven candidemia. Candidemia that responds rapidly to removal of the device and institution of IV amphotericin B can be reliably treated with a daily dose of 0.3 to 0.5 mg/kg and a total dose of 3 to 5 mg/kg.[173] If a lipid-associated formulation of amphotericin B is being used, a daily dose of 1 to 2 mg/kg and a total dose of 10 to 20 mg/kg should be sufficient in most cases.[104] If the patient has septic thrombosis of the central vein, associated with high-grade candidemia and florid sepsis, or infection caused by non-*albicans* species, a higher dose of IV amphotericin B is recommended, 0.7 mg/kg/day and 20 mg/kg or more total conventional amphotericin, 2 to 3 mg/kg/day and 20 to 30 mg/kg total, for a lipid-associated formulation.[173]

Fluconazole (400 mg/day) has been shown to be as effective as IV amphotericin B in randomized trials in nongranulocytopenic patients,[174,175] and has further been shown to be comparable to amphotericin B in observational studies of granulocytopenic patients with *Candida* IVDR BSIs,[104] but should not be used in IVDR BSIs associated with septic thrombosis and high-grade candidemia or in BSIs caused by azole-resistant species.

Infections caused by fluconazole-resistant organisms, such as *Candida krusei* and *Candida glabrata*, have become all too common, with many centers reporting that more than 50% of their *Candida* isolates are non-*albicans* species that are usually resistant to azoles.[164] Caspofungin was recently shown to be at least as effective as IV amphotericin B in a prospective randomized double-blind trial in patients with deep *Candida* infections, most of whom had candidemia[176]; most notably, caspofungin was associated with a greatly reduced rate of study drug withdrawal because of adverse events (2.6% versus 23.2%; $P = 0.003$). Intravenous caspofungin, which has a low incidence of side effects and can be given once daily, can now be considered a first-line drug for initial treatment of deep invasive candidal infection in centers with high rates of infection caused by non-*albicans* species, pending identification and susceptibility of the bloodstream isolate.

Hepatosplenic candidiasis is a more indolent form of visceral candidiasis that typically presents as persistent fever in a cancer patient who is recovering from granulocytopenia.[177] Blood cultures are usually negative; however, imaging with CT demonstrates multiple small nodules in the liver and spleen (Figure 76.8), and occasionally in the lungs, kidneys, or bone as well. Cultures of material obtained by percutaneous aspiration or biopsy can confirm the diagnosis but because of the small size of the infected nodules may be negative. Therefore, most clinicians initiate therapy (see Table 76.11) on the basis of radiographic findings and only proceed to invasive diagnostic procedures when patients remain refractory to treatment.

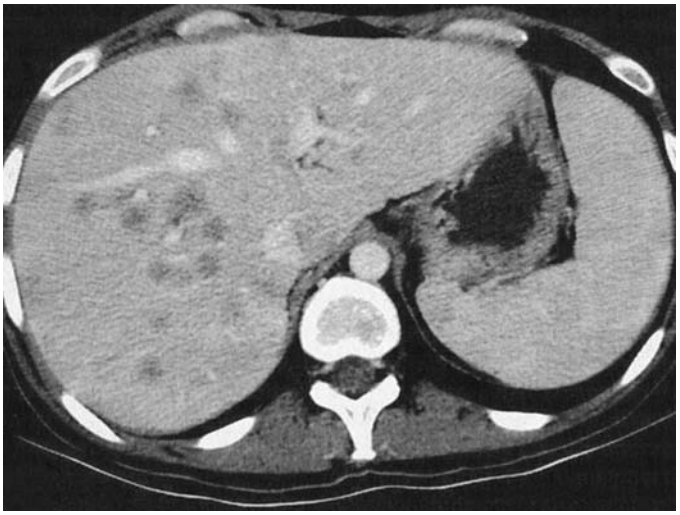


FIGURE 76.8. Hepatosplenic candidiasis in a patient with acute myelogenous leukemia seen on computed tomography (CT) scan. Multiple nodules can be seen in the liver and spleen. [By permission of Marchetti O, Calandra T. Infections in the neutropenic cancer patient. In: Cohen J, Powderly WG (eds) Infectious Diseases, 2nd ed. St. Louis: Mosby, 2004:1083.]

Aspergillus

Aspergillus spp. are ubiquitous environmental organisms, encountered most often in rural areas but also found throughout most hospitals. Invasive infections caused by *Aspergillus* spp. are an increasing problem in many hematology and solid organ transplant centers, with incidence rates of 5% to 24% among patients with acute leukemia.[178] Invasive aspergillosis is most often a complication of severe and prolonged granulocytopenia, and the duration of granulocytopenia is the most powerful predictor of risk of invasive aspergillosis. The median time to onset of disease in patients with severe granulocytopenia is 17 days and, historically, the majority of cases occur within 90 days in patients undergoing BMT,[163] although recent studies have found an increasing number of patients with invasive aspergillus that developed in 90 days or more.[179,180] Other risk factors associated with invasive aspergillosis include receipt of OKT3 antibodies, active CMV disease, and renal failure.[163] The most commonly isolated species have been *Aspergillus fumigatus* (more than 90% of all proven infections), *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*.

Aspergillus can infect any organ, but sinopulmonary disease is the most common manifestation. Infections often present insidiously in patients with granulocytopenia and fever may be the only manifestation. Dull chest pain that may become pleuritic in nature, cough, and sinus congestion are also common. Hemoptysis, although suspicious for invasive pulmonary aspergillosis, is relatively uncommon. Up to half of patients with lung involvement have disseminated disease that can involve the central nervous system, gastrointestinal tract, kidney, liver, or skin.[163] Less common presentations include isolated skin lesions, often at sites of vascular catheter insertions[181] or isolated gastrointestinal involvement,[163] possibly the result of ingestion of water containing these organisms.[182] Despite advances in diagnosis and treatment, mortality in patients with invasive aspergillosis remains high, 90% in BMT patients and nearly 80% in patients with leukemia.[183]

The diagnosis of invasive *Aspergillus* infection remains a formidable challenge. Chest radiographs are completely normal in 10% of patients with documented infection.[184] Chest CT is read as normal in only 3% of cases, and up to 85% of infected patients have characteristic radiographic findings, such as a "halo"[185] or "crescent"[186] sign. *Aspergillus* species are rarely isolated from expectorated sputum, and cultures of bronchoalveolar lavage (BAL) fluid are positive in only 20% of cases in most series; however, a positive culture for *Aspergillus fumigatus* has a very high positive predictive value for invasive disease in high-risk patients, in excess of 75%.[187] Transbronchial biopsy increases the diagnostic yield to 75%.[184] Molecular diagnostic tests that detect the presence of circulating galactomannan, a fungal cell wall constituent, and PCR techniques to detect ribosomal genetic material conserved across *Aspergillus* species, may eventually abrogate the need for invasive tests.[163] The sequential use of an ELISA to detect galactomannan was found to have an 87.5% positive predictive value and a 98.4% negative predictive value in a recent prospective trial in neutropenic BMT patients.[188]

The treatment of invasive aspergillosis has also undergone evolution. Traditional therapy has relied upon IV amphotericin B deoxycholate in doses of 1 to 1.5 mg/kg/day (Table 76.12); however, at these doses, nephrotoxicity is ubiquitous.

TABLE 76.12. Treatment options for patients with invasive infections caused by *Aspergillus* species.

Drug	*Route*	*Dose*	*Duration*
Amphotericin B deoxycholate	IV	1.0–1.5 mg/kg daily	Until evidence of infection has resolved
Liposomal amphotericin B (Ambisome)	IV	5.0–7.5 mg/kg daily; doses as high as 15 mg/kg daily have been used safely	Same
Amphotericin B lipid complex (ABLC)	IV	5.0 mg/kg daily	Same
Amphotericin B colloidal dispersion (ABCD)	IV	3–4 mg/kg daily	Same
Caspofungin	IV	70 mg loading dose 50 mg daily	Same
Itraconazole (suspension)	IV PO	6–12 mg/kg daily 200 mg bid	Same Same
Voriconazole	IV PO	6 mg/kg q12 for 2 doses 4 mg/kg bid thereafter IV load as above 200 mg bid thereafter	Same Same
Combination therapy	Investigational		

Despite the use of lipid-based agents, such as liposomal amphotericin B and amphotericin B lipid complex, in daily doses of 5 to 10 mg/kg, treatment-related side effects have remained high, prompting a search for less toxic alternatives. Caspofungin, a member of a new class of drugs that inhibit the synthesis of 1,3-β-glucan, an integral component of the fungal cell wall, was approved for the treatment of invasive aspergillosis refractory to treatment with other agents in 2001.[189] Itraconazole also possesses activity against *Aspergillus* spp. and appeared to be equivalent to amphotericin B deoxycholate in a retrospective analysis[190]; however, bias toward treatment of less severely ill patients limits the generalizability of this report, and we do not believe that clinicians should rely upon itraconazole alone for the treatment of invasive aspergillus infections at this time.[190] On the other hand, the newly released triazole, voriconazole, was recently shown to be superior, in terms of fewer side effects and improved clinical response (53% versus 32%) and patient survival (71% versus 58%), compared to amphotericin B deoxycholate in a large multicenter randomized trial.[191] As a result, voriconazole is now widely considered the standard of therapy for patients with documented *Aspergillus* infections. The use of antifungal drug combinations for treatment of invasive aspergillosis is currently under investigation, with caspofungin combined with lipid-based amphotericin B or voriconazole showing the most promise.[192,193]

Zygomycetes

Zycomycosis, known more commonly as mucormycosis, is a devastating infection caused by a variety of filamentous fungi in the order Mucorales. Risk factors for mucormycosis include diabetic ketoacidosis, iron overload, and, increasingly, prolonged granulocytopenia.[194] Rhinocerebral disease is the most common presentation in patients with diabetic ketoacidosis; however, pulmonary involvement, very similar to that seen with invasive aspergillosis, appears to be the most common manifestation of Mucorales infection in patients with cancer.[194] A black eschar may be seen on the nasal mucosa or soft palate in rhinocerebral disease, or on the skin in disseminated disease (Figure 76.9), or at sites of intravascular catheter insertion.[195] Involvement of the central nervous system can occur either as a result of direct extension from the sinuses, with rhinocerebral disease, or hematogenously, in disseminated disease.

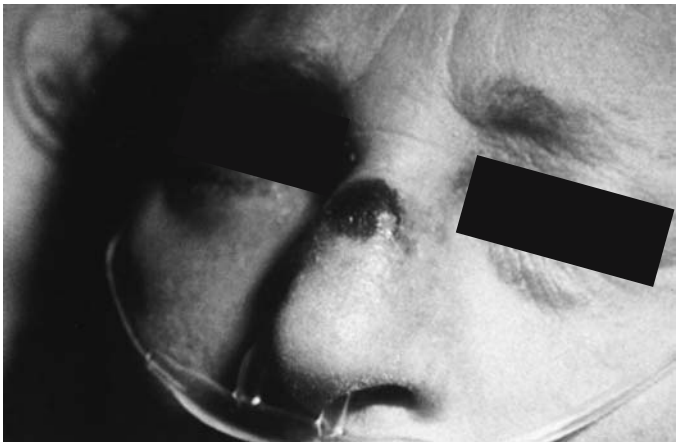


FIGURE 76.9. Necrotizing rhinocerebral infection with *Rhizopus*. Note the black eschar on the nose. [By permission of Stone DR, Gorbach SL (eds) Atlas of Infectious Diseases. Philadelphia: Saunders, 2000.]

Diagnosis of Mucorales infection rests on histopathologic examination or culture of a biopsy specimen, as blood and respiratory tract specimens are almost always culture negative, and the radiographic presentation may not be distinguishable from that seen with invasive pulmonary aspergillosis. It is important to recognize that the newer antifungals, voriconazole and caspofungin, have no activity against zygomycetes. Treatment begins with aggressive debridement whenever possible, combined with the use of conventional (1.0 to 1.5 mg/kg/day) or lipid-based amphotericin B (5 to 7.5 mg/kg/day). Despite treatment, mortality is greater than 75% in cancer patients.[163]

Fusarium

Fusarium species are soil saprophytes that have been increasingly implicated as a cause of fatal infection in patients with cancer, primarily patients with acute leukemia or those undergoing BMT.[196] Colonization originating from contaminated hospital water systems has been described,[197] although the significance of this finding has been challenged.[198] Fusariosis may be acquired either as a result of inhalation, with the development of pulmonary disease indistinguishable from invasive pulmonary aspergillosis, or from direct inoculation through the skin or an IVD access site. In all settings, hematogenous dissemination with widespread cutaneous involvement is common, and blood cultures are positive in up to 50% of patients with documented systemic fusariosis.[163] Recovery from granulocytopenia is critical to patient survival: a recent study found that all patients who had refractory granulocytopenia died of fusarium infection.[199]

Fluconazole and itraconazole are inactive against *Fusarium* species, and amphotericin B (1.0 to 1.5 mg/kg/day) is still considered the first line of therapy. Voriconazole possesses activity against *Fusarium* species in vitro, and its clinical use was associated with a complete or partial response in 43% of patients in a recent small trial.[194] Granulocyte infusions may have an important adjunctive role in infected patients with refractory granulocytopenia.[199]

Other Fungal Infections

A variety of unusual fungal organisms has been increasingly reported in infected patients with cancer.[163] Infections caused by these rare organisms have recently been reviewed by Walsh and Groll.[200] Table 76.13 lists some of the more prevalent emerging fungal pathogens and possible therapeutic options, although it is important to note that the outcome with most of these infections has been poor, and reported successes with treatment modalities have been anecdotal.

Evaluation of the Granulocytopenic Patient with Fever[6]

Infection in the granulocytopenic patient can progress very rapidly; hence, a thorough evaluation of the granulocytopenic patient with fever must be undertaken without delay. Characteristic signs and symptoms of inflammation may be minimal or absent,[201] and careful examination is necessary to detect subtle findings, especially in the periodontium; the

TABLE 76.13. Emerging fungal pathogens in patients with cancer.

Organism	*Treatment*
Dematiaceous (dark-walled) fungi	
Alternaria	Amphotericin B + flucytosine, itraconazole
Bipolaris	Itraconazole, voriconazole
Cladosporium	Amphotericin B, itraconazole
Curvularia	Amphotericin B, itraconazole, terbinafine
Scedosporium apiospermum (Pseudallescheria boydii)	Voriconazole, amphotericin B + itraconazole
Wangiella (Exophilia) dermatidis	Amphotericin + itraconazole, itraconazole
Hyaline fungi	
Acremonium	Amphotericin B, voriconazole
Geotrichum	Amphotericin B ± 5-flucytosine, itraconazole
Paecilomyces lilacinus	Amphotericin B, terbinafine
Paecilomyces variotii	Itraconazole or fluconazole
Penicillium	Amphotericin B, fluconazole, itraconazole
Trichophyton	Itraconazole or fluconazole
Yeasts	
Blastoschizomyces capitatus	Fluconazole
Trichosporon beigelii	Amphotericin B

pharynx; the lower esophagus; the lung; the perineum, including the anus; the eye (fundus); and the skin, including bone marrow aspiration sites, vascular catheter access sites, and tissue around the nails.

Bacterial cultures of blood should be obtained, including one drawn through the IVD; if a catheter insertion site has exudate, the material should be also be sent for Gram stain and culture. If the exudate is chronic, the material should also be analyzed for fungi and mycobacteria. A sample for urine microscopy and culture should also be obtained.

The evaluation of infectious diarrhea is based on whether it is community acquired, nosocomial, or chronic. For community-acquired diarrhea, stool specimens should be cultured for *Salmonella*, *Shigella*, *Campylobacter*, and *Escherichia coli* O157:H7. The major cause of nosocomial diarrhea is *Clostridium difficile*, which has been addressed in an earlier section; for diarrhea after 3 or more days of hospitalization, stool cultures for common community-acquired enteric pathogens have very low yield and are rarely necessary.[202] Persistent infectious cryptogenic diarrhea may warrant evaluation for giardia and cryptosporidium infection.

New, abnormal skin lesions in granulocytopenic patients often represent invasive bacterial or fungal infection and should be aspirated, or better, biopsied, and a Gram stain, bacterial and fungal culture, and histopathologic examination should be performed.

Chest radiographs should be obtained whenever signs or symptoms point toward a respiratory tract process. Some experts recommend chest radiography for all persons who are to be treated as outpatients, even without clinical evidence of pulmonary infection. A baseline radiograph may be helpful for granulocytopenic patients who subsequently develop respiratory symptoms or evidence of an infiltrate but may not be cost-effective on a routine basis. Of note, high-resolution CT will reveal evidence of pneumonia in more than one-half of febrile granulocytopenic patients who have normal findings on chest radiograph.

Examination of CSF is not recommended as a routine procedure unless the patient has severe headache, meningismus, or altered mental status. However, in general, a CT scan with and without intravenous contrast should be obtained before performing a lumbar puncture because of the risk of intracranial hemorrhage in patients with drug-induced thrombocytopenia and to rule out central fungal infection.

Complete blood cell counts and determination of the levels of serum creatinine and urea nitrogen are needed to plan supportive care and to monitor antiinfective drug toxicity. These tests should be done at least every 3 days during the course of intensive antiinfective therapy; more frequent monitoring may be required if amphotericin B is also being given.

Initial Empiric Antimicrobial Therapy

Empiric antimicrobial therapy should be instituted without delay in all granulocytopenic patients with fever, ideally, within 2 hours of the clinical evaluation. Afebrile patients who are granulocytopenic, but who have signs or symptoms suggestive of infection, should also receive empirical antimicrobial therapy, begun in the same manner as for febrile patients. The choice of initial antimicrobial regimens should be based on knowledge of the most common infecting pathogens in that center or patient population and the antibiotic susceptibilities at that institution. The major pathogens causing infection in granulocytopenic patients are shown in Table 76.3. *Because of the ever-present risk of life-threatening infection by* Pseudomonas aeruginosa, *all initial antimicrobial regimens must include at least one drug with antipseudomonal activity*.

Despite a plethora of randomized trials, no single empiric regimen can be recommended for the treatment of all patients with granulocytopenic fever. Comparing numerous studies is difficult because of differing definitions of disease and criteria used to assess the response to treatment.

The 2002 IDSA Guideline offers three options for initial intravenous antimicrobial therapy that are considered to be of comparable efficacy,[6] with the caveat that one may be more appropriate for certain patients or in certain institutions than the others: single-drug therapy (monotherapy), two-drug

therapy without a glycopeptide (vancomycin), and therapy with glycopeptide (vancomycin) plus one or two other antiinfective drugs.

Monotherapy

Multiple studies have shown no outcome differences between monotherapy and multidrug combinations for empiric treatment of uncomplicated fever in granulocytopenic patients, that is, those without clinical evidence of local infection or sepsis at the outset. Two recent meta-analyses encompassing more than 4,000 patients, found that patients with uncomplicated granulocytopenic fever treated with a beta-lactam alone, as contrasted with a beta-lactam plus an aminoglycoside found no significant difference in all-cause mortality (RR, 0.85–0.87; $P = 0.057$).[203,204] Although rates of superinfection in both groups were similar, the frequency of adverse events was higher in patients receiving combination therapy. Another meta-analysis, using clinical failure of antimicrobial therapy as the outcome measure, also found beta-lactam monotherapy to be comparable to aminoglycoside-containing combinations in uncomplicated granulocytopenic fever.[205]

The antimicrobial agents that have been best studied for monotherapy include a third-generation (ceftazidime) or fourth-generation cephalosporin (cefepime) or a carbapenem (imipenem-cilastatin or meropenem). The emergence of extended-spectrum β-lactamases (ESBL) in *Enterobacteriaceae* has reduced the utility of ceftazidime for monotherapy.[206] Imipenem-cilastatin, meropenem, and cefepime, unlike ceftazidime, are active against ESBL-producing *Enterobacteriaceae* and also have excellent activity against viridans streptococci and pneumococci. A prospective double-blind study of 411 patients with cancer showed that the rate of clinical response was higher in febrile granulocytopenic patients treated with meropenem than it was in those treated with ceftazidime.[207]

It is important to recognize that the spectrum of any of these drugs does not usually encompass coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and some strains of multiresistant *Streptococcus pneumoniae* or viridans streptococci. Therefore, close monitoring of the clinical response to treatment is important, and antiinfective therapy may need to be adapted to institutional susceptibilities, and modified, based on the susceptibilities of the organisms recovered in culture.

Current evidence to support the use of fluoroquinolones as monotherapy is limited and the results of the few studies have been conflicting.[208] The widespread use of fluoroquinolones for prophylaxis in granulocytopenic patients also limits their utility for initial empiric therapy, and this class of drugs cannot be recommended for initial monotherapy in patients with granulocytopenia and fever. Treatment with aminoglycosides alone is also suboptimal and not recommended.

Two-Drug Combination Therapy

Two-drug combination therapy most often comprises an aminoglycoside (gentamicin, tobramycin, or amikacin) plus an antipseudomonal penicillin (ticarcillin-clavulanate or piperacillin-tazobactam) or an antipseudomonal cephalosporin (cefepime or ceftazidime), or an an aminoglycoside plus a carbapenem (imipenem-cilastatin or meropenem). These regimens have been shown to have comparable efficacy in numerous trials.[204] Because of intrinsic and growing acquired resistance in many species of gram-negative bacteria causing serious infections,[209] and the high mortality associated with these infections, combination antimicrobial therapy, most commonly with two drugs, is intuitively appealing. However, as noted, the studies to date have not shown combination therapy to be superior to monotherapy *if there is no clinical obvious source of infection at the time therapy is begun.*[31,204] Moreover, there are disadvantages to using combination antiinfective therapy, including increased toxicity and cost and, possibly, an increased likelihood of a superinfection with even more resistant bacteria or fungi.

Although the combination of ciprofloxacin with piperacillin-tazobactam was found to have efficacy comparable to tobramycin and piperacillin-tazobactam in a large multicenter randomized trial,[210] in our opinion, fluoroquinolones in initial empiric regimens should not be used *if* the patient has had heavy exposure to this class of drugs in the past, such as for prophylaxis or treatment of a recent infection.

Vancomycin-Containing Regimens

There has been much controversy regarding the inclusion of vancomycin in the initial empiric regimen for the febrile granulocytopenic patient to provide a drug active against methicillin-resistant staphylococci, enterococci, and *Corynebacterium* species. Comparative trials have found that inclusion of vancomycin in the initial regimen does reduce the frequency of secondary nosocomial BSIs with these organisms during therapy[211]; however, these studies have not shown reduced morbidity and mortality. A recent prospective trial randomized 165 granulocytopenic patients with persistent fever despite piperacillin/tazobactam to the addition of vancomycin or placebo; no statistically significant differences were noted regarding time to defervescence or additional episodes of gram-positive bacteremia.[212]

In general, heavy use of vancomycin in the absence of a clear clinical indication is undesirable because of the risk of promoting vancomycin resistance in enterococci or *S. aureus*. Thus, routine use of vancomycin in the initial antimicrobial regimen for the febrile granulocytopenic patient is not recommended unless (1) the hospital has a high rate of nosocomial infection with MRSA or the patient is known to have previously been colonized or infected by MRSA, (2) there are reasons to suspect overwhelming alpha-hemolytic viridans streptococcal bacteremia, that is, shock with respiratory distress, (3) the patient shows evidence of infection at the exit site or tunnel of a CVC, or (4) the patient is at risk for endocarditis, that is, has a prosthetic heart valve.[213]

For microbiologically confirmed infections with coagulase-negative staphylococci or other resistant gram-positive organisms, vancomycin should be added to the initial regimen. Linezolid, the first U.S. Food and Drug Administration (FDA)-approved oxazolidinone, offers promise for treatment of resistant gram-positive bacterial infections, including those caused by VRE, although reversible drug-related myelosuppression can be seen, mainly with prolonged courses. Quinupristin-dalfopristin, another drug that has recently been approved by the FDA, is also effective against vancomycin-resistant *E. faecium* (but not *E. fecalis*) and other gram-positive bacteria.[214] However, further studies are needed

before recommendations can be made for the use of these drugs in initial empiric regimens in patients with cancer.

Oral Antimicrobial Therapy

Until recently, the accepted standard of care for the cancer patient with granulocytopenic fever, has been immediate hospitalization for parenteral administration of antibiotics, with close monitoring for complications and response to therapy.[215] As a result, there has been a dramatic decrease in mortality among febrile granulocytopenic patients. Recent investigations have shown that granulocytopenic patients with fever are a heterogeneous population, with varying risks relative to the response to therapy, the occurrence of serious medical complications, and mortality.[216,217]

Over the past decade, subsets of febrile granulocytopenic patients at low risk for complications have been identified, which have impelled studies of using oral antimicrobials, entirely in the outpatient setting or in the hospital, usually following a brief course of parenteral broad-spectrum antiinfective therapy. Table 76.14 summarizes the randomized controlled trials that have been undertaken to examine the efficacy and safety of oral antimicrobial therapy for low-risk patients with granulocytopenic fever.

These trials should be interpreted within the context of their limitations. Assessment of risk of infection, antimicrobial regimens used, and location of antimicrobial therapy (inpatient or outpatient) varied widely. Moreover, the outcome "success of therapy" was not uniformly defined. Nonetheless, the results of these important studies show

TABLE 76.14. Randomized controlled trials assessing the efficacy of oral antibiotic therapy in granulocytopenic patients with fever.

Author	*Patient population*	*Location of group treated orally*	*Antimicrobial regimen Oral treatment*	*Resolution of infection Inpatient parenteral*	*Oral treatment parenteral*	*RR Inpatient*	*Relative risk*
Minotti 1999[284]	Adults	Outpatient	Ciprofloxacin	Ceftriaxone	82%	75%	1.09
Paganini 2000[285]	Children	Outpatient	Ceftriaxone then cefixime	Ceftriaxone + amikacin	98%	98%	1.00
Paganini 2001[286]	Children	Outpatient	Initial ceftriaxone then ciprofloxacin	Ceftriaxone + amikacin followed by cefixime	100%	98%	1.02
Paganini 2003[287]	Children	Outpatient	Ciprofloxacin	Ceftriaxone[a]	85%	82%	1.03
Shenep 2001[288]	Children	Inpatient	Cefixime	Ticarcillin + tobramcyin + vancomycin	72%	73%	0.98
Mullen 1999[289]	Children	Outpatient	Ciprofloxacin	Ceftazidime[a]	80%	94%	0.85
Hidalgo 1999[290]	Adults	Outpatient	Ofloxacin	Ceftazidime + amikacin	89%	91%	0.97
Innes 2003[291]	Adults	Outpatient	Ciprofloxacin + amoxicillin-clavulanate	Gentamicin + piperacillin-tazobactam	84%	90%	0.93
Petrilli 2000[292]	Children	Outpatient	Ciprofloxacin	Ceftriaxone[a]	83%	75%	1.16
Freifeld 1999[293]	Adults	Inpatient	Ciprofloxacin + amoxicillin-clavulanate	Ceftazidime	71%	67%	1.05
Kern 1999[294]	Adults	Inpatient	Ciprofloxacin + amoxicillin-clavulanate	Ceftriaxone + amikacin	86%	84%	1.02
Engervall 1996[295]	Adults	Outpatient	Trimethoprim-sulfamethoxazole + amikacin	Ceftazidime	30%	36%	0.83
Velasco 1995[296]	Adults	Inpatient	Ciprofloxacin and penicillin	Amikacin + carbenicillin	94%	93%	1.01
Giamarellou 2000[208]	Adults	Inpatient	Ciprofloxacin	Ceftazidime + amikacin	50%	50%	1.00
Malik 1992[297]	Adults	Inpatient	Ofloxacin as outpatient	Ofloxacin as inpatient	81%	83%	0.97
Rubenstein 1993[298]	Adults	Inpatient	Ciprofloxacin + clindamycin	Clindamycin + aztreonam[a]	88%	95%	0.92
Johnson 1992[299]	Adults	Outpatient	Ciprofloxacin	Azlocillin + netilmicin	38%	42%	0.90
Flaherty 1989[300]	Adults	Outpatient	Ciprofloxacin + azlocillin	Ceftazidime + amikacin	35%	56%	0.62
Chan 1989[301]	Adults	Outpatient	Ciprofloxacin + netilmicin	Piperacillin + netilmicin	59%	62%	0.95
Rolston 1995[302]	Adults	Outpatient	Ciprofloxacin + amoxicillin-clavulanate	Clindamycin + aztreonam	90%	87%	1.03

[a] Parenteral regimen was provided on an outpatient basis.

that, in general, the outcomes for low-risk patients treated with oral antimicrobial therapy are generally equivalent to those for similar-risk patients treated with intravenously administered therapy. Oral therapy has the advantages of reduced cost, the potential for outpatient management, and avoidance of intravenous access, thereby obviating the risk of IVDR BSI. The oral regimens that have been most thoroughly evaluated are ofloxacin alone, ciprofloxacin alone, and ciprofloxacin plus amoxicillin-clavulanate.

Pivotal to the success of this approach in clinical practice is to accurately identify patients at low risk. Clinical prediction rules have been developed for this purpose. The hypothesis of Talcott et al. that granulocytopenic patients with controlled cancer and no serious comorbidity who developed fever in an outpatient setting are at low risk and can safely be treated as outpatients, was validated in a prospective study.[217] Klastersky et al. developed a Multinational Association for Supportive Care in Cancer risk index; a score of more than 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%.[218] The variables comprising this index are summarized in Table 76.15.

Summary Recommendations for Initial Empiric Therapy

Figure 76.10 summarizes the IDSA 2002 Guideline Recommendations for Initial Empiric Antimicrobial Therapy in Granulocytopenic Patients with Fever.[6] The first step is to determine whether the patient is at low or high risk for serious life-threatening infection, on the basis of the criteria observed at the time of presentation (see Table 76.15). If the risk is high, IV antimicrobials must be used; if risk is low, the patient may be treated with either intravenous or oral drugs. Second, decide whether the patient qualifies for vancomycin therapy. If the patient qualifies, begin treatment with a two- or three-drug combination, with vancomycin plus cefepime, ceftazidime, or a carbapenem, with or without an aminoglycoside. If vancomycin is not indicated, begin monotherapy with a cephalosporin (cefepime or ceftazidime) or a carbapenem (meropenem or imipenem-cilastatin), administered intravenously for uncomplicated cases. Two-drug combinations are recommended for management of complicated cases or if antimicrobial resistance is strongly suspected.

Adults selected for oral therapy may receive ciprofloxacin plus amoxicillin-clavulanate. Selection of patients for outpatient therapy must be done carefully from the low-risk group, depending on the capabilities of the medical center and the feasibility of close follow-up. Initial therapy with oral antimicrobials alone in the outpatient setting is not recommended for children because of a lack of sufficient evidence.

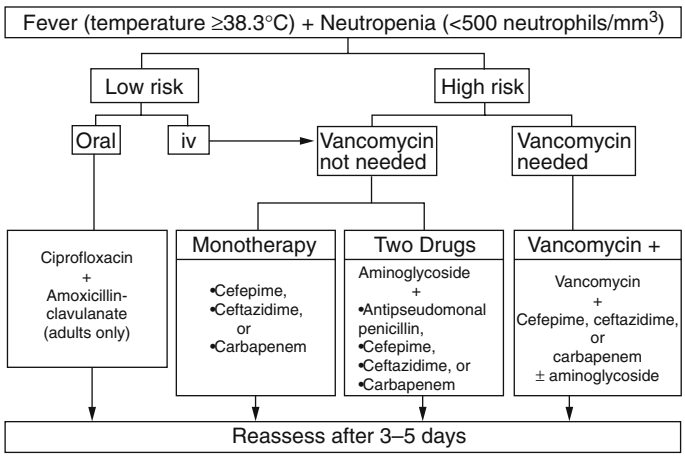


FIGURE 76.10. Algorithm for initial management of febrile granulocytopenic patients. (From Hughes et al.,[6] by permission of *Clinical Infectious Diseases.*)

Modification of Empiric Therapy

The majority of patients with febrile granulocytopenia will not have a microbiologically documented infection. Therefore, duration of therapy usually cannot be guided by monitoring clinical resolution of a local infection or clearance of bacteremia. Scientific evidence to answer this important question is scant and does not permit definitive conclusions. The evidence-based 2002 IDSA Guideline for the management of granulocytopenic fever stratifies patients by duration of fever and, for patients who become afebrile by day 3, recommends discontinuation of antiinfective therapy if the patient's granulocyte count is 500 cells/mm^3 or higher for 2 consecutive days, there is no definite site of infection, and cultures remain negative. If the patient's granulocyte count is still less than 500 cells/mm^3 by day 7, but the patient was initially at low risk and there are no subsequent complications, therapy may be stopped when the patient is afebrile for 5 to 7 days. However, if the patient was initially considered to be high risk, antiinfective therapy should be continued (Figure 76.11).[6]

Patients with persistent fever for more than 3 days after initial therapy, for whom no infected site of organism has been identified, pose the greatest challenge. Persistent fever suggests that the patient has a nonbacterial, especially fungal, infection, a bacterial infection resistant to or slow to respond to the drug or drugs being given, the emergence of a superinfection, inadequate serum and tissue levels of the antibiotic(s), drug fever, or need for source control (e.g., an abscess or infected IVD). Although some patients with microbiologically defined bacterial infections, even when appropriately

TABLE 76.15. Scoring index for identification of low-risk febrile granulocytopenic patients at time of presentation with fever.[a]

Characteristic	*Score*
Extent of illness[b]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age less than 60 years	2

[a] Does not apply to patients 16 years of age or less. Initial monocyte count of 100 cells/mm^3 or more, no comorbidity, and normal chest radiograph findings indicate children at low risk for significant bacterial infections.

[b] Choose one item only. Highest theoretical score is 26. A risk index score of 21 or more indicates that the patient is likely to be at low risk for complications and morbidity.

Source: Adapted from Hughes et al.,[6] by permission of *Clinical Infectious Diseases.*

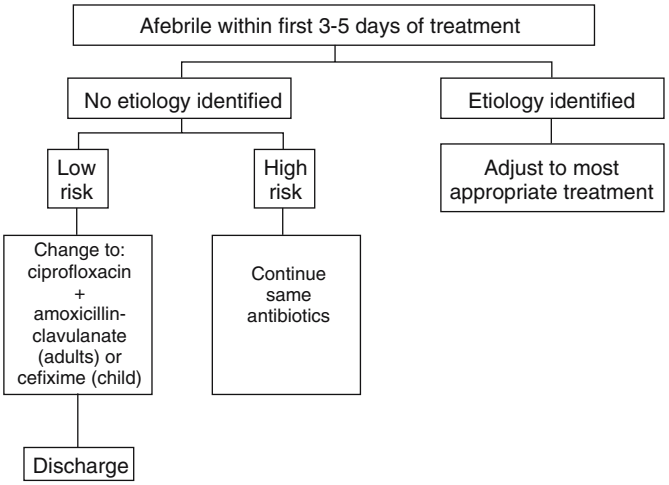


FIGURE 76.11. Guide for management of patients who become afebrile in the first 3 to 5 days of initial antibiotic therapy. See Table 7.15 for rating patients at low risk. (From Hughes et al.,[6] by permission of *Clinical Infectious Diseases.*)

treated, may require 5 days of therapy before defervescence occurs, a comprehensive reassessment should be undertaken if the patient fails to respond to initial therapy within 3 days, to include a review of all culture results, physical examination, chest radiograph, culturing of additional blood samples, and samples from clinically suspected sites of infection, and diagnostic imaging of any deep organ suspected of harboring infection. Ultrasonography or high-resolution CT are especially helpful for patients with suspected pneumonia, sinusitis, or typhlitis.

If fever persists after 5 days of antimicrobial therapy and reassessment does not yield a cause, there are three possible approaches (Figure 76.12): (1) continue treatment with the initial antibiotics, (2) modify the initial regimen, or (3) add an antifungal agent to the regimen, with or without modification of the antibacterial regimen.

If no discernible improvement in the patient's condition has occurred (i.e., the patient remains febrile but stable) during the first 4 to 5 days of initial antimicrobial therapy, and if reevaluation yields no new information to the contrary,

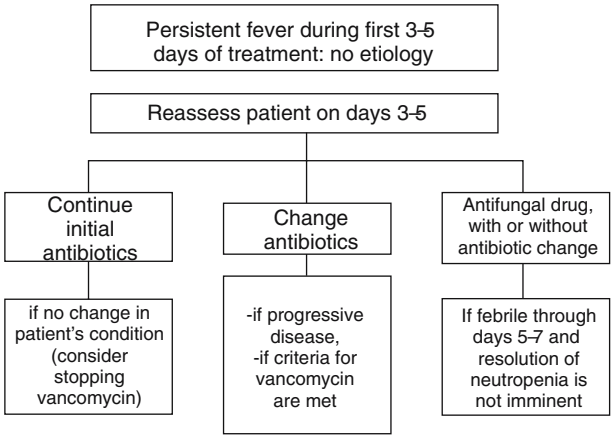


FIGURE 76.12. Guide to treatment of patients who have persistent fever after 3 to 5 days of treatment and for whom the cause of the fever is not found. (From Hughes et al.,[6] by permission of *Clinical Infectious Diseases.*)

the initial regimen can be continued. This decision will be strengthened if the granulocytopenia can be expected to resolve within the ensuing 5 days.

If evidence suggests clinical deterioration or a complication (such as the onset of abdominal pain from enterocolitis or typhlitis, new or worsening mucosal lesions, or drainage from an IVD exit site or pulmonary infiltrates) during the initial antimicrobial course, consideration should be given to adding appropriate antibiotics or changing to a different regimen.

If the initial regimen is monotherapy or two drugs without vancomycin, vancomycin may be considered if any of the criteria for use of vancomycin previously mentioned has been met. If a blood- or site-specific pathogen is isolated, the most appropriate antibiotic should be used while continuing broad-spectrum coverage.

The third decision to consider is the addition of empiric antifungal therapy. Amphotericin B is usually the drug of first choice (see Figure 76.12). Studies in 1982[219] and 1989[220] suggested that up to one-third of febrile granulocytopenic patients who do not respond to a 1-week course of empiric antimicrobial therapy have a systemic fungal infection that, in most cases, is caused by *Candida* or *Aspergillus* species. The empiric use of IV amphotericin B deoxycholate in patients with prolonged febrile granulocytopenia, was shown to reduce the incidence of invasive fungal infection and improve patient survival.[221,222] Although clinicians disagree when amphotericin B therapy should be initiated empirically, most believe that the patient who remains febrile and profoundly granulocytopenic for 5 days, despite administration of antimicrobial therapy in adequate doses, is a candidate for antifungal therapy.[6] However, every effort should be made to determine whether systemic fungal infection exists, by biopsy of suspicious lesions, radiographs of chest and sinuses, nasal endoscopy to investigate sinusitis, and CT of the abdomen and chest, before amphotericin B therapy is started.

Comparative trials show that lipid formulations of amphotericin B can be used as alternatives to amphotericin B deoxycholate for empiric therapy. Although they do not appear to be any more effective therapeutically,[223] lipid formulations of amphotericin are associated with much less infusion-related toxicity and, especially, nephrotoxicity.[224,225]

The use of azoles—fluconazole, itraconazole, or voriconazole—in patients with febrile granulocytopenia has been less well studied. Small trials have demonstrated equivalency between amphotericin B deoxycholate and fluconazole[226] or itraconazole[227]; however, both these studies were performed in populations with low rates of filamentous fungal infection.

The new triazole, voriconazole, has also been compared to liposomal amphotericin B in a large randomized multicenter study.[228] The use of voriconazole was associated with a reduced incidence of documented invasive fungal infections; however, voriconazole was found to be inferior to liposomal amphotericin, based on a five-part composite primary endpoint. As a result, voriconazole has not been licensed by the FDA for the empiric therapy of febrile granulocytopenia.[229]

Duration of Antimicrobial Therapy

The most important guides to successful discontinuation of antibiotics are the granulocyte count and defervescence

TABLE 76.16. Recommendations for duration of empiric antimicrobial therapy for patients with granulocytopenic fever.

Duration	*Recommendation*
Afebrile by day 3–5	
ANC >500 per 2 consecutive days	Stop antibiotics 48 hours after afebrile and ANC >500
ANC <500 by day 7	
Initially considered low-risk patient and clinically well	Stop antibiotics when afebrile for 5–7 days
Initially considered high risk, or profoundly granulocytopenic, or with mucositis or clinically unstable	Continue antibiotics
Persistent fever without identifiable source or pathogen	
ANC >500	Stop antibiotics 4–5 days after ANC >500 and reassess
ANC <500	Continue antibiotics for 2 weeks; reassess and stop if no disease is found

Source: Adapted from Hughes et al.,[6] by permission of *Clinical Infectious Diseases.*

(Table 76.16). As noted earlier, if no infection is identified, if the granulocyte count is 500 cells/mm^3 or more for 2 consecutive days, and the patient is afebrile for 48 hours or more, empiric antimicrobial therapy may be stopped at that time.

If the patient becomes afebrile but remains granulocytopenic, the best course is less well defined and no consensus exists. Some authorities recommend continuation of antibiotics, given intravenously or orally, until granulocytopenia has resolved; others suggest that for granulocytopenic patients who appear healthy clinically, who are in a low-risk category at onset of treatment, and who have no radiographic or laboratory evidence of infection may have systemic antimicrobial therapy stopped after 5 to 7 afebrile days, or sooner with hematologic recovery.[230] If antibiotics are stopped while the patient has granulocytopenia, the patient must be monitored very closely and intravenous antibiotics resumed immediately with the recurrence of fever or other evidence of bacterial infection.[231] *In general, antibiotic therapy should be continued throughout the granulocytopenic period in patients with profound granulocytopenia (less than 100 cells/mm^3), mucous membrane lesions of the mouth or gastrointestinal tract, unstable vital signs, or other identified risk factors.*

In patients with prolonged granulocytopenia in whom hematologic recovery cannot be anticipated, one can consider stopping antibiotic therapy after 2 weeks if no site of infection has been identified and the patient can be observed carefully (see Table 76.16).

The duration of amphotericin B therapy differs. If a systemic fungal infection has been identified, the course of antifungal therapy will be determined by the causative agent, the extent of the disease, and the clinical and microbiologic response. However, if no fungal infection is found, it is less clear how long empiric amphotericin B or other antifungal drugs should be continued. Experience is limited predominantly to amphotericin B. When granulocytopenia has resolved, the patient is clinically well, and CT of the abdomen and chest reveal no suspicious lesions, amphotericin B may be discontinued.[232] For clinically well patients with prolonged granulocytopenia, it is suggested that, after 2 weeks of daily doses of amphotericin B, if no discernible lesions can be found by clinical evaluation, chest radiography (or CT of the chest), and CT of the intraabdominal organs,[233] the drug can be stopped. In the patient who appears ill or is at high risk, one should consider continuation of therapy with antibiotics *and* amphotericin B throughout the period of granulocytopenia, assuming that hematologic recovery can be anticipated.

Predictors of Response to Antimicrobial Therapy

Elting et al. assessed predictors of outcome in 909 episodes of bacteremia selected from 10 randomized clinical trials of antimicrobial therapy for infection in patients with cancer and granulocytopenia.[234] Extensive tissue infection significantly compromised response to initial therapy (74% versus 38%; P less than 0.0001), ultimate outcome of infection (94% versus 73%; P less than 0.0001), and survival (94% versus 75%; P less than 0.0001). Log regression showed that shock (OR, 18.0; P less than 0.0001) and bacteremia caused by *P. aeruginosa* species (OR, 7.0; $P = 0.03$), *Clostridium* species (OR, 9.0; $P = 0.006$), or a pathogen resistant to antibiotics used for initial therapy (OR, 3.0; P less than 0.0001), were each independently associated with a poor outcome. Recovery of the granulocyte count predicted a favorable outcome (OR, 0.4; P less than 0.0001). Although the overall mortality rate was not significantly increased when patients with bacteremia caused by gram-negative organisms initially received monotherapy or when patients with bacteremia due to gram-positive organisms received delayed vancomycin therapy, these strategies increased the duration of therapy by 25%. Patients with bacteremia caused by alpha-hemolytic streptococcus were more likely to die if vancomycin was not included in the initial empirical regimen ($P = 0.004$).

Hematopoietic Growth Factors

Hematopoietic growth factors have been studied as an adjunct to antimicrobial therapy for granulocytopenic fever in several randomized trials. Although the duration of granulocytopenia was consistently shorter in these studies, it did not translate into clinically relevant improved outcomes. In a meta-analysis of 13 randomized, controlled trials comparing antibiotics and granulocyte colony-stimulating factor (G-CSF) with antibiotics alone for granulocytopenic fever, Clark et al. found a decrease in length of hospitalization [RR, 0.63; 95% confidence interval (CI), 0.40–0.82; P less than 0.001] and a shorter time to granulocyte recovery (RR, 0.32; 95% CI, 0.23–0.46; P less than 0.001); however, no effect on either overall mortality (OR, 0.68; 95% CI, 0.43–1.08; $P = 0.05$) or infection-related mortality (OR, 0.85; 95% CI, 0.33–2.20; $P = 0.7$) was observed.[235] Based on the available evidence, recent guidelines[6,236] that have addressed the use of G-CSF and granulocyte macrophage colony-stimulating factors (GM-CSF) in patients with cancer recommend against the routine use of hematopoietic growth factors. However, under certain conditions, with a worsening of the course and expected delay in marrow recovery, use of these agents may be appropriate with pneumonia, hypotension, or shock, severe cellulitis or sinusitis, systemic fungal infections, or multiorgan dysfunction secondary to sepsis.[6] Therapy with colony-stimulating factors

could also be considered for patients who remain severely granulocytopenic and have documented infections that have failed to respond to appropriate antimicrobial therapy, such as gram-negative cellulitis.

Granulocyte Transfusions

Existing evidence does not support the routine use of granulocyte transfusions in patients with granulocytopenic fever. The major indication for granulocyte transfusion support at the present time is the patient with profound granulocytopenia and overwhelming gram-negative bacillary infection, especially major soft tissue infection that is unresponsive to antiinfective therapy.[237]

Supportive Therapy

Treatment of infection, especially associated with sepsis or early multiple organ dysfunction (MODS) syndrome, does not stop with source control and antiinfective therapy but demands the highest skills of the clinician to keep the patient alive until the infection can be controlled.

Circulatory Support

The importance of very early and aggressive circulatory support of the septic patient with large volumes of fluids, with or without cardiovascular pressor drugs, cannot be overemphasized.[238] The most experienced clinician cannot by physical examination alone reliably assess a critically ill patient's cardiac performance vis-à-vis ventricular filling pressures or cardiac output. Thus, if an infected patient exhibits hypoxemia or hypotension refractory to initial fluid resuscitation, a flow-directed, balloon-tipped, pulmonary artery catheter (PAC) can be helpful to guide fluid therapy and decisions on choice of pressors and inotropic drugs, with the physiologic goal of optimizing oxygen delivery and uptake. Recent fear, based on a retrospective study, that PACs increase mortality in critically ill patients[239] has been dispelled by a large, multicenter randomized trial in older adult surgical patients showing that PACs can be used safely without increased mortality.[240]

There are no data to indicate that colloid solutions, such as albumin, plasma protein fraction, or hydroxyethyl starch (hetastarch) are superior to crystalloids, such as 0.9% normal saline or Ringer's lactate, for support of the failing circulation in the patient with septic shock. Crystalloids should be the IV fluid of choice for treatment of sepsis and in the patient with shock and should be given aggressively in the first 4 to 6 hours, guided by the central venous pressure, to minimize mortality.[238]

Novel Adjunctive Therapies

For nearly 40 years, despite advances in antiinfective therapy and in ICU care, the mortality of septic shock has declined only marginally, pointing up the need to modulate the severe systemic inflammatory response syndrome that underlies shock, multiorgan dysfunction, and death.[213]

Patients who have been receiving long-term corticosteroid therapy who develop sepsis need supplemental stress doses of corticosteroids, hydrocortisone 50 to 75 mg IV every 6 hours, to prevent acute adrenal crisis. However, there is growing evidence to suggest that these doses of hydrocortisone will improve survival in patients with severe sepsis. A recent multicenter, double-blind randomized trial in France found, in patients with severe sepsis or septic shock, that adjunctive therapy with hydrocortisone 50 mg IV every 6 hours and fludrocortisone 5 μg per day orally reduced mortality 30%.[241]

It has long been recognized that most patients with septic shock have low levels of the essential physiologic anticoagulant, protein C. A recent international, multicenter trial was undertaken to assess the therapeutic effect of repleting protein C with a recombinant activated form (rhAPC) in patients with severe sepsis, 75% with shock.[242] The choice of protein C was influenced by knowledge of its capacity to modulate inflammation through inhibition of monocyte production of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1b, inhibition of neutrophil activation, and downregulation of endothelial expression molecules, intercellular adhesion molecule ICAM-1, E-selectin, and VCAM-1. In the double-blind trial in 1,640 patients, a continuous infusion of rhAPC 24 μg/kg/min, begun within 24 hours of the onset of severe sepsis and continued for 96 hours, was associated with a 19% reduction in 28-day all-cause mortality ($P = 0.005$). There was a slight increase in bleeding complications in recipients of rhAPC (serious bleeding, 3.5% versus 2.0%; $P = 0.06$); however, rhAPC was well tolerated, considering the critical illness of most of the recipients.[242] The major contraindications to adjuvant use of rhAPC in cancer patients are active bleeding, severe thrombocytopenia (less than 30,000), or chronic renal or hepatic failure.

Prevention of Infection in the Patient with Cancer[213]

Protective Isolation

Profound and prolonged granulocytopenia, whether caused by the primary hematologic malignancy or its therapy, puts the patient at great risk for severe infection. Approximately 70% of deaths from acute nonlymphoblastic leukemia (ANLL) are ascribed to infection, the risk of which is inversely related to the absolute granulocyte count. Prevention of infection may allow patients to receive more intensive chemotherapy and thereby increase the rates of remission and overall survival. Concerted efforts have been made to protect the granulocytopenic patient from nosocomial infection during chemotherapy or bone marrow transplantation. Randomized trials have prospectively evaluated various procedures for protection of the granulocytopenic patient, including protective environments, the use of prophylactic nonabsorbable antibiotics, or both.[243]

Most programs have been based on elaborate protocols for protection against both extrinsic and endogenous pathogens, typically isolating the patient in a room or tent with filtered ultraclean air and requiring persons entering the room to wear sterile overgarments, gloves, shoe covers, and masks. Such protocols have been supplemented by regular applications of cutaneous and orificial disinfectants, use of food and water low in microbial content, and continuous administration of prophylactic oral nonabsorbable antibiotics. Because the

expense of such complex programs is prohibitive for most hospitals, simple protective isolation (or reverse precautions) requiring that the person entering the room wear a clean gown, gloves, and mask is widely used as an alternative means to protect the granulocytopenic patient from infection. A prospective, randomized unblinded study to assess the efficacy of protective isolation in 37 granulocytopenic patients with 43 episodes of infection found no statistically significant differences in the overall incidence of infection, time to onset of first infection, or days with fever.[244] Neither response to antileukemic therapy nor survival was improved with isolation.

These randomized trials are difficult to compare because of differing isolation protocols, different antileukemic or antibiotic regimens; moreover, criteria of infection have not been consistently defined. In general, however, comparative studies have shown that patients in whom some method or protection was used, either a protective environment or antibiotics alone or in combination, had fewer infections, fewer days of fever, and often reduced mortality from infection. However, more importantly, these measures have failed to find improvement in rates of leukemic remission or overall survival.

Prevention of Nosocomial Transmission of Resistant Organisms

Isolation of infected and colonized patients is widely regarded as the most important measure to prevent spread of resistant pathogens through the healthcare institution.[245,246] The most recent CDC Guideline categorizes isolation precautions: (1) standard precautions and (2) transmission-based precautions.[247] Standard precautions specify the use of gloves for any anticipated contact with blood, any body fluid, secretions or excretions (except sweat), nonintact, skin or mucous membranes. Gowns are recommended if patient care activities are likely to generate splashes of blood, body fluids, and secretions. Hand hygiene is expected after removing gloves and between patients. Standard precautions apply to *all* patients, without regard to clinical diagnosis.

Transmission-based precautions include contact, droplet, and airborne precautions, each based on the mode of transmission of the infectious agent within the healthcare setting. Acknowledging that multiresistant nosocomial pathogens, particularly MRSA and VRE, are spread primarily by direct (and indirect) contact with healthcare workers, the Guideline specifies that patients known to be colonized or infected by resistant bacteria are to be placed in contact isolation, which requires a private room for the patient (or pairing the patient in a semiprivate room with another patient who is also colonized or infected by the same organism). Healthcare workers are expected to wear gloves on entry to the room, and gowns as well if substantial contact with the patient or the environment is anticipated. Gloves and gowns should be removed and hands treated with a medicated hand hygiene product while still in the isolation room. Noncritical patient care items should be dedicated; if reused, they must be disinfected between patients.

Unfortunately, the existent paradigm for preventing spread of resistant organisms in the hospital—waiting until colonization or infection by MRSA, VRE, or some other resistant organism is serendipitously identified by the clinical laboratory, following which the patient is placed in isolation, usually in a single room, requiring gloves, with or without a gown, for all contacts with the patient—is failing dismally, viewing the inexorable growth in antimicrobial resistance.[49,248,249]

A recent Guideline from the Society for Healthcare Epidemiology of America[250] recommends that surveillance cultures to detect silent VRE or MRSA carriage be performed in roommates of VRE- or MRSA-colonized or -infected patients and other high-risk patients, at the discretion of infection control staff; patients found to be colonized must *also* be placed in contact isolation.[250] If these measures fail to contain spread, efforts should be intensified in the highest risk areas, such as the ICU. Grouping of staff and screening of staff for carriage, if epidemiologic data point to a link, is recommended. Verification that environmental disinfection procedures are effective, by environmental surveillance cultures before and after cleaning areas containing VRE- or MRSA-colonized or -infected patients, is also recommended.

Strategies designed to proactively identify the reservoir of asymptomatic colonized patients by routine surveillance cultures of patients at high risk for MRSA or VRE carriage, rather than relying solely on clinical cultures driven by suspicion of infection, followed by isolation only if cultures indicate the presence of a resistant organism,[251,252] have had variable results; most before-and-after studies have shown that this strategy has been useful in containing institutional spread of multiresistant organisms,[251,253,254] but others have found limited benefit.[255–257] It is notable that no randomized trial has yet been undertaken to assess the effectiveness of prospective microbiologic surveillance beyond the outbreak setting.

Eradication of VRE or MRSA from the hospital is most likely to succeed when the rate of colonization or infection is still low or confined to a single unit.[258,259] A comprehensive multifaceted infection control program, consisting of contact isolation (gowns, gloves) for patients found to be colonized in weekly screening of all patients, handwashing, dedicated use of noncritical equipment, and intensive education, was highly successful in reducing the prevalence of VRE colonization from 2.2% to 0.5% in the Siouxland region of Iowa, Nebraska, and South Dakota, where VRE was only recently detected for the first time.[258] Once hyperendemicity has occurred, eradication is very difficult and costly. The continued reintroduction of new multiresistant strains into the institution from interinstitutional transfers of unrecognized colonized patients has fueled the continued spread of multiresistant nosocomial organisms. Infection control policies must find ways to prevent both intra- and interinstitutional spread.

The majority of patients admitted to ICUs have multiple risk factors for colonization or infection by resistant organisms,[23] which mandates screening a very large proportion of the patients or, better, all of them. Weekly surveillance cultures, as performed in the majority of studies that have used this approach, requires substantial microbiologic support and is labor intensive.[260] By the time the results of surveillance cultures showing colonization by a resistant organism become available, and isolation precautions can be implemented, precious time has passed, providing opportunities for further spread of the organism. Moreover, targeted screening for only one nosocomial pathogen, such as VRE,

ignores the possibility that the patient might be colonized by nosocomial pathogens other than VRE, such as MRSA, resistant gram-negative bacteria, or *Clostridium difficile*, which obviously facilitates their spread.

We believe that a simpler strategy for preventing spread of all types of multiresistant bacteria, is the preemptive use of barrier isolation precautions (gowns and gloves) and dedicated patient care items, such as stethoscopes and sphygmomanometers, in *all* high-risk patients from the time of admission, to prevent healthcare workers from acquiring hand contamination by multiresistant organisms when having contact with patients with unrecognized colonization or infection, and thus, to block transmission to other, as yet uncolonized, patients. Numerous studies have shown that the preemptive use of barrier precautions, also called "protective isolation," can effectively prevent the spread of multiresistant organisms, such as MRSA or VRE, in an epidemic setting,[261,262] and other studies have shown the effectiveness of protective isolation in high-risk populations, such as patients in an ICU, for prevention of endemic nosocomial infection, including spread by multiresistant organisms.[256,263–267] Three prospective randomized trials have been conducted to assess the efficacy of preemptive barrier precautions[263,264,268]; two showed benefit with a reduction in all nosocomial infections in ICU patients (relative risk reduction, 52% to 81%).[263,264]

Antimicrobial Prophylaxis

Prophylactic antimicrobials during granulocytopenia have been shown to reduce the frequency of febrile episodes; however, enthusiasm for the use of prophylactic antimicrobials has been damped by the adverse consequences of such a strategy, particularly emergence of multiresistant bacteria, superinfection by fungi, and toxicity from the antimicrobials used.

Combinations of nonabsorbable drugs, such as aminoglycosides, polymyxins, and vancomycin, have been used for infection prophylaxis in the past. However, recent prospective, randomized trials have consistently found that trimethoprim-sulfamethoxazole (TMP-SMZ) and fluoroquinolones are more effective and better tolerated.[269,270]

A recent meta-analysis of nine prospective, randomized trials (1,202 patients) to assess the benefit of adding an agent for gram-positive coverage (vancomycin, penicillin, amoxicillin, roxithromycin, or rifampin) to prophylactic fluoroquinolones found that although the frequency of infections caused by gram-positive bacteria (coagulase-negative staphylococci and streptococci) was reduced, overall mortality attributable to infection was similar in both groups.[271] Side effects occurred twice as frequently in the group receiving additional prophylaxis against gram-positive bacteria. As such, the routine use of prophylactic antibiotics for prevention of infection in patients with cancer and granulocytopenia is not recommended.

Invasive fungal infection is associated with considerable morbidity and mortality especially in patients with hematologic malignancy. Because these infections are difficult to diagnose and have high mortality, prophylaxis against fungal infections is an attractive approach for patients expected to have prolonged granulocytopenia. Numerous randomized trials assessing the efficacy of antifungal agents, most often fluconazole, itraconazole, or amphotericin have been undertaken. The results are difficult to compare because of differing patient populations, myelosuppressive regimens, drug dosage and routes of administration, varying durations of prophylaxis, and lack of uniform case definitions. Nonetheless, most trials have found benefit for prevention of invasive fungal infections; however, a survival benefit was not consistently demonstrated.[272,273]

The risk of developing a potentially fatal invasive fungal infection increases in patients with hematologic (rather than solid organ) malignancy, duration of granulocytopenia, prolonged corticosteroid therapy, allogeneic and autologous bone marrow and stem cell transplantation, graft-versus-host disease, and concomitant viral infections.[274,275] Therefore, the best studies of antifungal prophylaxis have focused on these high-risk groups. Fluconazole has been the most widely studied agent for prophylaxis in doses ranging from 50 to 400 mg daily. Goodman et al. found that 400 mg/day of fluconazole was superior to placebo in reducing both the incidence of invasive fungal infection and attributable mortality.[276] In the second trial, performed in pediatric and adult bone marrow transplant recipients, fluconazole, given for 100 days posttransplantation, reduced the incidence of invasive fungal infection when compared with clotrimazole troches.[277]

Based on results from these and other studies that reported similar results, 400 mg/day fluconazole is recommended for patients undergoing allogeneic bone marrow or stem cell transplantation.

Fluconazole has dose-dependent activity against *Candida glabrata* and no activity against *Candida krusei* and *Aspergillus* species. An azole with a broader spectrum, itraconazole, has been studied in several trials. The oral suspension has superior bioavailability than capsules and has been shown to be more efficacious. The results of randomized trials indicate a reduction in the incidence of fungal infection; however, a mortality benefit was not consistently demonstrated. A recent meta-analysis of 13 randomized trials (3,597 patients) found that prophylaxis with itraconazole reduced the incidence of invasive fungal infection (RR, 40%; $P = 0.002$) and mortality from invasive fungal infection; however, no impact on overall mortality was observed.[278] As yet, the benefit of prophylaxis with itraconazole remains controversial, and it cannot be recommended universally.

Amphotericin B deoxycholate and lipid-based amphotericin B have each been studied in a limited number of trials, most of which employed historical controls or a small number of subjects.[279,280] Infusion-related toxicity with amphotericin B and the high cost of lipid-associated amphotericin B have limited the prophylactic use of these agents.

Two new antifungal agents, voriconazole and caspofungin, have recently become available for treatment of fungal infection; however, data on prophylaxis are as yet too limited to draw conclusions.[281] Recent recommendations regarding the use of antifungal prophyalxis have been published by the German Society of Hematology and Oncology[282] and are summarized in Table 76.17.

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TABLE 76.17. Summary of recommendations for antifungal prophylaxis in patients with malignancy.

Patient population	*Drug*	*Dosage*	*Level of evidence*
Conventional chemotherapy	Fluconazole	50–400 mg/day	C-I
	Itraconazole oral suspension	≤5 mg/kg/day	C-I
	Itraconazole capsules parenteral	Any dose	C-I
	amphotericin B deoxycholate parenteral	0.5–1.0 mg/kg every 48 hours	C-II
	amphotericin B deoxycholate	<0.5 mg /kg every 48 hours	C-II
Allogeneic transplant	Fluconazole	400 mg/day	A-I
	Fluconazole	50–200 mg/day	C-I
	Itraconazole	400 mg/day oral solution	C-I
	Liposomal amphotericin B	1.0 mg/kg/day	C-I
Solid tumors	Any antifungal	Any dose	C-I

Source: Adapted from Cornely et al.,[282] by permission of *Annals of Hematology*.

From the Infectious Diseases Society of America Guidelines for weighting recommendations based on the quality of scientific evidence.[283] Category: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation for use. Quality of evidence: I, evidence from one or more properly randomized controlled trial; II, evidence from one or more well-designed observational study, multiple time-series, or dramatic results of uncontrolled experiments; III, expert opinion, descriptive studies.

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