Chapter 84
Acute Infection in the Immunocompromised Host

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Advances in the management of neoplastic diseases, transplant immunology, and the therapy of autoimmune diseases have resulted in marked improvements in life expectancy and the quality of patients' lives. However, patients with either neoplasia or transplants are rendered highly susceptible to infection by virtue of their underlying diseases and their associated therapies, including chemotherapy, radiation therapy, and surgery. Infection has been and remains a leading cause of death in patients with leukemia and lymphoma and a major cause of morbidity and mortality in patients with solid tumors or transplants [1,2,3,4,5,6,7]. Rapid progression of fungal, bacterial, and mycobacterial infections occurs in patients given monoclonal antibodies to treat Crohn's disease and autoimmune diseases such as rheumatoid arthritis [8,9,10,11]. The epidemic of human immunodeficiency virus (HIV)-1 infection has added to the numbers of immunocompromised hosts by virtue of the central event of the virus's pathogenesis: a progressive, irreversible weakening of cell-mediated immunity unless the patient responds to antiretroviral agents (see Chapter 85).

Traditionally, infection has accounted for up to 75% of deaths in patients with acute leukemia or Hodgkin's disease [2,12] or in transplant recipients [4,13], but with advances in prophylaxis and management, deaths due to infections have decreased to about 50% while death due to graft versus host disease, relapse of malignancy, and multiorgan failure have increased [7,13,14,15]. Once patients require intensive care unit (ICU) care the mortality increases and the 1-year survival of cancer patients that require mechanical ventilation in the ICU is below 11% in some centers [16] with acute mortality between 44% to 65% [17,18,19,20]. Early ICU admission has been advocated based on one small study demonstrating that among patients initially thought to be too sick to benefit from ICU care many were subsequently admitted to the ICU and did well [21]. Additionally in this study, a fraction of patients initially thought to be too well to merit ICU care had high mortalities when they subsequently required ICU admission.

Although a great variety of microorganisms have been noted to cause severe, life-threatening infections in immunocompromised hosts, the clinician can formulate a diagnostic plan and decide on empiric therapy by giving careful consideration to the nature, duration, and severity of the immunosuppression that is causing the patient's predisposition to infection. Infection can arise as a consequence of derangement in host defenses that results from the primary disease, the medical and surgical treatment of the condition, or a combination of these factors. Additionally, immunocompromised patients are likely to manifest their infections in ways that are characteristically different from those of patients with intact immune responses.

Immune Defects and Associated Organisms and Infections

Underlying disease or treatments affect different aspects of the immune system and, depending on the type of defect, are associated with predisposition to infection with specific classes of organisms or disease syndromes. A level of suspicion of infection with certain organisms depends on the specific immune defect, the duration of immunosuppression, surgical and medical interventions, colonization with nosocomial pathogens, and previous latent or asymptomatic infections that may reactivate after immunosuppression. In general, the most

common sites of serious, definable infection in the immunocompromised host are the bloodstream (including infection related to intravenous access devices), lung, and mucocutaneous surfaces (including oral, gastrointestinal, skin, and perirectal areas) [3,5,22]. The diverse organismsfrequently or uniquely associated with infections in the compromised host are listed in Table 84-1. As for any patient in the ICU, the immunocompromised patient is susceptible to infection with common bacteria. The most common organisms found in patients with bloodstream infections are *Escherichia coli* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), followed by coagulase-negative staphylococci, enterococci, *Pseudomonas aeruginosa*, *Klebsiella* spp, *Enterobacter* spp, and various streptococci [23,24,25,26,27]. In patients with neutropenia and documented bacteremia, Gram-positive organisms predominate over Gram-negative bacilli in patients in most centers, and the presence of an intravascular device is associated with having a positive blood culture [28,29]. Fungal infections increase in frequency with increasing duration of the immunocompromised state and therapy with broad-spectrum antibiotics.

Anatomic Barriers

The skin and mucosal surfaces serve a primary role in the defense of the host against invasion by endogenous and exogenous microorganisms. Mucous membrane ulceration in the mouth and gastrointestinal tract can occur spontaneously in patients with acute leukemia, although this complication more

commonly arises after chemotherapy. In patients with solid tumors, disruption of mucocutaneous barriers can result from invasion, obstruction, or perforation by the malignancy. Iatrogenic disruption of the normal skin and mucosal barriers results from medical and surgical support interventions common to the ICU, including intravascular and urinary catheters [30,31] (see Chapters 81, 82). Organisms that most frequently cause infection of intravascular catheters include coagulase-negative staphylococci, *S. aureus*, enterococci, *Corynebacterium* spp (including *C. jeikeium*), and *Candida* spp [31,32,33]. Percutaneously inserted central catheters (PICC) are associated with an increased risk of both infection and thrombosis [34]. The risk of these infections can be reduced, although not eliminated, through the use of permanent, subcutaneously tunneled catheters (e.g., Hickman, Broviac, Groshung, or Portacath systems) [35,36]. Genitourinary tract infections are associated with disruption of the urinary

tract integrity, as occurs with urinary catheter drainage, pelvic tumors, or radiation with resultant ureteral obstruction, or after renal transplant.

Table 84-1. Organisms Commonly or Uniquely Associated with Acute Infection in the Immunocompromised Host

Organism	*Type of Immune Deficiency Most Likely to Predispose to This Organism*
Bacteria	
Enteric Gram-negative bacilli (*Escherichia coli,*	All immunocompromised patients, especially those with neutropenia and

Klebsiella, Enterobacter, or *Proteus* spp)	those on mechanical ventilation or medications that suppress gastric acid
Staphylococcus aureus	All immunocompromised patients especially those with skin infections or intravascular catheters
Pseudomonas aeruginosa	All immunocompromised patients especially neutropenic patients and those on mechanical ventilation
Listeria monocytogenes	All immunocompromised patients, HIV/AIDS patients
Legionella pneumophila and related organisms	All immunocompromised patients especially those in units with ongoing construction
Skin/mucous membrane saprophytes	All immunocompromised patients
Corynebacterium jeikeium	All immunocompromised patients, splenectomized patients
Capnocytophaga spp	All immunocompromised patients, splenectomized patients
Eikenella corrodens	All immunocompromised patients
Coagulase-negative staphylococci	Patients with indwelling vascular catheters or prosthetic material
Nocardia spp	All immunocompromised patients
Streptococcus pneumoniae	Patients with immunoglobulin deficiencies or hyposplenism

Haemophilus influenzae	Patients with immunoglobulin deficiencies or hyposplenism
Neisseria meningitidis	Patients with immunoglobulin deficiencies or hyposplenism
Mycobacteria	Patients with a history of high-risk exposure for tuberculosis (lived in an endemic area or history of a positive tuberculin skin test) or long-standing immune defects and/or chronic lung disease
Fungi	
Candida albicans and other *Candida* spp	Patients with vascular catheters, after abdominal surgery including liver transplantation, and those receiving intravenous hyperalimentation
Candida glabrata	Same as Candidiasis, increased in patients with diabetes and urinary tract colonization
Aspergillus spp	Patients with neutropenia, after transplantation, or on medications such as steroids and cytotoxic agents
Zygomycetes spp	Patients with neutropenia, after transplantation, with diabetes, or on medications such as steroids and cytotoxic agents
Trichosporon spp	Patients with neutropenia, after transplantation, or on medications such as steroids and cytotoxic agents, with vascular catheters and those receiving intravenous

	hyperalimentation
Fusarium spp	Patients with neutropenia, after transplantation, or on medications such as steroids and cytotoxic agents, with vascular catheters and those receiving intravenous hyperalimentation
Pneumocystis jiroveci	All immunocompromised patients especially those receiving steroids, antirejection agents, or with lymphocytic leukemia
Endemic fungi and yeasts	
Cryptococcus neoformans	Patients with HIV/AIDS, after transplantation, or receiving steroids
Histoplasma capsulatum	Patients from an endemic area
Coccidioides immitis	Patients from an endemic area
Protozoa	
Toxoplasma gondii	Patients with HIV/AIDS, after transplantation, or on medications such as steroids and cytotoxic agents
Parasites	
Strongyloides stercoralis	Patients from an endemic area and after transplantation, or on medications such as steroids and cytotoxic agents

Viruses	
Cytomegalovirus	Patients after bone marrow or solid organ transplantation
Varicella-zoster virus	All immunocompromised patients especially those not receiving antiviral prophylaxis with cancer, or after bone marrow or solid organ transplantation
Herpes simplex virus	All immunocompromised and ICU patients especially those not receiving antiviral prophylaxis especially those with cancer, or after bone marrow or solid organ transplantation

HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ICU, intensive care unit.

The gastrointestinal tract is a source of occult bacteremia or fungemia, as chemotherapy and neutropenia cause breakdown in normal mucosal defenses of the gut, facilitating entry of bacteria or yeast into the bloodstream. Clinically apparent intestinal problems seen in neutropenic patients include typhlitis, anorectal cellulitis/fasciitis/abscess, necrotizing colitis, and *Clostridium difficile*–associated colitis caused by chemotherapy or antibiotics [37,38]. Typhlitis, an inflammatory disease of the cecum, may lead to toxic megacolon and perforation and requires a high index of suspicion and prompt diagnosis. Unusually severe and prolonged viral gastroenteritis caused by cytomegalovirus, adenovirus, rotavirus, and Coxsackie virus has been observed in marrow transplant recipients [22,39,40]. Herpes simplex virus (HSV) should be suspected as a possible cause for any lesion of mucous membranes in an immunocompromised host. Herpes simplex may also cause fatal hepatitis [41]. Adenovirus may cause hepatitis, pneumonitis, or hemorrhagic cystitis [22], and BK and JC viruses may cause persistent fever and renal insufficiency [42,43]. Necrotizing gingivostomatitis caused by oral anaerobes as well as severe periodontal infection may also complicate neutropenia [44].

Defective Phagocytosis

Neutrophils and macrophages provide defense against infection by bacteria and many fungi. Patients with leukemia, particularly an acute type of leukemia, commonly have a reduction in their absolute number of circulating neutrophils; qualitative defects of neutrophil function have also been described in these patients. Aplastic anemia, as well as extensive bone marrow involvement caused by lymphoma or metastatic solid tumors, may result in neutropenia. By far

the most common cause of neutropenia, however, is cytotoxic chemotherapy. Patients whose neutrophils are reduced in number by malignancy or chemotherapy are at risk for development of spontaneous bacteremia. The risk becomes significant at absolute neutrophil counts that are persistently below 500 per mm^3 (or below 1,000 per mm^3 and falling) and increases dramatically at counts below 100 per mm^3 [22,45].

Invasive and disseminated fungal infections also may be a consequence of neutropenia and become more common after the neutropenic patient has received broad-spectrum antibiotic therapy [22,46,47,48]. *Candida* and *Aspergillus* species are the most common fungal pathogens observed in neutropenic hosts, but unusual genera such as *Fusarium, Trichosporon, Scedosporium* (*Pseudallescheria*), and *Cunninghamella* have been described with increasing frequency [49,50,51,52].

Altered Humoral Immunity

B-cell lymphocytic function and antibody production may be impaired in untreated patients with chronic lymphocytic leukemia, multiple myeloma, and lymphoma [53]. Acquired deficits in antibody production may also be encountered in otherwise healthy patients (e.g., immunoglobulin A deficiency, common variable immunodeficiency). Hypogammaglobulinemia or impaired antibody response predisposes patients to infections attributable to encapsulated bacteria, such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis*; moreover, these infections are likely to be sudden, severe, and associated with fulminant bacteremia [22]. Infections caused by enteric Gram-negative bacilli and *P. aeruginosa* also may be seen in previously untreated patients with defective humoral immunity secondary to B-cell malignancies.

Impaired Cell-Mediated Immunity

T cell–mediated immunity includes cytotoxic (killer) T cells, activated macrophages, and antibody-dependent cellular cytotoxicity. These critical components of immunity are impaired in patients with Hodgkin's disease [54] and other lymphomas and in those taking antirejection drugs (e.g., cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, and antilymphocyte antibodies), antibodies against tumor necrosis factor-α, or corticosteroids [4,9,11,55]. Patients infected with HIV-1 experience a progressive and devastating loss of T cell–mediated immunity. This virus selectively infects and lyses $CD4^+$ lymphocytes that play a central role in governing humeral and cellular immune responses. Herpes viral infections after transplantation and other natural occurring viral infections such as measles result in a decrease of cellular immunity [56]. Defects in cell-mediated immunity are commonly associated with primary or reactivation of infection by herpes viruses (varicella-zoster virus, cytomegalovirus [CMV], HSV), protozoa (*Toxoplasma gondii* and *Cryptosporidium* spp), fungi (*Pneumocystis jiroveci*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Candida* spp), helminths (*Strongyloides stercoralis*), mycobacteria (*M. tuberculosis, M. avium-intracellulare, M. kansasii, M. chelonae*), and other intracellular bacteria (*Listeria monocytogenes*, *Salmonella*, and *Legionella* spp) [4,54,57].

Immunosuppressive Medications

Cytotoxic chemotherapy, corticosteroids, anticytokine antibodies, and other immunosuppressive therapeutic regimens can alter host defenses in several ways. Immunosuppressive effects depend on the class of drug, dose and duration of therapy, and timing relative to other therapeutic modalities (e.g., radiation, which may contribute to neutropenia). Several new inhibitors of cytokines and cytokine activation (including anti-TNF

and anti-IL-1 antibodies) have been marketed for a variety of autoimmune disorders. Use of these agents has resulted in the reactivation of latent tuberculosis [9]. Disseminated histoplasmosis and invasive aspergillosis have been described in patients receiving anti-TNF agents [58,59]. Physicians need to be aware of the fact that patients on such agents have a risk of reactivation of intracellular organisms.

Antimicrobial Therapy

Antibiotic therapy is highly effective in the management of documented infections and febrile episodes in the compromised host. These agents are double-edged swords, however, and promote a shift toward increasing frequency of infections caused by progressively more resistant organisms, including *P. aeruginosa, Enterobacter* spp, expanded spectrum β-lactamase producing *Klebsiella* spp, multiply resistant enterococci, methicillin-resistant *S. aureus*, and fluconazole resistant *Candida* spp. Unusual, intrinsically resistant bacteria (e.g., *Capnocytophaga* and

Corynebacterium spp) and fungi (e.g., *Scedosporium* and *Fusarium* spp) are being seen with increasing frequency in oncology centers [29,50,60,61].

Splenectomy

Splenectomy, which results in the loss of the reticuloendothelial capacity to clear organisms from the bloodstream, predisposes patients to fulminant, overwhelming bacteremia caused by encapsulated bacteria (*S. pneumoniae, H. influenzae*, and *N. meningitidis*) as well as *S. aureus*. Although the syndrome of overwhelming postsplenectomy infection is most common in patients whose splenectomy was for malignancy or reticuloendothelial disease, overwhelming postsplenectomy infection can occur in any splenectomized patient regardless of underlying disease or interval since surgery [62,63] (see Chapter 83). Accordingly, fever higher than 38°C in the splenectomized patient warrants immediate investigation and empiric therapy for possible bacteremia or focal bacterial infection. Consideration of ICU admission and presumptive antibiotic therapy is appropriate if the patient appears systemically toxic. A third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) is reasonable empiric therapy, although if skin or skin structure infection is present vancomycin should be added because of the increasing likelihood of community acquired methicillin-resistant *S. aureus* [64,65].

Diagnostic Approach to Fever

In the evaluation of acutely ill, immunocompromised patients with fever in the ICU, a meticulous and thorough history and physical examination must be performed initially and repeated daily. Particular attention should be directed to sites of high risk, such as the oropharynx, anorectal region, lungs, skin, optic fundi, and vascular catheter sites [22,66]. Patients with focal abnormalities such as solid tumors, organ transplants, or recent surgery need to have these specific sites investigated with special care. Patients with neutropenia and infection exhibit fewer and less striking physical findings of infection (e.g., local warmth, swelling, adenopathy, exudate, or fluctuance) than are ordinarily encountered in immunocompetent individuals (see Chapter 76).

Initial laboratory studies that should be performed in the evaluation of the acutely ill, febrile, compromised host include (a) cultures of blood (b) cultures of urine if there are symptoms or abnormal urinalysis (c) routine sputum culture, if the patient has symptoms or signs of pulmonary disease (d) swab, aspiration, or biopsy of suspect skin, mucous membrane, or other lesions for smears, cultures, and pathologic examination; (e) semiquantitative culture of

intravenous (IV) catheters in place when fever develops; if possible (if the cannula is a critical lifeline or a subcutaneously tunneled device that shows no local signs of infection, removal can be deferred pending results of routine blood cultures), blood should be obtained by catheter for blood culture as well; (f) chest radiography; and (g) serum chemistries (i.e., electrolytes, liver chemistries, creatinine), in part to detect possible visceral involvement or multiorgan failure caused by disseminated infection and also to serve as baselines for monitoring possible adverse reactions to subsequent antimicrobial therapy.

Patients with defects in cell-mediated immunity (e.g., HIV-1 infection, lymphoma, transplant recipients) often harbor organisms that are best diagnosed by histological examination (e.g., *Pneumocystis jiroveci, T. gondii*) or special culture techniques (e.g., mycobacteria, viruses). In instances in which such organisms are high in the differential diagnosis, initial evaluation often entails immediate biopsy of the pathologic process. Localizing symptoms and signs may indicate the need for other studies, such as computed tomography (CT), magnetic resonance imaging (MRI), or nuclear medicine scans (e.g., gallium-67 scan to detect *P. jiroveci* pneumonia [PCP]). Tachypnea warrants arterial blood gas studies because progressive hypoxemia in the absence of radiographic findings can be an early indicator of pulmonary infection, especially PCP, and may indicate a need for bronchoscopy [67]. Depending on the nature of the abnormality and the state of immunosuppression, consider lung biopsy and/or quantitative culture of washings or protected brushings obtained through the bronchoscope if patient presents with pulmonary symptoms and a new finding on chest radiography [68,69].

Approach to Specific Infectious Disease Presentations

Acute Fever Without Obvious Source: Neutropenia

In patients with fever and neutropenia, shock may be an early complication of bacteremia. Although only one third of febrile neutropenic patients have documented infection [29,45], multiple randomized trials and consensus guidelines support the initiation of empiric broad-spectrum antibiotic therapy as indicated for all patients with fever greater than 38°C and absolute neutrophil counts less than 500 per mm^3 (or less than 1,000 per mm^3 and falling) [45,46,66,70]. The immediate institution of such therapy in these patients (even in the absence of documentation of bacterial infection) dramatically reduces morbidity and mortality. The most rapidly fatal infectious agents that are documented to cause acute fever in the critically ill neutropenic cancer patient are enteric Gram-negative bacilli (e.g., *E. coli*, *Klebsiella* spp, *Proteus* spp), *P. aeruginosa*, and *S. aureus* [45,46,71]. In the patient without an obvious site of infection, initial empiric antibiotic therapy should be directed against these pathogens (Table 84-2). Such therapy should take into consideration idiosyncrasies of the antimicrobial susceptibility patterns of organisms in the institutions where the patient has resided in the months before infection.

Despite the testing of hundreds of antibacterial regimens for use in patients with fever and neutropenia, there is no consensus on one best regimen. For patients who have not received prior antibiotic prophylaxis or therapy, a single antipseudomonal third-generation cephalosporin (for example, ceftazidime or cefepime), piperacillin/tazobactam, or a carbapenem (imipenem or meropenem) constitutes an appropriate regimen [46,70,72]. Although the use of piperacillin/tazobactam alone or cefepime is somewhat controversial, none of the β-lactam agents mentioned above are clearly preferred except as dictated by local resistance patterns or cost [66,73]. In comparative trials of ceftazidime or piperacillin/tazobactam monotherapy versus traditional combination therapy, no increase in mortality was seen in the monotherapy groups [70,74]. One study of 750 febrile

episodes in 567 patients showed equivalent response rates between imipenem monotherapy and ceftazidime with amikacin; addition of amikacin to imipenem failed to improve the outcome [75].

Table 84-2. Empiric Regimens for Initial Therapy of Critically Ill, Febrile, Adult Intensive Care Unit Patients with Neutropenia and Cancer (dosages provided for patients with normal renal function)

Choice of β-lactam or monobactama	Plus or minus additional antimicrobial to treat skin/soft tissue infections if present (must use for patients given aztreoman) or patient suspected of having staphylococcal infectiona	Plus or minus an aminoglycosidea
Piperacillin/tazobactam 3.375 g IV q4 or 4.5 g IV q6h OR	Vancomycin 1 g to 1.5 g IV q12 (weight based–15 mg/kg q12h)	Gentamicin or tobramycin 1.5 to 1.75 mg/kg q8h or 5–7 mg/kg once daily
Ceftazidime or cefepime 2 g IV q8h OR	(alternatives for allergic patients include linezolid, daptomycin, quinupristin/dalphopristin or clindamycin)	OR
Imipenem/cilastatin 500–750 mg IV q6h OR Meropenem 1 g IV q 8 h		Amikacin 7.5 mg/kg q12h or 15–20 mg/kg once daily
For penicillin and cephalosporin allergic patients: Aztreonam, 2 g IV q6–8h, plus vancomycin, 2 g/d (divided q6–12h)		

[a]The choice of regimen should be based on local resistance patterns and the individual patient's most recent prior antimicrobial therapy.

In a patient in septic shock who is admitted to the ICU or in institutions with endemic resistant Gram-negative bacteria, a two-drug regimen is indicated. An antipseudomonal β-lactam antibiotic such as piperacillin (3 g IV every 4 hours), piperacillin/tazobactam (3.375 to 4.5 g IV every 4 to 6 hours), cefepime (2 g IV every 8 hours), or ceftazidime (2 g IV every 8 hours) can be coupled with gentamicin or tobramycin (4 to 5 mg per kg per day IV divided every 8 hours or 6 to 7 mg IV every 24 hours), or amikacin (15 mg per kg per day IV divided every 12 hours) to provide superior activity against Gram-negative bacilli [66,70,76]. In critically ill patients, an initial loading dose of aminoglycoside is advisable (tobramycin or gentamicin, 2 mg per kg, or amikacin, 10 mg per kg). Alternatively, administration of a single, large, once-daily dose of aminoglycoside (tobramycin or gentamicin, 6 to 7 mg per kg, or amikacin, 15 to 20 mg per kg) to patients with normal renal function may reduce nephrotoxicity. For patients with immediate hypersensitivity reactions to cephalosporins and penicillins, aztreonam has activity equivalent to that of β-lactam drugs against Gram-negative bacilli and can be used with an aminoglycoside. Vancomycin typically is added to this regimen because aztreonam has no Gram-positive activity. Some recent guidelines have recommended routine inclusion of vancomycin in empiric regimens, particularly in patients on antimicrobial prophylaxis and those with evidence for skin or skin structure infections or with inflammation at the site or dysfunction of indwelling plastic venous access catheters [66]. Randomized controlled trials have demonstrated no benefit to continuing vancomycin after 72 hours unless patients demonstrated a Gram-positive infection [66,77,78,79,80].

Most standard regimens are designed for patients who have not previously received antibiotics. The development of fever with systemic symptoms such as shock or respiratory distress in a patient on antibiotic therapy requires a change in therapy to include organisms that are known to be resistant to classes of antibacterials the patient has received. For example, in choosing the aminoglycoside component of a multidrug regimen for a patient who has received gentamicin, the physician should consider choosing amikacin. Similarly, in a patient who recently has received cephalosporins, the choice of piperacillin, piperacillin/tazobactam, or imipenem may be preferable over ceftazidime or cefepime especially if expanded spectrum β-lactamase producing organisms are established flora in the local ICU. In ICU patients, vancomycin should be considered as a third agent if MRSA are a serious consideration and may be discontinued if no longer needed once cultures results are available.

After initial evaluation of the patient and initiation of empiric antibiotic therapy, subsequent management is based on (a) identification of a focus of infection, (b) isolation of an etiologic agent, (c) defervescence versus continued fever, and (d) duration of neutropenia. In the patient for whom an infection has been documented clinically or by culture, antibiotics should be continued as appropriate for the site of infection, susceptibility profile of pathogens, and the patient's clinical response [66]. Even when a specific pathogen is identified by culture in patients who are neutropenic, a broad-spectrum regimen usually is maintained for the duration of neutropenia [46,81]. In patients likely to have permanent or extremely prolonged granulocytopenia, attempts to stop therapy are reasonable but should be made with continuing close clinical observation [66,82].

If fever has not been eliminated or the patient continues to have evidence of ongoing sepsis, the search should continue for potential sites of focal infection (skin, optic fundi, oropharynx, chest, abdomen, and perirectal area). The serial, empiric addition of one antibiotic after another without culture data is not efficacious in most settings and may lead to confusion in the event that an adverse reaction occurs [66]. Cephalosporins and vancomycin can cause bone marrow suppression and lead to colonization with resistant organisms. The addition or sequential substitution of multiple cephalosporins may induce β-lactamase production by some organisms.

Persistent or Recurrent Fever Without Obvious Source: Neutropenia

Should fevers persist for 4 to 7 days of neutropenia, randomized controlled trials have found that empiric antifungal therapy with an amphotericin B preparation, voriconazole or anechinocandin [83,84,85,86,87,88] is appropriate. The rationale for such therapy is that it is difficult to culture fungi before they cause disseminated disease and that the mortality from disseminated fungal disease in neutropenic hosts is high. *Candida* and *Aspergillus* species are common pathogens, and *Fusarium, Trichosporon*, and *Bipolaris* species are seen occasionally but are becoming more common [49,51,89,90,91]. The use of the serum assay for galactomannan as a marker for aspergillus infection is controversial and does not clearly identify patients more quickly than traditional surveillance methods and may be false positive in patients receiving piperacillin [92,93].

Patients at particularly high risk of disseminated fungal disease include those with (a) prolonged granulocytopenia, (b) parenteral nutrition, (c) *Candida* colonization in oropharynx or urine, (d) corticosteroid therapy, and (e) advancing multiple organ dysfunction (renal, hepatic, or pulmonary). Moreover, multiorgan failure often is a reflection of disseminated candidiasis [94]. The use of antifungal prophylaxis with the imidazoles (fluconazole or itraconazole) has caused a shift in the species of *Candida* causing infection from *C. albicans* and *C. tropicalis* to the more imidazole-resistant *C. krusei* and *C. glabrata* [95,96,97], and with the use of voriconazole a shift has started to occur to more infections due to zygomycetes [98]. Hepatosplenic (also called *chronic disseminated*) candidiasis presents with fevers and elevation of serum alkaline phosphatase that continue through the return of neutrophils to greater than 1,000 cells per mm^3 [99]. Multiple embolic lesions are present in liver and spleen, and prolonged therapy with amphotericin B, itraconazole, fluconazole, caspofungin, or a combination of these agents including an azole or caspofungin and amphotericin is beneficial [100].

Based on the findings from a randomized clinical trial of primary therapy and randomized studies of salvage therapy, voriconazole is the new drug of choice for infections caused by *Aspergillus* [101]. However, an amphotericin preparation continues to be the drug of choice when a fungal infection is suspected in patients already receiving an antifungal (voriconazole or fluconazole) [98]. Amphotericin has activity against *Aspergillus*, the zygomycetes, and many other filamentous fungi. According to data from randomized clinical trials, the newer preparations of amphotericin B appear to decrease renal toxicity while maintaining efficacy: Therefore, amphotericin B complexed with cholesteryl sulfate, with liposomal vesicles, or with a bilayered lipid membrane have become standard for use in patients on other nephrotoxic drugs or those with impaired renal function, despite their higher cost [102] (see Chapter 77). Prognosis remains poor, however, for patients treated for documented invasive fungal infection in the setting of persistent neutropenia [89,103]. Most ICU patients who remain febrile and neutropenic after 4 to 7 days of broad spectrum antibacterials should be treated with either voriconazole, an amphotericin B preparation, or an echinocandin, although in selected low-risk patients itraconazole or fluconazole are equally efficacious as shown in open randomized clinical trails and endorsed in expert reviews of these studies [87,104,105,106,107].

Pneumonia in the Compromised Host

The lung is one of the most common identifiable sites of infection in immunocompromised patients [6,68,108]. Pulmonary disease can be caused by a wide variety of agents, including bacteria, protozoa, helminths, viruses, fungi, and mycobacteria (Table 84-3) (see Chapter 67).

The differential diagnosis is made even more difficult by the various noninfectious pulmonary complications that can present abruptly with acute respiratory symptoms and fever. These include underlying malignancy or vasculitis, drug toxicity, interstitial fibrosis, diffuse alveolar hemorrhage, radiation pneumonitis, cardiogenic pulmonary edema, bronchiolitis obliterans organinzing pneumonia, pulmonary alveolar proteinosis, and pulmonary embolism [108,109,110]

Pneumonia in the immunocompromised patient often presents without the symptoms and signs seen in normal hosts. Regardless of cause, fever and progressive shortness of breath (and concomitant tachypnea and arterial hypoxemia) tend to be common symptoms; in the neutropenic patient, cough, sputum production, and physical examination (as well as radiographic) findings are likely to be unimpressive or absent. Chest radiographs should be obtained promptly in the compromised patient with fever or dyspnea. High resolution CT or MRIs will often reveal infiltrates or masses that cannot be appreciated on conventional radiographs and thus are recommended in cases in which there is question about the diagnosis.

Differential Diagnosis

Developing an appropriate differential diagnosis for the causative agents of pneumonia in the immunocompromised host rests first on an appreciation of the nature, severity, and duration of the immune suppression. In addition to being susceptible to conventional respiratory tract pathogens (*S. pneumoniae, H. influenzae*) hospitalized immunocompromised hosts are prone to Gram-negative bacillary pneumonia; those with prolonged (greater than 7 days) or profound (less than 100

neutrophils per mm^3) neutropenia may become infected with *Aspergillus* or *Zygomycetes* spp [6,110]. T-cell–deficient hosts (e.g., patients with HIV infection, transplant, or lymphoma) are more likely to acquire PCP [111] or infection with CMV, HSV [112,113,114], endemic fungi (*Cryptococcus, Histoplasma*) [59,115,116], *Nocardia* spp, or intracellular bacteria (mycobacteria, *Legionella* spp) [117,118,119,120,121]. Patients who have resided in tropical countries may reactivate latent infection by *Strongyloides stercoralis* in the setting of altered cell-mediated immunity. Pulmonary infiltrates, polymicrobial bacteremia, and bacterial meningitis are the hallmarks of this syndrome [122]. Patients with deficient neutrophil and T-cell function (e.g., bone marrow transplant recipients) may be at risk for all of these pathogens.

Table 84-3. Common Causes of Acute Pulmonary Disease in Immunocompromised Patients

Infectious causes
Bacteria
Streptococcus pneumoniae
Haemophilus influenzae
Pseudomonas aeruginosa
Enteric Gram-negative bacilli
Staphylococcus aureus

- *Legionella* spp
- *Nocardia* spp
- Mycobacteria
- Fungi
  - *Aspergillus* spp
  - *Pneumocystis jiroveci*
  - *Candida* spp
  - *Zygomycetes* spp
  - *Cryptococcus neoformans*
- Viruses
  - Cytomegalovirus
  - Herpes simplex virus
- Protozoa
  - *Toxoplasma gondii*
- Parasite
  - *Strongyloides stercoralis*

Noninfectious causes

- Primary disease
  - Malignancy
    - Primary
    - Metastatic
  - Vasculitis
- Drug toxicity
  - Bleomycin
  - Busulfan
  - Cyclophosphamide
- Hemorrhage
- Congestive heart failure
- Radiation

Although chest radiographs may provide useful clues, focal or multifocal infiltrates tend to suggest infections by bacteria and those caused by *Aspergillus* or *Zygomycetes*. CT scanning often provides more information, including the detection of lesions not seen on routine chest radiograph [68]. Diffuse disease is more characteristic of viral causes (HSV, CMV), PCP, or noninfectious processes (drug toxicity, lymphangitic carcinomatosis, and radiation pneumonitis). Cavitary disease can be seen with certain of the necrotizing Gram-negative bacilli such as *P. aeruginosa* as well as *S. aureus* and anaerobes (e.g., postaspiration or postobstructive). Cavities also can be a late finding with pneumonia due to *Aspergillus, Zygomycetes*, and *Nocardia* spp. It is impossible, however, to make firm rules with regard to radiographic patterns. Gram-negative bacilli or *Legionella* may progress to diffuse disease or incite the acute respiratory distress syndrome. Patients with severe defects in cell-mediated immunity may manifest a miliary pattern caused by disseminated tuberculosis or histoplasmosis. Conversely, radiation pneumonitis may present as focal, sharply demarcated infiltrates confined to the irradiated portion of the lung [110].

Diagnostic Approach and Empiric Therapy

The diagnostic approach to pulmonary disease in the immunocompromised host also depends on the nature of the immune deficit. As a general rule, all accessible sites (blood, urine, and sputum) should be cultured, although sputum of high quality is obtained rarely in these circumstances. In neutropenic hosts, empiric antibacterial therapy is begun at the outset regardless of radiographic pattern, using one of the regimens discussed previously for fever and neutropenia [45,46]. In the case of ventilated inpatients, treatment of pneumonia must include antibiotic(s) that are effective against organisms that are typically resistant to conventional antibiotics. These regimens typically contain more than one antibiotic, and they should be adjusted based on the cumulative susceptibility report of the hospital or unit. Although logical, the use of “protected specimen brushes” has not been shown to be of clear clinical value and should not be a reason to perform an invasive procedure in an immunocompromised patient [123].

If a clinical response occurs in a neutropenic patient, therapy is continued until neutropenia resolves. In the setting of persistent neutropenia, a clinical picture of progressive pulmonary disease despite antibiotic therapy suggests invasive disease caused by fungi found in the environment (a variety of “saprophytic” fungi are a major concern, especially *Aspergillus*, but also *Rhizopus, Fusarium*, and *Trichosporon* spp) [49,50,51]. Expectorated sputum, protected bronchial brush specimen cultures, or bronchial lavage fluid may provide presumptive evidence of these pathogens, but prompt definitive diagnosis often requires open or thoracoscopically guided lung biopsy. Transbronchial biopsy is often nondiagnostic [124]. Typically, pneumonia caused by *Aspergillus* or *Zygomycetes* spp causes areas of lung infarction that may be missed by transbronchial biopsy [110,125]. CT scans may show the classic “crescent” sign in patients with aspergillosis, but this is a sign of late disease, and although it may be helpful diagnostically in patients who are recovering, early diagnosis is important to prevent mortality in persistently neutropenic patients. Unlike bacteria, which are usually easy to culture, fungi are often not isolated in cases where histopathology eventually demonstrates their presence. Although PCR-based techniques have yet to be of demonstrated clinical usefulness in these clinical situations, measurements of polysaccharide antigen in serum or other body fluids has been of demonstrated utility in the diagnosis of both *Cryptococcus*- and *Histoplasma*-associated pneumonia. Antigen tests for pneumococcal and *Aspergillus* antigens have been marketed and may be useful in some settings, but large randomized trials showing efficacy are still in process at this time.

The standard approach to therapy of confirmed pulmonary disease caused by *Aspergillus* is to treat with voriconazole as this agent has been shown to be superior to treatment with amphotericin B preparations [101]. Although the use of combinations of antifungal agents (including echinocandins and azoles as well as echinocandins and amphotericin) has rationale support from animal data and anecdotal human experience, large trials have yet to be performed, making it difficult to recommend this approach at this time unless single agents have failed. There is no established therapy for some emerging fungal pathogens such as *Trichosporon* or *Fusarium* spp, although encouraging results have been reported in a few cases using the new imidazoles, such as posaconazole or voriconazole [126].

In patients with compromised T-cell immunity, the list of diagnostic possibilities is longer and more diverse, making satisfactory empiric therapy a virtual impossibility. Expectorated or induced sputum may demonstrate the organism by special stains in a minority of cases (*P. jiroveci, M. tuberculosis, Nocardia asteroides*), but flexible bronchoscopy with lavage or transbronchial biopsy and open or thoracoscopically assisted lung biopsy may be required in order to make a diagnosis for these patients [68,127,128] (see Chapter 68). Bronchoscopy is

particularly helpful for diffuse or interstitial disease, in which it provides not only lavage fluid with reasonable diagnostic accuracy for infectious agents such as *P. jiroveci* and bacteria but pathologic specimens that may allow diagnosis of CMV infection, drug pneumonitis, hemorrhage, or lymphangitic carcinomatosis. In patients with focal or nodular disease, thoracopically assisted biopsy is likely to yield the best results.

In the immunocompromised host (non-HIV infected) the diagnosis of PCP often requires bronchoscopy with bronchoalveolar lavage with or without biopsy. A variety of other infections also require biopsy for diagnosis. It is reasonable to treat (empirically) with trimethoprim-sulfamethoxazole (15 to 20 mg per kg of the trimethoprim component IV daily divided every 6 or 8 hours) while arrangements are made for diagnostic procedures, as the organisms persist for the first few days of treatment. It is usually an error to postpone performing bronchoscopy (with biopsy) or thoracoscopically guided lung biopsy in severely ill immunocompromised patients with pulmonary infiltrates in the hope that they will improve, because clinical

deterioration may make the procedure (and the diagnosis) impossible. If PCP is confirmed and the patient has severe renal insufficiency, serum drug concentration monitoring, if available, should be used to adjust therapy to obtain a serum sulfamethoxazole level of 100–200 µg per mL or trimethoprim levels of 5 to 8 mg per µL [129]. An alternative diagnosis, established by histologic or microbiologic diagnosis, allows institution of specific therapy, such as acyclovir for HSV pneumonia, ganciclovir for CMV pneumonia, trimethoprim-sulfamethoxazole for nocardiosis, or corticosteroids for radiation pneumonitis, bronchiolitis obliterans with organizing pneumonia, or drug-induced disease [68,109,124,127].

Prevention of Infection

Increasing emphasis is being placed on the prevention of opportunistic infections in immunocompromised hosts. These strategies have taken many different forms. Early efforts were directed at modifications of the environment of neutropenic patients through laminar airflow, nonabsorbable antibiotics, and elaborate efforts at disinfecting the inanimate environment. These approaches have proven expensive and laborious and since they did not affect either disease remission or mortality, they have been abandoned by most centers.

Oral fluoroquinolone (and trimethoprim-sulfamethoxazole) administration has been studied in patients with prolonged neutropenia [130,131]. These agents reduce levels of aerobic Gram-negative bacilli in the gut lumen, the major reservoir for dissemination of infection in the neutropenic host. Although the incidence of Gram-negative bacillary infections is favorably affected by these regimens, they have had no proven effect on morbidity or mortality. Potential disadvantages include the development of resistant bacterial strains and a possible increase in infections caused by Gram-positive species or fungi. However, several recent studies document the efficacy of levofloxacin in preventing infections and hospitalizations in patients with chemotherapy induced neutropenia, and this prophylactic approach to preventing infections in patients anticipated to have prolonged neutropenia is the current standard of care [132,133].

Antifungal prophylaxis with oral fluconazole (400 mg orally daily or 200 mg IV every 12 hours) has proved effective in reducing infection by *Candida* spp in bone marrow transplant recipients [81] (see Chapter 191). Recent studies suggest that posaconazole, which has a much broader spectrum than fluconazole (including aspergillus), is efficacious in preventing fungal infections in severely neutropenic patients and those with graft versus host disease [134,135].

Antiviral prophylaxis with acyclovir has been shown to reduce mucositis and mucocutaneous infections by HSV in transplant recipients and in patients with leukemia [136,137]. Although prophylactic administration of ganciclovir has been demonstrated to decrease CMV disease in

solid organ transplant recipients, the administration of this agent to bone marrow transplant patients results in neutropenia. Consequently, most centers are now using “preemptive” treatment with ganciclovir (beginning treatment only when CMV-DNA is detected in the serum of hematology patients at risk) (see Chapters 189 and 191).

Administration of hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-monocyte colony-stimulating factor (GM-CSF) has been shown to hasten bone marrow recovery and shorten the duration of neutropenia in patients receiving chemotherapy. Although these agents have decreased the duration of neutropenia in febrile and in afebrile patients, and in vitro, they can augment antibacterial and antifungal efficacy of neutrophils, they have had no consistent effect on important clinical outcomes such as mortality, hospitalization rates, or number of culture-positive infections, and the use of these agents is only recommended for patients with prolonged neutropenia [66,138].

Table 84-4. Advances in Management of Infection in the Immunocompromised Host Based on Randomized Controlled Clinical Trials

- Acute Fever without Obvious Source: Neutropenia
  Broad-spectrum antibiotic therapy should be started for all immunocompromised patients with fever greater than 38°C and absolute neutrophil counts less than 500 per mm^3 (or less than 1,000 per mm^3 and falling) [45,46,66,71].
- There is no benefit to continuing vancomycin after 72 hours unless a Gram-positive infection is documented [66,78,79,80].
- Empiric antifungal with an amphotericin B preparation, voriconazole or caspofungin should be added to therapy for the immunocompromised patient with neutropenia and fever of 4 to 7 days duration on broad spectrum antibacterials [83,84,85,86,87,88].
- An oral fluroquinolone (levofloxacin) is useful in preventing infections and hospitalizations in patients anticipated to have prolonged neutropenia after chemotherapy [132,133].
- Voriconazole is the new drug of choice for documented infections due to *Aspergillus* [101].

Advances in infection in the immunocompromised host, based on randomized, controlled trials or metaanalyses of such trials, are summarized in Table 84-4.

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