Chapter

54 Critically Ill Immunosuppressed Host

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As the population of patients with cancer, organ transplants, vasculitides, and human immunodeficiency virus (HIV) infection has grown, intensivists are seeing more and more patients with altered immunity. These patients may come to the intensive care unit (ICU) because of life-threatening opportunistic infections, or they may develop life-threatening infection while in the ICU for an unrelated problem. Intensivists must recognize how these patients differ from immunologically normal patients in terms of clinical presentation and management of these infections.

This chapter emphasizes the important ways in which immunosuppressed patients differ from immunologically normal individuals in terms of infectious complications. Clearly, however, immunosuppressed patients also develop complications from their underlying diseases and the drugs used to treat these underlying processes. These noninfectious complications are not the focus of this chapter but are reviewed in Chapter 81.

DEFINITION

Patients who are at increased risk for infectious complications because of a deficiency in any of their host defense mechanisms are referred to as *compromised hosts*. Patients in ICUs are almost universally compromised either by virtue of their underlying disease or by virtue of the invasive devices utilized to support and monitor them. Patients are termed *immunocompromised* or *immunosuppressed* if their defect specifically involves immune response. Often, patients who have deficient inflammatory response (e.g., neutropenia) are grouped into the category of immunocompromised or immunosuppressed, although technically they have a different category of deficient host response. Patients in ICUs are often immunosuppressed as a result of their underlying disease, therapy, or nutri-

tional status. This chapter focuses specifically on patients who are immunocompromised or immunosuppressed.

HOST DEFENSE MECHANISMS

The microbial complications that any patient develops are determined by general, nonspecific barriers; innate immunity; acquired specific immunity; and environmental exposures. Nonspecific barriers include anatomic barriers such as intact skin and mucous membranes; chemical barriers such as gastric acidity or urine pH; and flushing mechanisms such as urinary flow or mucociliary transport. Organisms that breach these barriers encounter nonspecific and innate host factors termed the *acute phase response*. Acute phase responses include trigger molecules and effector molecules. Organisms also encounter acquired specific immune response systems including mononuclear phagocytes and antibodies.[1]

Infections that occur may result from normal flora that colonize mucosal or cutaneous surfaces. Infections may result from abnormal flora that have invaded or replaced normal flora because of environmental exposures, disrupted barriers, or selective pressure of antimicrobial agents. Table 54-1 lists organisms that cause disease when specific anatomic defenses are disrupted in individuals with normal microbial flora.

Infections may also result from common defects in the inflammatory or immunologic systems; examples are detailed in Table 54-2.[1-9] Inflammatory and immunologic barriers can be disrupted by the primary disease process (e.g., tumor can invade the bone marrow, immunologic abnormalities associated with aplastic anemia or collagen vascular disease can destroy cells either in the bone marrow or the periphery). Inflammatory and immunologic mechanisms can also be disrupted by drugs. Cytotoxic drugs, for instance, can reduce neutrophil number and function. Certain monoclonal antibodies can destroy lymphocyte populations or interfere with cytokine attachment to receptor sites. Some agents such as corticosteroids have multiple effects on neutrophils, lymphocytes, and soluble factors. Infections may result from organisms that are usually not pathogenic, but become opportunistic because of poor host defense mechanisms. Opportunistic infections are defined as those that occur with enhanced frequency or severity in a specific patient population compared with a normal patient population. *Pneumocystis jiroveci,* for example, never causes disease

Table 54-1. Normal Flora That Can Cause Disease When Anatomic Barriers Are Disrupted

Compromised Host Defense: Anatomic Disruption	Bacteria	Fungi
Oral cavity, esophagus	α-Hemolytic streptococci, oral anaerobes	*Candida* species
Lower gastrointestinal tract	Enterococci Enteric organisms Anaerobes	*Candida species*
Skin	Gram-positive bacilli Staphylococci, streptococci *Corynebacterium, Bacillus* species *Mycobacterium fortuitum, Mycobacterium chelonei*	*Candida* species *Aspergillus*
Urinary tract	Enterococci Enteric organisms	*Candida* species

Table 54-2. Infections Associated with Common Defects in Inflammatory or Immunologic Response

Host Defect	Examples of Diseases or Therapies Associated with Defects	Common Etiologic Agents of Infections
Inflammatory Response		
Neutropenia	Hematologic malignancies, cytotoxic chemotherapy, aplastic anemia	Gram-negative bacilli, *Staphylococcus aureus, Candida* species, *Aspergillus* species
Complement System		
C3	Congenital liver disease Systemic lupus erythematosus	*S. aureus, Staphylococcus pneumoniae* *Pseudomonas* species, *Proteus* species
Alternate pathway	Sickle cell disease	*S. pneumoniae, Salmonella*
Immune Response		
T lymphocyte deficiency/ dysfunction	Thymic aplasia, thymic hypoplasia, Hodgkin's disease, sarcoid Human immunodeficiency virus Mucocutaneous candidiasis	*Listeria monocytogenes, Mycobacterium* species, *Candida* species, *Aspergillus* species, *Cryptococcus neoformans,* herpes simplex, herpes zoster *Pneumocystis jiroveci,* cytomegalovirus, herpes simplex, *Mycobacterium avium* complex, *C. neoformans, Candida* species *Candida* species
B-cell deficiency/ dysfunction	Splenectomy, chronic lymphocytic leukemia, hypogammaglobulinemia, chronic lymphocytic leukemia, multiple myeloma, dysgammaglobulinemia Selective IgA deficiency	*S. pneumoniae,* other streptococci, *Haemophilus influenzae, Neisseria meningitidis, Babesia* sp. *Capnocytophaga, Giardia lamblia, P. jiroveci,* enteroviruses *G. lamblia,* viral hepatitis, *S. pneumoniae, H. influenzae*
Mixed T- and B-cell deficiency/dysfunction	Common variable hypogammaglobulinemia	*P. jiroveci (carinii),* cytomegalovirus, *S. pneumoniae, H. influenzae,* varicella, other bacteria

in immunologically normal individuals but can cause frequent episodes of pneumonia in certain immunosuppressed patients. *Candida* can cause mild mucosal disease in normal patients receiving antibacterial drugs but causes more frequent and more severe mucositis when patients have impaired cell-mediated immunity.

Recognition of which host defense mechanisms are disrupted enables the clinician to focus diagnostic, therapeutic, and prophylactic management and optimize patient outcome. For instance, if a patient presents with severe hypoxemia and diffuse pulmonary infiltrates, a health care provider who recognizes a prior splenectomy as the major predisposition to infection would focus the diagnostic evaluation and the empiric therapy on *Streptococcus pneumoniae* and *Haemophilus influenzae*. By contrast, if the patient's major predisposition to infection were HIV infection with a CD4+ T lymphocyte count below 50 cells/μL, the health care provider would focus on *Pneumocystis jiroveci* and *S. pneumoniae;* if a cytomegalovirus (CMV)-negative patient's major predisposition were a recent allogeneic stem cell transplant from a CMV-positive donor, then CMV would be a prime consideration.[2-9]

Immune competence should ideally be measurable by objective laboratory parameters. In fact, the risk for opportunistic infection in patients with HIV infection can be assessed by clinical laboratories with a high degree of accuracy by measuring the number of circulating CD4+ T lymphocytes.[5] The susceptibility of cancer patients to opportunistic bacterial and *Candida* infections can be assessed by measuring the number of circulating neutrophils.[7,10,11] The predisposition of patients with certain congenital immunodeficiencies can be assessed by measuring

serum immunoglobulin levels.[12] Unfortunately, however, for a large number of immunodeficiencies, no objective laboratory measures have been validated as predicting the risk of infection. Moreover, laboratory measures must be interpreted in context. CD4+ T lymphocyte counts have great prognostic value in patients with HIV infection but not in most other patient populations; neutrophil counts are relevant in all patient populations, but low counts are associated with disrupted mucosal surfaces compared with those with intact mucosa. Thus laboratory parameters must be interpreted in the context of the patient's underlying disease—risk is not always easily manageable by measuring one laboratory parameter.

Most importantly, most patients have multiple overlapping predispositions to infection. Knowledge of the infectious complications associated with specific diseases, specific immune defects, and specific laboratory abnormalities is helpful for predicting and managing infectious complications. However, a specific diagnosis should be established in each patient: knowledge of the immune defect helps guide empiric therapy or helps determine therapy if a diagnostic procedure is not safe to perform.

GENERAL APPROACH TO MANAGEMENT

Immunocompromised patients, by definition, are susceptible to a broader array of pathogens than immunocompetent patients. Understanding the specific immune defect can be enormously helpful in understanding the likely location and source of infection. However, the immune defect must be assessed in the context of the specific disease: the clinical manifestations of HIV infection, for instance, are quite different from the clinical manifestations of patients with other diseases that alter cell-mediated immunity such as lymphoma. The immune defect must also be interpreted with the understanding that predisposition to infection is usually multifactorial: in addition to neutropenia or lymphocyte depletion, patients often have impaired mucosal barriers, poor ciliary function, or breaches in their skin (i.e., from catheters) that can increase their risk of infection.

Effective management of opportunistic infections requires understanding of several basic tenets of care.

1. Diseases may present with subtle symptoms and signs, and patients are predisposed to deteriorate precipitously.

   Because immunocompromised patients may lack inflammatory and/or immunologic mediators, the clinical manifestations of infections are often less prominent and less impressive than immunocompetent patients with similar complications. Thus clinicians must recognize that even subtle changes in skin color, catheter site appearance, chest radiograph, or abdominal examination may warrant an aggressive diagnostic evaluation and early institution of broad-spectrum empiric therapy. Although all ICU patients demand prompt attention and vigorous diagnostic and therapeutic management, many types of immunosuppres-

sion can be associated with especially precipitous clinical deterioration despite their innocuous presentation.

2. Fever is not invariably present when patients are infected.

   Although fever is not invariably present in any patient population with infection, immunosuppressed patients are notorious for developing infection in the absence of fever. Thus infection must be considered as part of the differential diagnosis among patients with afebrile syndromes that might not appear to be infectious. Conversely, patients with fever may not have infection: Fever may be a manifestation of the underlying disease, an allergic response to a drug, or an underlying neoplastic or collagen vascular disease.

3. Diagnostic evaluation needs to be prompt and definitive.

   As indicated earlier, patients with life-threatening infection may present with subtle symptoms and signs that progress rapidly: these early manifestations merit aggressive attempts to define the anatomy of the lesion and the causative microbial pathogen. Because the spectrum of potential pathogens includes a wide array of microorganisms (e.g., viruses, fungi, protozoa, or bacteria), clinicians must be certain that appropriate specimens are obtained and the appropriate microbiologic and histologic tests are ordered to identify common, as well as uncommon or unusual, pathogens. Invasive diagnostic techniques such as bronchoalveolar lavage or tissue biopsies should be performed with less hesitancy than in immunologically normal patients. Patients often have enhanced risk factors for invasive procedures, such as thrombocytopenia, coagulation factor deficiencies, or compromised organ function. However, the benefit of definitive diagnosis often outweighs these risks when the procedures are performed by experienced operators.

4. The threshold for initiating broad-spectrum empiric therapy should be low.

   Because patients can deteriorate rapidly and because they are susceptible to such a wide array of microbial pathogens, clinicians should have little hesitation in instituting empiric antimicrobial therapy. This therapy must be directed at the full range of bacterial, fungal, viral, protozoal, and helminthic infections to which patients are predisposed. This therapy should be administered promptly, preferably within an hour of suspecting an infectious process. Clinicians should initiate comprehensive regimens: antimicrobial agents can be discontinued or reduced when culture results and clinical events clarify the scenario.

5. Foreign bodies and infectious foci should be addressed.

   Patients may need careful imaging to be certain that they do not have an obstructed viscus or localized collection that should be drained. Such imaging is appropriate even when signs or symptoms are unimpressive. Similarly, patients often have multiple intravascular catheters that may need to be removed, as discussed in Chapter 51.

6. Consideration should be given to augmenting the immune or inflammatory response.

There may be opportunities to augment immunologic or inflammatory responses by administering pharmacologic or biologic agents such as granulocyte colony-stimulating factor (G-CSF) or intravenous immunoglobulin.[12-15] Eliminating immunosuppressive drugs or reducing the dose can also improve the patient's prognosis.

7. Efficacy and toxicity of therapy should be assessed serially.

ICU patients characteristically require attentive monitoring to assure the adequacy and safety of therapy. Immunocompromised patients often have multiple prior and concurrent insults to their renal and hepatic function, and they often receive multiple drugs that can produce drug-drug interactions. Thus monitoring the pharmacokinetics and assessing potential toxicities are especially important in these patient populations. Moreover, because response to therapy may be less robust than in immunocompetent patients, antigen titers or PCR titers, as well as serial imaging studies, can be important to assure the adequacy of the management plan. Therapy must often be continued longer than in immunologically normal patients.

MANAGEMENT OF SPECIFIC PATIENT POPULATIONS

Patients with Neutropenia

General Principles

Cytotoxic therapy–induced neutropenia is a major predisposition to infection.[7,11] Counts below 500 cells/mm³ (the total of polymorphonuclear neutrophils and bands) increase susceptibility to infection in a linear fashion (i.e., the lower the neutrophil count, the greater the degree of susceptibility). The absolute neutrophil count is not the only factor that determines susceptibility, however, because some patients with cyclic neutropenias, drug-induced neutropenias, or HIV-induced neutropenias, for example, are not nearly as susceptible to infection as are cancer patients receiving cytotoxic therapy. Other important contributors to susceptibility, in addition to the absolute neutrophil count, are the duration of neutropenia, the functional capability of neutrophils, the integrity of physical barriers such as the skin and gastrointestinal mucosa, the patient's microbiologic environment (endogenous and exogenous flora), and the status of other immune mechanisms. For example, a patient with vancomycin-induced neutropenia during therapy for a staphylococcal infection may not develop any complications if the neutropenia is brief and defense mechanisms are otherwise intact. A patient with HIV-induced neutropenia may have prolonged or even lifelong neutrophil counts below 500/μL yet suffer few serious bacterial complications.[14] The presence of intact physical defense barriers is a major difference compared with cancer patients, whose skin and mucous membranes are disrupted by cytotoxic therapy in which the skin and gastrointestinal tracts are portals of entry for infections that are not controlled by diminished host immunologic or inflammatory defenses. Thus the patient with HIV infection is usually at a much lower risk for a bacterial infection than is a cancer patient, despite a comparable neutrophil count.

In the 1960s and 1970s, aerobic gram-negative bacilli such as *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* predominated as pathogens in neutropenic patients. Anaerobic bacteria and aerobic gram-positive cocci were recognized less commonly. Aerobic gram-negative bacillus infections were also associated with a poorer outcome than infections from gram-positive cocci. Given the spectrum of pathogenic organisms that were seen in that era, combination therapy was usually advocated.[11,16-24] A number of reasons were proposed to justify combination therapy: (1) broad coverage of potential pathogens; (2) prevention of emergence of resistance; and (3) synergy. In general, these principles are reasonable concepts on which to base a preference for using combination therapeutic regimens. However, no study unequivocally demonstrated that combination therapy provided better outcomes than did monotherapy, assuming that both study arms contained drugs that had activity against the causative organism. In addition, predicting synergy proved difficult.[25]

In the 1990s the spectrum of causative pathogens in neutropenic patients shifted from a predominance of gram-negative bacilli to a majority of gram-positive cocci including streptococci, staphylococci (including oxacillin-resistant *Staphylococcus aureus*), and enterococci (including vancomycin-resistant *enterocci*).[20,24,26] The development of potent broad-spectrum β-lactam and quinolone drugs in the 1980s and 1990s has provided single agents that can probably provide comparable outcomes to combination therapy when used empirically or specifically. In the current era the choice of single or combination regimens is based predominantly on the spectrum of organisms that needs to be covered rather than attempting a strategy of trying to obtain more potency through additive or synergistic combinations.[10,27]

Promptly initiating broad-spectrum antibacterial therapy for all cancer patients who are febrile and who are neutropenic (neutrophil count <500/mm³) as a result of cytotoxic chemotherapy is standard practice.[7,10,27] For febrile neutropenic patients who have no apparent source of infection, there is no evidence that the initial antibacterial regimen is any more effective if a broad-spectrum antibacterial regimen consisting of two or more drugs is used instead of a single broad-spectrum antibacterial drug. For stable "low-risk" patients outside the ICU, an oral regimen is now considered a reasonable approach.[7,10,17] Such oral regimens would not be used for inpatients in most circumstances and would not be appropriate for high-risk or unstable patients.[7,10] Antifungal and antiviral drugs are generally not used empirically when neutropenic patients are initially treated unless there is a specific reason to have a high suspicion for a fungal or viral process.

Historically, an infectious cause of fever has been found in about two thirds of febrile, neutropenic cancer patients. When a specific causative organism is identified, antimicrobial therapy is modified to include an agent or agents determined to be active by in vitro susceptibility tests and that penetrate to the site of the infection.[10] Combination therapy is advocated by some authorities for the specific (compared with empiric) therapy of either gram-positive or gram-negative bacteria, although, as noted earlier, there are little data for most pathogens that indicate that a combination regimen produces a better outcome than an appropriate single agent. Therapy is generally not narrowed in terms of spectrum, however, because alteration of broad-spectrum coverage to focused therapy has been associated with more complications (e.g., "breakthrough bacteremias") unless the neutropenia resolves. Whenever fever persists, therapy has generally been continued during the entire course of neutropenia because cessation of antimicrobial therapy has been associated with recurrent bacteremia resulting from the initial causative organism or a newly identified pathogen. A 10- to 14-day course of antibacterial therapy is usually the minimum recommended if a causative infection is identified. Therapy is usually stopped promptly when the neutrophil count exceeds 1000 cells/µml if fever resolves and no source was ever identified.

Empiric antibacterial therapy has been a successful strategy for reducing morbidity resulting from bacterial processes but has been associated with the emergence of fungal infections, as well as resistant bacterial pathogens. *Candida* and *Aspergillus* organisms, in particular, have become major causes of morbidity and mortality over the past 2 decades. These fungal processes can be difficult to diagnose because they are not always associated with detectable fungemia. The emergence of fungi as important pathogens, especially in patients with prolonged neutropenia, has led to the recommendation that empiric antifungal therapy be added to neutropenic patients who do not have an identified bacterial process and who do not defervesce within 4 to 7 days of empiric antibacterial therapy.[7,10] Fluconazole or an amphotericin B compound (e.g., liposomal amphotericin B) are often used, although echinocandins or certain other azoles such as voriconazole are being used by some investigators and clinicians.[28-31]

As patients receive chemoprophylaxis with quinolones and/or azoles during periods of intense neutropenia or immunosuppression, breakthrough pathogens are more and more likely to be resistant to the prophylactic agents.[32,33] Thus empiric regimens must be chosen with keen attention to the drugs that patients have received in the recent past, as well as pathogens they have previously been colonized or infected with.[34]

Diagnostic Approach

Patients with fever and neutropenia require aggressive diagnostic efforts to identify the cause of fever so that the appropriate antimicrobial agent is used and appropriate procedures (e.g., surgical drainage, removal of foreign body such as a catheter) can be performed. Regular physical examination is necessary to identify sites that merit more focused investigation: With impaired inflammatory response, findings on examination may be subtle. Knowledge of the specific immunologic defect is important so that when cultures of blood, sputum, urine, or other appropriate body fluids or body sites are performed, special microbiologic approaches can be used to detect viruses, fungi, helminths, protozoa, and bacteria. Imaging studies are also important because intra-abdominal, intrathoracic, intracerebral, or musculoskeletal processes can be clinically subtle and may not be associated with identifiable organisms in the bloodstream. A growing array of antigen, nucleic acid, and gene detection systems including polymerase chain reaction and microarray gene assays are being investigated to facilitate diagnosis. Some antigen or nucleic acid detection systems for blood or other body fluids can be useful for detecting cryptococcus, histoplasma, hepatitis B and C, HIV, mycobacteria, pneumococci, and *Legionella*. Some of these approaches, despite their promising initial reports, are not yet clinically practical because of their level of sensitivity, specificity, or the cost or expertise required to perform them adequately.

Careful attention to antimicrobial susceptibility patterns is also important. Patients are exposed to repeated courses of antimicrobial agents. Patients come into contact with contaminated environments in a variety of health care settings. Resistance is no longer an issue exclusively for aerobic gram-negative organisms but is a concern for anaerobes, gram-positive cocci, viruses, fungi, and protozoa. Clinicians must recognize that pathogens may be resistant when they are acquired by the patient, or they may become resistant during therapy if there is an inducible resistance mechanism or drug concentrations are not adequate to inhibit or kill the organism.

Antimicrobial Therapy

A broad-spectrum agent used as monotherapy for febrile, neutropenic patients should have activity against aerobic gram-positive cocci and aerobic gram-negative bacilli including *P. aeruginosa*.[7,10,19,35] Potential drugs for this indication include certain cephalosporins (e.g., cefepime), carbapenems (e.g., imipenem or meropenem), and β-lactam/β-lactamase combination agents (e.g., piperacillin-tazobactam). Ceftazidime is an option chosen by some, but its poor activity against gram-positive cocci has caused some clinicians to use other agents.[18] Intensivists must recognize, however, that these monotherapy regimens may not be appropriate in an ICU. Patients in ICUs, by definition, are either unstable hemodynamically or have a potentially life-threatening process such as diffuse pneumonia or are "fragile" because of concurrent processes. Thus combination regimens are preferred by many authorities in ICU settings, even though no study clearly documents superior outcomes from such combination regimens. The decade that started in 2000 is an era when microbial resistance is becoming an increasingly important problem for many types of bacteria including aerobic gram-positive cocci and anaerobes, as well as aerobic gram-negative bacilli. Multiple drug empiric regimens are more likely than monotherapy regimens to include an agent

with activity against the offending pathogen(s). Thus in a situation in an ICU when failure to use an active drug is more likely to be lethal than in other settings, and when enhanced potency is a logical goal, combination therapy is prudent as an initial management strategy. Thus adding vancomycin or linezolid or daptomycin for better gram-positive coverage, adding a quinolone for better gram-negative bacillus coverage, and adding metronidazole to cefepime would be prudent in this patient population pending results of initial diagnostic studies. Of note, however, is that although this strategy is logical, no study has shown convincingly that such an approach improves outcome.[22]

A substantial number of febrile, neutropenic patients fail to improve in terms of fever or other manifestations. Failure to improve may result from poor immune response, a need for drainage or necessity to remove foreign bodies, the use of drugs without activity against the causative organism, or a noninfectious process including drug allergy (i.e., fever resulting from a drug including an antimicrobial agent). The potential causative processes need to be aggressively reassessed on a regular basis by physical examination, history, cultures, and imaging techniques. Most centers add antifungal therapy empirically at day 4 or day 7 of therapy if patients remain febrile.[10,27,29,36,37] Fluconazole, liposomal amphotericin B, caspofungin, or voriconazole may be used: In some situations fluconazole would be less attractive either because the patient has received fluconazole prophylaxis or because molds are suspected.[28,38,39] The toxicity profile of amphotericin B, even in its liposomal form, has led many clinicians to prefer voriconazole or one of the echinocandins (i.e., caspofungin, micafungin, or anidulafungin).[30,40,41]

After empiric antimicrobial therapy is initiated, the optimal duration of therapy is a complex issue that depends on the type and severity of the infectious process and the duration and severity of immunosuppression, especially the neutropenia. If a causative bacterium is identified, a minimum of 7 to 10 days of therapy is generally advocated, with at least 3 to 4 days being administered after neutropenia has resolved. Longer courses may be required in certain settings. The duration of antifungal therapy is a complex issue and depends on the specific mycosis, the location and extent of disease, and the patient's immune status.[15] This is discussed in Chapter 53. The use of combination therapy for fungal diseases remains controversial.[42,43]

A common problem in febrile, neutropenic patients is managing indwelling intravascular lines.[44-46] In general, these lines can be left in place initially if examination of the site reveals no indication of infection. Blood cultures should be drawn through the catheter. Although some experts advocate drawing a culture through each port of each catheter, obtaining this many blood cultures is often not feasible. If a patient is hemodynamically unstable and fails to respond promptly to fluid administration, it is prudent to remove the line in case an infected catheter is the source of the sepsis. Failure to remove the foreign body in this situation probably increases the likelihood of an unfavorable outcome. Should blood cultures become

positive and should the suspicion be high that the catheter is the source, antibacterial therapy may be successful in some settings (e.g., if the pathogen is a bacteria that is relatively sensitive to antibacterial therapy), thus avoiding the need to remove the catheter. Situations suggesting that catheter removal is necessary include hemodynamic instability despite aggressive fluid resuscitation, tunnel infection, or infections resulting from fungi or relatively antibiotic-resistant bacteria such as *P. aeruginosa.*

A major determinant of prognosis is the immunologic status of the patient. Prompt return of neutrophil number to normal improves the outcome. The use of G-CSF or granulocyte-monocyte colony-stimulating factor (GM-CSF), if not contraindicated by the underlying disease, can improve clinical status by hastening the return of neutrophil numbers and function.[12-15,47] Granulocyte transfusions have not been proved useful in most clinical settings because of the inability to administer a large number of cells with adequate frequency.[48] The manipulation of immune response with cytokines, cytokine inhibitors, or immunoglobulins is the subject of considerable investigation: Such interventions may reduce the duration of fever or the incidence of infections when used empirically, but in no setting have they been clearly shown to improve survival when administered after an infection has been documented.

An algorithm for managing fever in neutropenic patients is provided in Figure 54-1. Table 54-3 suggests modifications of standard empiric regimens in certain common clinical scenarios.

Prevention of Infection

Given the experience with frequent and severe infectious complications in cancer patients with neutropenia, it has been logical to attempt to prevent infection.[33] Most microorganisms causing disease in this patient population arise from endogenous gastrointestinal, cutaneous, or respiratory flora. Total protected environments probably reduce frequency of infection, but this approach is expensive and inconvenient. Trying to prove a consistent beneficial impact on survival has been difficult, and thus such isolation is rarely used anymore. Some experts are enthusiastic about placing patients in positive pressure rooms so that pathogens do not enter via particles and droplets from outside the room. This type of isolation has not clearly improved outcome, however, and is not a standard of care.

Prophylactic bacterial therapy has also been controversial.[32] Systemic antibacterial prophylaxis and systemic antifungal prophylaxis have been shown in some studies to reduce the number of infections, but their lack of effect on patient survival, their cost, and their impact on the emergence of resistance have made many clinicians reluctant to use them. Selective gastrointestinal decontamination has not consistently improved survival and thus is not recommended by most authorities in the United States. Antipneumocystis prophylaxis is, in contrast, highly effective in susceptible populations. Prophylaxis for CMV is highly effective in well-defined, high-risk patients (e.g., some recipients of organ transplants who are either sero-
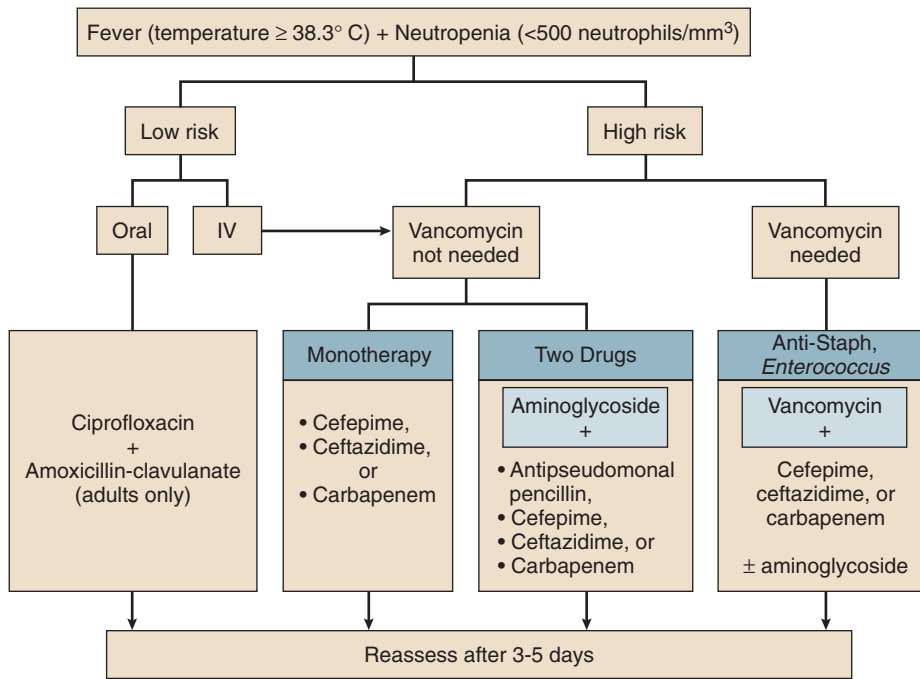
Figure 54-1. Algorithm for management of patients with febrile neutropenia. (From Hughes WT, Armstrong D, Bodey GP, et al: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Disease 2002;34:730-751.)

Table 54-3. Modification of Standard Empiric Therapy in Patients with Neutropenia	
Clinical Event	**Possible Modifications of Standard Empiric Therapy**
Breakthrough bacteremia	If gram-positive isolate (e.g., *Staphylococcus aureus*), add vancomycin until susceptibility pattern of isolate is known. If gram-negative isolate, add two new agents likely to have activity until susceptibility pattern of pathogen is known.
Cellulitis or catheter-associated infection	Add vancomycin.
Severe necrotizing mucositis or gingivitis	Add specific antianaerobic agent (e.g., metronidazole, meropenem, imipenem, or piperacillin-tazobactam) plus agent with activity against streptococci; consider acyclovir.
Ulcerative mucositis or gingivitis	Add acyclovir and anaerobic coverage.
Esophagitis	Add fluconazole or caspofungin; consider adding acyclovir.
Pneumonitis, diffuse or interstitial	Add trimethoprim-sulfamethoxazole and azithromycin or levofloxacin or moxifloxacin (plus broad-spectrum antibiotics if the patient is granulocytopenic).
Perianal tenderness	Include anaerobic agents such as metronidazole, imipenem, meropenem, or piperacillin-tazobactam.
Abdominal involvement	Add antianaerobic agent (e.g., metronidazole, meropenem, imipenem, or piperacillin-tazobactam).

positive for CMV or who are seronegative but received a graft from a seropositive donor).[2,4,49] Strategies that reduce the period of immunologic susceptibility (e.g., reduce the duration of neutropenia), such as adding G-CSF to a regimen or reducing the intensity of chemotherapeutic regimens, are promising. Table 54-4 summarizes general strategies of infection prevention in immunosuppressed patients including patients with neutropenia.

Patients with HIV Infection

Because so many patients are receiving highly active anti-retroviral therapy (HAART), opportunistic infections are not complicating the course of HIV infection to the same degree that they did in the 1980s and early 1990s.[50-53] Opportunistic infections continue to occur, however, in three groups of HIV-infected patients: (1) those who are unaware of their HIV status until they develop a clinical syndrome; (2) those who are unable or unwilling to receive appropriate therapy; and (3) those who fail HAART and opportunistic infection prophylaxis. Although HAART has dramatically reduced the incidence of opportunistic infections, a surprisingly large fraction of patients either never respond virologically and immunologically or lose their response within the first 12 to 24 months of therapy. These patients, most of whom have dominant viral quasispecies that are highly resistant to currently licensed antiretroviral drugs, will likely experience immunologic decline over the next few years and will again become more susceptible to opportunistic infections.

Table 54-4. Prevention of Infectious Complications in Compromised Patients

Ways to Prevent Acquisition of, Suppress, or Eliminate Microbial Flora	Examples
Isolation	
	Total protective isolation with high-efficiency particulate air filters and absorbable or nonabsorbable antibiotics for bone marrow–transplant recipient
Prophylactic Antibacterial Drugs	
Norfloxacin	Reduce bacterial infections in neutropenic patients
Trimethoprim-sulfamethoxazole	Suppress flora in chronic bronchitis patients
Penicillin	Reduce frequency of streptococcal infections after splenectomy or rheumatic valvular disease or graft-versus-host disease
Rifabutin	Prevention of *Mycobacterium avium* complex in patients with advanced HIV disease
Isoniazid	Prevention of tuberculosis in PPD-positive individuals
Nonabsorbable broad-spectrum agents (i.e., aminoglycoside, plus bacitracin)	Gut decontamination for neutropenic patients
Prophylactic Antiviral Drugs	
Oral acyclovir or valganciclovir, or IV ganciclovir	Reduce frequency of CMV disease following transplantation
Rimantadine, oseltamivir	Prevent influenza
Prophylactic Antifungal Drugs	
Fluconazole	Prevent recurrent candidiasis
Liposomal amphotericin B or voriconazole or caspofungin	Prevent *Candida* or mold infections
Trimethoprim-sulfamethoxazole	Prevent *Pneumocystis* pneumonia
Prophylactic Antiprotozoal/Anthelmintic Drugs	
Albendazole or ivermectin	Prevent disseminated strongyloidiasis in high-risk patients
Augment Host Defenses	
Immunization	Pneumococcal and *Haemophilus* vaccine for patients before splenectomy
Immune serum globulin	Augment levels in deficient patients (e.g., common variable immunodeficiency)
Fresh frozen plasma	Augment complement levels in deficient patients
Neutrophil transfusions	Augment inflammatory response in neutropenic patients or patients with chronic functional neutrophil disorders
Lymphocyte or other mononuclear cell transfusions	Experimental therapies for tumors, various immunodeficiencies
Bone marrow or stem cell transplant	Reconstitute patients with congenital immunodeficiencies or certain acquired cytopenias
Bone marrow human stem cell stimulation	G-CSF or GM-CSF to increase neutrophil or mononuclear cell quantity and function
Gene therapy	Replace genes to allow normal function

AIDS, acquired immunodeficiency syndrome; *CMV,* cytomegalovirus; *G-CSF,* granulocyte colony-stimulating factor; *GM-CSF,* granulocyte-monocyte colony-stimulating factor; *HIV,* human immunodeficiency virus; *PPD,* purified protein derivative.

Spectrum of Clinical Manifestations

Patients with HIV infection develop clinical disease as a result of three basic processes: the direct effect of HIV on specific organs (e.g., cardiomyopathy, enteropathy, dementia); immunologically mediated processes (e.g., glomerulonephritis, thrombocytopenia); or opportunistic infections and tumors that are enabled by HIV-induced immunosuppression.

HIV appears to cause direct organ damage.[50,53-57] This damage may be mediated by cytokines, lymphocytes, monocytes, or inflammatory cells. Cardiomyopathy, for example, can be a profound and lethal process that can lead to ICU admission or complicate other processes.[55] When patients present with or develop pulmonary manifestations such as shortness of breath or diffuse bilateral infiltrates on chest radiograph, cardiogenic causes must be considered. HIV also causes a diffuse pneumonitis,[56] profound encephalopathy,[54] and a diffuse enteropathy.[57] Patients with compatible syndromes need a comprehensive evaluation to look for other specific opportunistic infections or tumors,

especially those that can be specifically treated. In all of the HIV-caused syndromes, HIV as the etiology remains a diagnosis of exclusion. The institution of antiretroviral therapy appears to be beneficial for patients with susceptible isolates, although data regarding such effects for these HIV-related entities are largely anecdotal.

HIV-related thrombocytopenia and anemia appear to be immunologically mediated.[58,59] Both can be severe: platelet counts below 10,000/mm^3 and hemoglobins below 10 g/dL can be seen with the expected complications. These disorders are related to the development of antigen-antibody complexes and may improve dramatically with the institution of antiretroviral therapy and a decline in viral load. For thrombocytopenia, intravenous immunoglobulin (or anti RhD antibody), corticosteroids, or splenectomy may also be useful. Hemolytic anemia can also be severe: hemoglobin levels below 5 g/dL can be seen.

The most prominent manifestations of HIV continue to be the opportunistic infections and tumors that occur as a consequence of HIV-induced immunosuppression. The CD4+ T lymphocyte cell number is a useful marker for predicting the occurrence of opportunistic infections in patients with HIV infection.[5,9] This relationship of CD4+ T lymphocyte count to the occurrence of opportunistic infection continues to be as valid in the era of HAART as it was before the licensing of the first antiretroviral agent, zidovudine, in 1987.[60-62] Figure 54-2 demonstrates the typical relationship of CD4+ T lymphocyte counts to the occurrence of opportunistic infections. Knowledge of this relationship permits the focusing of diagnostic, therapeutic, and prophylactic management. For instance, if a patient with HIV infection and a CD4+ T lymphocyte count of 700 cells/μL presents with diffuse pulmonary infiltrates, the diagnostic evaluation and empiric antimicrobial regimen should focus on *S. pneumoniae; H. influenzae; Mycoplasma, Legionella,* and *Chlamydia*

organisms, as well as common community-acquired viruses. In contrast, if the same patient had a CD4+ T lymphocyte count of 50 cells/μL, the evaluation and empiric regimen would focus on pneumocystosis and CMV, although the previously mentioned processes that occur at high CD4+ T lymphocyte counts can also occur at lower CD4+ T lymphocyte counts. Keeping in mind that CD4+ T lymphocyte counts are useful predictors of susceptibility to infection is important, but they are not perfect. Occasionally, patients will develop opportunistic infections at "uncharacteristically" high CD4+ T lymphocyte counts. For instance, 5% to 10% of cases of pneumocystosis occur at CD4+ T lymphocyte counts greater than 200 cells/μL.[61] Clinical parameters can provide additional clues; for example, oral candidiasis, a previous opportunistic infection, a prior episode of pneumonia, or high viral load are independent risk factors for the occurrence of *Pneumocystis jiroveci carinii* pneumonia (PCP), and logically for other infections as well.[9]

A frequent question is whether an HIV-infected patient's prior CD4+ T lymphocyte count nadir affects the likelihood of an opportunistic infection occurring if HAART has stimulated a CD4+ T lymphocyte count rise. Specifically, if a patient has a CD4+ T lymphocyte count of 400 cells/μL while receiving HAART and that patient's CD4+ T lymphocyte count was 50 cells/μL before HAART, is that patient at greater risk for developing an opportunistic infection than another patient whose current CD4+ T lymphocyte count is 400 cells/μL but whose nadir before HAART was 250 cells/μL? The data suggest that these two patients have comparable risk (i.e., the current CD4+ T lymphocyte count is the most important predictor of risk and the earlier nadir has only minor influence on opportunistic infection susceptibility).[62]

In evaluating the differential diagnosis of infectious syndromes in patients with HIV (and in every other patient

DISTRIBUTION OF CD4+ T LYMPHOCYTE COUNTS AT DIAGNOSIS OF OPPORTUNISTIC INFECTION
1990-1994
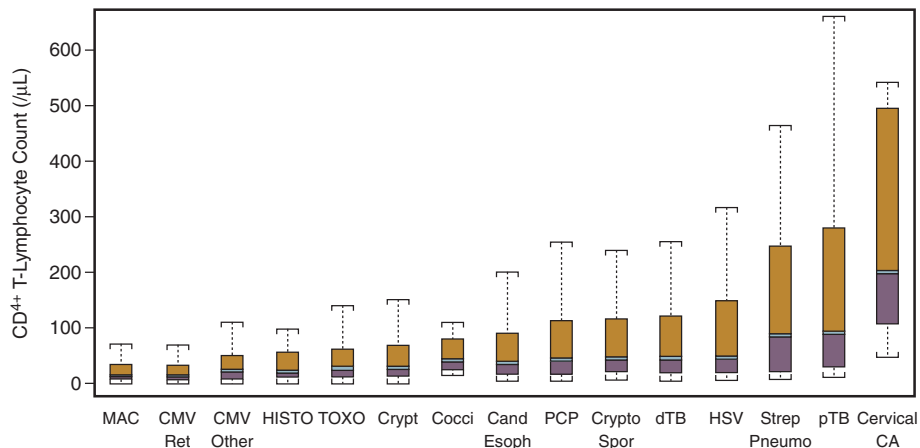
Figure 54-2. CD4+ cell count range for common manifestations of acquired immunodeficiency syndrome. Cand Esoph, *Candida* esophagitis; cervical CA, cervical cancer; CMV Other, other cytomegalovirus diseases; CMV Ret, cytomegalovirus retinitis; Cocci, coccidiorycosis; Crypt, cryptococcosis; Crypto Spor, cryptosporidiosis; dTB, disseminated tuberculosis; HISTO, histoplasmosis; NSV, *herpes simplex virus*; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystic carinii* pneumonia; pTB, pulmonary tuberculosis; Strep Pneumo, *Streptococcus pneumonia*; TOXO, toxoplasmosis.

population as well), geography is an important part of the history. Tuberculosis is always a concern because of the extraordinary susceptibility of HIV-infected patients for developing active disease.[63] In many urban settings in the United States, each pulmonary evaluation should include smears and cultures for *M. tuberculosis,* both to diagnose the appropriate cause of the pulmonary dysfunction and to assist in determining what respiratory precautions are appropriate. In some areas of the country, such as the Ohio River Valley and Indianapolis, histoplasmosis is as common as pneumocystosis in causing diffuse pulmonary infiltrates.[64] In the southwestern United States, coccidioidomycosis must be recognized as a cause of pulmonary infiltrates. The clinical presentations of tuberculosis, histoplasmosis, coccidioidomycosis, and other processes such as CMV can be clinically indistinguishable from PCP. Thus for patients with pulmonary infiltrates in an ICU, prolonged empiric therapy is discouraged in favor of vigorous efforts to establish a specific diagnosis.

HIV-infected patients are admitted to ICUs for several major syndromes: respiratory insufficiency, cerebral dysfunction, septic shock, hepatic or renal failure, and drug toxicities.[50] However, patients with HIV infection also come to ICUs for routine procedures and routine postoperative care. In those situations their management ordinarily requires no extraordinary measures, with two exceptions. First, the staff must be fully aware of how HIV is transmitted, the danger of injuries resulting from sharp objects, and the procedure for managing injuries involving sharp objects contaminated with blood or other biologic fluids from infected or potentially infected patients.[65] Second, drug interactions involving drugs used during procedures and certain antiretroviral drugs can have important clinical consequences.[66,67] Many of the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors that are now the backbone of antiretroviral therapy can inhibit or enhance the metabolism of drugs that depend on the cytochrome P450 system. Thus the half-lives of certain analgesics, sedatives, and hypnotics can be prolonged in HIV-infected patients who are taking ritonavir, for example. This pharmacokinetic effect is also relevant for a host of other therapeutic agents used in the ICU and may affect their efficacy or safety. Clinicians need to be familiar with these interactions when selecting new therapies for procedures or for clinical entities. Table 54-5 summarizes therapeutic and prophylactic approaches to managing patients with HIV-related opportunistic infections.[72]

Respiratory Insufficiency

Patients with HIV infection can develop severe pulmonary dysfunction because of common community-acquired pathogens such as *S. pneumonia, Legionella, Mycoplasma,* and *Chlamydia;* adenovirus; influenza; or respiratory syncytium virus, as well as other opportunistic viruses and fungi. Thus the diagnostic evaluation needs to be comprehensive, emphasizing direct smears of sputum or bronchoalveolar lavage. It is important to recognize that the clinical presentations produced by many causative agents can be similar. For instance, histoplasmosis,

tuberculosis, and nonspecific interstitial pneumonitis can present identically to PCP.[50,61,63,64,68] Thus although empiric diagnosis and empiric therapy may be reasonable as initial approaches to some patients with HIV infection and mild pneumonitis, such an approach is usually not appropriate for patients in an ICU.

Evaluation of induced sputum is the first step in the diagnostic approach to PCP. Sensitivity can be 80% to 95% at many hospitals (at some institutions the yield is considerably lower).[69] Specificity should be 100% in an experienced laboratory. Other pathogens, including mycobacteria, fungi, and routine bacteria, can be identified in sputum as well. For intubated patients, respiratory secretions obtained by deep intratracheal suctioning are also likely to be useful, although they have not been as carefully studied as induced sputum. Should the diagnosis not be established by evaluation of sputum or intratracheal secretions, bronchoscopy should be performed. Bronchoalveolar lavage should diagnose almost 100% of cases of PCP, even if patients have received 7 to 10 days of empiric therapy.[70] A diagnosis of PCP is established by visualizing one or more clusters of organisms.

Diagnostic criteria for other opportunistic infections are reviewed in Chapters 12 and 43. In patients with HIV, CMV merits special mention. Culture of sputum or bronchoalveolar lavage does not provide useful information because patients with CD4+ T lymphocyte counts below 100 cells/μL will predictably have CMV present in their secretion independent of whether or not pulmonary disease is present.[71] A diagnosis of CMV pneumonia in this patient population is suggested by cytology and confirmed by the presence of multiple inclusion bodies in lung tissue obtained by transbronchial or open lung biopsy. Similarly, *Mycobacterium avium* complex (MAC) and HSV can often be found in respiratory secretions, but these organisms almost never cause pneumonia in patients with HIV infection. In other patient populations they can clearly cause pneumonia, but the dearth of CMV, MAC, and HSV pneumonia in this patient population emphasizes the point that it is important to know from published literature what the clinical likelihood is for different microbial processes.

Fungal pneumonias other than PCP are generally diagnosed by direct microscopy or culture of respiratory secretions (sputum or lavage). *Candida* organisms almost never cause pneumonia in patients with HIV infection. The frequency of *Cryptococcus, Histoplasma, Blastomyces,* and *Coccidioides* organisms as causes of pneumonia depends on the geographic exposure of the patient. Among these mycoses, antigen detection techniques can be useful for finding *Cryptococcus* and *Histoplasma* organisms.

Mycobacteria frequently infect the respiratory tract of patients with HIV infection. As noted earlier, *M. avium* complex almost never causes pulmonary dysfunction in this patient population. When acid-fast bacilli are seen (as opposed to cultured) in respiratory secretions or tissue, *M. tuberculosis* is almost always the pathogen; *M. kansasii* and other mycobacteria less commonly cause disease. Screening all patients with acid-fast bacillus smears is important for preventing transmission of tuberculosis and

Table 54-5. Treatment of HIV-Associated Opportunistic Infections Among Adults

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
Pneumocystis jiroveci Pneumonia (PCP)	Acute therapy ■ Trimethoprim-sulfamethoxazole (TMP/SMX): [15-20 mg TMP and 75-100 mg SMX]/kg body weight/day IV administered q6h or q8h or ■ Same daily dose of TMP/SMX PO in 3 divided doses; or ■ TMP-SMX DS 2 tablets 3 times a day Total duration—21 days Chronic maintenance therapy (Secondary prophylaxis) *First choice:* ■ Trimethoprim-sulfamethoxazole (TMP-SMX) 1 double-strength tablet (DS) PO QD; or ■ TMP-SMX 1 single-strength tablet (SS) PO QD *Alternatives:* ■ Dapsone 50 mg PO twice daily or 100mg PO daily; or ■ Dapsone 50 mg PO daily plus pyrimethamine 50 mg PO weekly plus leucovorin 25 mg PO weekly; or ■ Dapsone 200 mg PO plus pyrimethamine 75 mg PO plus leucovorin 25 mg PO weekly; aerosolized pentamidine 300 mg every month via Respingard nebulizer (manufactured by Marquest, Englewood, Colorado); or ■ Atovaquone 1500 mg PO QD; or ■ TMP-SMX 1 DS PO TIW	For severe PCP: ■ Pentamidine 4 mg/kg QD infused over at least 60 minutes, some specialists reduce dose to 3 mg/kg IV QD because of toxicities For mild-to-moderate PCP: ■ Dapsone 100 mg PO QD and TMP 15 mg/kg/day PO (3 divided dose); or ■ Primaquine 15-30 mg (base) PO QD and clindamycin 600-900 mg IV q6h to q8h or clindamycin 300-450 mg PO q6h to q8h; or ■ Atovaquone 750 mg PO BID with food	Indications for corticosteroids: PaO_2 <70 mm/Hg at room air; or alveolar-arterial O_2 gradient >35 mm/Hg Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy): 40 mg BID days 1-5, 40 mg QD days 6-10, then 20 mg QD days 11-21 IV methylprednisolone can be administered as 75% of prednisone dose Chronic Maintenance Therapy (Secondary prophylaxis) should be discontinued if $CD4^+$ T lymphocyte count increases in response to ART from <200 to >200 cells/μL for ≥3 months
Toxoplasma gondii encephalitis (TE)	Acute therapy Pyrimethamine 200 mg POx1, then 50 mg (<60 kg body weight) to 75 mg (≥60 kg) PO QD and sulfadiazine 1000 (<60 kg) to 1500 mg (≥60 kg) PO q6h plus leucovorin 10-20 mg PO QD (can increase ≥50 mg) Total duration for acute therapy is at least 6 weeks Chronic maintenance therapy (Secondary prophylaxis) *First choice* ■ Sulfadiazine 500-1000 mg PO QID plus pyrimethamine 25-50 mg PO QD plus leucovorin 10-25 mg by mouth daily *Second choice* ■ Clindamycin 300-450 mg PO every 6-8 hours plus pyrimethamine 25-50 mg PO QD plus leucovorin 10-25 PO QD; or ■ Atovaquone 750 mg PO every 6-12 hours with or without pyrimethamine 25 mg PO QD plus leucovorin 10 mg PO QD	■ Pyrimethamine (leucovorin) and clindamycin 600 mg IV or PO q6h; or ■ TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX) IV or PO bid; or ■ Atovaquone 1,500 mg PO BID with meals (or nutritional supplement) and pyrimethamine (leucovorin); or ■ Atovaquone 1500 mg PO BID with meals (or nutritional supplement) and sulfadiazine 1000-1,500 mg PO q6h; or ■ Atovaquone 1500 mg PO BID with meals; or ■ Pyrimethamine (leucovorin) and azithromycin 900-1200 mg PO QD For severely ill patients who cannot take oral medications TMP-SMX IV and pyrimethamine PO For other regimens with limited experience, see text.	Adjunctive corticosteroids (e.g., dexamethasone) should be administered when clinically indicated for treatment of mass effect attributed to focal lesions or associated edema and discontinued as soon as clinically feasible Anticonvulsants should be administered to patients with a history of seizures Secondary prophylaxis may be discontinued if ■ Free of TE signs and symptoms; and sustained $CD4^+$ T lymphocyte count of >200 cells/μL for >8 months of ART

Table 54-5. Treatment of HIV-Associated Opportunistic Infections Among Adults—cont'd

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
Mycobacterium tuberculosis (MTB)	For drug-sensitive MTB *Initial phase (8 weeks)* Isoniazid (INH) 5 mg/kg body weight (max: 300 mg) PO QD and [rifampin 10 mg/kg (max: 600 mg) PO QD or rifabutin 300 mg PO QD] (or dose adjusted based on concomitant meds) and pyrazinamide (PZA) (dose based on weight) PO QD and ethambutol (EMB) (dose based on weight) PO QD *Continuation phase (19 weeks)* ■ INH 5 mg/kg (max: 300 mg) PO QD and [rifampin 10 mg/kg (max: 600 mg) or rifabutin 300 mg PO QD]; or ■ INH 15 mg/kg (max: 900 mg) PO BIW or TIW plus [rifampin 10 mg/kg (max: 600 mg) or rifabutin 300 mg PO TIW] In patients with delayed clinical or microbiologic response to initial therapy (e.g., sputum culture (+) after 2 months or if cavitary pulmonary lesions are present), total duration up to 9 months	Treatment for drug-resistant MTB: *Resistant to INH* ■ Discontinue INH (and streptomycin, if used) ■ Rifamycin, PZA, and EMB for 6 months; or rifamycin and EMB for 12 months (preferably with PZA during at least first 2 months *Resistant to rifamycin* ■ INH and PZA and EMB and a fluoroquinolone (e.g., levofloxacin 500 mg/day) for 2 months, followed by 10-16 additional months with INH and EMB and fluoroquinolone *Multidrug resistant (MDR) TB—both INH and rifamycin resistant* ■ Therapy should be individualized based on resistance pattern and with close consultation with experienced specialist TB treatment in patients with liver disease *If AST ≥3 times normal before treatment initiation* ■ Standard therapy with frequent monitoring; or ■ Rifamycin and EMB and PZA for 6 months ■ INH and rifamycin and EMB for 2 months, then INH and rifamycin for 7 months *For patients with severe liver disease* ■ Rifamycin and EMB for 12 months (preferably with another agent such as fluoroquinolone for first 2 months)	Treatment by directly observed therapy (DOT) is strongly recommended for all HIV patients Rifabutin has less drug interaction potential and can be used in place of rifampin Rifapenthe administered once weekly can result in development of resistance. It is not recommended among HIV patients Twice weekly intermittent regimen containing rifamycin might lead to rifamycin resistance, particularly among advanced HIV patients with CD4+ T-cell count <100 cells/μL; in this situation, therapy must be administered as daily or three times weekly For paradoxical reaction that is not severe, may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) without change in TB or HIV medications
Candidiasis (mucosal)	Oropharyngeal candidiasis Initial episodes (7-14 day treatment) ■ Fluconazole 100 mg PO QD; or ■ Itraconazole oral solution 200 mg PO QD; or ■ Clotrimazole troches 10 mg PO 5 times daily; or ■ Nystatin suspension 4-6 mL QID or 1-2 flavored pastilles 4-5 times daily Esophageal candidiasis (14-21 days) ■ Fluconazole 100 mg (up to 400 mg) PO or IV QD; or ■ Itraconazole oral solution 200 mg PO QD ■ Voriconazole 200 mg PO BID ■ Caspofungin 50 mg IV QD Vulvovaginitis ■ Topical azoles (clotrimazole, butoconazole, miconazole, ticonazole, or terconazole) for 7-10 days ■ Topical nystatin 100,000 units/day as vaginal tablet for 14 days ■ Oral itraconzaole 200 mg BID for 1 day or 200 mg QD for 3 days ■ Oral fluconazole 150 mg for 1 dose	Fluconazole-refractory oropharyngeal candidiasis ■ Itraconazole oral solution ≥200 mg PO QD; or ■ Amphotericin B suspension 100 mg/mL (not available in U.S.)—1 mL PO QID; or ■ Amphotericin B deoxycholate 0.3 mg/kg IV QD Fluconazole-refractory esophageal candidiasis ■ Caspofungin 50 mg IV QD; or ■ Voriconazole 200 mg PO or IV BID ■ Amphotericin B 0.3-0.7 mg/kg IV QD; or ■ Amphotericin liposomal or lipid complex 3-5 mg/kg IV QD	Suppressive therapy—generally not recommended unless patients have frequent or severe recurrences ■ Oropharyngeal candidiasis—fluconazole or itraconazole oral solution may be considered ■ Vulvovaginal candidiasis—daily topical azole for recurrent cases ■ Esophageal candidiasis—fluconazole 100-200 mg QD. Chronic or prolonged use of azoles might promote development of resistance

Cryptococcus neoformans meningitis	**Acute infection (induction therapy)** ■ Amphotericin B deoxycholate 0.7 mg/kg body weight IV QD and/or flucytosine 25 mg/kg PO QID for 2 weeks; or ■ Liposomal amphotericin B 4 mg/kg IV QD and/or flucytosine 25 mg/kg PO QID for 2 weeks **Consolidation therapy** ■ Fluconazole 400 mg PO QD for 8 weeks or until CSF cultures are sterile **Chronic maintenance therapy (Secondary prophylaxis)** ■ Fluconazole 200 mg PO QD;	**Induction therapy (alternative)** ■ Amphotericin B 0.7 mg/kg/day IV for 2 weeks; or ■ Fluconazole 400-800 mg/day (PO or IV) for less severe disease ■ Fluconazole 400-800 mg/day (PO or IV) and flucytlosine 25 mg/kg PO QID for 4-6 weeks **Consolidation therapy (alternative)** ■ Itraconazole 200 mg PO BID **Chronic maintenance therapy (alternative)** ■ Itraconazole 200 mg PO QD—for patients intolerant of or failed fluconazole	Repeated lumbar puncture might be indicated as adjunctive therapy among patients with increased intracranial pressure Discontinuation of antifungal therapy can be considered among patients who remain asymptomatic, with CD4$^+$ T-lymphocyte count >100-200 cells/µL for ≥6 months Some might consider performing a lumbar puncture before discontinuation of maintenance therapy
Histoplasma capsulatum infections	**Severe disseminated** **Acute phase (3-10 days or until clinically improved)** ■ Amphotericin B deoxycholate 0.7 mg/kg body weight IV QD; or ■ Liposomal amphotericin B 4 mg/kg IV QD **Continuation phase (12 weeks)** ■ Itraconazole 200 mg capsule PO BID **Less severe disseminated** ■ Itraconazole 200 mg capsule PO TID for 3 days, then 200 mg PO BID for 12 weeks **Meningitis** ■ Amphotericin B deoxycholate or liposomal for 12-16 weeks **Chronic maintenance therapy (secondary prophylaxis)** ■ Itraconazole capsule 200 mg PO QD	**Severe disseminated** **Acute phase (alternative)** ■ Itraconazole 400 mg IV QD **Continuation phase (alternative)** ■ Itraconazole oral solution 200 mg PO BID ■ Fluconazole 800 mg PO QD **Mild disseminated** ■ Fluconazole 800 mg PO QD	Acute pulmonary histoplasmosis among HIV-1–infected patients with CD4$^+$ T-lymphocyte count >500 cells/µL might require no therapy Insufficient data to recommend discontinuation of chronic maintenance therapy.
Herpes simplex virus (HSV) disease	**Orolabial lesions and initial or recurrent genital HSV** Famciclovir 500 mg PO BID or valacyclovir 1 g PO BID or acyclovir 400 mg PO TID for 7-14 days **Moderate-to-severe mucocutaneous HSV infections** ■ Initial therapy acyclovir 5 mg/kg body weight IV q8h ■ After lesions begin to regress, change to famciclovir 500 mg PO BID or valacyclovir 1 g PO BID or acyclovir 400 mg PO TID; continue therapy until lesions have completely healed **HSV keratitis** ■ Trifluridine 1% ophthalmic solution, one drop onto the cornea every 2 hours, not to exceed 2 drops per day, for no longer than 21 days **HSV encephalitis** ■ Acyclovir 10 mg/kg IV q8h for 14-21 days	**Acyclovir-resistant HSV** ■ Foscarnet 120-200 mg/kg/day IV in 2-3 divided doses until clinical response ■ Cidofovir 5 mg/kg IV weekly until clinical response **Alternative for acyclovir-resistant HSV infections** ■ Topical trifluridine ■ Topical cidofovir Note: Neither of these topical preparations is commercially available; extemporaneous compounding of these topical products can be prepared using trifluridine ophthalmic solution and cidofovir for intravenous administration	Chronic suppressive therapy with oral acyclovir, famciclovir, or valacyclovir might be indicated among patients with frequent or severe recurrences

Table 54-5. Treatment of HIV-Associated Opportunistic Infections Among Adults—cont'd

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
Varicella zoster virus (VZV) disease	Primary VZV infection (chickenpox) ■ Acyclovir 10 mg/kg body weight IV q8h for 7-10 days ■ Switch to oral therapy (acyclovir 800 mg PO QID or valacyclovir 1 g TID or famciclovir 500 mg TID) after defervescence if no evidence of visceral involvement exists Local dermatomal herpes zoster ■ Famciclovir 500 mg or valacyclovir 1 g PO TID for 7-10 days Extensive cutaneous lesion or visceral involvement ■ Acyclovir 10 mg/kg IV q8h, continue until cutaneous and visceral disease clearly resolved Progressive outer retinal necrosis (PORN) ■ Acyclovir IV 10 mg/kg q8h and foscarnet 80 mg/kg IV q8h		Corticosteroids for dermatomal zoster are not recommended
Coccidioidomycosis	Nonmeningeal infection Acute phase (diffuse pulmonary or disseminated disease) ■ Amphotericin B deoxycholate 0.5-1.0 mg/kg body weight IV QD; continue until clinical improvement, usually 500-1,000 mg total dose Acute phase (milder disease) ■ Fluconazole 400-800 mg PO QD; or ■ Itraconazole 200 mg PO BID Meningeal Infections ■ Fluconazole 400-800 mg IV or PO QD Chronic maintenance therapy (Secondary prophylaxis) ■ Fluconazole 400 mg PO QD; or ■ Itraconazole 200 mg capsule PO BID	Nonmeningeal infection Acute phase (diffuse pulmonary or disseminated disease) ■ Some specialists add azole to amphotericin B therapy Meningeal infection ■ Intrathecal amphoterin B	Insufficient data to recommend discontinuation of chronic maintenance therapy
Invasive aspergillosis	Voriconazole 400 mg IV or PO q12h for 2 days, then 200 mg q12h Duration of therapy based on clinical response	■ Amphotericin B deoxycholate 1 mg/kg body weight/day IV; or ■ Lipid formulations of amphotericin B 5 mg/kg/ day IV	Not enough data to recommend chronic suppression or maintenance therapy

Cytomegalovirus (CMV) disease		

CMV retinitis

For immediate sight-threatening lesions

Ganciclovir intraocular implant and valganciclovir 900 mg PO QD

For peripheral lesions

Valganciclovir 900 mg PO BID for 14-21 days, then 900 mg PO QD

Chronic maintenance therapy (Secondary prophylaxis)

First choice

■ Valganciclovir 900 mg PO QD

■ Foscarnet 90-120 mg/kg body weight IV QD

CMV esophagitis or colitis

■ Ganciclovir IV or Foscarnet IV for 21-28 days or until signs and symptoms have resolved; oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption

■ Maintenance therapy is generally not necessary, but should be considered after relapses

CMV pneumonitis

■ Treatment should be considered in patients with histologic evidence of CMV pneumonitis and who do not respond to treatment of other pathogens

■ The role of maintenance therapy is not yet established

CMV neurologic disease

■ Ganciclovir IV and Foscarnet IV continue until symptomatic improvement

■ Maintenance therapy should be continued for life

CMV retinitis

■ Ganciclovir 5 mg/kg IV q12h for 14-21 days, then 5 mg/kg IV QD; or

■ Ganciclovir 5 mg/kg IV q12h for 14-21 days, then valganciclovir 900 mg PO QD; or

■ Foscarnet 80 mg/kg IV q8h or 90 mg/kg IV q12h for 14-21 days, then 90-120 mg/kg IV q24h; or

■ Cidofovir 5 mg/kg IV for 2 weeks, then 5 mg/kg every other week; each dose should be administered with IV saline hydration and oral probenecid; or

■ Repeated intravitreal injections with fomivirsen (for relapses only, not as initial therapy)

Chronic maintenance therapy

■ Cidofovir 5 mg/kg IV every other week with probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g); or

■ Fomivirsen 1 vial (330 mg) injected into the vitreous, then repeated every 2-4 weeks

Choice of initial therapy for CMV retinitis should be individualized on the basis of location and severity of the lesion(s), level of immunosuppression, and other factors such as concomitant medications and ability to adhere to treatment

Initial therapy among patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include optimization of antiretroviral therapy (ART)

Some specialists recommend delaying ART among patients with CMV neurologic disease because of concerns about worsening of condition as a result of immune recovery inflammatory reaction

Pre-emptive treatment of patients with CMV viremia without evidence of organ involvement is generally not recommended

Maintenance therapy for CMV retinitis can be safely discontinued among patients with inactive disease and sustained CD4$^+$ T lymphocyte (>100-150 cells/μL^3 for $\geq$8 months); consultation with ophthalmologist is advised

Patients with CMV retinitis who discontinued maintenance therapy should undergo regular eye examination for early detection of relapse

Ganciclovir intraocular implants might need to be replaced every 6-8 months for patients who remain immunosuppressed with CD4$^+$ T lymphocyte counts <100-150 cells/μL

Immune recovery uveitis (IRU) might develop in the setting of immune reconstitution; treatment of IRU; periocular corticosteroids or short courses of systemic steroid.

Because of its poor oral bioavailability and with the availability of valganciclovir, oral ganciclovir should not be used

should be considered as part of a routine respiratory evaluation for patients with radiographic infiltrates in most areas of the United States.

Therapy of opportunistic infections is summarized in Table 54-5.[72] While awaiting a specific diagnosis, it is reasonable to initiate empiric therapy in patients ill enough to merit admission to an ICU. For patients with a CD4+ T lymphocyte count greater than 250 to 300 cells/μL, azithromycin and ceftriaxone or azithromycin and ampicillin-sulbactam would be reasonable choices. For patients with CD4+ T lymphocyte counts below 200 to 250 cells/μL, levofloxacin or moxifloxacin plus trimethoprim-sulfamethoxazole or pentamidine plus levofloxacin or moxifloxacin would be potential regimens. If PCP is documented, trimethoprim-sulfamethoxazole is always the drug of choice in patients who can tolerate it. Table 54-5 lists alternatives for sulfa-intolerant individuals. Regardless of which specific antipneumocystis regimen is used, corticosteroid therapy is indicated for any patient who presents with an oxygen pressure (PO$_2$) below 70 mm Hg or an alveolar-arterial gradient higher than 30 mm Hg.[73-76] Patients with an initial PO$_2$ lower than 70 mm Hg are the subgroup with substantial mortality for whom corticosteroids have been shown to provide a survival benefit. Corticosteroids may provide more rapid and perhaps more complete resolution of pulmonary manifestations in patients who present with better pulmonary function, but survival in this population is so high that clinical trials have not been able to show survival benefit. Some experts are concerned that corticosteroid use will be associated with reactivation of latent infections such as CMV or tuberculosis. However, reactivation of life-threatening infections has not been associated with this corticosteroid regimen.

How should a patient with AIDS-associated PCP be managed if there is no improvement, or if there is deterioration, after 5 to 10 days of therapy? The median time to improvement in clinical variables is 4 to 8 days; therefore, changes in therapy are probably not warranted before 5 to 10 days. At that point the accuracy of the diagnosis should be reassessed: Consideration should be given to repeat bronchoscopy with transbronchial biopsy to determine if CMV, fungi, mycobacteria, or a nosocomial bacterial process is present. Noninfectious processes such as congestive heart failure or tumor (e.g., Kaposi's sarcoma) must also be considered. If pneumocystosis is the only causative process that can be identified, corticosteroids should be added to the regimen if they have not been already. Whether switching from one antipneumocystis agent to another or whether adding a second agent is helpful has not been determined by clinical trials. Some human pneumocystosis isolates are resistant to sulfonamides, but such testing is available only in a few research centers. Most clinicians add parenteral pentamidine to trimethoprim-sulfamethoxazole. Parenteral trimetrexate or clindamycin-primaquine could be used as salvage regimens as well. Patients who have not improved after 14 to 21 days of therapy with specific chemotherapy plus corticosteroids have an exceedingly poor prognosis.

Should patients with AIDS-related PCP be intubated and provided with mechanical ventilation? Mortality for such patient populations was 70% to 80% in several series in the early 1980s.[77-80] Since that era, supportive care has improved, and treatment modalities for concurrent infectious and noninfectious processes have become more effective. Patient selection for ventilatory support is probably also improving. Patients who have multiple active opportunistic infections, substantial weight loss, and no response to 14 days of therapy have a worse prognosis than ambulating patients who develop respiratory failure the third day of therapy. Thus decisions about ICU support for patients with HIV infection and respiratory failure need to be individualized on the basis of a realistic assessment of prognosis, the availability of resources, and the preference of the individual patient.

A frequent question for any HIV-infected patient in the ICU is whether antiretroviral drugs should be continued or initiated during the critical or life-threatening illness. Although there is no specific study of various strategies, most authorities discourage the use of antiretroviral drugs in the ICU because of drug interactions and drug toxicities. In addition, the initiating HAART can be associated with dramatic "immune reconstitution" syndromes that can complicate the process that brought the patient to the ICU.[81-83] Finally, almost all antiretroviral drugs that are commercially available are oral: In most situations it is better to discontinue all antiretroviral drugs for a few days or weeks or months rather than risk poor absorption and suboptimal serum levels. The latter would enhance the emergence of drug-resistant HIV.

Central Nervous System Dysfunction

An important cause of admitting HIV-infected patients into the ICU is either seizures or altered mental status. Either can result from infectious or neoplastic processes caused by meningeal disease or parenchymal involvement. The differential diagnosis of meningeal disease includes pneumococcal and staphylococcal meningitis, cryptococcal meningitis, tuberculous meningitis, and lymphomatous meningitis, as well as involvement from other endemic mycoses and common community-acquired viral and bacterial processes.[24,84] Diffuse central nervous system parenchymal disease can be caused by HIV itself, by progressive multifocal leukoencephalopathy, and occasionally by herpes viruses such as CMV or herpes simplex virus. Focal mass lesions may be caused by toxoplasmosis or lymphoma. Less often, tuberculosis, fungi, conventional bacterial abscesses, nocardia, and other tumors are the cause of focal lesions. These lesions can be difficult to distinguish clinically and radiologically. The CD4+ T lymphocyte count can help narrow the differential diagnosis, but CSF or brain tissue is usually necessary for definitive diagnosis.

The routine therapies for many of these processes are outlined in Table 54-5. Toxoplasmosis deserves particular mention because of its frequency.[85-87] Toxoplasmosis occurs mainly in patients with HIV infection who have CD4+ T lymphocyte counts below 100 cells/μL, have a positive IgG antibody titer against toxoplasma, and who

have not been receiving trimethoprim-sulfamethoxazole or dapsone prophylaxis. Patients present with altered cognition, focal motor or sensory deficits, or seizures. Lesions may be unifocal or multifocal. They usually enhance with contrast, but this is not invariably true. For patients who fit the profile for high risk of toxoplasmosis, and with a compatible presentation, it is reasonable to establish an empiric diagnosis and institute specific therapy with sulfadiazine plus pyrimethamine or, for patients unable to tolerate sulfa, clindamycin plus pyrimethamine. Corticosteroids may be needed for patients with considerable intracerebral edema or elevated intracranial pressure. Antiseizure medication is usually instituted only after a seizure has occurred rather than prophylactically. Most patients improve clinically and radiologically within 7 to 10 days. If patients fail to improve, a stereotactic needle biopsy is appropriate, especially because the prevalence of lymphoma is increasing. Organisms can be difficult to see in brain specimens obtained by this technique.

Hypotension

Patients with HIV infection develop hypotension resulting from the same types of disorders as with non-HIV infected individuals—sepsis from a primary infection or a wound or device (especially an intravascular access device), fluid depletion from vomiting or diarrhea, and hemorrhage from a gastrointestinal lesion are examples of common causes. The evaluation of hypotension in a patient with HIV infection must take into account factors particular to this patient population: It is susceptible to opportunistic infections; it undergoes many procedures that can be associated with infectious complications; and it receives an array of drugs, some of which have cardiovascular effects. Thus evaluating hypotension in this patient population requires a comprehensive and thorough approach. A differential diagnosis of the major causes is shown in Table 54-6. Adrenal function always deserves special attention because several viral processes, fungal and mycobacterial diseases, HIV, and drugs can suppress the adrenal axis and either cause hypotension or exacerbate it.

Prevention of Opportunistic Infection

Patients with HIV infection typically receive several antimicrobial agents to reduce the likelihood they will acquire opportunistic infections.[9] *Primary prophylaxis* is the term used to indicate strategies that reduce the likelihood of an initial episode of a disease process. *Secondary prophylaxis* is the term used to indicate strategies that prevent recurrences or relapses. *Chronic suppressive therapy* is identical to secondary prophylaxis: This refers to regimens that are continued after the initial therapeutic course to prevent relapses.

All patients with HIV infection and CD4+ T lymphocyte counts below 200 cells/µL typically receive antipneumocystis prophylaxis. Trimethoprim-sulfamethoxazole is the regimen of choice. Patients who actually take this drug have very few breakthroughs of PCP and receive considerable protection against toxoplasmosis and certain routine bacterial infections. Alternative regimens include monthly dapsone, weekly dapsone-pyrimethamine, or

Table 54-6. Causes of Hypotension in Patients with HIV Infection	
Process	**Examples of Causes**
Distributive Shock	
Septic shock	
Bacterial	*Pneumococcus* or *Haemophilus* organism pneumonia Vascular access infection Surgical wound
Viral	CMV, disseminated VZV
Fungal	*Histoplasma, Coccidioides, Cryptococcus* organisms Vascular access–related candidemia *Pneumocystis jiroveci* pneumonia
Adrenal Insufficiency	Tuberculosis, fungi, CMV, HIV
Oligemic Shock	
Dehydration	Bacterial diarrhea *C. difficile* diarrhea
Gastrointestinal hemorrhage	CMV colitis Gastrointestinal lymphoma
Cardiogenic Shock	
Cardiomyopathy	HIV
Endocarditis	Bacterial pathogens related to IV drug abuse
Extracardiac Obstruction	
Pericardial tamponade	Lymphoma, Kaposi's sarcoma, primary effusion lymphoma Fungus, tuberculosis
Pericardial constriction	Tuberculosis, fungus
Massive pulmonary embolus	Inactivity, inanition
CMV, cytomegalovirus; *HIV,* human immunodeficiency virus; *VZV,* varicella-zoster virus.	

daily aerosol pentamidine. Prophylaxis against *M. avium* complex is recommended for patients with CD4+ T lymphocyte counts under 100 cells/µL; clarithromycin and azithromycin are currently the drugs of choice.[9] Many clinicians also use fluconazole or acyclovir prophylaxis to reduce the frequency of fungal and viral processes, respectively, although this is not recommended because of issues of cost, pill burden, and the emergence of resistant pathogens. Isoniazid prophylaxis is important for any patient with a tuberculin skin test that shows more than 5 mm of induration or a history of substantial recent exposure.[9]

Transmission of HIV-Related Pathogens in the ICU

Transmission of tuberculosis from patients to other patients, from patients to staff, or from staff to patients is an urgent concern in ICUs. Patients with HIV infection are extraordinarily susceptible to tuberculosis. Thus an infected patient poses a substantial risk, especially when

hospitalized for pneumonia or when undergoing procedures at high risk for producing aerosols such as intubation, bronchoscopy, sputum induction, or aerosol pentamidine treatment. Identifying potentially infected patients early and placing them in appropriate isolation until their tuberculosis status is fully examined is important. In many centers, patients with syndromes compatible with pulmonary or upper airway tuberculosis are maintained in isolation at least until three specimens of respiratory secretions have been examined for tuberculosis. HIV-infected health care practitioners need to carefully assess their risk of acquiring tuberculosis by their exposure in the ICU.

Transmission of HIV

Transmission of HIV is an issue that requires attention in the ICU.[65] No evidence exists that HIV-infected health care professionals can infect patients, regardless of what procedure they perform, outside of two unusual events. HIV patients pose a risk to health care professionals, however. This risk can be substantially reduced by education, by strict monitoring for compliance with universal precautions, and by having proper equipment. Almost all HIV transmission in an occupational setting occurs as a result of injuries involving sharp instruments (e.g., needles, scalpels). The risk of such injuries is about one case of HIV transmission per 250 injuries, but the likelihood of transmission in an individual accident depends on the amount of viremia at the time of the accident (late-stage patients generally have more circulating virus than do early-stage patients) and the nature of the accident. Most authorities

recommend immediate prophylaxis if a significant injury occurs involving an HIV-infected patient. Considerable debate exists over the optimal choice of drugs and the optimal duration of therapy, but it is clear that initiating therapy within a period of hours rather than days is best. Many authorities now advocate a HAART regimen for any situation when the patient and health care provider determine that therapy is appropriate, and continue that for 4 to 6 weeks.

Human Stem Cell, Bone Marrow, and Solid Organ Transplant Recipients

Increasingly, ICUs are caring for organ transplant recipients, either in the period immediately after the procedure or during a crisis that occurs days, weeks, months, or years after engraftment. Managing each type of organ transplant recipient has unique features depending on whether bone marrow, kidney, heart, lungs, liver, or other organs are transplanted.[2,6] Laboratory monitoring provides useful predictive information about the status of cellular immunity, humoral immunity, and neutrophil number and function. Ultimately, however, clinical experience is necessary with each type of organ transplant and each immunosuppressive regimen to predict the most likely pathogens, when they most characteristically occur in relation to the transplant procedure, and what influence each immunosuppressive therapy has. An example of the temporal pattern of infectious complications after bone marrow transplantation is shown in Figure 54-3.[9] Although such figures are useful conceptually, however, the immunosuppressive regimens are changing rapidly, and such figures

PHASES OF OPPORTUNISTIC INFECTIONS AMONG ALLOGENEIC HSCT RECIPIENTS
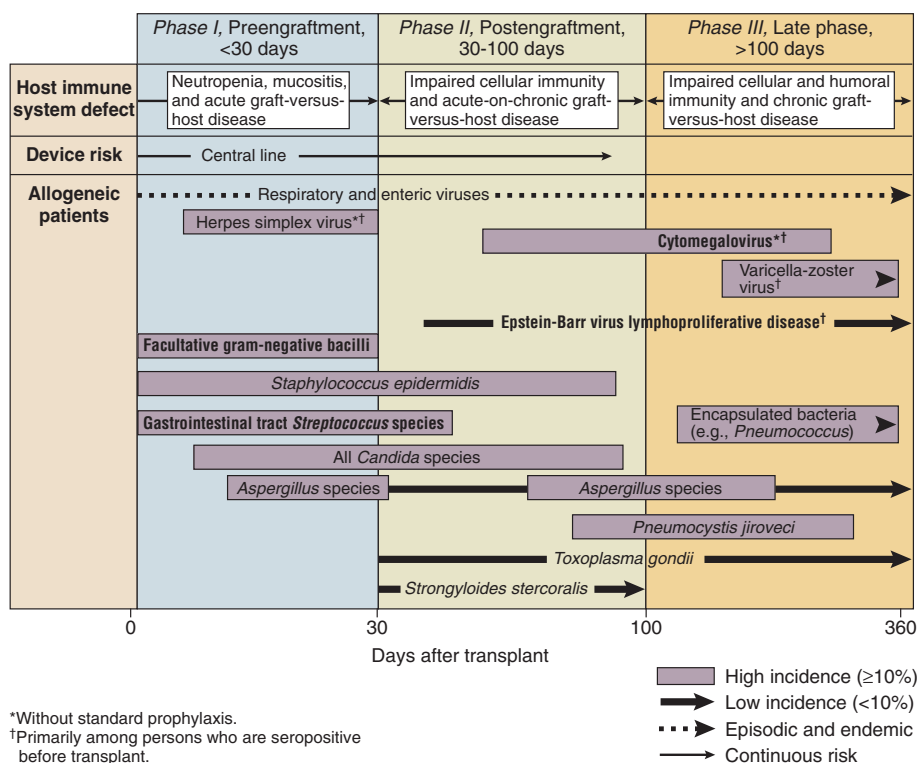
Figure 54-3. Usual sequence of infection after organ transplantation; precise period of susceptibility depends on organ transplanted, immunosuppressive regimen, and concomitant complications. (Adapted from Fishman JA, Rubin RH: Infection in organ-transplant recipients. Infection in organ-transplant recipients. N Engl J Med 1998;338:1741.)

*Without standard prophylaxis.
†Primarily among persons who are seropositive before transplant.

may be misleading when applied to current transplantation protocols.

Organ transplant recipients share a complex interaction between immunosuppression and infection. Immunosuppression is usually necessary in allogeneic transplantation to permit graft survival. The more potent the immunosuppression, the more likely infection is to occur. Strategies that use antimicrobial agents (drugs, vaccines, and other biologic products) aggressively may reduce the risk of and damage from infection in a manner that allows more potent immunosuppression and better graft survival. Such approaches may include prophylactic antibacterial and antiretroviral treatment, as well as prompt empiric therapy for emerging febrile episodes.

Patients receiving hematopoietic stem cell transplantation (HSCT) or solid organ transplants are often receiving antimicrobial prophylaxis. Acyclovir for HSV, valacyclovir for CMV, fluconazole for yeast, voriconazole for yeast and molds, trimethoprim-sulfamethoxazole for PCP, and quinolones for bacteria are used in various combinations at different transplant programs. These agents dictate which organisms will break through to cause disease, and what their antibiotic susceptibility patterns will be.

Several pathogens deserve special mention. CMV is one of the most prominent pathogens for solid organ and bone marrow transplant recipients.[88-90] Most disease is secondary (i.e., disease results from reactivation of a previously acquired, latent infection) in a seropositive organ recipient. In urban areas of the United States, 60% to 70% of the population is seropositive for CMV, and thus 60% to 70% of the transplant recipients will have latent infection that could potentially be reactivated. Some CMV seronegative patients acquire primary infections from a CMV-infected organ or from CMV-infected blood or blood products. A few CMV seropositive individuals develop superimposed CMV disease from CMV acquired through a seropositive donor. Laboratory monitoring of patients for evidence of CMV disease by using a DNA amplification assay, or surveillance of CMV antigen in buffy coat smears, is an important feature in efforts to reduce morbidity and mortality resulting from CMV.[89,91-95] Intensivists need to understand how to interpret these assays in terms of starting empiric, pre-emptive, or definitive therapy. Strategies to reduce the frequency of CMV disease with acyclovir, intravenous or oral ganciclovir (or oral valganciclovir), the investigational agent proganciclovir, or immune globulin are used by many programs. CMV disease can cause substantial morbidity and mortality including fever, hypotension, pneumonitis, hepatitis, glomerulitis, enteritis, and allograft injury. The availability of ganciclovir, foscarnet, and cidofovir has enabled these conditions to be treated successfully in many instances, although all three of these drugs are associated with substantial toxicity. Whether immune globulin (either immune globulin or specific hyperimmune globulin) adds anything to the potency of therapeutic regimens is not clear, although these products are usually administered when they are available.

PCP has been reported in recipients of most types of organ transplants. Most organ transplant programs use PCP prophylaxis.[6,33,96] Trimethoprim-sulfamethoxazole is usually the prophylactic agent of choice because it is more effective than other agents, is well tolerated, and reduces the frequency of urinary tract infections and other potential complications (e.g., disease resulting from *Nocardia, S. pneumoniae,* and *Haemophilus* organisms).

Fungal infections have been common, but the causative pathogens are changing because of changes in prophylactic regimens. With the use of fluconazole, *Candida albicans* infections became less common. Molds, especially *Aspergillus,* became more important pathogens, as did fluconazole-resistant *Candida*. Some programs are now using voriconazole prophylaxis. For such patients, mucormycosis and *non-albicans Candida* are becoming more prominent causes of morbidity. Thus clinicians must know what antifungal prophylaxis has been used in order to anticipate which complications will occur. Mold infections can be difficult to diagnose: serum galactomannan assays can yield specific information, but the test has low sensitivity. Mold infections almost never cause fungemia. Thus diagnosis depends on cultures, which can be highly suggestive if obtained from sources such as bronchoalveolar lavage or biopsy.

Viral respiratory infections require particular mention because some are treatable and most are transmissible. Community-acquired respiratory viruses such as adenoviruses, coronaviruses, or influenza can occur in immunocompetent or immunosuppressed patients. When respiratory infections occur in immunocompromised patients, health care professionals need to be certain that a transmissible virus is not the cause because of the potential to infect other patients, families, or hospital staff. Of the respiratory infections, RSV deserves special attention in HSCT patients. Although RSV can, like other community-acquired viruses, cause disease in any patient population, it is especially lethal in solid organ, bone marrow, and stem cell transplants. Thus RSV must be specifically sought in this patient population, as well as their visitors and health care providers, so that it does not spread to highly susceptible patients.

Similarly, when caring for immunosuppressed patients, attention to *Mycobacterium tuberculosis* is important because this pathogen can also spread to other patients, families, and hospital staff. With more immigrants in the United States and more patients having travel exposure, *M. tuberculosis* needs to be considered in the differential diagnosis and specifically sought by gene probe, smear, or culture where appropriate.

Diagnosis and therapy of opportunistic infections and nosocomial infections should follow the guidelines given in Chapters 43, 51, and 54. In choosing therapies, attention must be focused on the toxicities of antimicrobial agents and how they influence the outcome of the transplanted organ. In addition, drug interactions are important, especially with cyclosporine. Drugs that alter hepatic metabolism, such as rifampin, rifabutin, and fluconazole, can have substantial influence on cyclosporine levels and thus need to be used with careful pharmacologic attention. Finally, clinicians must recognize that new immunosuppressive regimens and changing prophylactic regimens

are changing the spectrum of infectious complications. As mentioned earlier, fungal infections are increasingly likely to be caused by species other than *C. albicans: non-albicans Candida, Fusarium,* and *Rhizopus* are recognized with increasing frequency. Similarly, prophylaxis with valganciclovir is reducing CMV disease and pushing disease that does occur later and later in relation to the transplant procedure. Viruses such as HHV-6 and BK virus are causing disease. Thus clinicians need to look for changing spectrum of pathogens, as well as changing manifestations if the morbidity and mortality caused by infection is to be managed optimally.

KEY POINTS

- Knowledge of a patient's specific defects in immunologic and inflammatory response helps predict which opportunistic pathogens are most likely to occur.

- ICUs are increasingly successful in enabling immunosuppressed patients to survive acute crises, especially if the defect in immunologic or inflammatory function is reversible over time or by replacement therapy.

- For neutropenic patients, gram-positive cocci are becoming more frequent than gram-negative bacilli as causes of life-threatening illness.

- Resistance to antimicrobial agents is becoming a major problem including bacteria (e.g., vancomycin-resistant enterococci and penicillin-resistant pneumococci), fungi (e.g., fluconazole-resistant *Candida* organisms), as well as PCP, and viruses (e.g., acyclovir-resistant herpes simplex and ganciclovir-resistant CMV).

- In neutropenic patients, combination therapy should be considered when treating any life-threatening bacterial process.

- A substantial fraction of HIV-infected patients with PCP-related respiratory failure can survive mechanical support and be discharged from the hospital.

- Adjunctive corticosteroid therapy is indicated for respiratory failure related to PCP.

- Tuberculosis is a concern in any immunologically abnormal individual with pulmonary disease but is a special concern in HIV-infected patients. Tuberculosis in these cases often warrants respiratory isolation until appropriate specimens are evaluated for mycobacteria.

- Organ transplant recipients develop opportunistic infections at relatively predictable points depending on the type of transplantation and the specific immunosuppressive regimen used.

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