

guidelines are useful in the initial treatment of neutropenic patients with fever (Fig. 104-2):

1. In the initial regimen, it is necessary to use antibiotics active against both gram-negative and gram-positive bacteria (Table 104-4).
2. Monotherapy with an aminoglycoside or an antibiotic lacking good activity against gram-positive organisms (e.g., ciprofloxacin or aztreonam) is not adequate in this setting.
3. The agents used should reflect both the epidemiology and the antibiotic resistance pattern of the hospital.
4. If the pattern of resistance justifies its use, a single third-generation cephalosporin constitutes an appropriate initial regimen in many hospitals.
5. Most standard regimens are designed for patients who have not previously received prophylactic antibiotics. The development of fever in a patient who has received antibiotics affects the choice of subsequent therapy, which should target resistant organisms and organisms known to cause infections in patients being treated with the antibiotics already administered.
6. Randomized trials have indicated the safety of oral antibiotic regimens in the treatment of “low-risk” patients with fever and neutropenia. Outpatients who are expected to remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen.
7. Several large-scale studies indicate that prophylaxis with a fluoroquinolone (ciprofloxacin or levofloxacin) decreases morbidity and mortality rates among afebrile patients who are anticipated to have neutropenia of long duration.

Commonly used antibiotic regimens for the treatment of febrile patients in whom prolonged neutropenia (>7 days) is anticipated include (1) ceftazidime or cefepime, (2) piperacillin/tazobactam, or (3) imipenem/cilastatin or meropenem. All three regimens have shown equal efficacy in large trials. All three are active against *P. aeruginosa* and a broad spectrum of aerobic gram-positive and gram-negative organisms. Imipenem/cilastatin has been associated with an elevated rate of *C. difficile* diarrhea, and many centers reserve carbapenem antibiotics for treatment of gram-negative bacteria that produce extended-spectrum β -lactamases; these limitations make carbapenems less attractive as an initial regimen. Despite the frequent involvement of coagulase-negative staphylococci, the initial use of vancomycin or its automatic addition to the initial regimen has not resulted in improved outcomes, and the antibiotic does exert toxic effects. For these reasons, only judicious use of vancomycin is recommended—for example, when there is good reason to suspect the involvement of coagulase-negative staphylococci (e.g., the appearance of erythema at the exit site of a catheter or a positive culture for methicillin-resistant *S. aureus* or coagulase-negative staphylococci). Because the sensitivities of bacteria vary from hospital to hospital, clinicians are advised to check their local sensitivities and to be aware that resistance patterns can change quickly, necessitating a change in approach to patients with fever and neutropenia. Similarly, infection control services should monitor for basic antibiotic resistance and for fungal infections. The appearance of a large number of *Aspergillus* infections, in particular, suggests the possibility of an environmental source that requires further investigation and remediation.

The initial antibacterial regimen should be refined on the basis of culture results (Fig. 104-2). Blood cultures are the most relevant basis for selection of therapy; surface cultures of skin and mucous membranes may be misleading. In the case of gram-positive bacteremia or another gram-positive infection, it is important that the antibiotic be optimal for the organism isolated. Once treatment with broad-spectrum antibiotics has begun, it is not desirable to discontinue all antibiotics because of the risk of failing to treat a potentially fatal bacterial infection; the addition of more and more

antibacterial agents to the regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Planned progressive therapy (the serial, empirical addition of one drug after another without culture data) is not efficacious in most settings and may have unfortunate consequences. Simply adding another antibiotic for fear that a gram-negative infection is present is a dubious practice. The synergy exhibited by β -lactams and aminoglycosides against certain gram-negative organisms (especially *P. aeruginosa*) provides the rationale for using two antibiotics in this setting, but recent analyses suggest that efficacy is not enhanced by the addition of aminoglycosides, while toxicity may be increased. Mere “double coverage,” with the addition of a quinolone or another antibiotic that is not likely to exhibit synergy, has not been shown to be of benefit and may cause additional toxicities and side effects. Cephalosporins can cause bone marrow suppression, and vancomycin is associated with neutropenia in some healthy individuals. Furthermore, the addition of multiple cephalosporins may induce β -lactamase production by some organisms; cephalosporins and double β -lactam combinations should probably be avoided altogether in *Enterobacter* infections.

ANTIFUNGAL THERAPY

Fungal infections in cancer patients are most often associated with neutropenia. Neutropenic patients are predisposed to the development of invasive fungal infections, most commonly those due to *Candida* and *Aspergillus* species and occasionally those caused by *Mucor*, *Rhizopus*, *Fusarium*, *Trichosporon*, *Bipolaris*, and others. Cryptococcal infection, which is common among patients taking immunosuppressive agents, is uncommon among neutropenic patients receiving chemotherapy for AML. Invasive candidal disease is usually caused by *C. albicans* or *C. tropicalis* but can be caused by *C. krusei*, *C. parapsilosis*, and *C. glabrata*.

For decades, it has been common clinical practice to add amphotericin B to antibacterial regimens if a neutropenic patient remains febrile despite 4–7 days of treatment with antibacterial agents. The rationale for this empirical addition is that it is difficult to culture fungi before they cause disseminated disease and that mortality rates from disseminated fungal infections in granulocytopenic patients are high. Before the introduction of newer azoles into clinical practice, amphotericin B was the mainstay of antifungal therapy. The insolubility of amphotericin B has resulted in the marketing of several lipid formulations that are less toxic than the amphotericin B deoxycholate complex. Echinocandins (e.g., caspofungin) are useful in the treatment of infections caused by azole-resistant *Candida* strains as well as in therapy for aspergillosis and have been shown to be equivalent to liposomal amphotericin B for the empirical treatment of patients with prolonged fever and neutropenia. Newer azoles have also been demonstrated to be effective in this setting. Although fluconazole is efficacious in the treatment of infections due to many *Candida* species, its use against serious fungal infections in immunocompromised patients is limited by its narrow spectrum: it has no activity against *Aspergillus* or against several non-*albicans* *Candida* species. The broad-spectrum azoles (e.g., voriconazole and posaconazole) provide another option for the treatment of *Aspergillus* infections (Chap. 241), including CNS infection. Clinicians should be aware that the spectrum of each azole is somewhat different and that no drug can be assumed to be efficacious against all fungi. *Aspergillus terreus* is resistant to amphotericin B. Although voriconazole is active against *Pseudallescheria boydii*, amphotericin B is not; however, voriconazole has no activity against *Mucor*. Posaconazole, which is administered orally, is useful as a prophylactic agent in patients with prolonged neutropenia. Studies in progress are assessing the use of these agents in combinations. **For a full discussion of antifungal therapy, see Chap. 235.**

ANTIVIRAL THERAPY

The availability of a variety of agents active against herpes-group viruses, including some new agents with a broader spectrum of activity, has heightened focus on the treatment of viral infections,