The Infectious Diseases Society of America 2002 Guidelines for the Use of Antimicrobial Agents in Patients with Cancer and Neutropenia: Salient Features and Comments

Kenneth V. I. Rolston
University of Texas M. D. Anderson Cancer Center, Houston, Texas

Infection remains the most common complication of chemotherapy-induced neutropenia. Bacterial infections predominate initially. Invasive fungal infections occur in patients with prolonged neutropenia. Chemoprophylaxis is recommended only for patients at high risk. Initial empirical therapy is based on local epidemiology and drug-susceptibility patterns. Patients at low risk can be treated as outpatients. Other patients need hospital-based, parenteral therapy. Several options are available, including combination regimens or monotherapy. Initial antimicrobial coverage against *Pseudomonas* species is necessary. Subsequent management depends on the nature of the febrile episode. If defervescence occurs within 3–5 days and no pathogen has been identified, the initial regimen or a suitable oral regimen can be used to complete a 7- to 10-day course. If the etiology has been established, therapy can be adjusted for optimal coverage (activity against gram-negative organisms must be maintained). If fever persists for longer than 3–5 days, assessment for a fungal infection, a resistant organism, or a new infectious focus should be conducted and empirical antifungal therapy instituted.

Infection is the most common complication associated with neutropenia and accounts for substantial morbidity and mortality. The principles that guide the management of patients with neutropenia are different from those for immunocompetent patients. The Infectious Diseases Society of America (IDSA) initially developed guidelines for the use of antimicrobial agents in to treat neutropenic patients with cancer more than a decade ago and has produced 2 subsequent revisions [1–3]. Here I highlight the salient features of the IDSA guidelines and also synthesize information presented in the preceding 3 articles in this supplement issue of *Clinical Infectious Diseases* [4–6].

**DEFINITIONS**

**Fever.** Fever has been defined as an oral temperature of ≥38.3°C. Rectal temperature measurement is not recommended, because it may precipitate bacteremia, particularly in patients with mucositis, hemorrhoids, anal fissures, or other localized lesions. Occasionally, neutropenic patients with infection may be afebrile or even hypothermic. This includes patients infected by certain organisms (e.g., *Clostridium septicum*, *Pseudomonas aeruginosa*, and *Acinetobacter* species), patients with septic shock, and patients who are receiving corticosteroids or other immunosuppressive agents known to blunt the inflammatory response.

**Neutropenia.** Neutropenia is defined as an absolute neutrophil count of either ≤500 cells/mm³ or ≤1000 cells/mm³ with a predictable decline to ≤500 cells/mm³ in 24–48 h. The incidence and severity of infection is inversely proportional to the number of circulating neutrophils. The duration of neutropenia is another important determinant of the risk of infec-
SPECTRUM OF INFECTION

Currently, gram-positive organisms cause bacteremia in patients with neutropenia more often than do gram-negative organisms [9, 10]. However, bacteremia occurs in only 15%–20% of neutropenic patients with documented infections [11]. Gram-negative organisms are isolated more frequently from other sites of infection, such as the urinary tract, respiratory tract, and gastrointestinal tract (in cases of enterocolitis or perirectal infection). These sites of infection should also be considered to achieve a more accurate picture of the spectrum of bacterial infections. In addition, ~25%–30% of infections are polymicrobial, and ~80% of these have a gram-negative organism as a component [12]. When these are taken into account, gram-positive organisms are not as predominant as they appear to be. For reasons that are poorly understood, anaerobic bacteria are isolated infrequently from patients with neutropenia. Invasive fungal infections, particularly those caused by molds such as Aspergillus species, tend to occur later in the course of neutropenia than do bacterial infections. The herpes group of viruses (herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6), and community-acquired respiratory viruses (respiratory syncytial virus, influenza virus, and parainfluenza virus) have emerged as important pathogens in selected subsets of patients (hematopoietic stem cell transplant recipients), and some of these infections have a seasonal distribution [13].

INITIAL EVALUATION OF FEBRILE NEUTROPENIC PATIENTS

A thorough history and physical examination is of paramount importance. Useful bits of historical information include the nature and duration of antineoplastic therapy (some regimens are more myelosuppressive or immunosuppressive than others and may be associated with infection with different pathogens), administration of prophylactic or broad-spectrum antibiotics (because these are likely to alter the patient’s microflora), previous infections, medical procedures, allergies, and/or drug-drug interactions. The physical examination should entail a careful search for potentially infected sites, including the gastrointestinal tract (oropharynx, esophagus, and perineum), skin, nails and nailbed, eyes, lungs, vascular access sites, and bone marrow or other biopsy sites.

Laboratory evaluation recommended for all febrile neutropenic patients includes 2 sets of blood samples for culture for bacteria and fungi, 1 from peripheral blood and 1 from each catheter lumen, if present. Although quantitative cultures with lysis centrifugation techniques are not done in most institutions, they might provide useful information regarding the severity of infection and might help determine the duration of therapy [14]. Chemical analysis, including a complete blood cell count, an electrolyte panel, and liver and renal function panels, should be done at baseline and every 2 or 3 days as needed. Studies that provide useful information but are not necessary for all febrile neutropenic patients include chest radiography, if symptoms are present or outpatient management is being considered; culture of urine, if patients are catheterized or symptomatic; and culture of stool and screening for Clostridium difficile toxin in patients with diarrhea. Testing of CSF and joint fluid should be done only when signs of local infection are present. All drainage materials should be subjected to appropriate smears and cultures (including for detection of acid-fast bacilli and fungi). Screening for resistant organisms (e.g., methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci) is recommended only for infection control purposes. Measurements of levels of C-reactive protein, procalcitonin, and other cytokines may occasionally provide useful information but are not routinely recommended.

INITIAL ANTIBIOTIC THERAPY

The prompt administration of empirical antibiotic therapy based on local epidemiology and drug-susceptibility patterns is essential, because infections may progress rapidly in patients with neutropenia [3]. Initial therapy is directed primarily at bacterial pathogens, because fungal, viral, or protozoal organisms rarely cause the initial infection. Not all febrile neutropenic patients have the same risk of developing medical morbidity or serious complications during a febrile episode. A “low-risk” subset can be identified at the onset of the febrile episode by means of various risk prediction rules [15, 16]. These patients are candidates for outpatient management with oral or intravenous antibiotics [17]. Most outpatient regimens are quinolone-based combinations (e.g., ciprofloxacin plus amoxicillin-clavulanate or clindamycin). Monotherapy with newer, broad-spectrum quinolones (gatifloxacin and moxifloxacin) is being evaluated but cannot yet be recommended [18].

Patients not identified as being at low risk of serious complications need hospital-based, parenteral, broad-spectrum antibiotic therapy. When selecting empirical regimens, several factors need to be considered in addition to local epidemiology and drug-susceptibility patterns. Potential toxicities and allergies might limit the use of certain agents. The use of multiple nephrotoxic agents (e.g., cisplatin, cyclosporine, aminoglycosides, and polyenes) to treat the same patient should be avoided if possible. Blood levels of potentially toxic agents should be monitored to preempt toxicity. Most febrile neutropenic patients will have indwelling catheters in place for vascular access.
In general, these may be left in place unless there is evidence of tunnel infection or documented infection caused by *Bacillus* species, *Corynebacterium jeikeium*, *S. aureus*, *P. aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, or *Candida* species. Rotation of parenteral therapy through all lumens of multilumen catheters is also recommended.

Two general schemes of intravenous antibiotic therapy are used: monotherapy or combination therapy. Combination therapy is subdivided into regimens that do or do not contain a glycopeptide (i.e., vancomycin, or teicoplanin when available). Inclusion of agents such as linezolid or quinupristin-dalfopristin in empirical regimens has not been well studied and is not recommended.

**Combination therapy.** When combination regimens are being chosen, a decision regarding the initial inclusion of a glycopeptide needs to be made. If a glycopeptide is not deemed necessary, a combination regimen will usually consist of an aminoglycoside (amikacin, gentamicin, or tobramycin) plus an extended-spectrum cephalosporin (cefepime or ceftazidime), an antipseudomonal penicillin (piperacillin-tazobactam or ticarcillin-clavulanate), or a carbapenem (imipenem or meropenem). Combinations of 2 β-lactam agents have been used but have fallen out of favor because of increased potential for the emergence of resistance. When vancomycin is deemed necessary, any of the agents listed above can be combined with it, with or without an aminoglycoside. Combinations that include a quinolone should be used only for patients who have not received quinolone prophylaxis.

The advantages of combination therapy include potential synergistic activity against some organisms and a reduction in the emergence of drug-resistant strains during therapy, although data regarding this issue are conflicting. The major disadvantages are increased toxicity (e.g., nephrotoxicity, otoxicity, and rashes) and drug-drug interactions.

**Monotherapy.** Comparative studies have shown no significant differences between the outcomes of monotherapy and combination regimens when used empirically [3]. Agents recommended for monotherapy include cefepime and ceftazidime, among the cephalosporins (although resistance to ceftazidime has increased considerably at many institutions), and the carbapenems imipenem and meropenem (but not ertapenem) [19–21]. The quinolones are not recommended for monotherapy, although the potential of some newer quinolones (gatifloxacin and moxifloxacin) for monotherapy for low-risk febrile neutropenic patients is being evaluated [18]. Aminoglycosides should not be used as single agents to treat patients with neutropenia under any circumstances [22]. The fixed combination piperacillin-tazobactam administered as a single agent has been less well evaluated but might be potentially useful for some patients [23–25]. Patients receiving monotherapy should be closely monitored for treatment response, adverse events, superinfections with organisms such as methicillin-resistant *S. aureus* and methicillin-resistant *Staphylococcus epidermidis*, vancomycin-resistant enterococci, and *S. maltophilia*, and the development of resistance while undergoing therapy [26]. It may be prudent to administer combination therapy to patients with complex, tissue-based infections and those with polymicrobial infections (pneumonia, perirectal infections, or enterocolitis) and monotherapy to patients with unexplained fever or simple infections [27].

**MANAGEMENT DURING THE FIRST WEEK OF THERAPY**

To determine the efficacy of the initial regimen, it is generally necessary to administer it for 3–5 days. Subsequent treatment and its duration will depend on the nature of the infection (i.e., whether it is pneumonia, bacteremia, or unexplained fever) and on whether the patient is in a low-risk or high-risk subset. Modification of the initial regimen before completion of 3 days of treatment is indicated if there is clinical deterioration or if it is mandated by microbiological information from a positive culture result.

If defervescence is achieved within 3–5 days, but no specific etiology has been established, low-risk patients can be discharged with treatment with an oral fluoroquinolone. High-risk patients should receive the initial regimen for at least 7 days before discontinuation of therapy. If a causative pathogen is identified, therapy can be adjusted to provide optimal coverage, but broad-spectrum coverage needs to be maintained to avoid breakthrough infections. Antibiotic treatment should be continued for a minimum of 7 days and/or until culture results indicate a microbiological response, infection has resolved at all sites, and the patient is asymptomatic. For documented infections, it is desirable for the neutrophil count to have risen to >500 cells/mm$^3$ before therapy is stopped. Careful monitoring is necessary if antibiotic therapy is stopped for patients with persistent neutropenia.

If fever persists for >3–5 days, the patient needs to be reassessed for the development of a drug-resistant organism or a new site of infection (e.g., an abscess or at a catheter site). Various tests, including additional cultures, radiographic studies, and, on occasion, invasive procedures, ought to be part of the reassessment. If this reassessment reveals a cause of the fever, a change in therapy should be made accordingly (e.g., strengthening antimicrobial coverage against gram-negative, gram-positive, or anaerobic organisms). If reassessment does not yield a cause, the addition of empirical antifungal therapy with or without modification of the antibacterial regimen is generally appropriate. This generally consists of a polyene (a standard or a lipid formulation of amphotericin B), particularly if a mold infection is suspected and for patients who received azole antifungal prophylaxis. Newer agents (i.e., voriconazole)
are being evaluated for empirical antifungal therapy but have not yet received US Food and Drug Administration approval for this indication [28, 29].

SUBSEQUENT MANAGEMENT AND DURATION OF THERAPY

Recovery from neutropenia is the most important factor influencing the duration of therapy, in the opinion of most (but not all) authorities [7, 30]. Therapy can be stopped if no specific infection has been documented, the neutrophil count has increased to ≥500 cells/mm^3 for 2 consecutive days, and the patient has been afebrile for at least 48 h. Therapy can also be discontinued if the patient is afebrile but still neutropenic, provided that close monitoring can be ensured. When a specific infection has been documented, appropriately adjusted therapy should be continued until the neutrophil count has recovered or improved, the patient has been afebrile for ~4 days, and there is clinical, microbiological, and radiographic evidence of resolution. Patients with persistent neutropenia should be treated for at least 2 weeks. Empirical antifungal therapy can be discontinued according to the same rationale mentioned above. Treatment of documented or strongly suspected fungal infections will depend on the specific fungal pathogen and the nature and the site of the infection. Empirical antiviral therapy is not recommended. The choice of specific therapy or preemptive therapy will depend on the specific pathogen being targeted. The antiviral armamentarium is expanding and includes newer agents such as cidovir, valganciclovir, and fomiviren. During winter months, infections with respiratory syncytial virus and influenza or parainfluenza viruses can put hematopoietic stem cell transplant recipients and some patients with hematologic malignancies at serious risk. These infections can be prevented or treated with suitable agents, such as ribavirin, zanamivir, oseltamivir, rimantidine, or amantidine. These strategies have been shown to have an impact on overall morbidity and mortality [31, 32].

The evaluation of patients who remain febrile after the resolution of neutropenia should focus on occult or undiagnosed infections of a fungal (e.g., chronic systemic infections with Candida or Aspergillus species or other molds, or histoplasmosis), mycobacterial, or viral nature, particularly for patients who have deficiencies in cell-mediated immunity and/or who are receiving immunosuppressive therapy.

OTHER CONSIDERATIONS

Colony-stimulating factors (i.e., granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) and granulocyte transfusions are not recommended for routine use. Situations in which they might be helpful include documented infections refractory to appropriate therapy, severe uncontrollable fungal infections, and specific infections, such as pneumonia [33, 34]. Human activated protein C (i.e., drotrecogin alfa) is indicated for the reduction of mortality among patients with severe sepsis associated with acute and multiple organ dysfunction [35]. It has, however, not been fully evaluated in patients with neutropenia or thrombocytopenia and can increase the risk of bleeding. Routine antibacterial and antifungal prophylaxis for all patients with neutropenia is not recommended. High-risk patients may benefit from antibacterial prophylaxis, usually with a fluoroquinolone, and antifungal prophylaxis with fluconazole or itraconazole. Prophylaxis with trimethoprim-sulfamethoxazole (or an alternative agent in patients allergic to this agent) is recommended for all patients at risk for infection with Pneumocystis jiroveci. All prophylaxis should be given for the shortest duration possible.

CONCLUSIONS

Guidelines provide recommendations based on the best available evidence. They are not absolute or mandatory. They should not be considered to be legally binding. Finally, they should be revised at appropriate intervals, as new data become available.

References