GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

1997 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Unexplained Fever

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This is the first in a series of practice guidelines commissioned by the Infectious Diseases Society of America through its Practice Guidelines Committee. The purpose of these guidelines is to provide assistance to clinicians when making decisions on treating the conditions specified in each guideline. The targeted providers are internists, pediatricians, and family practitioners. The targeted patients and setting for the fever and neutropenia guideline are hospitalized individuals with neutropenia secondary to cancer chemotherapy. Panel members represented experts in adult and pediatric infectious diseases and oncology. The guidelines are evidence-based. A standard ranking system was used for the strength of the recommendations and the quality of the evidence cited in the literature reviewed. The document has been subjected to external review by peer reviewers as well as by the Practice Guidelines Committee and was approved by the IDSA Council. An executive summary, algorithms, and tables highlight the major recommendations. The guideline will be listed on the IDSA home page at http://www.idsociety.org.

—Peter A. Gross, MD for the IDSA Practice Guidelines Committee

Executive Summary

Definitions

Fever: A single oral temperature of >38.3°C (101°F); or ⩾38.0°C (100.4°F) over at least 1 hour.

Neutropenia: Neutrophil count, <500/mm^3 or <1,000/mm^3 with predicted decline to ⩽500/mm^3.

Evaluation: Cultures of blood (peripheral and catheter), lesions, and diarrheal stools; chest radiograph; complete blood count; determinations of levels of transaminases, Na, K, creatinine, and blood urea nitrogen. Other tests as indicated.

Guidelines for Treatment

Initial antibiotic therapy: One of three regimens.

- If vancomycin is needed (criteria given):
  1. Vancomycin + ceftazidime
- If vancomycin is not needed:
  2. Monotherapy: ceftazidime or imipenem (cefepime or meropenem)

  or
  3. Duotherapy: aminoglycoside + antipseudomonal β-lactam.

Afebrile within first 3 days of treatment:

- If no etiology identified:
  Low risk (defined): change to oral antibiotic (cefixime or quinolone).
  High risk (defined): continue same antibiotics.
- If etiology identified: adjust to most appropriate treatment.

Persistant fever during first 3 days of treatment:

- Reassess on day 4 or 5.
  If no change: continue antibiotics; consider stopping vancomycin if cultures are negative.
  If progressive disease: change antibiotics.
  If febrile on days 5–7: add amphotericin B with or without antibiotic changes.

Duration of antibiotic therapy:

Afebrile by day 3:

- If absolute neutrophil count, ⩾500/mm^3 by day 7: stop after 7 days.
- If absolute neutrophil count, <500/mm^3 by day 7:
  Low risk: stop when afebrile for 5–7 days.
  High risk: continue antibiotics.

Persistent fever:

- If absolute neutrophil count, ⩾500/mm^3: stop after 4–5 days, if absolute neutrophil count is >500/mm^3: reassess.

These guidelines are part of a series of updated and new guidelines from the IDSA that will appear in *CID*.

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- If absolute neutrophil count, $<500/mm^3$: continue for 2 weeks, reassess and stop if no disease sites.

Use of antivirals: Not routine.

Use of colony-stimulating factors: Not routine; consider in certain cases with predicted worsening of course (defined).

Antibiotic prophylaxis in afebrile neutropenic patients:

- Not routine, except for *Pneumocystis carinii* pneumonitis prophylaxis.

Economics issues: Suggestions for cost containment.

Introduction

This paper is a revision and an update of a 1990 report by the Infectious Diseases Society of America (IDSA), which provided guidelines for the antimicrobial management of febrile episodes in severely neutropenic patients [1]. Although most of the information and recommendations made in that report are still valid, treatment and preventive measures have evolved, and new problems have emerged in the management of the immunocompromised host. New issues to be addressed in this revision are: (1) the increasing frequency of infections due to antibiotic-resistant bacteria such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus,* and *Streptococcus pneumoniae* that is resistant to penicillin and cephalosporins; (2) the use of immunomodulators such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF); (3) the use of oral antibiotics and outpatient management; and (4) approaches to cost containment in the treatment of febrile neutropenic patients.

The guidelines that follow are general and must be applied wisely with respect to individual variations and types of infections, settings where patients are being treated, antimicrobial susceptibility patterns, underlying causes of neutropenia, and expected time to recovery. The recommendations made herein are based on scientific publications and peer-reviewed information that has been formally presented at national or international meetings, whenever possible. When firm recommendations cannot be made, usually because adequate scientific data are lacking, the Guidelines Panel of the IDSA has offered suggestions based on the consensus of its members, all of whom have extensive experience in the treatment of neutropenic patients.

Table 1. Categories reflecting the strength of each recommendation for or against the use of antimicrobial agents in febrile neutropenic patients.

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

NOTE. Data are from [4].

Table 2. Categories indicating the quality of evidence on which recommendations for antimicrobial therapy in febrile neutropenic patients are made.

Grade	Definition
I	Evidence from at least one properly randomized controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees

NOTE. Data are from [4].

These guidelines have been derived predominantly from knowledge of and experience with the hematopoietic and lymphoproliferative malignancies but can be applied in general to febrile neutropenic patients with other neoplastic diseases.

Members of the Panel have indicated their estimate of the validity of a particular recommendation or statement by the use of the weighting system described in other consensus reports [2–4]. Basically, a ranking of A through E is used to reflect the *strength* of the recommendation (table 1), and roman numerals I through III (table 2) are used to show the *quality of evidence* forming the basis for a specific comment or recommendation. We emphasize that no specific scheme, no specific drug or combination of drugs, and no specific period of treatment can be unequivocally applied to all febrile neutropenic patients. The essentials for optimal patient care include meticulous attention to detail, repeated examination, thoughtful consideration of the microbiological data, and recognition of institutional trends. When possible, it is advisable to involve an infectious diseases specialist who is knowledgeable and interested in infections of the immunocompromised host. It is imperative that patients be considered as individuals and that guidelines herein be adapted or modified as needed for the optimal benefit of the patient.

Clinical Features of the Neutropenic Host

Between 48% and 60% (or more) of neutropenic patients who become febrile have an established or occult infection, and ~16%–20% (or more) of patients with neutrophil counts of $<100/mm^3$ have bacteremia [5–7]. With the onset of fever, bacteremia is most frequently due to aerobic gram-positive cocci (in particular, coagulase-negative staphylococci, viridans streptococci, or *S. aureus*) or aerobic gram-negative bacilli (especially *Escherichia coli, Klebsiella pneumoniae,* or *Pseudomonas aeruginosa*) (table 3). Fungi are common causes of secondary infections among neutropenic patients who have received courses of broad-spectrum antibiotics but, on occasion, these organisms can be the cause of primary infection. Neutropenic patients are difficult to evaluate because a marked

Table 3. Bacterial causes of febrile episodes in neutropenic patients.

Common	Intermediately frequent	Uncommon
Gram-positive cocci and bacilli		
Staphylococcus		*Bacillus* species
Coagulase positive (*S. aureus*)		*Listeria monocytogenes*
Coagulase negative (*S. epidermidis* and others)		*Stomatococcus mucilagnosus*
Streptococcus		
S. pneumoniae		
S. pyogenes		
Viridans group		
Enterococcus faecalis/faecium		
Corynebacterium species		
Gram-negative bacilli and cocci		
Escherichia coli	*Enterobacter* species	*Flavobacterium* species
Klebsiella species	*Proteus* species	*Chromobacterium* species
Pseudomonas aeruginsa	*Salmonella* species	*Pseudomonas* (other than *P. aeruginosa*)
	Haemophilus influenzae	*Legionella* species
	Acinetobacter species	*Neisseria* species
	Stenotrophomonas maltophilia	*Moraxella* species
	Citrobacter species	*Eikenella* species
		Kingella species
		Gardenerella species
		Shigella species
		Erwinia species
		Serratia marcescens
		Hafnia species
		Flavimonas oryzihabitans
		Achromobacter xylosoxidans
		Edwardsiella species
		Providencia species
		Morganella species
		Yersinia enterocolitica
		Capnocytophaga species
Anaerobic cocci and bacilli		
	Bacteroides species	*Peptococcus* species
	Colstridium species	*Veillonella* species
	Fusobacterium species	*Peptostreptococcus* species
	Propionibacterium species	

decrease in the number of neutrophils is associated with a diminished inflammatory response. Therefore, the signs of inflammation are muted, requiring special consideration during history-taking and physical examination.

Relatively few anatomical sites are affected, and the cause of these infections is limited to relatively few types of organisms. The primary sites of infection often include the alimentary tract, where cancer chemotherapy–induced mucosal damage allows invasion of opportunistic organisms. However, patients with chronic hereditary neutropenia tend to have upper respiratory tract infections, periodontal infections, and skin infections in patterns different than those for patients with cytotoxic therapy–induced neutropenia. Similarly, damage to the integument by invasive procedures, such as placement of vascular access devices, may serve as a portal for infection.

Definitions

The precise definition of fever and neutropenia may vary slightly from center to center. In general, a temperature clearly above the normal temperature for the patient constitutes a febrile state. A single oral temperature of $\geq$38.3°C (101°F) in the absence of obvious environmental causes is usually considered fever. A temperature of $\geq$38.0°C (100.4°F) over at least 1 hour indicates a febrile state. This definition has also been recommended for use in studies to evaluate drugs for the treatment of febrile neutropenic patients [8]. It is important to avoid the use of a rectal thermometer in neutropenic patients. Although uncommon, a neutropenic patient who is afebrile but who has signs and symptoms compatible with infection (e.g., abdominal pain) should be considered at risk for infection. For example, infections due to *Clostridium septicum* may occur in neutropenic patients without initial fever.

When the neutrophil count decreases to $<$1,000 cells/mm^3, increased susceptibility to infection can be expected, with the frequency and severity generally inversely proportional to the neutrophil count [5, 6]. Patients with neutrophil counts of $\leq$500/mm^3 are at considerably greater risk for infection than those with counts of 1,000/mm^3, and patients with counts of $\leq$100/mm^3 are at greater risk than those with counts of

500/mm^3. In addition to the number of circulating neutrophils, the rate of decline in count to low levels and the duration of neutropenia are important determinants of infection. A rapid decrease in the neutrophil count and protracted neutropenia (neutrophil count, $<$500 cells/mm^3 for 10 days) are major risk factors for impending infection [5, 9]. In addition to quantitative changes in neutrophil counts, abnormalities of phagocytic function or other deficits in the immune response may further increase the risk for infection in a neutropenic host.

Evaluation

Empirical administration of broad-spectrum antibiotics is necessary for febrile neutropenic patients because the currently available diagnostic tests are not sufficiently rapid, sensitive, or specific for identifying or excluding the microbial cause of a febrile episode. If untreated, these infections may be rapidly fatal in the neutropenic host. Although molecular diagnostic technology provides considerable promise, it has added little useful support to the immediate evaluation of febrile neutropenic patients to date.

Physicians should attempt to relate the day of the onset of fever to the day of cytotoxic therapy dated from the first day of the last cycle of chemotherapy. This information permits an estimate of the expected duration of neutropenia. In addition, some physicians believe that in the absence of a definable clinical focus of suspected infection, a fever observed within 6 hours of the administration of a blood product is less likely to be of infectious origin.

A search should be undertaken for subtle signs and symptoms of inflammation at the sites most commonly infected. These sites are the periodontium; pharynx; lower esophagus; lung; perineum, including the anus; skin lesions; bone marrow aspiration sites; the eye (fundoscopic); vascular catheter access sites; and tissue around the nails. Specimens for culture should be collected during or immediately after an interview for historical information and physical examination. Two cultures of blood for bacteria and fungi should be performed for all patients.

If a central venous catheter is in place, some authorities recommend that blood samples for culture are obtained from each lumen as well as from a peripheral vein (C, III). Other investigators are of the opinion that only a culture of blood from a peripheral venipuncture is adequate [10]. Quantitative blood cultures, although not necessarily recommended routinely for patients, may be helpful for comparing venous catheter and peripheral vein specimens [11]. If a catheter entry site is inflamed or draining, exuding fluid should be examined by gram staining and culture for bacteria and fungi. If such lesions are persistent or chronic, stains and cultures for nontuberculous mycobacteria should be obtained [12].

Very little clinically useful information is gained from performing routine cultures of the anterior nares, oropharynx, urine, and rectum when lesions or disease processes are absent. However, for infection control purposes, anterior nasal cultures may reveal colonization with methicillin-resistant *S. aureus,* penicillin-resistant pneumococcus, or *Aspergillus* species; and rectal cultures may yield *P. aeruginosa,* multidrug-resistant gram-negative bacilli, or vancomycin-resistant enterococci. Such results may be useful collectively for infection control.

Diarrheal stools believed to be of infectious etiology should be tested for *Clostridium difficile* toxin and for bacteria (species of *Salmonella, Shigella, Campylobacter, Aeromonas/Plesiomonas,* and *Yersinia*), viruses (rotavirus or cytomegalovirus), or protozoa (*Cryptosporidium* species). Identification of these organisms is important for the prevention of nosocomial transmission. Some investigators suggest testing first for *C. difficile* toxin; and if this test is negative, additional studies should be considered. Urine cultures are indicated if signs or symptoms of urinary tract infection exist, a urinary catheter is in place, or the urinalysis results are abnormal. Pyuria may be absent in the presence of urinary tract infection in neutropenic patients. Examination of CSF is not recommended as a routine procedure but may be considered if CNS infection is suspected; however, meningeal inflammation and pleocytosis may be absent in neutropenic patients with meningitis. The performance of cultures and stains of CSF for bacteria and fungi may be valuable if such infections are suspected. Chest radiographs should be obtained whenever any signs or symptoms of respiratory tract abnormality are present, and a baseline radiograph is helpful for neutropenic patients who subsequently develop respiratory symptoms or evidence of an infiltrate. Skin lesions suspected of being infected should be aspirated or biopsied for cytology, gram staining, and culture [13].

Complete blood counts and determinations of the levels of serum transaminases, sodium, potassium, creatinine, and urea nitrogen are needed to plan supportive care and to monitor for the possible occurrence of drug toxicity. These tests should be done at least every third day during the course of intensive antibiotic therapy. The use of some drugs, such as amphotericin B, will require more frequent measures of electrolyte and creatinine levels.

Imaging techniques provide powerful aids in the identification of infectious processes. Ultrasonography, CT, MRI, and radionuclide imaging are often useful in the care of febrile neutropenic patients, especially those with persistent fever or signs of infection. However, it is beyond the scope of this report to deal with specific indications for these studies. Even with the most skilled physicians and with state-of-the-art diagnostic capabilities, infection may not be recognizable in some neutropenic patients who actually are infected [14].

Initial Antibiotic Therapy

Because of the high risk of life-threatening bacterial infections, all febrile patients with neutrophil counts of $<$500/mm^3 and those with counts of 500–1,000/mm^3 in whom a further decrease can be anticipated should be treated with broad-spectrum bactericidal antibiotics promptly by the intravenous route and in maximal therapeutic dosages (A, II). Afebrile patients who are profoundly neutropenic (neutrophil count, $<$500/mm^3)

but have signs or symptoms compatible with an infection should receive empirical broad-spectrum antibiotics.

Concomitant polymicrobial and sequential infections are not uncommon. Systemic fungal infections, especially candidiasis and aspergillosis, often occur during the course of prolonged broad-spectrum antibiotic therapy.

Patients who receive broad-spectrum antibiotics may have a sufficient reduction in the number of bacteria in the intestinal flora that synthesize menaquinones, especially *E. coli* and *Bacteroides fragilis,* to cause hypoprothrombinemia and bleeding [15, 16]. The administration of oral vitamin K should be considered for those patients receiving certain broad-spectrum antibiotics, where antagonism of prothrombin carboxylase might occur, or for those with evidence of a bleeding tendency due to vitamin K deficiency (B, II).

In selecting the initial antibiotic regimen, physicians should consider the type, frequency, and antibiotic susceptibilities of the bacterial isolates found in similar patients at the local hospital. Special circumstances, such as drug allergy or organ (e.g., renal or hepatic) dysfunction, may limit the use of certain antibiotics. Combinations of drugs such as cisplatin, amphotericin B, cyclosporine, and aminoglycosides should be avoided, if possible, because of additive renal toxicity. Drug plasma concentrations should be monitored when prediction of therapeutic success and toxicity (e.g., aminoglycosides causing renal failure) is needed.

During the past decade there have been changes in the organisms that cause infection in neutropenic patients. Historically, infection has been clinically documented in only ~48%–60% of febrile episodes, and infection has been microbiologically documented in only one-half of these episodes. In the 1990s, sites of infection have commonly been defined less frequently, especially in patients receiving oral prophylactic antibiotics. Gram-positive organisms now account for ~60%–70% of microbiologically documented infections. Many of these gram-positive organisms may be methicillin-resistant and hence are susceptible only to vancomycin and teicoplanin. These infections are often more indolent (e.g., those due to coagulase-negative staphylococci or *Corynebacterium jeikeium*), and a few days' delay in administration of specific therapy may not be detrimental, although it may prolong hospitalization. Other resistant organisms (*S. aureus,* viridans streptococci, and pneumococci) may cause fulminant infections that result in serious complications or death if they are not treated promptly [17].

Vascular access devices (e.g., Hickman-Broviac catheters or subcutaneous ports) may be left in place during antibiotic treatment in most patients, even if a local entry-site infection or catheter-related bacteremia is detected (A, II). *S. aureus* and coagulase-negative staphylococci are the most frequent causes of catheter-associated infections [18, 19], and these infections often respond to parenteral antibiotic therapy, without removal of the catheter, unless a catheter-tunnel infection has become established (B, II). Catheter-related infections due to *S. aureus* do not respond to antibiotics alone as well as do coagulase-negative staphylococcal infections; therefore, catheter removal may be required for cure of the infection if the response to antibiotics is slow. Evidence of a subcutaneous-tunnel or periport infection, septic emboli, hypotension associated with catheter use, or a nonpatent catheter is an indication for removal of the catheter and prompt administration of antibiotics (A, II).

Catheter removal is also advisable for patients with atypical mycobacterial infections [20] (A, II). Bacteremia due to *Bacillus* species, *P. aeruginosa,* or *C. jeikeium,* and fungemia due to *Candida* species [21] often respond poorly to antimicrobial treatment, and removal of the line is recommended (A, II). Established infections with *Stenotrophomonas maltophilia* and *Acinetobacter* species also often require removal of the infected catheter.

Administration of antibiotics through each lumen of the involved catheter is suggested to avoid treatment failure due to microbial sequestration (B, III). Rotation of antibiotic delivery through multilumen catheters has been recommended. At some centers, antibiotic-containing heparin-lock solutions (''antibiotic lock therapy'') are used to supplement systemic therapy, but data are not available to assess benefits and risks of this procedure. The routine supplemental use of urokinase in patients with catheter-related infections is not recommended.

Because a large armamentarium of highly effective antibiotics is currently available (appendix 1) [22–115], it is difficult to recommend a single antibiotic or a single combination of antibiotics over all others for the initial treatment of febrile patients with neutropenia. In addition, despite the fact that rather extensive clinical studies have been conducted over the past two decades, the results from study to study are often not comparable because the definitions of infectious diseases and the criteria used to assess response to therapy vary considerably.

Although it is generally agreed that many antibiotic regimens are effective in the control of infection and no striking differences in toxicity can be identified, careful selection may enhance efficacy and minimize adverse effects. For example, several studies have indicated that not all β-lactam antibiotics are equally effective, at least at some institutions. Aminoglycosides should be avoided in patients with impaired renal function, and patients with penicillin allergy should not be given antipseudomonal penicillins or imipenem. Antibiotic resistance among gram-negative bacilli may limit the efficiency of some β-lactams at some institutions [59, 111, 116, 117]. Furthermore, some febrile episodes are caused by nonbacterial pathogens including fungi (*Candida* species or *Aspergillus* species) and viruses (herpesviruses).

Herein, we consider three general schemes, with the caveat that one may be more appropriate for certain patients and in certain institutions than are the other schemes. These schemes are single-drug therapy (monotherapy), two-drug therapy (duotherapy) without vancomycin, and vancomycin plus one or two other drugs [52, 55, 67, 103, 118] (figure 1).

Monotherapy (A, I)

Several studies have shown that for initial antibiotic regimens in the treatment of uncomplicated episodes of fever in

neutropenic patients, before the etiology of the infection is known, there are no striking differences between monotherapy and multidrug combinations, and monotherapy can be considered a standard of therapy [27, 69, 109, 119–121]. Ceftazidime or imipenem/cilastatin may be used as monotherapy in most cases. Regardless of whether monotherapy or a combination of antibiotics is used, patients must be monitored closely for nonresponse, emergence of secondary infections, adverse effects, and the development of drug-resistant organisms. Addition of other antibiotics may be necessary as the course progresses. In particular, it should be kept in mind that these drugs do not usually provide coverage for coagulase-negative staphylococci, methicillin-resistant *S. aureus,* vancomycin-resistant or vancomycin-susceptible enterococci, some strains of penicillin-resistant *S. pneumoniae,* and viridans streptococci. Ceftazidime may be used in the presence of mild or moderate renal dysfunction, without dose modification, and in patients receiving treatment with nephrotoxic drugs such as cisplatin, cyclosporine, or amphotericin B. Quinolones, such as ciprofloxacin, also have been evaluated as monotherapy in limited studies showing both favorable [64, 70] and unfavorable results [58]. Currently, quinolone monotherapy cannot be recommended for routine initial therapy.

A promising new ''fourth-generation'' cephalosporin with enhanced activity against gram-positive and gram-negative organisms, cefepime [52, 55, 67], and a new carbapenem, meropenem [103, 118], have recently been approved by the U.S. Food and Drug Administration (FDA) for use in the United States. Other drugs that have shown promise in other countries are cefpirome and cefoperazone/sulbactam.

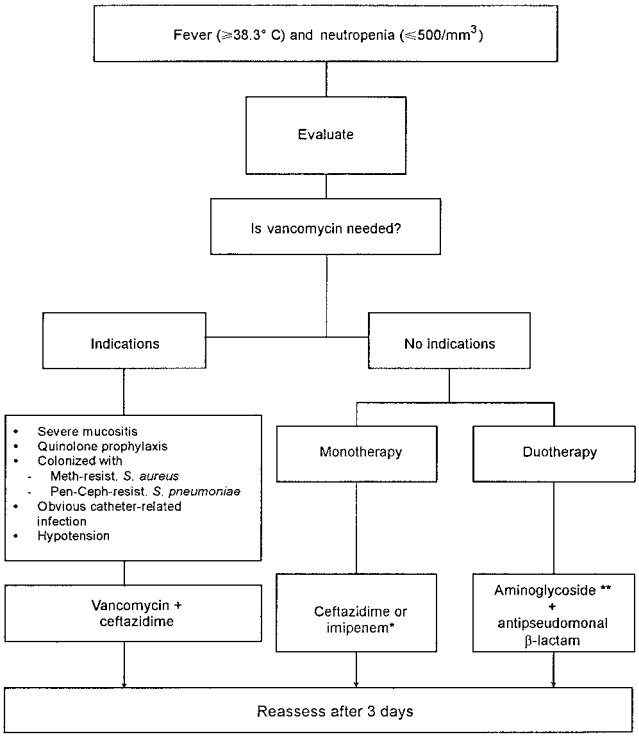

Figure 1. Guide to the initial management of the febrile neutropenic patient. See tables 1 and 2 for rating system. (*) Recent studies [52, 55, 67, 103, 118] plus U.S. Food and Drug Administration approval suggest cefepime or meropenem may be as effective as ceftazidime or imipenem as monotherapy. (**) Avoid if patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (poor blood-brain perfusion). Meth-resist. = methicillin-resistant; Pen-Ceph-resist. = penicillin-cephalosporin resistant.

Duotherapy Without Vancomycin (A, I)

Regimens containing two β-lactam antibiotics have been used at some centers and have generally been found to be as effective as the combination of an aminoglycoside plus a β-lactam drug (appendix 1). The availability of carbapenems, the frequency of methicillin-resistant gram-positive infections (especially in patients with vascular devices), and the higher cost of these regimens has made them less attractive. The exception would be the combination of aztreonam or ceftazidime plus a β-lactam drug with gram-positive activity (nafcillin or oxacillin) in institutions where methicillin-resistant, gram-positive and anaerobic infections are infrequent or are unlikely to be the cause of the fever or for patients who are allergic to other antibiotics.

The most commonly used duotherapy, excluding regimens with vancomycin, is an aminoglycoside (gentamicin, tobramycin, or amikacin) with an antipseudomonal carboxy penicillin or ureidopenicillin (ticarcillin with or without clavulanic acid, azlocillin, mezlocillin, or piperacillin) or an aminoglycoside with a third-generation antipseudomonal cephalosporin such as ceftazidime. The more recent publications summarized in appendix 1 show that generally, the two-drug combinations yield similar results when differences in experimental design, definitions, endpoints, and underlying primary diseases are taken into consideration. Advantages of combination therapy are potential synergistic effects against some gram-negative bacilli [122] and gram-positive bacteria, activity against anaerobes, and minimal emergence of resistant strains during treatment [123, 124]. The major disadvantages of combination therapy are a lack of activity against some gram-positive bacteria (the combination of ticarcillin/clavulanate and cefepime is an exception) and the nephrotoxicity, ototoxicity, and hypokalemia associated with aminoglycoside compounds and carboxy penicillins. Serum levels of the aminoglycoside should be monitored as needed, and dosages should be adjusted until optimal therapeutic concentrations are achieved.

Treatment with aminoglycosides alone is not recommended, even though a bacterium may be susceptible in vitro. Ceftazidime is the preferred cephalosporin because of its antipseudomonal activity, in contrast to ceftriaxone, which lacks activity against *P. aeruginosa.* However, some studies have shown that a single daily dose of an aminoglycoside in combination with ceftriaxone is as effective as multiple daily doses of these

drugs [88, 125] or as effective as monotherapy with ceftazidime [26].

Studies of quinolone drugs in combination with other antibiotics are limited, and no convincing conclusions can be drawn. The role of macrolide drugs such as erythromycin, clarithromycin, and azithromycin in the empirical management of febrile episodes in neutropenic patients has not been delineated.

Vancomycin Plus One or Two Drugs (A, I)

There has been considerable debate about whether vancomycin should be included in the initial antimicrobial regimen for febrile neutropenic patients. This dilemma has resulted from the increased frequency of infections caused by gram-positive organisms that are susceptible only to vancomycin. These infections can be fulminant and can lead to death in <24 hours if not promptly treated. Although vancomycin has not been shown to influence the overall mortality associated with infections due to gram-positive cocci as a group, the mortality associated with viridans streptococcal infections may be higher among patients who are not initially treated with vancomycin [126, 127]. Some strains of viridans streptococci are resistant to or tolerant of penicillin. However, there is also concern about the emergence of vancomycin-resistant organisms, especially enterococci, which are generally associated with excessive use of vancomycin in the hospital. It is suggested that hospital infection control practitioners adopt the recent recommendations of the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention for preventing the spread of vancomycin resistance [128]. The study by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada showed that vancomycin is not a necessary part of initial empirical antibiotic therapy [109]. At institutions where these fulminant infections are rare, vancomycin should not be routinely used unless the results of cultures indicate the need for this antibiotic.

At institutions where fulminant gram-positive bacterial infections are common, vancomycin may be incorporated into initial therapeutic regimens for some high-risk patients, but vancomycin therapy should be discontinued 3–4 days later if no such infection is identified. It would probably be prudent to start with vancomycin therapy in selected patients with clinically obvious, serious catheter-related infections; intensive chemotherapy that produces substantial mucosal damage (i.e., high-dose cytarabine which increases the risk for penicillin-resistant streptococcal infections, particularly those due to viridans streptococci); prophylaxis with quinolones before the onset of the febrile episode; known colonization with pneumococci that are resistant to penicillin and cephalosporins or methicillin-resistant *S. aureus;* a blood culture positive for gram-positive bacteria before final identification and susceptibility testing; hypotension or other evidence of cardiovascular impairment (A, II) (figure 2).

Several studies have evaluated vancomycin in combination with other drugs in neutropenic patients with fever; these combinations include vancomycin/imipenem [129], vancomycin/amikacin/ticarcillin [126], vancomycin/ciprofloxacin [113], vancomycin/aztreonam [112, 115], vancomycin/ceftazidime [104–107, 110], vancomycin/ceftazidime/amikacin [130], vancomycin/tobramycin/piperacillin [114, 131], vancomycin/ticarcillin [111], and vancomycin/ceftazidime/ticarcillin [111]. Because the combination of ceftazidime/vancomycin has been studied most extensively, provides broad-spectrum coverage, and has a wide margin of safety, it is recommended as the combination of choice for initial therapy when vancomycin is needed (A, I).

Teicoplanin has been evaluated as an alternative to vancomycin (appendix 1) in limited clinical trials, but the drug has not received FDA approval in the United States, and additional studies are needed to place it in proper perspective.

The Panel suggests selection of patients based on the criteria mentioned above for inclusion of vancomycin in the initial antibiotic regimen and omission of the drug for patients at lower risk. Empirical vancomycin therapy should be discontinued if initial cultures are negative for gram-positive organisms after 24–48 hours.

Management of the Antibiotic Regimen During the First Week of Therapy

At least 3 days of antibiotic treatment are usually required to determine efficacy of the initial regimen. At this point, further treatment is based on whether the fever has resolved and whether the patient's condition has deteriorated (figure 2). The conditions

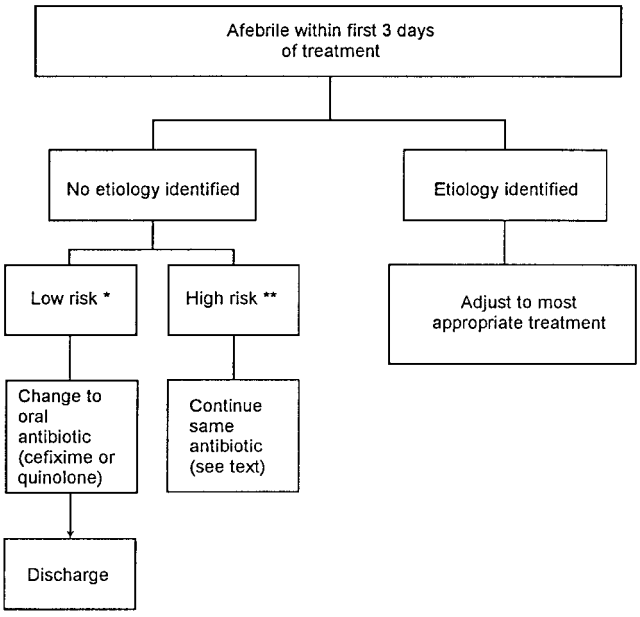

Figure 2. Management of patients who become afebrile in first 3 days of initial antibiotic therapy. (*) = Clinically well; (**) = Absolute neutrophil count, <100/mm^3; mucositis; unstable signs (see text).

of some patients may deteriorate rapidly in <3 days, necessitating reassessment of the patient and the empirical regimen.

It must be pointed out that the times-to-defervescence for febrile neutropenic cancer patients who receive antibiotic regimens including ceftazidime, ciprofloxacin, imipenem, and piperacillin (with or without aminoglycosides) are 2–7 days (median time, 5 days) [109, 110, 125, 132]. These data should be taken into account in assessing the need to change antibiotics for individual patients.

Afebrile within 3 days of treatment (A, II). If a causative microbe is identified, the antibiotic regimen can be changed, if necessary, to provide optimal treatment with minimal adverse effects and lowest cost, but broad-spectrum coverage should be maintained [133]. Antibiotic treatment should be continued for a minimum of 7 days, or until culture results indicate eradication of the causative organism, all sites of infection have resolved, and the patient is free of significant symptoms and signs. It is desirable for the neutrophil count to be $>500/mm^3$ before treatment is stopped. However, if the neutropenia is prolonged and the aforementioned responses have been achieved, consideration can be given to discontinuation of treatment before the neutrophil count of $500/mm^3$ is reached. This approach can be taken if the patient can be carefully observed, the mucous membranes and integument are intact (e.g., no mucositis, ulcerations, evidence of catheter-site infection, or bleeding sites are present), and no invasive procedures or ablative chemotherapy are impending.

If no organism is isolated, treatment with the initial antibiotic or antibiotic combination should be continued for a minimum of 7 days. More-prolonged antibiotic therapy may be required if the neutropenia persists, but the above-mentioned guidelines can be applied to terminate therapy during neutropenia when no causative agent has been found and the patient remains afebrile.

In the absence of discernible infectious disease (e.g., pneumonitis, enterocolitis, typhlitis, endocarditis, central-catheter-associated infection, or severe cellulitis) and positive cultures, treatment for compliant patients may be changed after ⩾2 days of intravenous therapy to an oral antibiotic such as cefixime [134], a quinolone such as ciprofloxacin or ofloxacin, or a drug combination of clindamycin and ciprofloxacin or amoxacillin/clavulanic acid plus pefloxacin (appendix 1), and the patient can be observed closely as an outpatient. Patients who lack signs of sepsis (chills, hypotension, and requirement for fluid resuscitation) at the time of admission, are afebrile at 48 hours, and have a neutrophil count of $\geqslant 100/mm^3$ are at low risk for complications; such patients could be discharged and continue to receive oral antibiotics [7]. Alternatively, the discharged patient may continue to receive intravenous antibiotics through a home program.

Some investigators have advocated discontinuing antibiotic therapy for patients without documented infections and with signs of early marrow recovery [135–137]. There is currently not enough evidence or experience with this approach to endorse its use.

It is important to realize that the suggestions made herein are somewhat arbitrary, and a comprehensive assessment is essential for each patient. Antibiotic therapy alone, in the presence of persistent neutropenia, may suppress but not eradicate the infection.

Persistent fever throughout the first 3 days of treatment (A, II). Fever that persists >3 days in patients for whom no infected site or organism has been identified suggests a nonbacterial infection, a bacterial infection resistant to the antibiotic(s) in use, the emergence of a second infection, inadequate serum and tissue levels of the antibiotic(s), drug fever, or infection at an avascular site (e.g., ''abscesses'' or catheters). In reassessing the patient's condition on day 4 or 5, the physician should attempt to identify one or more of these factors that might account for nonresponsiveness (figure 3). However, it should be noted that some patients with microbiologically defined bacterial infections, even when adequately treated, may require 4–5 days of therapy before defervescence occurs.

Reassessment includes a review of all previous culture results, a meticulous physical examination, chest and sinus radiographs, status of vascular catheters, reculture of blood and specific sites of infection, and diagnostic imaging of any organ suspected of infection. If possible, the determination of serum concentrations of antibiotics, especially aminoglycosides, may be useful in assessment of drug therapy. Ultrasonography and CT are generally used for reassessment. Additional studies may be done to identify relatively infrequent causes of fever such as infection with *Toxoplasma gondii,* herpes simplex virus, cytomegalovirus, Epstein-Barr virus, enterovirus, enteric protozoa, *Mycobacterium tuberculosis,* nontuberculous mycobacteria, and *Chlamydia pneumoniae* if the presence of these organisms is suggested by clinical features. However, the results of these studies must be evaluated cautiously because positive results alone may not be diagnostic of the febrile episode. If reassessment yields a cause of the fever or strongly suggests

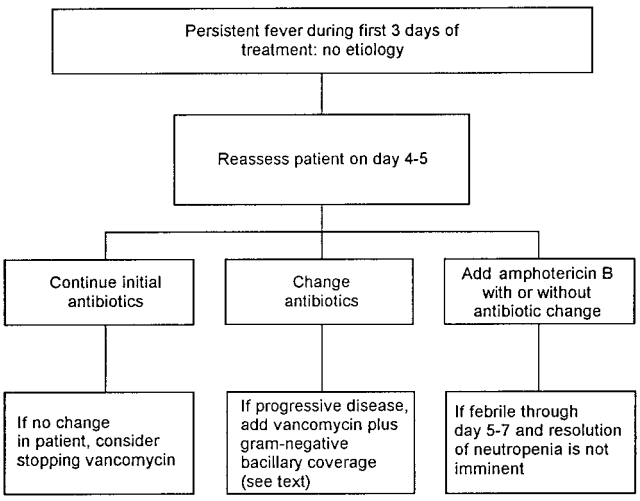

Figure 3. Treatment of patients who have persistent fever after 3 days of treatment and for whom the etiology of the fever is not found.

a cause not adequately covered by the initial antibiotic regimen, a change should be made accordingly.

If the fever persists after 4–7 days of antibiotic therapy and reassessment does not yield a cause, one of three choices of management should be made: (1) continue treatment with the initial antibiotic(s); (2) change or add antibiotic(s); or (3) add amphotericin B to the regimen, with or without changing the antibiotics. A fourth choice of withdrawing all antimicrobial drugs will not be considered as a valid option for these general guidelines, although in some highly individualized cases (such as those in which the fever is proven to be of noninfectious origin) physicians may elect to stop antibiotic therapy.

If no discernible changes in the patient's condition have occurred (i.e., the patient remains febrile but stable) during the first 4–5 days of initial antibiotic treatment and reevaluation yields no new information to the contrary, the initial antibiotic regimen could be continued (B, III). This decision would be strengthened if the neutropenia can be expected to resolve within the ensuing 5 days.

If evidence of progressive disease becomes apparent (such as the onset of abdominal pain due to enterocolitis or cecitis, new or worsening mucous membrane lesions, drainage or reactions around catheter entry and/or exit sites, pulmonary infiltrates, toxicity or other adverse effects due to the drugs, or changes in the bacteria in the mucous membranes—e.g., acquisition of *P. aeruginosa* since admission cultures were performed) during the initial antibiotic course, consideration should be given to either the addition of appropriate antibiotics or to a change to different antibiotics. Whether a change is indicated will also depend on the initial antibiotic regimen.

Resistance to commonly used antibiotic regimens has become a serious problem at some institutions, and persistent fever due to such organisms is becoming increasingly frequent. Hence, attention to the results of repeated cultures is important.

If the initial antibiotic therapy is monotherapy or duotherapy without vancomycin, vancomycin should be given if blood or site-specific isolates of coagulase-negative staphylococci, methicillin-resistant *S. aureus, Corynebacterium* species, enterococcus, or viridans streptococcus are recovered or if there is evidence of life-threatening sepsis.

If the initial treatment included vancomycin as a part of the therapeutic regimen, consideration should be given to the withdrawal of vancomycin to minimize antibacterial resistance to this important drug. By day 3, the results of admission cultures will be available to support a decision to stop vancomycin therapy. The other initial antibiotics may be continued if there is no evidence of disease progression, or if the patient is in a low-risk category (figure 2), an oral antibiotic may be given, even if the patient is febrile.

The third choice to consider is the addition of antifungal therapy (A, I), since ⩽33% [138] of febrile neutropenic patients who do not respond to a 1-week course of antibiotic therapy will have systemic fungal infections that are due in most cases to *Candida* or *Aspergillus* species. While clinicians disagree as to when, and even if, amphotericin B therapy should be introduced empirically, most are of the opinion that the patient who remains febrile and profoundly neutropenic for 1 week despite the administration of broad-spectrum antibiotics in adequate dosages is a candidate for amphotericin B therapy. Individual cases may have clinical features that will direct the use of amphotericin B earlier, later, or not at all. Such an exception might be a patient who has no discernible fungal lesion, has neither *Candida* nor *Aspergillus* species isolated from any site, and is expected to have an increased neutrophil count within a few days; in this case, amphotericin B therapy could be withheld and the patient monitored carefully, if clinically stable. Every effort should be made to determine whether or not systemic fungal infection exists (e.g., lesions should be biopsied; radiographs of chest and sinuses should be obtained; nasal endoscopy should be performed to detect sinusitis; and cultures, certain serological tests for antibody and antigens, and CT of the abdomen and chest should be performed) before amphotericin B therapy is started because the empirical decision to start treatment with the drug is not as difficult as the decision to discontinue the drug. It must be kept in mind that the administration of amphotericin B does not always prevent the emergence of fungal infection [21].

Fluconazole may be an acceptable alternative to amphotericin B as an empirical antifungal agent at institutions where mold infections (e.g., those due to *Aspergillus* species) and drug-resistant *Candida* species are uncommon, especially if the patient does not have symptoms of sinusitis and there is no radiographic evidence of pulmonary infection; however, the efficacy of fluconazole as an empirical agent has not been documented. The choice of fluconazole is less attractive if the patient has received fluconazole prophylaxis and if rates of isolation of *Candida krusei* and/or *Candida glabrata* are high in a given institution, since these species are frequently resistant to fluconazole. In patients with clinical features strongly suggestive of systemic mycoses, most physicians strongly prefer to use amphotericin B until evaluations are complete. Fluconazole may provide an alternative for some patients who have renal dysfunction or who may not be able to tolerate amphotericin B.

Duration of Antimicrobial Therapy (B, II)

The single most important determinant of the duration of therapy is the patient's neutrophil count (figure 4). If the neutrophil count exceeds 500/mm^3 by day 7 and the patient is afebrile, antibiotic therapy may be stopped at that time. If the patient becomes afebrile but remains neutropenic, the proper antibiotic course is less well defined. Some specialists recommend continuation of antibiotics if there are no signs of hematologic recovery and the patient remains profoundly neutropenic [139, 140]. This approach may increase the risk for drug toxicity and superinfection with fungi or resistant bacteria and requires prolonged hospitalization for intravenous administration of the drugs [141]. It is reasonable to stop systemic antibiotic therapy for neutropenic patients who have been afebrile for 5–7 days and appear well clinically, have no discernible infectious lesions,

and have no radiographic or laboratory evidence of infection. If antibiotic therapy is stopped during neutropenia, the patient must be monitored closely and intravenous treatment restarted immediately on the recurrence of fever or other evidence of bacterial infection [142]. Clinicians should consider continuous antibiotic therapy throughout the neutropenic period for patients with profound neutropenia (<100 cells/mm^3), mucous membrane lesions of the mouth or gastrointestinal tract, and unstable vital signs. Some experts suggest a change from the therapeutic regimen to one of the prophylactic schemes described below [139, 143], but this change is not recommended for routine use.

For patients who remain febrile and neutropenic, it has been suggested that treatment with amphotericin B be started empirically. If a systemic fungal infection has been identified, the course of antifungal therapy will be determined by the causative agent and the extent of the disease. However, if no fungal infection is found, how long should amphotericin B be administered? No firm answer can be given. It has been suggested that after daily doses of amphotericin B have been given for 2 weeks, treatment with the drug can be stopped if no discernible lesions can be found by clinical evaluation, chest radiography, and, preferably, CT of the abdominal organs [144, 145]. Antibiotics also can be stopped at this time. In exceptional cases, amphotericin B may need to be continued because of unexplained lesions or impending ablative chemotherapy. Another approach, preferred by other experts, is to terminate antibiotic therapy after ~4 days of initial antibiotic therapy if no evidence of infection is found. Under these conditions, which include close, continuous monitoring of patients, subsequent infections may occur, but most can be adequately treated [142].

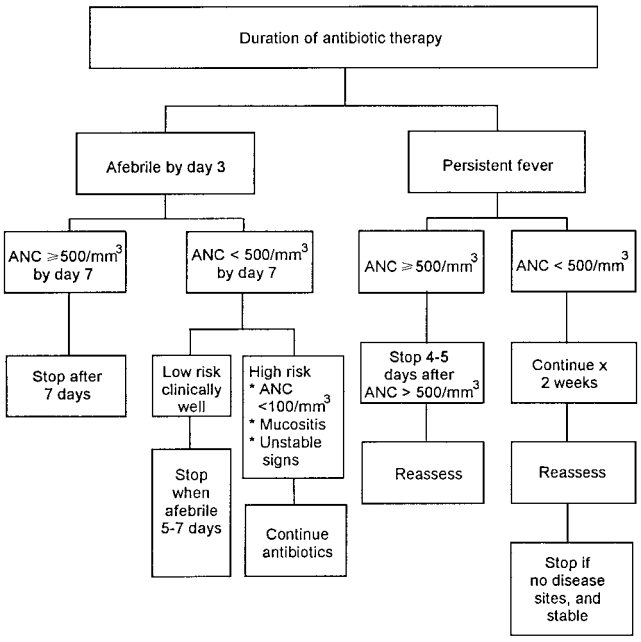

Figure 4. Duration of antibiotic therapy. ANC = absolute neutrophil count.

For patients who remain febrile after their neutrophil counts have recovered to >500/mm^3 and broad-spectrum antibacterial therapy has been administered, reassessment for undiagnosed infection should be directed at fungal infections (especially chronic systemic candidiasis, histoplasmosis, and trichosporonosis), or viral infection should be considered a possibility until proven otherwise [146]. Antibiotics can generally be stopped 4–5 days after the neutrophil count reaches $\geqslant 500$/mm^3, despite persistent fever, if no infectious lesions are identified. CT of the abdomen may be useful for the detection of systemic fungal infections. Splenic, hepatic, and/or renal lesions may become apparent or enlarged as the neutrophil count increases.

The Use of Antiviral Drugs (B, II)

There is usually no indication for the empirical use of antiviral drugs in the treatment of febrile neutropenic patients without evidence of viral disease. However, if skin or mucous membrane lesions due to herpes simplex virus or varicella-zoster virus are present, even if not the cause of fever, treatment with acyclovir is indicated. The intent is to enhance the healing of these lesions that provide portals of entry for bacteria and fungi during the neutropenic period. Lack of response or resistance to acyclovir is uncommon. Foscarnet is generally effective in treating infections due to acyclovir-resistant herpesvirus. Newer agents such as valaciclovir and famciclovir, which are better absorbed after oral administration than is acyclovir, might be indicated instead of oral acyclovir. In patients with low CD4 lymphocyte counts, pneumonitis and encephalitis may rarely be due to herpes simplex virus. Systemic infections and disease due to cytomegalovirus are uncommon causes of fever in neutropenic patients, with the exception of those who have undergone bone marrow transplantation. Cytomegalovirus infection is treated with ganciclovir or foscarnet. Ganciclovir, foscarnet, and high-dose acyclovir also have been useful for preventing cytomegalovirus infection in transplant patients. The role of a new drug, cidofovir, has not been adequately studied, and thus no comment on its use can be made at this time.

If certain viral respiratory tract infections are identified in febrile neutropenic patients, use of suitable antiviral agents is usually warranted (e.g., ribavirin for respiratory syncytial virus infection and rimantadine or amantadine for influenza A infections).

Granulocyte Transfusions (C, III)

The routine use of granulocyte transfusions is not usually advocated [147]. However, for certain patients with profound neutropenia in whom the microbiologically documented causative bacteria cannot be controlled with optimal antibiotic therapy or by administration of a granulocyte colony-stimulating factor (G-CSF), some investigators believe granulocyte transfusions may be useful. Transfusion of high counts of granulo-

cytes, obtained after administration of G-CSF to the donor, are under study and are being used by some clinicians, but at this time there is no convincing evidence of efficacy.

Use of Colony Stimulating Factors (B, II)

The administration of G-CSF (filgrastin) and GM-CSF (sargramostim) may decrease the incidence and duration of febrile neutropenic episodes after chemotherapy in some, but not all, circumstances [148–152]. The use of these agents may also enhance the rapidity of engraftment in bone marrow transplant recipients. The American Society of Clinical Oncology has published guidelines for the use of these agents with cancer chemotherapy [153].

The routine use of hematopoietic colony stimulating factors as adjuvant therapy for neutropenic patients with unexplained fevers is not recommended. The likelihood of a good outcome for typical febrile neutropenic episodes is very high with standard antibiotic therapy, and recent advances in limiting therapy for patients at low risk further reduces the potential benefits of hematopoietic colony-stimulating factors. While some limited studies have shown reduced duration of neutropenia, shorter hospital stays, and cost savings [154, 155], others have not shown significant beneficial effects [156, 157]. No study has demonstrated a decrease in infection-related mortality.

While the routine use of colony-stimulating factors is not recommended, under certain conditions where worsening of the course is predicted and there is an expected long delay in recovery of the marrow, use of these agents may be indicated. Such conditions include pneumonia, hypotensive episodes, severe cellulitis or sinusitis, systemic fungal infections, and multiorgan dysfunction secondary to sepsis. Therapy with colony-stimulating factors should also be considered for patients who remain severely neutropenic and have documented infections that fail to respond to appropriate antimicrobial therapy.

If used, a colony-stimulating factor may be withdrawn once the neutrophil count is stabilized at $>500–1{,}000/mm^3$.

Antibiotic Prophylaxis for Afebrile Neutropenic Patients

Because profound neutropenia is a dependable herald for serious bacterial infection, the opportunity for administering antimicrobial prophylaxis exists. Whatever benefit may come from the administration of necessarily broad-spectrum antibiotics is countered by the deleterious effects from toxicity, the emergence of antibiotic-resistant bacteria, and fungal overgrowth. Of special concern is the increasing prevalence of antibiotic-resistant bacteria. Over the past two decades, many studies have shown that the frequency of febrile episodes as well as of infectious diseases can be reduced with the administration of antibiotics during the early afebrile period of neutropenia. An axiom for prophylaxis is that the antibiotic should be administered over as short a period as possible and to as few patients as possible.

Afebrile patients who are expected to be profoundly neutropenic (<100 cells/mm^3) are at greater risk for developing resistant infections than those with counts of $500/mm^3$. Additional significant risk factors include lesions that break the mucous membranes and skin, indwelling catheters, instrumentation (e.g., endoscopy), severe periodontal disease, dental procedures, postobstructive pneumonia, status of malignancy or organ engraftment, and compromise of other immune responses. Personal factors such as willingness to comply with the prescribed prophylaxis, hygienic habits, and environmental (hospital or home) circumstances must also be considered.

The potential adverse effects of prophylactic antibiotics must be weighed against the benefits for each patient. Chemoprophylaxis for neutropenia has been studied most extensively in patients with malignancies, especially leukemia, and the recommendations that follow are based on the results of these studies. The experiences at specific medical centers vary and may serve as an additional guide in making a decision.

Several prophylactic regimens have been studied (table 4) [158–175]. Preservation of the anaerobic flora of the alimentary tract while eliminating potentially pathogenic aerobic gram-negative bacilli has been considered by some investigators to be especially important [176]. The term *selective decontamination* has been applied to this approach [177]. Both oral nonabsorbable and absorbable antibiotics have been evaluated.

Combinations of nonabsorbable drugs such as aminoglycosides, polymyxins, and vancomycin have been used for infection prophylaxis in the past. Prospective, randomized trials have consistently shown that orally absorbable agents such as trimethoprim-sulfamethoxazole (TMP-SMZ) and quinolones are more effective and better tolerated for this purpose. In addition, the increasing frequency of antibiotic resistance necessitates reserving aminoglycosides and vancomycin for therapeutic use.

Two types of oral absorbable antibiotics may be considered for chemoprophylaxis. These are TMP-SMZ and the quinolones.

TMP-SMZ. Early studies of prophylaxis with TMP-SMZ were reviewed in the 1990 report of the Panel [1], and more recent studies are summarized in table 4. In most of these studies, the infection rates for TMP-SMZ-treated patients were considerably lower than those for placebo-treated controls, especially among patients who were neutropenic for >2 weeks after reinduction of cytotoxic therapy for leukemia. Adverse effects were few and insignificant, but bacterial resistance has been noted. TMP-SMZ has proven effective in the prevention of *Pneumocystis carinii* pneumonia in neutropenic and nonneutropenic patients [178].

Experts differ on recommendations for the routine use of TMP-SMZ during periods of neutropenia. These differences stem in great part from the magnitude of impact the prophylaxis may have on outcome for the patient. In some studies, periods of granulocytopenia were prolonged, and the rate of fungal colonization was increased among patients receiving the antibiotics [178]. At institutions with high prevalences of fungal infections and for patients at high risk for *P. carinii* pneumoni-

Table 4. Recent studies on antimicrobial prophylaxis in neutropenic patients, 1990–1995.

Year [reference]	No. of patients	Drugs	Most effective regimen
1990 [158]	62	Ofloxacin or vancomycin/polymyxin	Ofloxacin
1991 [159]	801	Norfloxacin or ciprofloxacin	Ciprofloxacin
1990 [160]	102	Ofloxacin or co-trimoxazole	Ofloxacin
1991 [161]	51	Ciprofloxacin + erythromycin or ciprofloxacin	Equal
1993 [162]	42	TMP-SMZ or placebo	Equal
1991 [163]	60	Vancomycin* or none	Vancomycin
1994 [164]	99	Ciprofloxacin + rifampin or then vancomycin* + tobramycin	Effective when compared to historical controls
1994 [165]	551	Pefloxacin or pefloxacin + penicillin	Pefloxacin + penicillin
1992 [166]	136	Norfloxacin or pefloxacin	Pefloxacin
1991 [167]	150	Pefloxacin + vancomycin or gentamicin + colistin + vancomycin	Pefloxacin + vancomycin
1994 [168]	62	Ciprofloxacin or G-CSF or none	Ciprofloxacin
1990 [169]	73	Ciprofloxacin + ketoconazole or polymyxin e + nystatin	Ciprofloxacin + ketoconazole
1991 [170]	128	TMP-SMZ or ofloxacin	Ofloxacin
1990 [171]	59	Ofloxacin or ciprofloxacin or co-trimoxazole + colistin	Equal
1994 [172]	238	Ciprofloxacin or ofloxacin or pefloxacin	Ciprofloxacin
1993 [173]	53	Ciprofloxacin or ciprofloxacin + amoxicillin	Equal
1994 [174]	46	Fluconazole or placebo	Fluconazole
1995 [175]	53	TMP-SMZ or TMP-SMZ + ciprofloxacin	TMP-SMZ + ciprofloxacin

NOTE. See [1] for summary of studies before 1990. G-CSF = granulocyte colony-stimulating factor; TMP-SMZ = trimethoprim-sulfamethoxazole.
* Given intravenously.

tis (e.g., those with childhood leukemias, histiocytosis, or AIDS), TMP-SMZ prophylaxis may be indicated to prevent the pneumonitis and thereby indirectly affect a decision to administer the drug during periods when neutropenia may or may not occur. Disadvantages of this regimen include adverse reactions due to sulfonamide drugs, myelosuppression in some cases, development of resistant bacteria, and oral candidiasis. Furthermore, the spectrum of TMP-SMZ does not include *P. aeruginosa.*

Quinolones. The oral quinolones are being used extensively for prophylaxis in febrile neutropenic patients. The results of comparative studies of ofloxacin or ciprofloxacin vs. TMP-SMZ suggest that the quinolones are equal to or superior to TMP-SMZ in the prevention of febrile episodes of infectious origin (table 4). Unfortunately, most of the studies have included an inadequate number of patients for sound statistical analysis. However, two studies of reasonable size are of interest. One hundred twenty-eight neutropenic patients were randomized to receive ofloxacin or TMP-SMZ in the study by Kern et al. [170]; gram-negative bacillary infections were significantly less frequent in the ofloxacin group, but no difference in the frequency of gram-positive bacterial and fungal infections was noted. Thus, a disadvantage of prophylaxis with quinolones is the inadequate coverage for gram-positive bacterial infections. In another study, the addition of penicillin significantly reduced the number of episodes of bacteremia primarily via a reduction in the frequency of streptococcal bacteremia in the penicillin group [165]. The emergence of quinolone-resistant gram-negative bacilli has been demonstrated in patients given quinolone prophylaxis [179–182]. The quinoline drugs have not been approved by the FDA for infants and children. Therefore, these antibiotics should not be used as prophylaxis where resistance has already been observed or if parenteral quinolones are part of empirical therapy for febrile episodes in neutropenic patients.

Vancomycin. Intravenous vancomycin has been used as prophylaxis for catheter-related or quinolone-related gram-positive infections. While this approach may be effective, it must be strongly discouraged because of the potential for the emergence of vancomycin-resistant organisms.

Antifungal drugs. The frequency of fungal infections has increased substantially in recent years. Because these infections are often difficult to diagnose and treat successfully, antifungal prophylaxis is appropriate in institutions where fungal infections are encountered frequently. Only the absorbable agent fluconazole has been shown to reduce the frequency of both superficial and systemic infections in bone marrow transplant patients. This reduction has not been demonstrated in leukemic patients, and mortality has not been affected [183, 184]. Fluconazole's efficacy is limited by its lack of activity against *C. krusei,* some strains of *C. glabrata,* and molds. Increased frequency of colonization by *C. krusei* and *C. glabrata* has been reported in a few institutions where fluconazole has been used [185]. Only HEPA (high efficiency particulate air) filtration has had any impact on reducing mold infections. While oral itraconazole has activity against *Aspergillus* species, its unreliable absorption by very sick patients has limited its usefulness as a prophylactic agent. No prospective, randomized study has demonstrated a reduction in the frequency of aspergillosis among patients receiving itraconazole prophylaxis. In addition, a recent placebo-controlled study showed that fluconazole reduced the duration of fever and prevented oropharyngeal

candidiasis but did not affect the frequency of deep mycoses [186].

Recommendation for prophylaxis (B, I). Although TMP-SMZ prophylaxis is recommended for patients at risk for *P. carinii* pneumonitis, there is no sound consensus among the Panel members to recommend it for routine use in afebrile neutropenic patients. This lack of consensus is based, in great part, on the current concern about the emergence of antibiotic-resistant bacteria due to overuse of antibiotics. Furthermore, while TMP-SMZ prophylaxis will reduce the infection rate, it has not been shown to reduce the mortality rate. Quinolones are not recommended for routine prophylaxis because of the emergence of resistant organisms. However, in some special cases of profound and prolonged neutropenia, a quinolone may be considered for short periods of time if the potential for resistant organisms is appreciated and outweighed.

The routine use of fluconazole or other antifungal drugs is not recommended. However, in certain circumstances where the frequency of systemic infection due to *C. albicans* is high and that due to other *Candida* species is low, some physicians may elect to administer fluconazole prophylaxis.

The Panel's recommendation on routine prophylaxis is in a sense paradoxical. Data that support the efficacy of prophylaxis with TMP-SMZ and the quinolones in reducing the number of infectious episodes during the neutropenic period are adequate and would warrant a rating of (**A**, **I**) from the standpoint of efficacy alone. However, the Panel's concern about the problem of emerging drug-resistant bacteria due to extensive antibiotic use, plus the fact that such prophylaxis has not been shown to reduce mortality rates, led to the recommendation that routine prophylaxis with these antibiotics in neutropenic patients be avoided. Physicians should consider these issues in the treatment of individual patients.

Economic Issues

Driven by potential savings of $5,000 or more per episode of febrile neutropenia [187, 188], several approaches to reduce the costs of treating neutropenic patients with unexplained fever have been explored [142, 187, 189–192]. Opportunities to reduce costs have proliferated because of an expanding armamentarium of oral and intravenous antimicrobials, the emergence of hematopoietic colony-stimulating factors, the advent of home antibiotic therapy services, and data suggesting that empirical therapy can be discontinued early in certain subsets of low-risk patients [135–137]. When economic studies are conducted, it is essential that the welfare of patients be paramount. It is not sufficient to simply demonstrate statistically significant cost savings, unless the impact on morbidity and mortality is also considered. The following points should be taken into account:

1. In deciding on cost effective empirical antibiotic therapy, the consideration of drug acquisition cost by itself is of limited value. Physicians must consider the relative effectiveness, side-effect rates, and overall hospital resource consumption of the available treatments. The results of a recent decision analysis suggest that even though the triple combination of cefazolin, tobramycin, and piperacillin has a higher initial cost, this combination may result in economically attractive therapy because of reduced future costs (i.e., modification of therapy or hospitalization) [193].
2. The dose of the drug should be considered with regard to cost. Without question, the most effective dose is basic for this decision. However, there is no need to exceed the optimal dose. The recommended dose of ceftazidime is 2.0 grams every 8 hours for severe, life-threatening infections. However, in some studies, lower doses of 1.0 gram every 8 hours have been used successfully in patients with solid tumors and with expected short periods of neutropenia [88].
3. Durations of antibiotic treatment beyond the reasonable periods mentioned herein will obviously add to the cost of treatment, and at this point, would not seem warranted except in special cases.
4. The stepdown from inpatient intravenous antibiotics to outpatient oral antibiotics is usually cost efficient.
5. The expensive colony-stimulating factors are frequently used routinely, when they should be used according to well thought-out guidelines such as those of the American Society of Clinical Oncology [153]. At this time, the approved dose of G-CSF is 5 μg/(kg·d). The manufacturer recommends that treatment with G-CSF be continued until the absolute neutrophil count reaches 10×10^9/L. However, there is new evidence that a G-CSF dosage of 2.0 μg/(k·d) is as effective as the higher dose [153]. In addition, it appears that treatment may be safely discontinued when the absolute neutrophil count reaches 5×10^9/L [194]. Such dosage modifications may have important implications with respect to the economically rational use of these compounds. As to the use of G-CSF prophylactically, there is retrospective evidence implying that oral ciprofloxacin is as effective as G-CSF in preventing fever-related morbidity secondary to chemotherapy, but at one-twentieth the cost [156]. The use of TMP-SMZ prophylaxis would lead to an even greater reduction in cost. Clearly, these outcomes are highly relevant in the current climate of fiscal restraint, and they need to be confirmed by well-designed, randomized comparative trials. However, costs associated with the emergence of resistant organisms during the administration of prophylactic antibiotics must also be considered.
6. The identification of ''low-risk'' patients who can be treated as outpatients offers great promise in making significant impact on the cost of managing fever in neutropenic patients. The studies by Talcott et al. [190], Lucas et al. [7], Malik et al. [23], Rolston et al. [189], as well as other studies that have not yet been published, will provide guides to more liberal use of outpatient treatment.
7. Avoidance of the indiscriminate use of antifungal and antiviral drugs during febrile neutropenic episodes requires adherence to the policy of use only when adequate scientific data support the indication.

8. A simplified approach to performing marginal cost-effectiveness analyses is detailed in a recent report from the Centers for Disease Control and Prevention and requires a description of the program and of the health outcomes averted and the timing of these health outcomes; the rates of health outcomes and the preventable fraction of the health outcomes averted; and the costs per unit of the intervention and the costs of the health outcomes prevented and the side effects incurred [195]. Because costs differ from one location to another, the cost-effectiveness of an intervention in the management of fever and neutropenia must be determined at physicians' respective hospitals.
9. Liposomal amphotericin B costs 10–20 times more than amphotericin B deoxycholate and should be used only for the FDA-approved indication, i.e., aspergillosis that does not respond to the conventional amphotericin B preparation and for patients who cannot tolerate the conventional drug or who have renal insufficiency.

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Appendix 1. Summary of studies of antibiotics for treatment of febrile neutropenic patients: 1990–1995.

Reference	Drugs	Efficacy*	No. of patients or cases
Single and multiple drugs without vancomycin			
[22]	Imipenem/cilastatin or		70
	imipenem/cilastatin + amikacin	■	
[23]	Oral ofloxacin	○	182
[24]	Ceftazidime or	E	90
	ceftazidime + amikacin	E	
[25]	Acylaminopenicillin + aminoglycoside or	E	1,573
	cephalosporin + aminoglycoside or	E	
	acylaminopenicillin + cephalosporin	E	
[26]	Ceftazidime or	E	580
	ceftriaxone + tobramycin	E	
[27]	Cefoperazone + piperacillin or	E	429
	ceftazidime + piperacillin or	E	
	imipenem	E	
[28]	Ceftazidime or	E	696
	piperacillin + tobramycin	E	
[29]	Ceftriaxone or	E	121
	latamoxef	E	
[30]	Pefloxacin + oral amoxicillin/clavulanic acid	○	68
[31]	Ofloxacin	○	82
[32]	Ceftazidime or	E	120
	ceftazidime + teicoplanin	E	
[33]	Ceftriaxone or	E	145
	imipenem/cilastatin	E	
[34]	Oral ofloxacin or	E	60
	piperacillin + amikacin	E	
[35]	Cefoxitin + amikacin + carbenicillin or		226
	ceftriaxone + amikacin	■	
[36]	Imipenem or	■	45
	antipseudomonal penicillin + cephalosporin		
[37]	Ticarcillin/clavulanate + gentamicin	○	56
[38]	Piperacillin + amikacin or	E	69
	ceftazidime	E	
[39]	Piperacillin + flucloxacillin or	E	98
	ceftazidime + flucloxacillin	E	
[40]	Imipenem or	■	91
	cefuroxime + tobramycin		
[41]	Piperacillin + ciprofloxacin	○	41
[42]	Imipenem/cilastatin or	E	50
	ceftriaxone + gentamicin	E	
[43]	Cephalosporin + aminoglycoside	○	26
[44]	Ceftriaxone + netilmicin or	E	47
	ceftriaxone + amikacin	E	
[45]	Ceftriaxone + amikacin	○	100
[46]	Ceftriaxone + amikacin or	E	50
	ceftazidime + amikacin	E	
[47]	Ceftriaxone + amikacin or	E	100
	ceftazidime + amikacin	E	
[48]	Teicoplanin + pefloxacin or	E	40
	teicoplanin + netilmicin	E	
[49]	Imipenem or	E	100
	latamoxef + tobramycin	E	
[50]	Imipenem	○	87
[51]	Ceftriaxone or	E	42
	ceftriaxone + teicoplanin	E	
[52]	Cefepime or	E	100
	ceftazidime	E	

Appendix 1. (*Continued*)

Reference	Drugs	Efficacy*	No. of patients or cases
[53]	Cefepime or	E	78
	piperacillin + gentamicin	E	
[54]	Ceftazidime + amikacin	○	166
[55]	Cefepime or	E	133
	ceftazidime	E	
[56]	Cefepime + amikacin or	E	353
	ceftazidime + amikacin	E	
[57]	Piperacillin + amikacin or	E	170
	ceftazidime + amikacin	E	
[58]	Ciprofloxacin or		101
	piperacillin + amikacin	■	
[59]	Ceftazidime or	E	750
	imipenem or	E	
	ceftazidime + amikacin or	E	
	imipenem + amikacin	E	
[60]	Teicoplanin + piperacillin + gentamicin or	E	98
	flucloxacillin + piperacillin + gentamicin	E	
[61]	Ceftazidime + teicoplanin or	E	100
	ceftazidime + amikacin	E	
[62]	Ceftazidime + ciprofloxacin or		86
	ceftazidime + ciprofloxacin + teicoplanin	■	
[63]	Azlocillin + gentamicin or	E	108
	azlocillin + ciprofloxacin	E	
[64]	Ciprofloxacin	○	42
[65]	Teicoplanin	○	53
[66]	Ciprofloxacin + penicillin or	E	97
	piperacillin + netilmicin	E	
[67]	Cefepime	○	84
[68]	Netilmicin + β-lactam antibiotics	○	116
[69]	Piperacillin + gentamicin or	E	234
	imipenem	E	
[70]	Ciprofloxacin or	E	113
	azlocillin + netilmicin	E	
[71]	Ticarcillin/clavulanic acid + gentamicin	○	42
[72]	Trimethoprim-sulfamethoxazole + amikacin or	E	55
	imipenem/cilastatin	E	
[73]	Mezlocillin + amikacin	○	30
[74]	Piperacillin/tazobactam + gentamicin	○	44
[75]	Ceftazidime + amikacin	○	50
[76]	Ceftriaxone or	E	100
	azlocillin + netilmicin	E	
[77]	Ceftazidime	○	38
[78]	Ceftriaxone + amikacin or	■	144
	ceftazidime + amikacin		
[79]	Imipenem/cilastatin or	E	106
	ceftazidime + tobramycin	E	
[80]	Piperacillin + pefloxacin	○	40
[81]	Ceftriaxone or	E	121
	latamoxef	E	
[82]	Cefpiramide + amikacin or	E	141
	piperacillin + amikacin	E	
[83]	Ceftriaxone + amikacin	○	115
[84]	Piperacillin + netilmicin	○	103
[85]	Piperacillin + netilmicin	○	203
[86]	Ceftriaxone + teicoplanin or	E	102
	ceftazidime + teicoplanin	E	
[87]	Ceftazidime or		89
	ceftazidime + tobramycin	■	
[88]	Ceftazidime + tobramycin	○	150

Appendix 1. (*Continued*)

Reference	Drugs	Efficacy*	No. of patients or cases
[89]	Ceftriaxone	○	41
[90]	Piperacillin + gentamicin or	E	100
	aztreonam + flucloxacillin	E	
[91]	Teicoplanin + ciprofloxacin or	■	80
	piperacillin + gentamicin		
[92]	Ceftriaxone + amikacin or	E	364
	ceftazidime + amikacin	E	
[93]	Piperacillin + amikacin or	E	76
	piperacillin + amikacin + teicoplanin	E	
[94]	Ceftriaxone + amikacin or	○	101
	ciprofloxacin		
[95]	Piperacillin/tazobactam + amikacin or	■	544
	ceftazidime + amikacin		
[96]	Ceftazidime or	E	399
	imipenem	E	
[97]	Ciprofloxacin + oral clindamycin or	E	580
	aztreonam + clindamycin	E	
[98]	Piperacillin + amikacin or	E	158
	piperacillin + amikacin + teicoplanin	E	
[99]	Teicoplanin + ciprofloxacin or	■	80
	piperacillin + gentamicin		
[100]	Piperacillin + amikacin + teicoplanin or	E	114
	piperacillin + amikacin + tazobactam	E	
[101]	Cefoperazone + aztreonam	○	478
[102]	Imipenem/cilastatin	○	150
[103]	Meropenem or	E	958
	ceftazidime + amikacin	E	
Vancomycin with single and multiple drug combinations			
[104]	Ceftazidime or	E	127
	ceftazidime + vancomycin	E	
[105]	Ceftazidime + vancomycin or	E	151
	ceftazidime + teicoplanin	E	
[106]	Ceftazidime or	E	102
	ceftazidime + amikacin or	E	
	ceftazidime + vancomycin	E	
[107]	Ceftazidime + amikacin or	E	148
	ceftazidime + amikacin + vancomycin	E	
[108]	Ceftazidime + amikacin + teicoplanin or	E	527
	ceftazidime + amikacin + vancomycin	E	
[109]	Ceftazidime + amikacin or	E	747
	ceftazidime + amikacin + vancomycin	E	
[110]	Imipenem or	E	89
	ceftazidime + vancomycin	E	
[111]	Ticarcillin/clavulanate + vancomycin or	E	535
	ceftazidime + vancomycin or	E	
	ticarcillin + ceftazidime + vancomycin	■	
[112]	Aztreonam + vancomycin or	E	61
	piperacillin + gentamicin	E	
[113]	Ciprofloxacin + vancomycin	○	12
[114]	Piperacillin + tobramycin + vancomycin or	E	50
	piperacillin + tobramycin + teicoplanin	E	
[115]	Aztreonam + vancomycin or	E	300
	imipenem + vancomycin	E	

NOTE. E = equally effective in comparative study; ○ = considered effective in non-comparative study; ■ = more effective than others studied.

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