



Complete Summary

GUIDELINE TITLE

2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer.

BIBLIOGRAPHIC SOURCE(S)

Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002 Mar 15; 34(6): 730-51. [191 references]

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SCOPE

DISEASE/CONDITION(S)

Febrile neutropenia

GUIDELINE CATEGORY

Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Pediatrics
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide assistance to internists, pediatricians, and family practitioners in the treatment of febrile neutropenic patients who have cancer and other underlying myelosuppressive diseases

TARGET POPULATION

Individuals with febrile neutropenia secondary to cancer chemotherapy and other myelosuppressive diseases

INTERVENTIONS AND PRACTICES CONSIDERED

1. Evaluation including physical examination, complete blood cell count, serum creatinine, urea nitrogen, transaminases, blood cultures, and chest radiograph (when indicated)
2. Initial regimens including intravenous and oral antibiotics as monotherapy, two-drug therapy without a glycopeptide (vancomycin), and therapy with glycopeptide (vancomycin) plus one or two drugs
3. Antifungal therapy
4. Antiviral therapy
5. Granulocyte transfusions
6. Colony stimulating factors
7. Trimethoprim-sulfamethoxazole (TMP-SMZ) therapy
8. Quinolone therapy

MAJOR OUTCOMES CONSIDERED

Infection-related morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence:

I - Evidence from ≥ 1 properly randomized, controlled trial

II - Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort, or case-controlled analytic studies (preferably from ≥ 1 center); from multiple time-series; or from dramatic results for from uncontrolled experiments

III - Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guideline recommendations were prepared by a panel of experts in oncology and infectious diseases.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of recommendation:

- 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
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

COST ANALYSIS

Economic Issues

Several approaches to reducing the cost of treating neutropenic patients with unexplained fever have been explored. 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. 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.

Outpatient treatment of low-risk episodes of fever and neutropenia is substantially less costly than inpatient care and is preferred by most patients and families. The panel has attempted to encourage outpatient management when it is safe and feasible. An assumption that hospitalization of a patient is the safest course to take is not necessarily correct, in light of the Institute of Medicine's recent report that 190,000 preventable deaths occur in hospitals in the United States each year.

The dosage of a drug should be considered with regard to cost. Without question, the most effective dosage is basic for this decision. However, there is no need to exceed the optimal dosage. For example, the recommended dosage of ceftazidime is 2.0 g given every 8 h for treatment of patients with severe, life-threatening infections. However, in some studies, the lower dosage of 1.0 g given every 8 h has been used successfully to treat patients with solid tumors who have expected short periods of neutropenia. Confirmation of such dosage schemes is needed before a practice standard is established.

Duration of antibiotic treatment beyond the reasonable periods mentioned in the original guideline document will obviously add to the cost of treatment and, at the time the guideline was developed, would not seem warranted, except in special cases. The step-down from inpatient intravenous antibiotics to outpatient oral antibiotics is usually cost-efficient.

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. Under some circumstances, such as high-dose chemotherapy with either bone marrow or peripheral blood stem cell support, colony-stimulating factors may be both clinically and economically effective.

Liposomal and lipid-complex amphotericin B cost 10–60 times more than does amphotericin B deoxycholate and should be used only for the FDA-approved indications: for cases of aspergillosis that do not respond to the conventional amphotericin B preparation and for patients who cannot tolerate the conventional drug or who have or are at high risk for renal insufficiency. Avoidance of the indiscriminate use of antifungal and antiviral drugs during the febrile neutropenic episode requires adherence to the policy of use only when adequate scientific data support the indication.

Because costs differ from location to location, the cost-effectiveness of an intervention in the management of fever and neutropenia must be determined at the physicians' respective hospitals.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines were peer-reviewed by an external group of knowledgeable practitioners, reviewed and approved by the Practice Guideline Committee, and approved as published by the Infectious Disease Society of America.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The strength (A-E) and quality (I-III) of the recommendations are defined at the end of the "Major Recommendations" field.

Definitions

Fever: A single oral temperature of ≥ 38.3 degrees C (101 degrees F); or ≥ 38.0 degrees C (100.4 degrees F) for ≥ 1 hour.

Neutropenia: Neutrophil count, $< 500/\text{mm}^3$ or $< 1,000/\text{mm}^3$ with a predicted decrease to $< 500/\text{mm}^3$.

Evaluation

Initial evaluation should consist of a thorough physical examination; a complete blood cell count; measurement of serum levels of creatinine, urea nitrogen, and transaminases; and culture of blood samples (obtained from a peripheral vein and/or a catheter). A chest radiograph is indicated for patients with respiratory signs or symptoms or if outpatient management is planned. (B-III)

Treatment

Initial Regimen

Figure 1 in the original guideline document shows an algorithm for initial management of febrile neutropenic patients. First, determine whether the patient is at low or high risk for serious life-threatening infection on the basis of the criteria observed at the time of presentation (see Table 3 titled "Factors That Favor A Low Risk For Severe Infection Among Patients With Neutropenia" and Table 4 titled "Scoring Index For Identification of Low-Risk Febrile Neutropenic Patients at Time of Presentation With Fever" in the original guideline document). If the risk is high, intravenous antibiotics must be used; if risk is low, the patient may be treated with either intravenous or oral antibiotics (A-II). Second, decide whether the patient qualifies for vancomycin therapy. If the patient qualifies, begin treatment with a 2- or 3-drug combination with vancomycin plus cefepime, ceftazidime, or a carbapenem, with or without an aminoglycoside. If vancomycin is not indicated, begin monotherapy with a cephalosporin (cefepime or ceftazidime) or a carbapenem (meropenem or imipenem-cilastatin) administered

intravenously for uncomplicated cases. Two-drug combinations may be used for management of uncomplicated cases or if antimicrobial resistance is a problem. Adults selected for oral therapy may receive ciprofloxacin plus amoxicillin-clavulanate. Selection of patients for outpatient therapy must be done carefully from the low-risk group, depending on the capabilities of the medical center and doctor-patient relationship. Initial therapy with oral antibiotics alone is not recommended for children. Use current antibiotic susceptibility patterns from your local hospital laboratory as an aid in antibiotic selection.

Afebrile Patients

Figure 2 in the original guideline document presents a guide for the treatment of patients who become afebrile within 3 to 5 days of starting treatment. Modify antibiotic therapy for specific organisms, if identified, and continue use of broad-spectrum antibiotics for ≥ 7 days, until cultures are sterile and the patient has clinically recovered. If the causative organism is not found and the patient is receiving drugs intravenously and was at low risk at the onset of treatment, treatment may be changed to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children after 48 hours, if clinically preferable. The same intravenous antibiotics should be continued for high-risk patients (B-II).

If Fever Persists for >3 Days

Figure 3 in the original guideline document summarizes recommendations for patients with fever that persist for >3 days. Begin diagnostic reassessment after 3 days of treatment. By day 5, if fever persists and reassessment is unrevealing, there are three options: (1) continue administration of the same antibiotic(s) if the patient's condition is clinically stable, (2) change antibiotics if there is evidence of progressive disease or drug toxicity, or (3) add an antifungal agent if the patient is expected to have neutropenia for longer than 5 to 7 more days (B-II).

Duration of Antimicrobial Therapy

Recommendations for duration of therapy are summarized in Figure 4 in the original guideline document. The single most important determinant of successful discontinuation of antibiotics is the neutrophil count. If no infection is identified after 3 days of treatment, if the neutrophil count is ≥ 500 cells/mm³ for 2 consecutive days, and if the patient is afebrile for ≥ 48 hours, antibiotic therapy may be stopped at that time (C-III). If the patient becomes afebrile but remains neutropenic, the proper antibiotic course is less well defined. Some specialists recommend continuation of antibiotics, given intravenously or orally, until neutropenia is resolved (B-II). This approach may increase the risk for drug toxicity and superinfection with fungi or drug-resistant bacteria. It is reasonable for neutropenic patients who appear healthy clinically, who were in a low risk category at onset of treatment, who have no discernible infectious lesions, and who have no radiographic or laboratory evidence of infection, to have their use of systemic antibiotics stopped after 5 to 7 afebrile days, or sooner, with evidence of hematologic recovery. If use of antibiotics is stopped while the patient has neutropenia, the patient must be monitored closely and intravenous antibiotics restarted immediately on the recurrence of fever or other evidence of bacterial infection (see Figure 4 in the original guideline document).

One should consider continuous administration of antibiotics throughout the neutropenic period in patients with profound neutropenia (<100 cells/mm³), mucous membrane lesions of the mouth or gastrointestinal tract, unstable vital signs, or other identified risk factors (C-III). In patients with prolonged neutropenia in whom hematologic recovery cannot be anticipated, one can consider stopping antibiotic therapy after 2 weeks, if no site of infection has been identified and the patient can be observed carefully (C-III). Some experts suggest a change from the therapeutic regimen to one of the prophylactic schemes described below in the section titled "Antibiotic Prophylaxis for Afebrile Neutropenic Patients."

The duration of amphotericin B therapy varies. 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, it is not clear how long amphotericin B or other antifungal drugs should be administered. Experience is limited predominantly to amphotericin B. When neutropenia has resolved, the patient is clinically well, and computed tomography (CT) of the abdomen and chest reveals no suspicious lesions, use of amphotericin B may be discontinued. For clinically well patients with prolonged neutropenia, it is suggested that, after 2 weeks of receipt of daily doses of amphotericin B, if no discernible lesions can be found by clinical evaluation, chest radiography (or computed tomography of the chest), computed tomography of abdominal organs, use of the drug can be stopped. In the patient who appears ill or is at high risk, one should consider continuation of therapy with antibiotics and amphotericin B throughout the neutropenic episode, assuming that hematologic recovery can be anticipated.

Another approach to clinically well patients with persistent fever, preferred by other experts, is to terminate initial antibiotic therapy after approximately 4 days if no evidence of infection is found and there is no response to therapy (C-III). Under these conditions, which include very close, continuous monitoring of patients, subsequently demonstrated infections may occur, but most infections can be adequately treated. Empirical amphotericin B administration should be considered for these patients, despite discontinuation of antibiotic therapy, if fever persists for 5 to 7 days after the start of initial therapy.

For patients who remain febrile after recovery of the neutrophil count to ≥ 500 cells/mm³ and despite receipt of broad-spectrum antibacterial therapy, reassessment for undiagnosed infection should be directed at fungal (especially chronic systemic candidiasis, aspergillosis, histoplasmosis, and trichosporonosis), mycobacterial, or viral infections. Antibiotic therapy can generally be stopped despite persistent fever 4 to 5 days after the neutrophil count reaches ≥ 500 cells/mm³ if no infectious lesions are identified. Ultrasonography (or, preferably, computed tomography or magnetic resonance imaging) 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.

Use of Antiviral Drugs

Antiviral drugs are indicated only if there is clinical or laboratory evidence of viral disease.

Granulocyte Transfusions

There are no specific indications for standard use of granulocyte transfusions (C-II).

Use of Colony-stimulating Factors

Colony-stimulating factors are not recommended for routine use to treat febrile or afebrile neutropenic patients. The Infectious Disease Society of America panel supports and endorses the American Society of Clinical Oncology guidelines (see National Guideline Clearinghouse (NGC) Summary [Recommendations for the Use of Hematopoietic Colony-stimulating Factors: Evidence-based, Clinical Practice Guidelines](#) (D-II).

Antimicrobial Prophylaxis

Trimethoprim-sulfamethoxazole (TMP-SMZ) therapy is recommended at risk for *Pneumocystis carinii* pneumonitis, regardless of whether they have neutropenia (A-I). However, there is no consensus to recommend TMP-SMZ or quinolones for routine use for all afebrile neutropenic patients. This lack of consensus is based, in great part, on the current concern about the emergence of antibiotic resistant bacteria that has resulted from the overuse of antibiotics. In some special cases, for patients with profound and prolonged neutropenia, a quinolone plus penicillin or TMP-SMZ may be considered for critical periods of time, if the potential for resistant organisms is appreciated and outweighed.

Routine use of fluconazole or itraconazole for all cases of neutropenia is not recommended (D-II). However, in certain circumstances in which the frequency of systemic infection due to *Candida albicans* is high and the frequency of systemic infection due to other *Candida* species and *Aspergillus* species is low, some physicians may elect to administer antifungal prophylaxis.

The Panel's recommendations for routine prophylaxis are, in a sense, paradoxical. Data supporting the efficacy of prophylaxis with TMP-SMZ, quinolones, fluconazole, and itraconazole 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, concern about the problem of emerging drug-resistant bacteria and fungi due to extensive antibiotic use, plus the fact that such prophylaxis has not been shown to consistently reduce mortality rates, leads to the recommendation that routine prophylaxis with these drugs in neutropenic patients be avoided, with the exception of the use of TMP-SMZ for patients at risk for *Pneumocystis carinii* pneumonitis. An axiom for prophylaxis is that the antibiotic used should be administered for as short a period as possible and to as few patients as possible.

Definitions:

Strength of Recommendation:

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

D - Moderate evidence to support a recommendation against use

E - Good evidence to support a recommendation against use

Quality of Evidence:

I - Evidence from ≥ 1 properly randomized, controlled trial

II - Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort, or case-controlled analytic studies (preferably from ≥ 1 center); from multiple time-series; or from dramatic results for from uncontrolled experiments

III - Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

CLINICAL ALGORITHM(S)

Algorithms are provided for the following:

- Initial management of febrile neutropenic patients
- Management of patients who become afebrile in first three-five days of initial antibiotic therapy
- Treatment of patients who have persistent fever after three-five days of treatment and for whom the cause of the fever is not found
- Duration of antibiotic administration

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified with each recommendation (see "Major Recommendations"). When firm recommendations cannot be made, usually because of inadequate scientific data, the Panel has offered suggestions based on the consensus of its members, all of whom have extensive experience in the treatment of neutropenic patients.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate empirical administration of broad spectrum antibiotics for febrile neutropenic patients

POTENTIAL HARMS

- Side effects of antimicrobial regimens
- Emergence of antibiotic resistant organisms
- Emergence of secondary infections

Subgroups Most Likely to Be Harmed:

- Aminoglycosides should be avoided in patients with impaired renal function.
- Patients with penicillin allergy should not be given antipseudomonal penicillins or imipenem.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- It is important to note that the guidelines are general and must be applied wisely with respect to variations in individual patients and types of infection, settings in which patients are being treated, antimicrobial susceptibility patterns, underlying causes of neutropenia, and expected time to recovery.
- The authors 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.
- Despite extensive clinical studies since the 1970s, no single empirical therapeutic regimen for the initial treatment of febrile patients can be recommended. 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.
- Caspofungin, an echinocandin, has recently been approved by the U.S. Food and Drug Administration (FDA) for the treatment of invasive aspergillosis refractory to amphotericin B and itraconazole. Data are not adequate for recommendations regarding its use for treatment of febrile neutropenic patients.
- The Panel's recommendations for routine prophylaxis are, in a sense, paradoxical. Data supporting the efficacy of prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ), quinolones, fluconazole, and itraconazole 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, concern about the problem of emerging drug-resistant bacteria and fungi due to extensive antibiotic use, plus the fact that such prophylaxis has not been shown to consistently reduce mortality rates, leads to the recommendation that routine prophylaxis with these drugs in neutropenic patients be avoided, with the exception of the use of TMP-SMZ for patients at risk for *Pneumocystis carinii* pneumonitis. An axiom for prophylaxis is that the antibiotic used should be administered for as short a period as possible and to as few patients as possible.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002 Mar 15;34(6):730-51. [191 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 (revised 2002 Mar 15)

GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

SOURCE(S) OF FUNDING

Infectious Diseases Society of America

GUIDELINE COMMITTEE

The Fever and Neutropenia Guidelines Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Walter T. Hughes; Donald Armstrong; Gerald P. Bodey; Eric J. Bow; Arthur E. Brown; Thierry Calandra; Ronald Feld; Philip A. Pizzo; Kenneth V.I. Rolston; Jerry L. Shenep; Lowell S. Young

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the most current release of the guideline.

This report updates a previously issued version: 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis 1997 Sep; 25[3]: 551-73).

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Infectious Diseases Society of America (IDSA) via the Clinical Infectious Diseases journal Web site:

- [HTML](#)
- [Portable Document Format \(PDF\)](#)
- [Postscript](#)

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001 Mar 15; 32(6): 851-4.

Electronic copies: Available from the [Infectious Diseases Society of America \(IDSA\) Web site](#).

- Gross PA. Practice guidelines for infectious diseases: Rationale for a work in progress. Clin Infect Dis. 1998 May; 26(5): 1037-41.

Electronic copies: Available in Portable Document Format (PDF) from the [IDSA Web site](#).

Print copies: Available from IDSA, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 15, 1999. The information was verified by the guideline developer as of March 22, 1999. This summary was

updated on June 10, 2002. The updated information was verified by the guideline developer as of June 18, 2002.

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