Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

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This document updates and expands the initial Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guideline that was published in 1997 and first updated in 2002. It is intended as a guide for the use of antimicrobial agents in managing patients with cancer who experience chemotherapy-induced fever and neutropenia.

Recent advances in antimicrobial drug development and technology, clinical trial results, and extensive clinical experience have informed the approaches and recommendations herein. Because the previous iteration of this guideline in 2002, we have a developed a clearer definition of which populations of patients with cancer may benefit most from antibiotic, antifungal, and antiviral prophylaxis. Furthermore, categorizing neutropenic patients as being at high risk or low risk for infection according to presenting signs and symptoms, underlying cancer, type of therapy, and medical comorbidities has become essential to the treatment algorithm. Risk stratification is a recommended starting point for managing patients with fever and neutropenia. In addition, earlier detection of invasive fungal infections has led to debate regarding optimal use of empirical or preemptive antifungal therapy, although algorithms are still evolving.

What has not changed is the indication for immediate empirical antibiotic therapy. It remains true that all patients who present with fever and neutropenia should be treated swiftly and broadly with antibiotics to treat both gram-positive and gram-negative pathogens.

Finally, we note that all Panel members are from institutions in the United States or Canada; thus, these guidelines were developed in the context of North American practices. Some recommendations may not be as applicable outside of North America, in areas where differences in available antibiotics, in the predominant pathogens, and/or in health care–associated economic conditions exist. Regardless of venue, clinical vigilance and immediate treatment are the universal keys to managing neutropenic patients with fever and/or infection.

EXECUTIVE SUMMARY

Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because signs and symptoms of inflammation typically are attenuated. Physicians must be keenly aware of the infection risks, diagnostic methods, and antimicrobial therapies required for management of febrile patients through the neutropenic period. Accordingly, algorithmic approaches to fever and neutropenia, infection prophylaxis, diagnosis, and treatment have been

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established during the past 40 years, guided and modified by clinical evidence and experience over time.

The Infectious Diseases Society of America Fever and Neutropenia Guideline aims to provide a rational summation of these evolving algorithms. Summarized below are the recommendations made in the 2010 guideline update. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guideline.

GUIDELINE RECOMMENDATIONS FOR THE EVALUATION AND TREATMENT OF PATIENTS WITH FEVER AND NEUTROPENIA

I. What Is the Role of Risk Assessment and What Distinguishes High-risk and Low-risk Patients with Fever and Neutropenia?

Recommendations

1. Assessment of risk for complications of severe infection should be undertaken at presentation of fever (**A-II**). Risk assessment may determine the type of empirical antibiotic therapy (oral vs intravenous [IV]), venue of treatment (inpatient vs outpatient), and duration of antibiotic therapy (**A-II**).
2. Most experts consider high-risk patients to be those with anticipated prolonged (>7 days duration) and profound neutropenia (absolute neutrophil count [ANC] ⩽100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy (**A-II**).
3. Low-risk patients, including those with anticipated brief (⩽7 days duration) neutropenic periods or no or few co-morbidities, are candidates for oral empirical therapy (**A-II**).
4. Formal risk classification may be performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system (**B-I**).

i. High-risk patients have a MASCC score <21 (**B-I**). All patients at high risk by MASCC or by clinical criteria should be initially admitted to the hospital for empirical antibiotic therapy if they are not already inpatients (**B-I**).

ii. Low-risk patients have a MASCC score ⩾21 (**B-I**). Carefully selected low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy (**B-I**).

II. What Specific Tests and Cultures Should be Performed during the Initial Assessment?

Recommendations

5. Laboratory tests should include a complete blood cell (CBC) count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin (**A-III**).
6. At least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing central venous catheter (CVC), if present, and from a peripheral vein site; 2 blood culture sets from separate venipunctures should be sent if no central catheter is present (**A-III**). Blood culture volumes should be limited to <1% of total blood volume (usually ~70 mL/kg) in patients weighing <40 kg (**C-III**).
7. Culture specimens from other sites of suspected infection should be obtained as clinically indicated (**A-III**).
8. A chest radiograph is indicated for patients with respiratory signs or symptoms (**A-III**).

III. In Febrile Patients With Neutropenia, What Empiric Antibiotic Therapy Is Appropriate and in What Venue?

Recommendations

General Considerations

9. High-risk patients require hospitalization for IV empirical antibiotic therapy; monotherapy with an anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended (**A-I**). Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen for management of complications (eg, hypotension and pneumonia) or if antimicrobial resistance is suspected or proven (**B-III**).
10. Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia (**A-I**). These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.
11. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (**B-III**). These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum β-lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.

i. MRSA: Consider early addition of vancomycin, linezolid, or daptomycin (**B-III**).

ii. VRE: Consider early addition of linezolid or daptomycin (**B-III**).

iii. ESBLs: Consider early use of a carbapenem (**B-III**).

iv. KPCs: Consider early use of polymyxin-colistin or tigecycline (**C-III**).

12. Most penicillin-allergic patients tolerate cephalosporins, but those with a history of an immediate-type hypersensitivity reaction (eg, hives and bronchospasm) should be treated with a combination that avoids β-lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin (**A-II**).

13. Afebrile neutropenic patients who have new signs or symptoms suggestive of infection should be evaluated and treated as high-risk patients (**B-III**).

14. Low-risk patients should receive initial oral or IV empirical antibiotic doses in a clinic or hospital setting; they may be transitioned to outpatient oral or IV treatment if they meet specific clinical criteria (**A-I**).

i. Ciprofloxacin plus amoxicillin-clavulanate in combination is recommended for oral empirical treatment (**A-I**). Other oral regimens, including levofloxacin or ciprofloxacin monotherapy or ciprofloxacin plus clindamycin, are less well studied but are commonly used (**B-III**).

ii. Patients receiving fluoroquinolone prophylaxis should not receive oral empirical therapy with a fluoroquinolone (**A-III**).

iii. Hospital re-admission or continued stay in the hospital is required for persistent fever or signs and symptoms of worsening infection (**A-III**).

IV. When and How Should Antimicrobials be Modified During the Course of Fever and Neutropenia?

Recommendations

15. Modifications to the initial antibiotic regimen should be guided by clinical and microbiologic data (**A-II**).

16. Unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly (**A-I**).

17. Documented clinical and/or microbiological infections should be treated with antibiotics appropriate for the site and for the susceptibilities of any isolated organisms (**A-I**).

18. If vancomycin or other coverage for gram-positive organisms was started initially, it may be stopped after 2 days if there is no evidence for a gram-positive infection (**A-II**).

19. Patients who remain hemodynamically unstable after initial doses with standard agents for neutropenic fever should have their antimicrobial regimen broadened to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria and fungi (**A-III**).

20. Low-risk patients who have initiated IV or oral antibiotics in the hospital may have their treatment approach simplified if they are clinically stable (**A-I**).

i. An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is felt to be adequate (**A-I**).

ii. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured (**B-III**). If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients (**A-III**).

21. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source (**A-II**).

V. How Long Should Empirical Antibiotic Therapy be Given?

Recommendations

22. In patients with clinically or microbiologically documented infections, the duration of therapy is dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until ANC is $\geq$ 500 cells/mm^3) or longer if clinically necessary (**B-III**).

23. In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an increasing ANC that exceeds 500 cells/mm^3 (**B-II**).

24. Alternatively, if an appropriate treatment course has been completed and all signs and symptoms of a documented infection have resolved, patients who remain neutropenic may resume oral fluoroquinolone prophylaxis until marrow recovery (**C-III**).

VI. When Should Antibiotic Prophylaxis be Given, and With What Agents?

Recommendations

25. Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC $\leq$100 cells/mm^3 for $>$7 days) (**B-I**). Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered to be roughly equivalent, although levofloxacin is preferred in situations with increased risk for oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli is recommended (**A-II**).

26. Addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended (**A-I**).

27. Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for $<$7 days (**A-III**).

VII. What Is the Role of Empirical or Pre-emptive Antifungal Therapy and Which Antifungal Should be Used?

Recommendations

High risk

28. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days **(A-I).** Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving anti-mold prophylaxis, but switching to a different class of anti-mold antifungal that is given intravenously should be considered **(B-III)**.

29. Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography (CT) signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi (such as *Candida* or *Aspergillus* species) from any body site may have antifungal agents withheld **(B-II)**. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified.

Low Risk

30. In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended **(A-III).**

VIII. When Should Antifungal Prophylaxis be Given and With What Agents?

Recommendations

High risk

31. Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant (HSCT) recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia **(A-I)**. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives.

32. Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients ⩾13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in whom the risk of invasive aspergillosis without prophylaxis is substantial **(B-I)**.

33. Prophylaxis against *Aspergillus* infection in pre-engraftment allogeneic or autologous transplant recipients has not been shown to be efficacious. However, a mold-active agent is recommended in patients with prior invasive aspergillosis **(A-III)**, anticipated prolonged neutropenic periods of at least 2 weeks **(C-III),** or a prolonged period of neutropenia immediately prior to HSCT **(C-III)**.

Low Risk

34. Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is <7 days **(A-III).**

IX. What Is the Role of Antiviral Prophylaxis and What Virus Infections Require Antiviral Treatment?

Recommendations

35. Herpes simplex virus (HSV)–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis **(A-I).**

36. Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease **(C-III).**

37. Respiratory virus testing (including testing for influenza, parainfluenza, adenovirus, respiratory syncytial virus [RSV], and human metapneumovirus) and chest radiography are indicated for patients with upper respiratory symptoms (eg, coryza) and/or cough **(B-III).**

38. Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer **(A-II).** Optimal timing of vaccination is not established, but serologic responses may be best between chemotherapy cycles (>7 days after the last treatment) or >2 weeks before chemotherapy starts **(B-III).**

39. Influenza virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible **(A-II)**. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically **(C-III).**

40. Routine treatment of RSV infection in neutropenic patients with upper respiratory disease should not be given **(B-III).**

X. What Is the Role of Hematopoietic Growth Factors (G-CSF or GM-CSF) in Managing Fever and Neutropenia?

Recommendations

41. Prophylactic use of myeloid colony-stimulating factors (CSFs; also referred to as hematopoietic growth factors) should be considered for patients in whom the anticipated risk of fever and neutropenia is ⩾20% **(A-II).**

42. CSFs are not generally recommended for treatment of established fever and neutropenia **(B-II)**.

XI. How are Catheter-Related Infections Diagnosed and Managed in Neutropenic Patients?

Recommendation

43. Differential time to positivity (DTP) >120 min of qualitative blood cultures performed on specimens simultaneously drawn from the CVC and a vein suggests a central line–associated blood stream infection (CLABSI) **(A-II).**

44. For CLABSI caused by *S. aureus*, *P. aeruginosa,* fungi, or mycobacteria, catheter removal is recommended in addition to systemic antimicrobial therapy for at least 14 days **(A-II).** Catheter removal is also recommended for tunnel infection or port pocket site infection, septic thrombosis, endocarditis, sepsis with hemodynamic instability, or bloodstream infection that persists despite ⩾72 h of therapy with appropriate antibiotics **(A-II)**.

45. For documented CLABSI caused by coagulase-negative staphylococci, the catheter may be retained using systemic therapy with or without antibiotic lock therapy **(B-III).**

46. Prolonged treatment (4–6 weeks) is recommended for complicated CLABSI, defined as the presence of deep tissue infection, endocarditis, septic thrombosis **(A-II)** or persistent bacteremia or fungemia occurring >72 h after catheter removal in a patient who has received appropriate antimicrobials (**A-II** for *S. aureus*, **C-III** for other pathogens).

47. Hand hygiene, maximal sterile barrier precautions, and cutaneous antisepsis with chlorhexidine during CVC insertion are recommended for all CVC insertions **(A-I).**

XII. What Environmental Precautions Should be Taken When Managing Febrile Neutropenic Patients?

Recommendations

48. Hand hygiene is the most effective means of preventing transmission of infection in the hospital **(A-II).**

49. Standard barrier precautions should be followed for all patients, and infection-specific isolation should be used for patients with certain signs or symptoms **(A-III).**

50. HSCT recipients should be placed in private (ie, single-patient) rooms **(B-III).** Allogeneic HSCT recipients should be placed in rooms with >12 air exchanges/h and high-efficiency particulate air (HEPA) filtration **(A-III)**.

51. Plants and dried or fresh flowers should not be allowed in the rooms of hospitalized neutropenic patients **(B-III)**.

52. Hospital work exclusion policies should be designed to encourage health care workers (HCWs) to report their illnesses or exposures **(A-II)**.

INTRODUCTION

This guideline provides a general approach to the management of patients with cancer who have neutropenia and present with fever, and it gives special attention to antimicrobial management. It updates the IDSA document that was last revised in 2002 [1].

Fever: Etiology and Epidemiology

Fever occurs frequently during chemotherapy-induced neutropenia: 10%–50% of patients with solid tumors and >80% of those with hematologic malignancies will develop fever during ⩾1 chemotherapy cycle associated with neutropenia [2]. Most patients will have no infectious etiology documented. Clinically documented infections occur in 20%–30% of febrile episodes; common sites of tissue-based infection include the intestinal tract, lung, and skin. Bacteremia occurs in 10%–25% of all patients, with most episodes occurring in the setting of prolonged or profound neutropenia (ANC, <100 neutrophils/mm^3) [3–5].

Substantial fluctuation in the epidemiologic spectrum of bloodstream isolates obtained from febrile neutropenic patients has occurred over the past 40 years. Early in the development of cytotoxic chemotherapy, during the 1960s and 1970s, gram-negative pathogens predominated. Then, during the 1980s and 1990s, gram-positive organisms became more common (Table 1) [6–7] because of increased use of indwelling plastic venous catheters, which can allow for colonization by and entry of gram-positive skin flora [1, 6]. Currently, coagulase-negative staphylococci are the most common blood isolates in most centers; Enterobacteriaciae (eg, *Enterobacter* species, *Escherichia coli* and *Klebsiella* species) and nonfermenting gram-negative rods (eg, *Pseudomonas aeruginosa* and *Stenotrophomonas* species) are isolated less often.

Drug-resistant gram-negative bacteria species are causing an increasing number of infections in febrile neutropenic patients [5, 8–9]. In some centers, this has led to an epidemiologic trend toward a predominance of gram-negative pathogens in the neutropenic population [5, 8–10].

ESBL genes, acquired primarily among *Klebsiella* species and *E. coli* strains, confer a broad range of β-lactam antibiotic resistance [11–12]. These ESBL pathogens are often only susceptible to

Table 1. Common Bacterial Pathogens in Neutropenic Patients

Common gram-positive pathogens
Coagulase-negative staphylococci
Staphylococcus aureus, including methicillin-resistant strains
Enterococcus species, including vancomycin-resistant strains
Viridans group streptococci
Streptococcus pneumoniae
Streptococcus pyogenes
Common gram-negative pathogens
Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinetobacter species
Stenotrophomonas maltophilia

carbapenems, such as imipenem or meropenem. Carbapenemase-producing isolates of *Klebsiella* species and *P. aeruginosa* have been reported to cause infections that are resistant to carbapenems [13]. Recognition of these resistant species requires careful interpretation of organism-specific antibiograms [5–7].

In addition, resistant gram-positive pathogens, such as MRSA and VRE, have become more common and are the most prevalent resistant isolates in some centers, accounting for 20% and slightly >50% of episodes, respectively [14–15]. Penicillin-resistant strains of *S. pneumoniae* and of viridans group streptococci are less common but may cause severe infections [16]. The bacterial pathogens that cause most bloodstream infections in the setting of neutropenia are listed in Table 1.

Fungi are rarely identified as the cause of first fever early in the course of neutropenia; rather, they are encountered after the first week of prolonged neutropenia and empirical antibiotic therapy. Yeasts, primarily *Candida* species, may cause superficial infections of mucosal surfaces (eg, thrush); chemotherapy-induced mucositis, in turn, may disrupt this barrier [5], allowing *Candida* to enter the bloodstream. Deep-tissue candidiasis, such as hepatic or hepatosplenic disease, esophagitis, or endocarditis, is much less common. Molds, such as *Aspergillus*, are most likely to cause life-threatening infection of the sinuses and lungs, typically after ⩾2 weeks of neutropenia.

The majority of patients who develop fever during neutropenia have no identifiable site of infection and no positive culture results. Nonetheless, the Panel recommends that every patient with fever and neutropenia receive empirical antibiotic therapy urgently (ie, within 2 h) after presentation, because infection may progress rapidly in these patients. In the febrile neutropenic patient, substantially better outcomes can be expected with prompt initiation of the critical management pathways discussed in this document [17].

Definitions

The definitions of fever and neutropenia in this guideline are general criteria that should be used to identify patients in whom empirical antibiotic therapy must be initiated. However, these definitions are not hard-and-fast rules. Clinical variations among patients mandate that clinical judgment play a critical role in identifying which patients require antibiotics during the risk period of neutropenia, even if those patients do not meet these specific definitions.

♦ *Fever*

Fever is defined as a single oral temperature measurement of ⩾38.3°C (101°F) or a temperature of ⩾38.0°C (100.4°F) sustained over a 1-h period.

Use of axillary temperatures is discouraged, because they may not accurately reflect core body temperature. Rectal temperature measurements (and rectal examinations) are avoided during neutropenia to prevent colonizing gut organisms from entering the surrounding mucosa and soft tissues.

♦ *Neutropenia*

Neutropenia is defined as an ANC of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 h.

The term ''profound'' is sometimes used to describe neutropenia in which the ANC is <100 cells/mm^3; a manual reading of the blood smear is required to confirm this degree of neutropenia. The term ''functional neutropenia'' refers to patients whose hematologic malignancy results in qualitative defects (impaired phagocytosis and killing of pathogens) of circulating neutrophils. These patients should also be considered to be at increased risk for infection, despite a ''normal'' neutrophil count.

The primary aim of the practice guideline is to assist practitioners in making decisions about appropriate care for neutropenic patients who present with signs and symptoms of potentially serious infections [18]. The recommendations are derived from well-tested patterns of clinical practice that have emerged from cancer therapy clinical trials; modifications of these recommendations are based upon careful review of data from recent scientific publications and peer-reviewed information whenever possible. When evidence-based recommendations cannot be made because of insufficient data, the Panel has provided guidance that is based on the consensus of its members, all of whom have extensive experience in the treatment of neutropenic patients. For example, it is recommended by Panel members that neutropenic patients who are not febrile but who have new signs or symptoms that suggest infection have empirical antibiotics initiated.

During fever and neutropenia, no specific drug or combination of drugs and no specific period of treatment can be unequivocally recommended for all patients. Rather, the recommendations outlined in these guidelines are generally applicable in most clinical situations but, in some instances, will require modifications according to circumstances and local epidemiologic data. For management of most patients, the Panel recommends involvement of an infectious diseases specialist knowledgeable about infections of the immunocompromised host. It is also essential that an antimicrobial stewardship program be in place at facilities where patients with cancer are routinely treated, to ensure appropriated and judicious antimicrobial use.

A major change in the current guideline is a more structured consideration of the level of risk for serious infectious complications that a given patient with fever and neutropenia might face. This recognition of the differences in patients' levels of risk (low risk and high risk) during the febrile neutropenic period directs all recommendations regarding evaluation, therapy, venue of therapy, and prophylaxis.

Prevention of infection in neutropenic patients is also an important focus of this guideline. The bacterial, viral, and fungal

prophylaxis recommendations herein reflect the Panel's interpretations of clinical trial results. However, as newer drugs and newer methods of delivery are developed, approaches to prophylaxis will evolve. Whatever new approaches may be developed, the central issue of prophylaxis remains unchanged: a balance must be struck between effective infection prevention and the risk of antimicrobial-resistant infections caused by overuse of antibiotics.

Finally, these guidelines contain new sections on the management of indwelling CVCs and environmental precautions for neutropenic patients.

The following 12 clinical questions are addressed in the guideline:

I. What is the role of risk assessment and what distinguishes high-risk and low-risk patients with fever and neutropenia?

II. What cultures should be collected and what specific tests should be performed during the initial assessment?

III. In febrile patients with neutropenia, what empirical antibiotic therapy is appropriate and in what setting?

IV. When and how should antimicrobials be modified during the course of fever and neutropenia?

V. How long should empirical antibiotic therapy be given?

VI. When should antibiotic prophylaxis be given and with what agents?

VII. What is the role of empirical antifungal therapy and what antifungals should be used?

VIII. When should antifungal prophylaxis or preemptive therapy be given and with what agents?

IX. What is the role of antiviral prophylaxis and how are respiratory viruses diagnosed and managed in the neutropenic patient?

X. What is the role of hematopoietic growth factors (G-CSF or GM-CSF) in managing fever and neutropenia?

XI. How are catheter-related infections diagnosed and managed in neutropenic patients?

XII. What environmental precautions should be taken when managing febrile neutropenic patients?

UPDATE METHODOLOGY

Panel Composition

The IDSA Standards and Practice Guidelines Committee reconvened many members of the original guideline panel, together with additional experts in the management of patients with fever and neutropenia. The Panel included experts in infectious diseases, oncology, and HSCT in both adult and pediatric patients. The Panel members are listed as authors of this document.

Process Overview

In evaluating the evidence regarding the management of patients with fever and neutropenia, the Panel used a systematic weighting of the level and grade of the evidence for making a recommendation (Table 2) [19].

Literature Review and Analysis

For the 2010 update, the Panel completed the review and analysis of data published since 2002. Computerized literature searches of the PUBMED database were performed. The searches of the English-language literature from 2002 through July 2009 combined the terms ''ANTIBIOTICS'' and ''FEVER'' and ''NEUTROPENIA.'' Data published after July 2009 were also considered in the final preparation of the manuscript. The searches were limited to human-only studies and to specific study design or publication type: clinical trial, randomized clinical trial, meta-analysis, or practice guideline.

Guidelines and Conflict of Interest

All members of the Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Panel completed the IDSA conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Consensus Development Based on Evidence

The Panel met on >10 occasions via teleconference (including subgroup calls) and once in person to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions, distribute writing assignments, and finalize recommendations. All members of the Panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee and the Board of Directors prior to dissemination.

Revision Dates

At annual intervals, the Panel Chair, the liaison advisor, and the Chair of the Standards and Practice Guidelines Committee will determine the need for revisions to the updated guideline on the basis of an examination of the current literature. If necessary, the entire Panel will reconvene to discuss potential changes. When appropriate, the Panel will recommend full revision of the guideline to the IDSA Standards and Practice Guidelines Committee and the Board for review and approval.

Table 2. Strength of Recommendation and Quality of Evidence

Category/Grade	Definition
Strength of Recommendation	
A	Good evidence to support a recommendation for *or against* use.
B	Moderate evidence to support a recommendation for *or against* use.
C	Poor evidence to support a recommendation.
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 from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

NOTE. Adapted from [19]. Reproduced with the permission of the Minister of Public Works and Government Services Canada.

GUIDELINE RECOMMENDATIONS FOR THE EVALUATION AND TREATMENT OF PATIENTS WITH FEVER AND NEUTROPENIA

I. What Is the Role of Risk Assessment and What Distinguishes High-risk and Low-risk Patients With Fever and Neutropenia?

Recommendations

1. Assessment of risk for complications of severe infection should be undertaken at presentation of fever **(A-II)**. Risk assessment may determine the type of empirical antibiotic therapy (oral vs IV), venue of treatment (inpatient vs outpatient), and duration of antibiotic therapy **(A-II)**.
2. Most experts consider high-risk patients to be those with anticipated prolonged (>7 days duration) and profound neutropenia (ANC ⩽100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy **(A-II)**.
3. Low-risk patients, including those with anticipated brief (⩽7 days duration) neutropenic periods or no or few co-morbidities, are candidates for oral empirical therapy **(A-II).**
4. Formal risk classification may be performed using the MASCC scoring system **(B-I).**

i. High-risk patients have a MASCC score <21 **(B-I).** All patients at high risk by MASCC or by clinical criteria should be initially admitted to the hospital for empirical antibiotic therapy if they are not already inpatients **(B-I).**

ii. Low-risk patients have a MASCC score ⩾21 **(B-I).** Carefully selected low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy **(B-I).**

Evidence Summary

Risk assessment

Patients who present with fever and neutropenia may have a variety of clinical outcomes. Most receive broad-spectrum empirical antibiotics and survive the episode without major incident. A minority of patients will develop significant infections or experience other life-threatening medical events.

Numerous studies have sought to stratify patients at presentation into those with high- versus low-risk for complications of severe infection. In addition, an ever-broadening clinical experience continues to inform clinical judgment. As noted previously, in this document, the term "high risk" will refer to patients who, in the experience of clinical experts, have an increased risk for severe infection. Typically, such patients have sustained, profound neutropenia anticipated to last >1 week or are clinically unstable (eg, experience uncontrolled pain, altered mental status, or hypotension) or have significant medical co-morbidities, such as uncontrolled cancer, chronic obstructive pulmonary disease, poor functional status, or advanced age. High-risk patients also may be identified by underlying cancer (eg, acute leukemia) and/or the intensity of chemotherapy undergone (eg, induction for acute leukemia or HSCT). Furthermore, the selection of patients who may benefit the most from antimicrobial prophylaxis (see Section VI) is based upon these criteria for being at high risk, which are derived from clinical trials [20–41]. Most clinicians (including Panel members) use and understand this clinically relevant categorization of "high-risk" in the context of fever and neutropenia. Low-risk patients are clinically defined by neutropenia anticipated to last ⩽7 days, are clinically stable, and have no medical comorbid conditions.

In addition to this clinical definition, the MASCC has developed a risk assessment scheme and a well-validated scoring method that can identify subgroups of febrile neutropenic patients with low or high risk of complications and death [2, 42–44]. The MASCC score is also a means to determine which patients require prolonged hospitalization and which may be candidates for oral or once-daily IV regimens and/or for early discharge from the hospital to complete the antibiotic course as outpatients. In this document, patients with increased risk as defined by MASCC

Table 3. The Multinational Association for Supportive Care in Cancer Risk-Index Score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms[a]	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease[b]	4
Solid tumor or hematologic malignancy with no previous fungal infection[c]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms[a]	3
Outpatient status	3
Age <60 years	2

NOTE. The maximum value of the score is 26. Adapted from [43]. Reproduced with permission of the American Society for Clinical Oncology.

[a] Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

[b] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

[c] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

criteria will be referred to as "high risk by MASCC criteria." A similar distinction will be applied to low-risk patients.

The MASCC scoring system is a summation of weighted risk factors, including patient age, history, outpatient or inpatient status, acute clinical signs, the presence of medical comorbid conditions, and severity of fever and neutropenia as assessed by "burden of illness." Low-risk patients are identified by a cumulative score ⩾21 points (Table 3). A fundamental difficulty with the MASCC system is the nebulous nature of one of its major criteria: the "burden of febrile neutropenia" and symptoms associated with that burden. This may be interpreted to be a measure of how "sick" the patient appears to be on presentation. However, without a clear standardized definition of this "burden" of disease, uniform application of the MASCC tool may be confusing [45].

In a validation study of the MASCC assessment tool, the rate of serious medical complications during the course of neutropenia was only 5% among 441 febrile neutropenic adult patients initially classified as low risk [42]. Of the patients with episodes that were predicted to be low risk, 189 (43%) were eligible for oral treatment, but only 79 patients (18%) met additional stringent criteria for discharge from the hospital and receipt of outpatient therapy (clinically stable or improving and with an adequate home environment and psychosocial status) after at least 24 h of observation in hospital. Only 3 patients required re-admission to the hospital for fever or other reasons, and there were no adverse events among the carefully selected outpatient subgroup.

The Panel recommends that either the clinical judgment criteria that have been based upon data derived from published clinical trials or the MASCC assessment tool can be used to stratify risk for patients presenting with fever and neutropenia. Risk assessment should then inform decisions about the type of regimen and appropriate venue for delivery of empirical antibiotics, as well as the timing of hospital discharge [42–44, 46]. Specific definitions of high and low risk are given below.

High-Risk Patient: Patients with any of the following criteria (based on clinical trial criteria from studies assessing risk in febrile neutropenic patients) are considered to be at high risk for serious complications during fever and neutropenia. Alternatively, a MASCC score <21 may be used to define individuals at high risk using MASCC criteria. High-risk patients should initially receive IV empirical antibiotic therapy in the hospital.

♦ Profound neutropenia (ANC ⩽100 cells/mm^3) anticipated to extend >7 days

♦ Presence of any co-morbid medical problems including but not limited to:

- Hemodynamic instability
- Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea
- Gastrointestinal symptoms, including abdominal pain, nausea and vomiting, or diarrhea
- Neurologic or mental-status changes of new onset
- Intravascular catheter infection, especially catheter tunnel infection
- New pulmonary infiltrate or hypoxemia, or underlying chronic lung disease

♦ Evidence of hepatic insufficiency (defined as aminotransferase levels >5 × normal values) or renal insufficiency (defined as a creatinine clearance of <30 mL/min).

It is important to note that the duration of neutropenia is not included as a criterion for risk in the MASCC assessment scheme; however, the Panel considers it to be an important determinant. In the initial multivariate analysis that led to the development of the MASCC criteria, longer neutropenia duration was not found to be a significant risk factor for poor

outcome [43]. Nonetheless, a review of the MASCC criteria applied to a large population at one US cancer center found that patients defined as low risk by the tool "predominantly are patients with solid tumors who are receiving conventional chemotherapy as outpatients who have minimal medical co-morbidity and an expected duration of neutropenia of ≤7–10 days" [41]. The Panel has agreed that cumulative clinical experience indicates that patients in whom prolonged neutropenia is expected as a consequence of HSCT preparation or induction chemotherapy for AML should be regarded as at high risk and always hospitalized initially for fever and neutropenia. Patients receiving autologous HSCT or consolidation therapy for leukemia may also have prolonged neutropenic periods but appear to be at somewhat lower risk for serious infections. If these patients attain a MASCC score that predicts low risk, it may be reasonable to prescribe antimicrobial management accordingly.

Low-Risk Patients: Low-risk patients are those with neutropenia expected to resolve within 7 days and no active medical co-morbidity, as well as stable and adequate hepatic function and renal function. These low-risk features are most commonly found among patients with solid tumors, although not exclusively so. In general, any patient who does not strictly fulfill criteria for being at low risk should be treated according to guidelines for high-risk patients. Patients who are at low risk by MASCC criteria have a MASCC score ⩾ 21.

II. What Specific Tests and Cultures Should be Performed during the Initial Assessment?

Recommendations

5. Laboratory tests should include a CBC count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin (**A-III**).
6. At least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing CVC, if present, and from a peripheral vein site; 2 blood culture sets from separate venipunctures should be sent if no central catheter is present (**A-III**). Blood culture volumes should be limited to <1% of total blood volume (usually ~70 mL/kg) in patients weighing <40 kg (**C-III**).
7. Culture specimens from other sites of suspected infection should be obtained as clinically indicated (**A-III**).
8. A chest radiograph is indicated for patients with respiratory signs or symptoms (**A-III**).

Evidence Summary

Physical Examination

Signs and symptoms of inflammation are often attenuated or absent in neutropenic patients. Accordingly, in neutropenic patients, bacterial infections of skin and soft-tissue may lack induration, erythema, warmth, or pustulation; a pulmonary infection may have no discernible infiltrate on a radiograph; CSF pleocytosis might be modest or altogether absent in the setting of meningitis; and a urinary tract infection may demonstrate little or no pyuria. Fever is often the only sign of a serious underlying infection.

A detailed history should include elicitation of new site-specific symptoms, information about antimicrobial prophylaxis, infection exposures, prior documented infections or pathogen colonization, and co-existence of noninfectious causes of fever, such as blood product administration. Underlying co-morbid conditions, such as diabetes, chronic obstructive lung disease, and/or recent surgical procedures, should be noted. The physical examination of febrile neutropenic patients requires a careful search to detect subtle symptoms and signs, especially at the sites that are most commonly infected: skin (especially sites of previous procedures or catheters, such as catheter entry and exit sites or bone marrow aspiration sites), oropharynx (including periodontium), alimentary tract, lungs, and perineum. Additional diagnostic tools include blood tests, microbiologic cultures, and radiographic studies.

Cultures The total volume of blood cultured is a crucial determinant of detecting a bloodstream infection [47]. Accordingly, at least 2 sets of blood culture specimens should be obtained, (a "set" consists of 1 venipuncture or catheter access draw of ~20 mL of blood divided into 1 aerobic and 1 anaerobic blood culture bottle). In pediatric patients weighing <40 kg, proportionately smaller volumes of blood culture samples are suggested. Some centers limit blood draws to no more than 1% of a patient's total blood volume. Because total blood volume is approximately 70 mL/kg, the total sample limit would be 7 mL for a 10-kg patient and 28 mL for a 40-kg patient [48]. Recently, 2 retrospective studies found that 2 blood culture sets detect 80%–90% of bloodstream pathogens in critically ill patients, whereas ⩾3 sets are required to achieve >96% detection [49–50]. In the neutropenic patient with cancer, collection of blood culture sets from all CVC lumens (if present), as well as 1 set from a peripheral vein, is advocated during the initial evaluation of fever. Some experts have suggested obtaining both sets of blood cultures from the CVC alone, without peripheral vein sampling. However, the Panel does not favor this approach for initial evaluation, because a catheter-related infection cannot be ruled out without the simultaneous peripheral culture [51–53]. If fever persists after empirical antibiotics have been started, then 2 sets of blood cultures (via catheter or periphery) may be obtained on each of the next 2 days. Beyond that, most experts would not continue daily blood cultures for persistent fever unless there is a clinical change in the patient. After initial defervescence occurs with empirical antibiotics, any recrudescent fever should be evaluated with cultures as a new episode of possible infection.

Culture of the sites listed below should be guided by clinical signs and symptoms but should not be performed routinely.

♦ Stool: A stool specimen in a patient with diarrhea should be evaluated with a *Clostridium difficile* toxin assay. There is limited value in sending a stool specimen for bacterial pathogen cultures or for ova and parasite examination for most patients treated in US hospitals unless there has been recent travel to or residence in areas of endemicity.

♦ Urine: Culture of urine samples is indicated if signs or symptoms of urinary tract infection exist, a urinary catheter is in place, or the findings of urinalysis are abnormal.

♦ CSF: Examination and culture of spinal fluid is indicated if meningitis is suspected. Platelet transfusion should be given prior to lumbar puncture if thrombocytopenia is a concern.

♦ Skin: Aspiration or biopsy of skin lesions suspected of being infected should be performed for cytological testing, Gram staining, and culture [54].

♦ Respiratory specimens: Sputum samples for routine bacterial culture should be sent if the patient has a productive cough. Lower respiratory tract specimens obtained by bronchoalveolar lavage (BAL) are recommended for patients with an infiltrate of uncertain etiology visible on chest imaging. Nasal wash or BAL specimens are recommended to evaluate for symptoms of respiratory virus infection, particularly during an outbreak or during winter. Assays should be sent for detection of adenovirus, influenza A and B virus, RSV, and parainfluenza virus.

Radiography

Patients with respiratory signs and symptoms should have a chest radiograph to rule out pneumonia. Pneumonia during neutropenia can progress rapidly to respiratory compromise and therefore should be managed in the inpatient setting. CT of other areas (head, sinuses, abdomen, and pelvis) should be performed as clinically indicated.

Other Laboratory Analysis

CBC counts and determination of the levels of serum 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 3 days during the course of intensive antibiotic therapy. At least weekly monitoring of serum transaminase levels is advisable for patients with complicated courses or suspected hepatocellular injury or cholestatic disease.

Serum Markers of Inflammation

Studies have demonstrated inconsistent results regarding the use of such markers of inflammation as C-reactive protein, interleukins-6 and -8, and procalcitonin in neutropenic patients with cancer [55–57]. The current data are not sufficient to recommend routine use of these tests to guide decisions about antimicrobial use.

III. In Febrile Patients With Neutropenia, What Empiric Antibiotic Therapy Is Appropriate and in What Venue?

Recommendations

General Considerations

9. High-risk patients require hospitalization for IV empirical antibiotic therapy; monotherapy with an anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended (**A-I**). Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen for management of complications (eg, hypotension and pneumonia) or if antimicrobial resistance is suspected or proven (**B-III**).

10. Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia (**A-I**). These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin and soft-tissue infection, pneumonia, or hemodynamic instability.

11. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (**B-III**). These include MRSA, VRE, ESBL-producing gram-negative bacteria, and carbapenemase-producing organisms, including KPC. Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.

♦ MRSA: Consider early addition of vancomycin, linezolid, or daptomycin (**B-III**).

♦ VRE: Consider early addition of linezolid or daptomycin (**B-III**).

♦ ESBLs: Consider early use of a carbapenem (**B-III**).

♦ KPCs: Consider early use of polymyxin-colistin or tigecycline (**C-III**).

12. Most penicillin-allergic patients tolerate cephalosporins, but those with a history of an immediate-type hypersensitivity reaction (eg, hives and bronchospasm) should be treated with a combination that avoids β-lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin (**A-II**).

13. Afebrile neutropenic patients who have new signs or symptoms suggestive of infection should be evaluated and treated as high-risk patients (**B-III**).

14. Low-risk patients should receive initial oral or IV empirical antibiotic doses in a clinic or hospital setting; they may be transitioned to outpatient oral or IV treatment if they meet specific clinical criteria (**A-I**).

i. Ciprofloxacin plus amoxicillin-clavulanate in combination is recommended for oral empirical treatment (**A-I**). Other oral regimens, including levofloxacin or ciprofloxacin monotherapy, or ciprofloxacin plus clindamycin, are less well studied but are commonly used (**B-III**).

ii. Patients receiving fluoroquinolone prophylaxis should not receive oral empirical therapy with a fluoroquinolone (**A-III**).

iii. Hospital re-admission or continued stay in the hospital is required for persistent fever or signs and symptoms of worsening infection (**A-III**).

Evidence Summary

General Considerations

The goal of initial empirical antibiotic therapy is to prevent serious morbidity and mortality due to bacterial pathogens, until the results of blood cultures are available to guide more-precise antibiotic choices. However, a recent prospective observational study involving >2000 patients revealed that only 23% of febrile neutropenic episodes are associated with bacteremia [44]. Frequencies of gram-positive, gram-negative, and polymicrobial bacteremia were approximately 57%, 34%, and 9%, respectively. Although isolation of gram-positive organisms was more common than isolation of gram-negative organisms, gram-negative bacteremias were associated with greater mortality (5% vs 18%). Coverage of *P. aeruginosa* has largely driven the recommended antibiotic choices for fever and neutropenia in the past because of the especially high mortality rates associated with this infection, and *P. aeruginosa* coverage remains an essential component of the initial empirical antibiotic regimen in the current era [58–59]. Furthermore, even if blood cultures remain negative, empirical antibiotics are considered vital to cover possible occult infections in febrile neutropenic patients.

Despite decades of well-performed clinical trials, no single empirical therapeutic regimen for the initial treatment of febrile patients with neutropenia has emerged as clearly superior to others [60]. All effective empirical antibiotic regimens (combination or monotherapy) share certain essential features, including bactericidal activity in the absence of white blood cells, anti-pseudomonal activity, and minimal toxicity. In recent years, an increasing incidence and array of antibiotic-resistant pathogens have become significant challenges in the treatment of neutropenic and other hospitalized patients [5–7, 11, 13–14, 61–62]. Routine empirical coverage of this broad range of bacteria is not possible. Rather, the aim is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infections in a given patient. This may be accomplished with a variety of antibiotic regimens, including both multidrug combinations and monotherapy regimens, but the ultimate selection of a particular empirical antibiotic regimen should be based on the risk status of the patient (low vs high); on localizing signs or symptoms of infection, such as pulmonary infiltrate or cellulitis; and especially on trends in the epidemiology of pathogens causing infections in neutropenic patients, with special attention to local and even individual patient patterns of bacterial colonization and resistance. Figure 1 depicts an algorithm for managing patients at high and low risk who present with fever and neutropenia. Once blood culture results and organism suscepibilities are available—usually within several days after blood samples are drawn—they may direct a more specific choice of antibiotics. In a majority of cases, however, blood culture results are negative. In these cases, empirical antibiotics are generally continued until ANC recovery is imminent or until an infection requiring alternative antimicrobial coverage is identified.

Initial Antibiotics for High-Risk Patients

High-risk patients require inpatient management with IV broad-spectrum antibiotic therapy that covers *P. aeruginosa* and other serious gram-negative pathogens. Monotherapy with an anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem (imipenem-cilastatin or meropenem), or piperacillin-tazobactam are each as effective as multidrug combinations and are recommended as first-line therapy [11–12, 20–21, 60, 63–92]. A recent meta-analysis found a significant advantage of β-lactam monotherapy over β-lactam plus aminoglycoside combinations, in that the former was associated with fewer adverse events and less morbidity, but with similar rates of survival [93]. Many centers have found that ceftazidime is no longer a reliable agent for empirical monotherapy of fever and neutropenia because of its decreasing potency against gram-negative organisms and its poor activity against many gram-positive pathogens, such as streptococci [61, 94–96]. Aminoglycoside monotherapy should not be used for either empirical coverage or for bacteremia during neutropenia because of the rapid emergence of microbial resistance to this class of agents.

Cefepime remains an acceptable monotherapy for empirical coverage of febrile neutropenia. However, a meta-analysis by Yahav et al [97] of 19 randomized clinical trials involving neutropenic patients noted an increased 30-day mortality associated with the use of cefepime, compared with other β-lactams, in this patient population (risk ration [RR], 1.41; 95% confidence interval [CI], 1.08–1.84), stirring doubt and controversy about the safety of the drug. The authors of this study were not able to provide a biologically plausible explanation for this apparent increased risk of death, and subsequent analyses have raised questions about the trial data included in the study [98–99]. In previously published prospective, randomized trials involving febrile neutropenic populations, an association between mortality and cefepime was not identified [98]. Nonetheless, concerns about continued cefepime use prompted the US Food and Drug Administration (FDA) to undertake a second comprehensive meta-analysis, using an expanded dataset of all cefepime-based studies involving fever

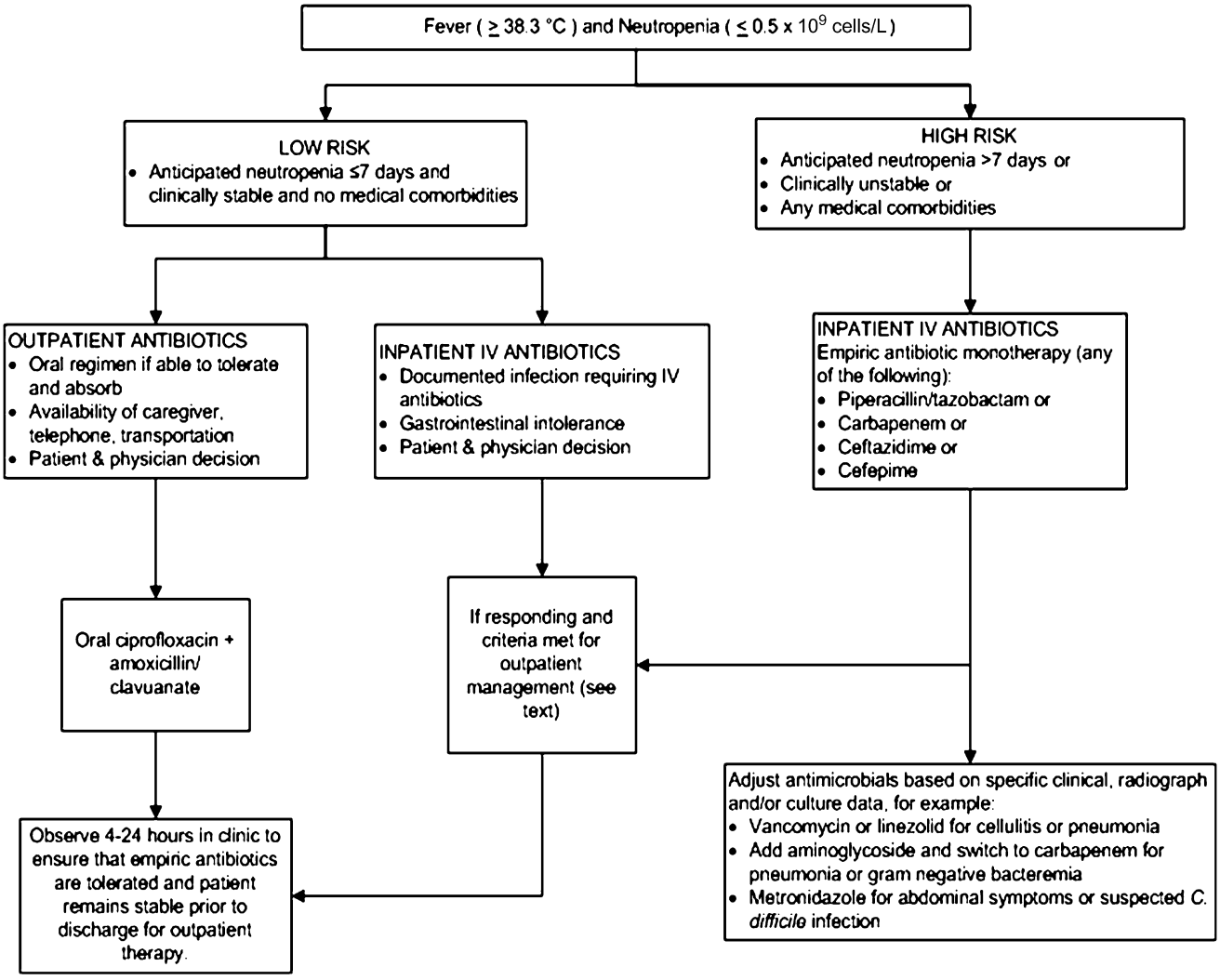

Figure 1. Initial management of fever and neutropenia. *Limited data to support recommendation. ANC, absolute neutrophil count; CT, computed tomography; MRI, magnetic resonance imaging.

and neutropenia (including many not included in the earlier meta-analysis) [336]. The FDA study, which included both trial data and patient-level data controlled for mortality-related risk factors, found no statistically significant increase in 30-day mortality associated with cefepime use (RR, 1.20; 95% CI, 0.82–1.76). Therefore, the Panel continues to consider cefepime a reliable first-line agent for empirical antibiotic coverage for fever and neutropenia.

Increasingly, drug-resistant gram-negative bacterial species are responsible for infections in febrile neutropenic patients. ESBL genes confer a broad range of β-lactam antibiotic resistance among these species, primarily among *Klebsiella* species and *E. coli* [11–12]. Carbapenemase-producing organisms, including *Klebsiella* species and *P. aeruginosa,* may also cause infections refractory to imipenem or meropenem [13]. Organisms producing KPCs are resistant to all β-lactam antibiotics and may require treatment with colistin or tigecycline [100–101]. Recognition of these resistant species requires careful interpretation of hospital and organism-specific antibiograms.

Vancomycin is not a standard part of empirical antibiotic therapy for fever and neutropenia. Despite the predominance of gram-positive organisms as the cause of bacteremia during fever and neutropenia, randomized studies comparing empirical regimens with and without vancomycin as part of the initial empirical regimen have shown no significant reductions in either the duration of fever or overall mortality [60, 62, 93, 102–103]. Coagulase-negative staphylococci, which are the most commonly identified cause of bacteremia in neutropenic patients, are weak pathogens that rarely cause rapid clinical deterioration, so there is usually no urgent need to treat such infections with vancomycin at the time of fever

[51]. A single blood culture positive for coagulase-negative staphylococci should generally be dismissed as attributable to a contaminant, assuming that a second set of blood specimens have been drawn that have negative culture results. The primary reason for the judicious use of vancomycin has been the epidemiological link between its overuse and the development of drug resistance in *Enterococcus* species and *S. aureus* [14, 60, 104–105]. However, there are specific circumstances that warrant the addition of vancomycin (or another antibiotic with enhanced gram-positive coverage) to the initial empirical regimen for fever and neutropenia (Table 4). Notably, monotherapy regimens, including cefepime, carbapenems and piperacillin-tazobactam, provide excellent coverage of viridans streptococci and are considered to be adequate solo agents for the treatment of febrile neutropenia in patients with oral mucositis, precluding the need for the addition of vancomycin to the regimen [106].

If vancomycin or another gram-positive active agent is added to the initial regimen for clinical reasons, it should be discontinued 2 or 3 days later if susceptible bacteria are not recovered from the patient. As with vancomycin, newer gram-positive agents, such as linezolid, quinupristin-dalfopristin, tigecycline, televancin, or daptomycin, have no proven role in routine empirical coverage. Some hazards related to use of these gram-positive agents include the emergence of linezolid-resistant *Enterococcoccus* species in neutropenic patients receiving the drug, marrow-suppression with linezolid, and severe arthralgias with quinupristin-dalfopristin [107–109]. Accordingly, they should be used only for targeted therapy of specific pathogens or for empirical use in HSCT recipients colonized with VRE who develop fever [15].

In view of the widespread presence of MRSA in both hospital and community settings, the Panel recognizes that there may be an increasing epidemiologic rationale for employing vancomycin as a part of the empirical regimen. Serious infections due to *S. aureus* are more often associated with septic shock than are infections due to coagulase-negative staphylococci [62]. Neutropenic patients who are colonized with MRSA may benefit from early empirical use of vancomycin (specifically, if they are hemodynamically unstable or if gram-positive cocci are detected in their blood cultures). However, vancomycin (or similar coverage for gram-positive organisms) is not endorsed as a routine component of the empirical antibiotic regimen.

Bacteremia due to viridans streptococci, which may be resistant to β-lactams and fluoroquinolones, may result in shock and adult respiratory distress syndrome [110–111]. Gastrointestinal mucositis, ceftazidime use, and prophylaxis with ciprofloxacin or levofloxacin are important risk factors for developing serious viridans streptococci bacteremia during neutropenia [112]. Ten percent to 25% of viridans group streptococci may be penicillin-resistant, and many viridans group streptococci have reduced susceptibility to fluoroquinolones [93, 113]. Early vancomycin treatment appears to reduce mortality [94]. Pneumococci may also cause fulminant infection if they are not recognized quickly and treated promptly with appropriate antibiotics; it may be prudent to add vancomycin to the treatment regimen until antibiotic susceptibilities are available and antimicrobial coverage is adjusted accordingly. *Stomatococcus mucilaginosis* is also a potentially virulent but rare gram-positive bloodstream pathogen in neutropenic patients [114–116]. VRE bloodstream infection is difficult to treat in the setting of fever and neutropenia, particularly in leukaemic patients and/or HSCT recipients, and it is an independent risk factor for death [64, 96–97, 117–119]. VRE colonization is an important risk factor for subsequent invasive disease [15]. Local and even individual patient patterns of bacterial colonization and resistance must be taken into account when choosing an initial empirical regimen for neutropenic patients at a given institution [112].

Table 4. Indications for Addition of Antibiotics Active Against Gram-Positive Organisms to the Empirical Regimen for Fever and Neutropenia

♦ Hemodynamic instability or other evidence of severe sepsis
♦ Pneumonia documented radiographically
♦ Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
♦ Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
♦ Skin or soft-tissue infection at any site
♦ Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae* (see text)
♦ Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

As noted above, ciprofloxacin monotherapy is not an adequate therapy for febrile neutropenic patients because of its weak activity against gram-positive organisms, especially viridans streptococci [12, 21, 120–122]. In combination with vancomycin or clindamycin, however, it is a suitable alternative for patients who are allergic to β-lactams [66]. Double β-lactam regimens are discouraged because of concerns about increased expense and toxicity without added benefit [123–124].

Initial Antibiotics for Low-Risk Patients

Carefully selected febrile adult neutropenic patients at low risk for complications during neutropenia may be treated initially with oral broad-spectrum antibiotics [2, 22–34, 42–43, 45, 104]. In general, the use of oral antibiotics may be considered only for patients who fulfill clear criteria for being at low-risk for complications during neutropenia, as defined above [42, 44–45]. In 2 large, placebo-controlled studies, outcomes for low-risk patients treated with an empirical oral combination of ciprofloxacin and

amoxicillin-clavulanate were comparable to those for patients treated with IV antibiotic regimens. Notably, because patients were managed as inpatients in both studies, neither trial examined the feasibility of outpatient oral therapy [23, 26].

Ciprofloxacin should not be employed as a solo agent because of its poor coverage of gram-positive organisms [12, 21, 114, 120–122]. Levofloxacin has better activity against gram-positive organisms but less potent anti-pseudomonal activity than does ciprofloxacin, which makes it a potentially attractive agent for oral empirical therapy in low-risk patients [125]. A recent survey found that practicing oncologists frequently employ levofloxacin monotherapy to treat low-risk patients with fever and neutropenia. However, a definitive clinical trial to evaluate its efficacy has not been performed [125]. The anti-pseudomonal activity of levofloxacin 500 mg daily is probably inadequate, but it may be sufficient at 750 mg daily because of the higher bactericidal drug concentrations that are achieved [126–128]. At present, there are not enough data to endorse either levofloxacin or other fluoroquinolone monotherapies.

Despite the obvious advantages of oral therapy, including reduced cost, lack of need for indwelling IV access, decreased toxicity, and improved patient acceptance [35], few studies have assessed the feasibility of managing patients solely in the outpatient setting. Rather, most studies have observed patients in the hospital during the first 24 h of empirical antibiotic therapy, although in a few studies patients have been discharged from the hospital as early as 6 h after the initial dose was administered [36–37]. An outpatient treatment course with oral or IV antibiotics may be considered after a brief inpatient stay, during which IV therapy is initiated, fulminant infection is excluded, the patient is deemed to be clinically stable and at low-risk for complications, assessment of family support is completed, and the status of initial culture specimens may be ascertained [42, 45, 66]. In one large series, oral outpatient treatment for low-risk fever and neutropenia was deemed to be successful in 80% of patients, with 20% of patients requiring re-admission to the hospital, primarily for persistent fever. Factors predicting re-admission included age >70 years, grade of mucositis >2, poor performance status, and ANC <100 cells/mm^3 at the outset of fever [66].

If outpatient management is prescribed, then vigilant observation and prompt access to appropriate medical care must also be ensured 24 h a day, 7 days a week. Preferably, patients whose clinical conditions worsen should be able to reach their local medical facility within 1 h. Recurrent fever or new signs of infection mandate hospital readmission and institution of a standard empirical regimen of broad-spectrum IV antibiotics. For many patients and for some institutions, outpatient therapy may not be advisable simply because of practical considerations, such as distance from the hospital or lack of a home caregiver or transportation. Patients with recovering neutrophil counts are better candidates for outpatient treatment than are patients with decreasing counts or no indication of marrow recovery.

Fluoroquinolone prophylaxis in a patient strictly precludes the subsequent use of fluoroquinolones for initial empirical therapy; such patients should receive a β-lactam agent if they become febrile during neutropenia.

IV. When and How Should Antimicrobials be Modified During the Course of Fever and Neutropenia?

Recommendations

15. Modifications to the initial antibiotic regimen should be guided by clinical and microbiologic data (**A-II**).

16. Unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly **(A-I).**

17. Documented clinical and/or microbiological infections should be treated with antibiotics appropriate for the site and for the susceptibilities of any isolated organisms (**A-I**).

18. If vancomycin or other coverage for gram-positive organisms was started initially, it may be stopped after 2 days if there is no evidence for a gram-positive infection (**A-II**).

19. Patients who remain hemodynamically unstable after initial doses with standard agents for neutropenic fever should have their antimicrobial regimen broadened to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria and fungi **(A-III).**

20. Low-risk patients who have initiated IV or oral antibiotics in the hospital may have their treatment approach simplified if they are clinically stable **(A-I).**

iii. An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is felt to be adequate **(A-I).**

iv. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured **(B-III).** If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients **(A-III).**

21. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source **(A-II).**

Evidence Summary Once they have initiated empirical antibiotics for fever, all neutropenic patients must be monitored closely for response, adverse effects, emergence of secondary infections, and the development of drug-resistant organisms. This involves daily physical examination, review of systems for new symptoms, cultures of specimens from suspicious sites,

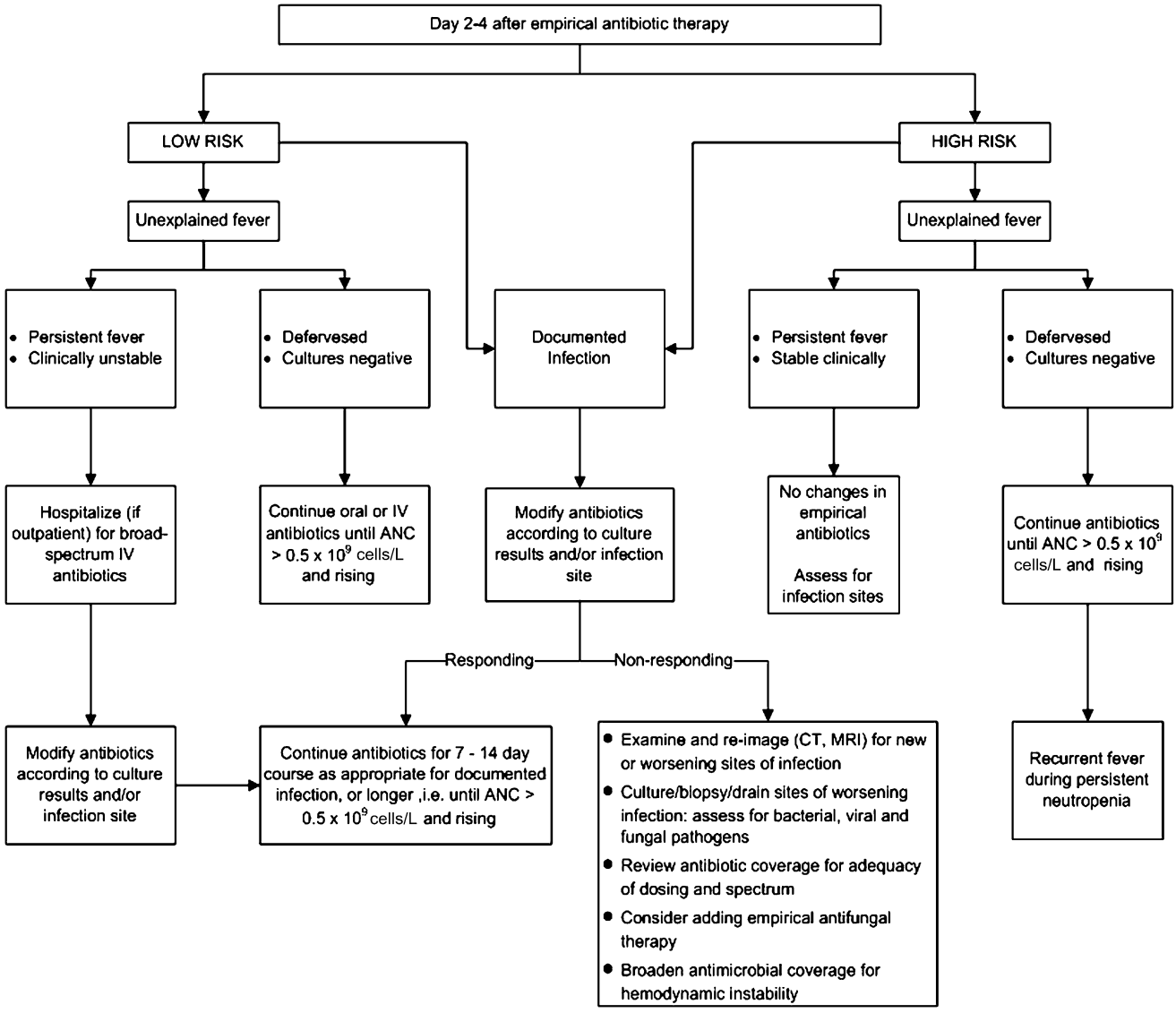

Figure 2. Reassess after 2-4 days of empirical antibiotic therapy. ANC, absolute neutrophil count; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging.

and/or directed imaging studies. With empirical antibiotics, the median time to defervescence in patients with hematologic malignancies, including HSCT, is ~5 days [63, 129–130], whereas for patients at lower risk with solid tumor, defervescence occurs at a median of 2 days [35]. This should be kept in mind when evaluating neutropenic patients who remain febrile after the initiation of empirical antibacterials. Persistent fever alone in a patient whose condition is otherwise stable is rarely an indication to alter the antibiotic regimen. Specific antimicrobial additions or changes to the initial regimen should be guided by clinical change or culture results rather than by the fever pattern alone. Broader decisions about when and how to modify antimicrobial coverage during the course of neutropenia should be based on the risk category (low or high), the source of fever in documented infections, and a clinical judgment about whether the patient is responding to the initial regimen. Figure 2 shows the algorithm for management of patients during days 2–4 after starting empirical antibiotic therapy, when most modifications will be made to the initial regimen.

Unexplained Fever

Patients with unexplained fever who are responding to initial empirical therapy may be maintained on that initial regimen until the recovery of ANC to >500 cells/mm^3. If they have initiated IV antibiotics, patients who meet criteria for being at low risk (Table 3) and can tolerate oral medications may be candidates for transitioning to combination oral antibiotics. As addressed above (see Section III), important issues to address before outpatient antibiotic treatment is assigned include

ascertainment of how long the patient should be observed in a controlled clinical setting before hospital discharge; the appropriateness and safety of the home environment; the type and frequency of clinical follow-up; and discrete indications for readmission to the hospital.

Persistent fever in an otherwise asymptomatic and hemodynamically stable patient is not a reason for undirected antibiotic additions or changes. Specifically, there is no proven advantage to adding vancomycin empirically in the setting of persistent or recrudescent fever and neutropenia. A randomized prospective study of vancomycin versus placebo added to initial empirical piperacillin-tazobactam after 60–72 h of persistent fever showed no difference in time-to-defervescence [131]. Similarly, effective monotherapies, such as cefepime and carbapenems, are also unlikely to benefit from the empirical addition of vancomycin for persistent fever, and this practice is discouraged. If treatment with vancomycin was added empirically at the outset of therapy, as part of the initial regimen, it should be stopped if blood cultures have incubated for 48 h and demonstrated no pathogenic gram-positive organisms [132]. A switch from one empirical monotherapy to another or the addition of an aminoglycoside to the treatment regimen is also not generally useful, unless there is a need for an expanded spectrum of coverage as dictated by clinical or microbiologic data. An important exception, as noted above, is for low-risk outpatients who are being treated with empirical oral or IV therapy. If they have not responded with improvements in fever and clinical symptoms within 48 h, they should be re-admitted to the hospital and re-evaluated, and an IV broad-spectrum antibacterial regimen should be initiated.

Recurrent or persistent fever >3 days in duration despite empirical antibiotic therapy should prompt a thorough search for a source of infection, including a new set of blood cultures and symptom-direction collection of other diagnostic tests. Breakthrough infections, such as *C. difficile*–associated diarrhea or a catheter-related skin or bloodstream infection, are not uncommon. Diarrhea should be assessed by analyzing a stool sample for *C. difficile* toxin using available tests, including enzyme immunoassays or the 2-step antigen assay for *C. difficile* and toxin, but other studies, such as stool white blood cell count, stool bacterial pathogen cultures, or tests for ova and parasites, are not necessary for hospitalized patients. Empirical treatment of *C. difficile* with oral vancomycin or metronidazole may be employed for patients with symptoms of abdominal cramping and diarrhea until diagnostic results are available or if *C. difficile* infection is strongly suspected clinically [133]. An abdominal CT may be helpful in patients with recrudescent neutropenic fever who have abdominal pain and/or diarrhea, to evaluate the possibility of neutropenic enterocolitis [134–135]. A CT of the chest and sinuses is recommended for high-risk patients, to further assess for occult invasive fungal infection (see Section VIII).

For patients with recurrent or persistent fever, consideration should also be given to noninfectious sources, such as drug-related fever, thrombophlebitis, the underlying cancer itself, or resorption of blood from a large hematoma. In many cases, no source of persistent fever is identified but the patient defervesces nonetheless, when the ANC increases to >500 cells/mm^3.

Hemodynamically unstable neutropenic patients with persistent fever without a clear source should have their antimicrobial regimen broadened to ensure adequate coverage for drug-resistant gram-negative and gram-positive organisms, as well as for anaerobes. This may be achieved by a change from an initial cephalosporin to an anti-pseudomonal carbapenem, such as imipenem or meropenem, as well as by the prompt addition of an aminoglycoside, ciprofloxacin, or aztreonam together with vancomycin. The addition of anti-*Candida* coverage with fluconazole or a newer antifungal agent (if fluconazole is already being given prophylactically) is also prudent in for patients who experience systemic inflammatory response syndrome during neutropenia.

High-risk patients who have persistent or recurrent fever after 4–7 days of treatment with broad-spectrum antibacterials and who are anticipated to have prolonged neutropenia lasting >10 days are candidates for the addition of empirical anti-mold therapy. A detailed discussion of this recommendation is provided in Section VIII.

Documented Infections

Identification of a clinically or microbiologically documented infection should guide any changes to the initial empirical antibiotic regimen. Antimicrobial modifications should be based on identified or suspected pathogens (if none can be cultured) and on available antimicrobial susceptibility data, including local susceptibility and resistance trends. Modifications for specific documented infections are discussed below, with the caveat that local patterns of susceptibility are the most critical factor in making final decisions.

Gram-negative bloodstream infections in patients with neutropenia may initially be treated with combinations of β-lactam or carbapenem agents plus aminoglycosides or fluoroquinolones to provide broad initial coverage of possible multidrug-resistant pathogens at the outset of treatment [136–137]. One recent study demonstrated that delaying appropriate antibiotic therapy for *P. aeruginosa* bacteremia for ⩾2 days was associated with a doubling of the 30-day mortality in nonneutropenic patients [138]. Once the patient is stable and in vitro susceptibilities are known, antibiotic treatment can be reduced to monotherapy with a β-lactam agent, which is adequate for most simple bacteremias during neutropenia [20–21, 68–69, 74–92, 139–140].

Pneumonia in neutropenic patients should generally be treated as a health care–acquired infection according to recent guidelines from the American Thoracic Society [141].

Immunosuppressed patients and those who have been hospitalized or received antibiotics within the preceding 90 days are considered to be among those at high risk for developing pneumonia with multidrug-resistant pathogens. An initial broad-spectrum treatment with combinations of a β-lactam or carbapenem plus an aminoglycoside or antipseudomonal fluoroquinolone is recommended for these patients. In severe cases of pneumonia, as documented by hypoxia or extensive infiltrates, or if MRSA is suspected, the addition of vancomycin or linezolid to the treatment regimen is in order. Although this triple combination provides broad coverage for *Legionella* species, drug-resistant gram-negative pathogens, and MRSA, it should be emphasized that the degree of immunocompromise, prior antibiotic and infection history, and local patterns of antibiotic resistance must be considered before deciding upon a specific regimen to treat pneumonia in a given neutropenic patient. Initiation of inadequate or limited regimens for health care–associated pneumonia is a major risk factor for excess mortality and prolonged length of stay [142]. When possible, pneumonia should be evaluated with BAL and biopsy. Adjustment of the empirical regimen can be guided by the identity and susceptibility of pathogens and by clinical progress [141].

For patients with gram-positive bloodstream isolates or with skin and soft-tissue infections, the early addition of vancomycin (or linezolid or daptomycin) to the treatment regimen is recommended until susceptibility results are available for the organism(s) that have been isolated. Linezolid may cause marrow suppression and thus impair ANC and platelet recovery, particularly when given for >14 days [143–144]. Elevations of creatine kinase level may be seen in patients who receive daptomycin treatment.

Other specific sites of documented infection should be covered according to the potential or identified pathogens. Oral ulcerations or symptoms of esophagitis may represent HSV or *Candida* esophagitis infections in high-risk patients, so empirical additions of acyclovir and/or fluconazole or another antifungal are appropriate. Diagnostic endoscopy rarely causes bacteremia [145] but generally should be avoided in neutropenic thrombocytopenic patients because of the risk of bleeding and perforation [146]. If it is still indicated after recovery of ANC and platelet count, the test can be performed. The onset of severe abdominal pain, typically in the right lower quadrant, suggests neutropenic enterocolitis (also referred to as "typhlitis"). A CT should be obtained for additional evaluation [147]. Patients who develop neutropenic enterocolitis should be treated with an expanded broad-spectrum regimen, although the most efficacious regimen is unknown. Because anaerobes and gram-negative organisms predominate in causing neutropenic enterocolitis, monotherapy with piperacillin-tazobactam or a carbapenem or a combination of an anti-pseudomonal cephalosporin plus metronidazole are appropriate antibiotic regimens. There is less evidence to support routine additions of vancomycin or an antifungal agent to antimicrobial regimens [146]. These patients should be evaluated by a surgeon in case a bowel resection is required for uncontrolled sepsis, bleeding, or ischemic bowel.

V. How Long Should Empirical Antibiotic Therapy be Given?

Recommendations

22. In patients with clinically or microbiologically documented infections, the duration of therapy is dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until ANC ⩾ 500 cells/mm^3) or longer if clinically necessary **(B-III).**
23. In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an increasing ANC that exceeds 500 cells/mm^3 **(B-II).**
24. Alternatively, if an appropriate treatment course has been completed and all signs and symptoms of a documented infection have resolved, patients who remain neutropenic may resume oral fluoroquinolone prophylaxis until marrow recovery **(C-III).**

Evidence Summary The traditional approach to duration of antibiotic therapy for a fever of unidentified etiology has been to continue broad-spectrum antibiotics until the patient has been afebrile for at least 2 days and the neutrophil count is >500 cells/mm^3 on at least one occasion but is showing a consistent increasing trend. Years of experience have proven this approach to be safe and effective. It is based on the principle that, although antibiotics are required to contain an occult infection during neutropenia, the return of adequate effector cells is necessary to protect the patient. Variables that can affect this basic approach include the expected duration of neutropenia and how quickly and reliably the patient's ANC recovers. The prophylactic use of CSFs and the overall state of the patient's marrow function also are important determinants of hematologic recovery that will aid in the decision about when antibiotics may be safely stopped.

Documented Infection

For documented infections, the duration of antibiotic therapy should be appropriate for effective eradication of the identified infection. Most bacterial bloodstream infections, soft-tissue infections, and pneumonias require 10–14 days of appropriate antibiotic therapy. Antibiotic treatment may therefore extend beyond resolution of fever and neutropenia. The antibiotic spectrum can be appropriately narrowed to specifically treat the defined infection once fever has resolved. In the absence of significant impairment of gastrointestinal function (eg, nausea, vomiting, diarrhea, malabsorption, and poor oral intake), an

oral antibiotic regimen may be undertaken to complete the full course of therapy. Several studies have indicated that, if the antibiotic course is finished but the patient remains neutropenic and afebrile, resuming fluoroquinolone prophylaxis is safe [67].

Unexplained Fever in Low-Risk Patients

In low-risk patients without documented infection, continuing antibiotic therapy until resolution of both fever and neutropenia is the standard approach. For those patients who have initiated IV antibiotic therapy, a step down to the oral regimen of ciprofloxacin plus amoxicillin-clavulanate is recommended for low-risk patients when they become afebrile after 3 days of treatment, are clinically stable, and have no discernable infection or positive culture results [148].

However, a number of studies, primarily involving pediatric patients, have supported the simpler alternative of stopping antibiotic therapy altogether before attaining the endpoint of an ANC $\geqslant$500 cells/mm^3 if cultures are negative at 48 h and patients remain afebrile for at least 24 h [25, 65, 149–150].

Certain predictive hematological criteria may be substituted as an endpoint for resolution of neutropenia, including a daily increase in the absolute phagocyte count (bands and mature neutrophils combined), the absolute monocyte count, or the reticulocyte fraction [22, 25, 27, 31, 104, 151–152]. The rationale is that these markers provide substantive evidence of marrow recovery, because they typically precede the ANC reaching 500 cells/mm^3 by several days. Particularly in patients who are receiving prophylactic CSFs, it is reasonable to expect that there will be an increase in neutrophils each day. Therefore, in low-risk patients who have defervesced after 3 days of empirical antibiotic therapy, evidence of imminent marrow recovery may direct cessation of broad-spectrum antibiotics prior to the ANC reaching 500 cells/mm^3.

Unexplained Fever in High-Risk Patients

Early discontinuation of antibiotic therapy while fever and neutropenia both persist is strongly discouraged for high-risk patients. In such cases, the clinician should search carefully for a potential source of infection and change antibiotic coverage on the basis of clinical or microbiologic evidence to add antifungal therapy empirically and/or should use CT of the chest to look for invasive fungal disease. A limited number of studies have demonstrated that neutropenic patients with persistent marrow suppression are at high-risk for recurrent fever and sepsis [153–154]. Therefore, patients with profound, persistent myelosuppression and no identifiable source of infection should continue antibiotic therapy until there is evidence of marrow recovery. Some experts advocate that patients with unexplained fever who remain afebrile for 4–5 days may have empirical antibiotics switched back to fluoroquinolone prophylaxis for the remaining duration of neutropenia [155]. Switching from an inpatient antibiotic regimen to outpatient oral or IV regimens for patients who have defervesced, combined with careful daily follow up, may also be a reasonable alternative to prolonged hospitalization of patients waiting for bone marrow recovery. Although these options are used in some centers, there are currently no published trials to confirm their efficacy and safety.

VI. When Should Antibiotic Prophylaxis be Given, and With What Agents?

Recommendations

25. Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC $\leqslant$100 cells/mm^3 for $>$7 days) **(B-I)**. Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered roughly equivalent, although levofloxacin is preferred in situations with increased risk for oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli is recommended **(A-II)**.

26. Addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended **(A-I).**

27. Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for $<$7 days **(A-III).**

Evidence Summary Since the 1980s, studies have demonstrated reductions in the frequency of febrile episodes and in the prevalence of some documented infections among patients who receive prophylactic antibiotics during the early afebrile period of neutropenia [156–157]. The strongest evidence has been for fluoroquinolone prophylaxis [158–163], which has demonstrated an association with reductions in febrile events, documented infections, and bloodstream infections due to gram-positive or gram-negative bacteria [158–163]. Until recently, however, trials have failed to show a survival advantage associated with antibiotic prophylaxis, which, when combined with concern regarding the promotion of antibiotic-resistant bacteria and fungal overgrowth, as well as the risk for drug-related adverse effects, has strengthened the argument against routine use [164–167].

Previously published guidelines by the IDSA [1], the Centers for Disease Control and Prevention, and the American Society for Blood and Marrow Transplantation (ASBMT) [168], as well as guidelines from professional societies in Japan [169], Chile [170], and Germany [171], have not recommended routine application of prophylactic antibiotics for fever and neutropenia. In contrast, the National Comprehensive Cancer Network guidelines and the updated ASBMT guidelines [172, 337] made the qualified recommendation to consider antibacterial chemoprophylaxis for certain high-risk patients who are

anticipated to have prolonged and profound neutropenia (ANC <100 cells/mm^3 for >7 days[337]) after publication of several studies suggesting a limited role for fluoroquinolone prophylaxis in selected high-risk patients [161, 173–175].

A meta-analysis of 17 placebo-controlled or no treatment–controlled trials of fluoroquinolone prophylaxis demonstrated a relative risk reduction of 48% and 62% in all-cause mortality and infection-related mortality, respectively, among fluoroquinolone recipients [161], especially among recipients of ciprofloxacin (RR, 0.32; 95% CI, 0.13–0.82) [175]. This survival advantage had not been shown in previous meta-analyses [158–160, 162–163]. The majority of patients included in these studies had hematologic malignancies or received HSCT, with durations of neutropenia typically >7 days, thus placing them at high risk for infection during neutropenia.

Levofloxacin prophylaxis was found by Bucaneve et al [173] to significantly reduce episodes of fever and the number of documented infections, most strikingly for gram-negative bacillary infections, in a prospective, randomized, double-blind, placebo-controlled trial performed exclusively among patients expected to have ANC counts <1000 cells/mm^3 for >7 days. This study, combined with the meta-analysis data demonstrating survival benefit [161], indicates a potentially important role for levofloxacin prophylaxis in high-risk patients with cancer expected to develop profound neutropenia >7 days in duration. Allogeneic HSCT recipients and patients undergoing induction therapy for acute leukemia are the primary constituents of this high-risk group. However, because of the heterogenicity of the patient populations studied, some controversy remains regarding precisely which patient groups are the most appropriate candidates for fluoroquinolone prophylaxis. For example, the randomized trial by Bucaneve et al [173] did not include allogeneic HSCT recipients, although it demonstrated beneficial effects in other patients with similar degrees of neutropenia. Furthermore, although autologous HSCT recipients also typically experience >7 days of neutropenia after conditioning, they appear to be at lower risk for serious bacterial infections. Accordingly, many experts do not recommend fluoroquinolone prophylaxis for neutropenic autologous HSCT recipients. Some clinicians are reluctant to routinely use fluoroquinolones in children because of preclinical studies in animals that have suggested musculoskeletal toxicity. Large surveys of fluoroquinolone use in children who do not have cancer have not identified serious problems, although the drugs may be associated with more musculoskeletal adverse effects, compared with other classes of antibiotics [176–178]. High-quality clinical trials have not assessed the risk-benefit ratio of fluoroquinolone prophylaxis in children, but it may be reasonable to use the drugs in very high-risk situations, such as allogeneic transplantation or induction therapy for acute leukemia. A second large randomized trial of levofloxacin prophylaxis examined only lower-risk patients with solid tumors or lymphoma and showed a 33% reduction in febrile episodes per chemotherapy cycle with prophylaxis but no effect on documented infections [174]. Given the low rate of fever in the placebo arm, up to 71 patients per chemotherapy cycle would be necessary to prevent one febrile neutropenic episode, without any impact on all-cause mortality [164]. Therefore, routine use of fluoroquinolone chemoprophylaxis in low-risk patient populations is not recommended.

The potential for bacterial resistance to fluoroquinolone-based chemoprophylaxis is a substantial concern [179–185]. High use of fluoroquinolones in oncology patients has been linked to increases in infections due to fluoroquinolone-resistant *E. coli* [181] and *C. difficile* enterocolitis [186–187], although recent meta-analyses have not shown an association [161, 175]. Individual cancer centers have reported increasing rates of resistance related to broad use of fluoroquinolones [175, 179, 181, 183]. In 2 centers, discontinuing routine fluoroquinolone prophylaxis among patients with hematologic malignancy led to prompt reductions in bacterial resistance rates without a significant impact on infection-related morbidity [181, 183]. One report, however, suggested that stopping fluoroquinolone prophylaxis in the setting of high rates of resistance may lead to an increase in morbidity [175].

Because staphylococci and microaerophilic viridans group streptococci are encountered among fluoroquinolone prophylaxis recipients, some authorities have advocated adding a gram-positive agent to the prophylactic regimen [159]. Combinations of a fluoroquinolone plus antibiotics with enhanced activity against gram-positive organisms, including penicillins, rifampin, or macrolides, may reduce infections due to staphylococci and streptococci, as well as reduce the incidence of neutropenic fever, but they do not affect infection-related mortality [159–160]. Increased rates of gastrointestinal upset and of breakthrough resistant gram-positive infections have limited the usefulness of this approach, and it is not recommended [159–160, 188].

The question of when to initiate and discontinue antibacterial chemoprophylaxis has not been systematically studied. Many clinicians begin prophylaxis treatment with the first day of cytotoxic therapy or the day following administration of the last dose of chemotherapy, and they stop at the termination of the neutropenic period or, for those patients who develop fever, at the initiation of empirical antibiotic therapy.

VII. What Is the Role of Empirical or Preemptive Antifungal Therapy and Which Antifungal Should be Used?

Recommendations

High risk

28. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics

and whose overall duration of neutropenia is expected to be >7 days (**A-I**). Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving antimold prophylaxis, but switching to a different class of antimold antifungal given intravenously should be considered (**B-III**).

29. Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus CT signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi (such as *Candida* or *Aspergillus* species) from any body site may have antifungal agents withheld (**B-II**). Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified.

Low Risk

30. In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended (**A-III**).

Evidence Summary In this document, "empirical" antifungal therapy refers to initiation of an antifungal agent at the first possible clinical evidence of fungal infection, which is usually persistent or recrudescent fever on or after day 4 of empirical antibiotic therapy. "Preemptive" antifungal therapy refers to more-targeted, less broad treatment of only those patients with additional findings suggestive of invasive fungal infection, such as serologic test results or chest CT findings. Figure 3 outlines a management algorithm for the use of empirical and preemptive antifungal therapy in persistently febrile neutropenic high-risk patients.

Empirical

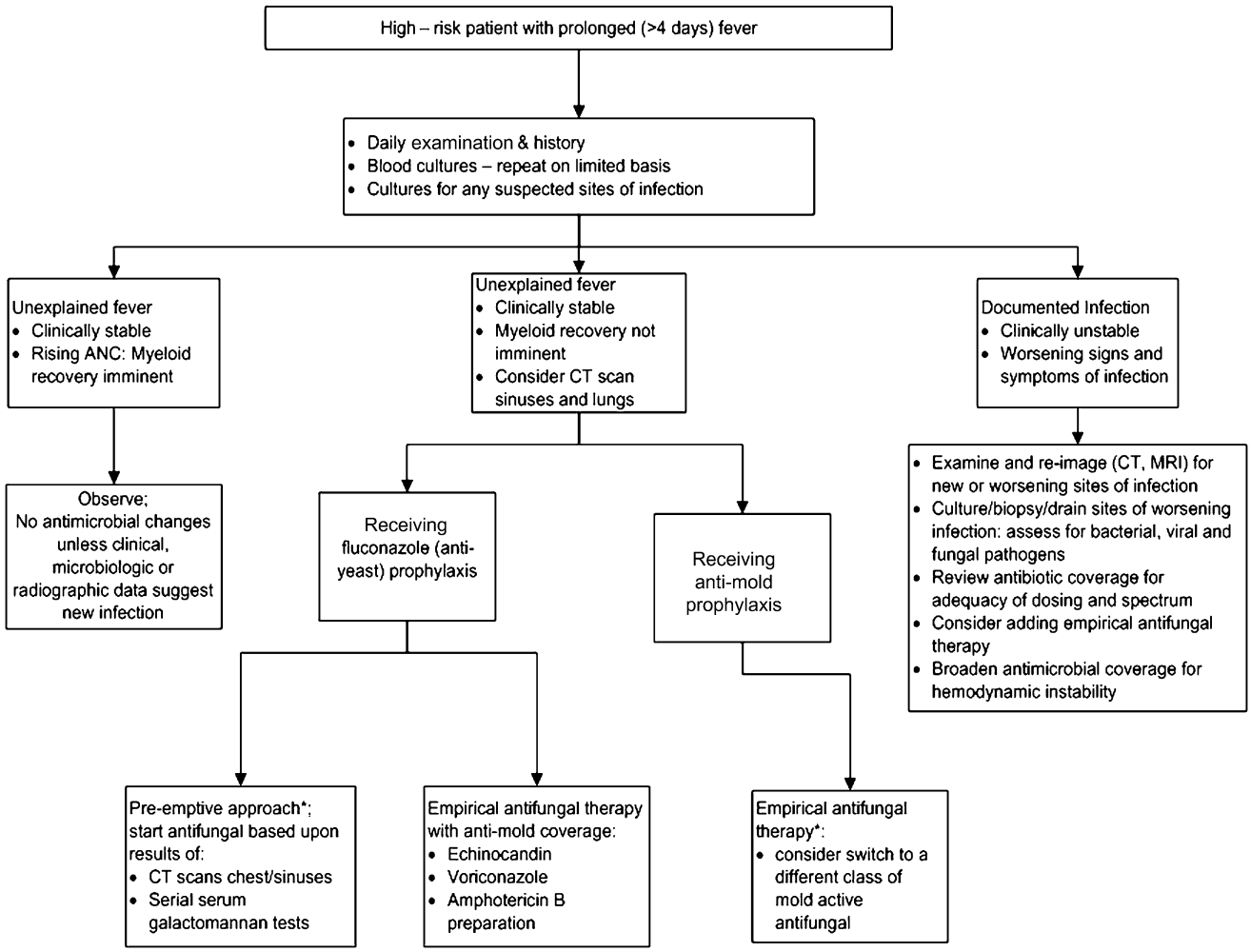

Figure 3. High-risk patient with fever after 4 days of empirical antibiotics. *C. difficile, Clostridium difficile*; IV, intravenous.

High-risk patients who have received intensive cytotoxic chemotherapy are at risk for invasive fungal infection. Yeast (primarily *Candida* species) and molds typically cause infections, which are manifested by persistent or recurrent fever in patients with prolonged neutropenia, rather than causing initial fever in the course of neutropenia [189]. Because *Candida* species are ubiquitous colonizers of human mucosal surfaces, they may cause bloodstream infection with mucosal barrier breakdown [190–192]. Azole prophylaxis, primarily with fluconazole, has significantly reduced the incidence of invasive *Candida* infections in certain high-risk patients with cancer, but breakthrough infections due to azole-resistant strains may occur [193–195]. Fluconazole lacks any activity against invasive mold infections, so it is useful only for *Candida* prophylaxis.

Invasive mold infections, including aspergillosis (the most common invasive mold infection), zygomycosis, and fusariosis, occur almost exclusively in high-risk patients with profound neutropenia ($\leqslant$100 cells/mm^3) lasting longer than 10–15 days [196–197]. At greatest risk are those treated for acute myelogenous leukemia, for whom the incidence of invasive mold infection is of the order of 20 times greater than that seen among patients with lymphoma and multiple myeloma [198]. Because clinical manifestations are nonspecific in the early stages of incubating infection, the diagnosis of invasive fungal infection is especially difficult. Fever may be the lone sign of invasive fungal infection; therefore, to prevent late initiation of treatment, empirical antifungal therapy for persistent or recrudescent neutropenic fever syndrome has been the standard approach for many decades [2, 199].

Empirical antifungal therapy is instituted for the treatment of "occult" fungal infection presenting as persistent neutropenic fever despite 4–7 days of empirical antibiotic therapy [200]. Approximately 22%–34% of neutropenic patients with cancer will receive an antifungal drug by these criteria, yet only ~4% have a demonstrated invasive fungal infection [201–204]. Given that fever is an especially nonspecific surrogate for invasive fungal infection, the true utility of requiring empirical antifungal therapy for every neutropenic patient on the basis of persistent fever alone must be questioned. The choice of empirical antifungal agent depends upon likely fungal pathogens, toxicities, and cost. If antifungal prophylaxis has not been given, then candidemia is initially the greatest concern. For patients receiving fluconazole prophylaxis, fluconazole-resistant *Candida* infections, such as those due to *Candida krusei* or *Candida glabrata*, or an invasive mold infection are more likely because the drug lacks anti-mold activity. Amphotericin B desoxycholate (a polyene antifungal) has been the standard empirical choice for over 3 decades; however, a number of trials have identified roles for other antifungal agents, including liposomal amphotericin B, amphotericin B colloidal dispersion, amphotericin B lipid complex (alternate formulations of amphotericin B), itraconazole or voriconazole (azoles with mold activity), and caspofungin (the first available echinocandin antifungal) [202, 204–207]. Although none of these alternatives have proven to have an efficacy advantage, they have generally been less toxic than the original parent drug, amphotericin B desoxycholate. Although voriconazole failed to meet the strict statistical measurement of noninferiority when compared with liposomal amphotericin B [203], most clinicians regard it as a reliable alternative [208–209]. There are insufficient data upon which to base a specific empirical antifungal choice for patients already receiving mold-active prophylaxis, but a switch to an IV anti-mold agent within a different antifungal class seems prudent. This suggestion is based on the evidence that fungal infection breakthroughs may be related to inadequate serum levels of voriconazole or posaconazole when they are given orally [210–211]. In the absence of changes visible on CT, and if serum levels of anti-mold azole prophylaxis are adequate, continuing the same mold-active prophylaxis may be an acceptable alternative.

Preemptive

Advances in the early detection of fungal infections have prompted a critical re-assessment of whether empirical antifungal therapy is mandatory for all persistently febrile neutropenic patients. Such approaches include serum tests for fungal antigens or DNA and high-resolution chest CT [212–214]. With preemptive treatment, antifungal therapy is given only when evidence of invasive infection is suggested by one of these tests. Although it is attractive, preemptive antifungal therapy currently remains largely experimental and is not standard of practice.

CT may reveal abnormalities in either the lungs or the sinuses. Macronodules with or without a halo sign are the most typical findings associated with invasive aspergillosis on chest CT at the initial diagnosis and are evident during neutropenia [212, 215–217]. The halo sign represents edema or blood surrounding the nodule [217]. Other later manifestations include nodular, wedge-shaped, peripheral, multiple, or cavitary lesions. An air-crescent sign is insensitive and generally appears late, if at all [215]. Preemptive initiation of antifungal therapy directed against *Aspergillus* on the basis of finding a halo sign has been associated with significantly improved survival [212–213, 218].

Two serum fungal diagnostic tests, the β-(1-3)-D glucan test and the galactomannan test, may aid in the detection of common invasive fungal infections. They are not recommended for low-risk patients. The sensitivity of a single serum test is extremely low, and a single negative result should not be used to rule out the diagnosis of an invasive fungal infection. Serial serum monitoring for either of these fungal wall elements can be used to guide initiation of preemptive antifungal therapy in high-risk patients.

The β-(1-3)-D glucan test detects most of the relevant fungal pathogens, including *Candida* species, *Aspergillus* species, *Pneumocystis* species, and *Fusarium* species (but not the zygomycetes agents or *Cryptococcus* species), with high levels of sensitivity and specificity reported in small studies [219–220]. Among patients with AML or MDS undergoing chemotherapy, β-(1-3)-D glucan assay has been found to be 63%–90% sensitive and >95% specific for early detection of proven or probable fungal infections, including candidiasis, fusariosis, trichosporonosis, and aspergillosis [219–221]. A positive test result preceded clinical symptoms of invasive fungal infection in many patients. Experience with use of the β-(1-3)-D glucan assay in HSCT recipients is limited [222] and requires further study. Of note, hemodialysis, hemolysis, serum turbidity, hyperlipidemia, visible bilirubin, use of blood products including immunoglobulin and albumin, bacteremia, and the specimen's exposure to gauze may confound interpretation of the test.

The galactomannan assay detects only *Aspergillus* species (and *Penicillium* species, which is a rare pathogen in the United States) and does not detect other pathogenic fungi, although cross-reactivity to *Histoplasma capsulatum* has been described [223]. In various studies of prospective serial serum galactomannan testing in high-risk patients, sensitivity has ranged widely among different patient populations and has depended upon the optical density cutoff used to define a positive test [224–233]. In patients with hematologic malignancies or HSCT, galactomannan sensitivity was only 58%–65% and specificity was only 65%–95% [234]. The test should be used only for patients at risk for *Aspergillus* infection. The performance of the galactomannan assay may be confounded by concomitant use of β-lactam/β-lactamase combinations, such as piperacillin-tazobactam (false positives) or anti-mold antifungal agents (false negatives) [225]. Preliminary work has suggested that galactomannan detection in BAL fluid [235] may be a useful adjunct with excellent specificity and ~80% sensitivity, compared with ~50% sensitivity for BAL fungal culture [236–237]. Polymerase chain reaction (PCR) assays for fungal detection in blood and BAL fluid are also being developed and tested, but none are yet commercially available [233]. The current evidence, reviewed below, suggests that evolving diagnostic methods may lead to better targeting of those febrile patients in need of preemptive antifungal therapy as an alternative to broad use of empirical antifungals [213].

Preemptive management, using a combination of clinical, serologic, and CT evidence to initiate antifungal therapy, has been evaluated in several trials. In a 2005 pilot study by Maertens et al [213], serial serum galactomannan tests and early CT were applied prospectively in a preemptive treatment algorithm that lead to a nearly 78% reduction (from 35% to 8%) in the use of antifungals among 41 neutropenic patients who would otherwise have qualified for empirical antifungal treatment on the basis of persistent or recurrent fever, without compromising outcomes. More recently, Cordonnier et al [238] demonstrated, in a randomized trial, that preemptive antifungal therapy was a safe alternative to empirical antifungal therapy in a selected group of high-risk neutropenic patients. Patients undergoing AML induction treatments, consolidation therapy, and autologous transplantation and other patients with prolonged neutropenia were evaluated, but allogeneic HSCT recipients were excluded. Preemptive therapy was initiated on the basis of clinical symptoms or chest CT findings suggestive of an invasive fungal infection and/or mycological evidence, such as *Aspergillus* colonization or a positive galactomannan test result. Although overall rates of mortality were not different between patients randomized to preemptive versus empirical antifungal therapy, there were more episodes of invasive fungal infection and a trend toward more fungal-related deaths among those treated with preemptive therapy [238]. The difference in invasive fungal infection was seen only in the subset of patients who were not given antifungal prophylaxis (55% of the patients entered into the study), which was administered at the discretion of each center. The outcome difference was due to more *Candida* infections occurring in the preemptive group, which did not receive antifungal prophylaxis [238–239]. Antifungal therapy was given to fewer patients in the preemptive arm than in the empirical therapy arm. Hebart and colleagues compared empirical antifungal therapy versus PCR-driven preemptive antifungal therapy after allogeneic stem cell transplant [214] in patients receiving anti-yeast prophylaxis. The investigators demonstrated increased use of anti-fungal therapy and reduced 30-day mortality in the PCR-driven arm, but no difference in proven/probable invasive fungal infections or 100-day survival. These and other studies support the concept that certain high-risk febrile neutropenic patients receiving anti-yeast prophylaxis may be exempted from automatic receipt of empirical antifungal therapy if in a structured monitoring program and if specific criteria are met [213, 240–241]. However, if a serum fungal antigen marker (galactomannan or 1,3-β-D-glucan), a chest or sinus CT, or specific clinical signs or symptoms implicate a possible invasive fungal infection, then antifungal therapy that covers a broader range of fungal pathogens, including molds, should be quickly applied using one of the broad-spectrum antifungals that has documented efficacy in the empirical setting. A number of important issues about preemptive therapy require further study: the optimal trigger (clinical or radiological manifestations versus a serum biomarker), which biomarker should be used (antigen or PCR test), timing (early before clinical manifestations or late after clinical manifestations), and which antifungals provide the most appropriate spectrum of activity. Another important unresolved question is use of the preemptive antifungal approach in patients who are already receiving anti-mold prophylaxis [242].

VIII. When Should Antifungal Prophylaxis be Given and With What Agents?

Recommendations

High-risk

31. Prophylaxis against *Candida* infections is recommended in patient groups in whom the risk of invasive candidal infections is substantial, such as allogeneic HSCT recipients or those undergoing intensive remission-induction or salvage induction chemotherapy for acute leukemia (**A-I**). Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives.

32. Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients ⩾13 years of age who are undergoing intensive chemotherapy for AML/MDS in whom the risk of invasive aspergillosis without prophylaxis is substantial (**B-I**).

33. Prophylaxis against *Aspergillus* infection in pre-engraftment allogeneic or autologous transplant recipients has not been shown to be efficacious. However, a mold-active agent is recommended in patients with prior invasive aspergillosis (**A-III**), anticipated prolonged neutropenic periods of at least 2 weeks (**C-III**), or a prolonged period of neutropenia immediately prior to HSCT (**C-III**).

Low-Risk

34. Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is <7 days (**A-III**).

Evidence Summary

Candida *infection*. Fluconazole prophylaxis is effective in reducing the risk of *Candida* infections in neutropenic patients, is well tolerated, and is available in both oral and IV formulations [194, 243–249]. The epidemiology of candidemia has changed with the broad use of fluconazole prophylaxis, which has led to an increase in *Candida* species (eg, *C. glabrata* and *C. krusei*) that are less susceptible to fluconazole [250]. *C. glabrata* infection is common in some centers. Accordingly, there is reason to limit fluconazole prophylaxis to only those patients who are at substantial risk for invasive infection. The threshold incidence of *Candida* infection at which fluconazole prophylaxis appears to be efficacious is 6%–10% in controlled studies and in meta-analyses of prophylaxis [245–247].

Candida infection rates at this level are usually seen among high-risk patients with cancer who are not receiving prophylaxis. These include pre-engraftment allogeneic HSCT recipients receiving myeloablative conditioning regimens, some autologous HSCT recipients unsupported by hematopoietic growth factors, and patients undergoing intensive induction chemotherapy regimens for AML with severe oral and gastrointestinal mucositis [245, 247]. Among lower-risk patient populations, invasive candidiasis is rare [245] and generally does not merit routine fluconazole prophylaxis. Voriconazole prophylaxis has also proven to be as effective as fluconazole or itraconazole for *Candida* prophylaxis in patients undergoing allogeneic stem cell transplant, and its ability to prevent possible fungal infections in high-risk leukaemic patients is promising [251–253].

Prophylaxis with micafungin or caspofungin is efficacious and well-tolerated for the prevention of candidiasis and invasive aspergillosis in high-risk patients [248, 254]. The high cost and need for parenteral administration are limitations of these agents. It should be emphasized that fluconazole will not provide preventive coverage against invasive aspergillosis or other molds. The toxicity of amphotericin B desoxycholate makes it less desirable for prophylactic use, despite its very broad antifungal activity. In trials of posaconazole prophylaxis for high-risk patients, in which the major goal was mold prevention, low rates of invasive candidiasis were observed; by inference, posaconazole is a reasonable recommendation for *Candida* prophylaxis in the high risk group [193, 201].

Aspergillus *infection*. The need for *Aspergillus* prophylaxis among neutropenic high-risk patients varies according to the disease and chemotherapy regimen (eg, induction for acute leukemia or myelodysplastic syndrome and pre-engraftment allogeneic HSCT); efficacy varies by antifungal agent (eg, itraconazole, voriconazole, and posaconazole) [193, 201, 247, 251, 253, 255–257].

Patients with AML. For patients with AML who experience induction therapy–related prolonged neutropenia, prophylaxis is beneficial when the baseline rate of invasive aspergillosis is at least 6% [193, 201]. This antifungal prophylactic benefit has not been established for post-remission consolidation therapy for acute leukemia and is not routinely recommended. Among adult and adolescent patients (>13 years of age) who receive induction chemotherapy for AML or intensive treatment for advanced MDS, posaconazole prophylaxis, compared with itraconazole or fluconazole, was associated with significantly fewer *Aspergillus* infections and improved survival but with more-serious adverse events, compared with a heterogeneous control group heavily weighted by fluconazole recipients [201]. Posaconazole is currently available only in an oral formulation, and its oral absorption is highly dependent upon concomitant intake of a high fat meal with each dose [211, 258]. Its bioavailability is variable and unreliable if not taken in conjunction with food [259–260]. Drug interactions with chemotherapy agents, such as cyclophosphamide, and the vinca alkaloids, such as vincristine, which are also metabolized by the liver, are a potential concern associated with posaconazole and other mold-active azoles that are used in acute leukemia therapy [261–263]. Co-administration of mold-active triazole-based prophylaxis with vinca alkaloids or high doses of cyclophosphamide and anthracyclines should be avoided until these interactions have been better studied.

Oral itraconazole has activity against *Aspergillus*, but its prophylactic utility is hampered by a paucity of clinical trial data showing an anti-*Aspergillus* effect. One meta-analysis demonstrated a protective effect limited to trials that used itraconazole oral solution doses of 200 mg twice a day; however, the oral solution is rarely employed because of poor tolerability [249, 255]. Although voriconazole is used for prophylaxis in some centers, no large randomized studies involving patients with AML or MDS have been performed to date.

Allogeneic HSCT Recipients. After allogeneic HSCT, there are 2 distinct periods of risk for invasive mold infections: the first during the neutropenic pre-engraftment phase and the second during the post-engraftment period, when a patient develops graft-versus-host disease (GVHD), which requires immunosuppressive treatment. The focus of this guideline is the initial risk period during neutropenia. Fluconazole is an effective prophylactic antifungal in allogeneic HSCT recipients when used from the onset of conditioning, through neutropenia, and extended to at least day 75 after receipt of transplant. However, fluconazole lacks anti-mold coverage; its prophylactic efficacy in the HSCT population can be attributed to prevention of invasive candidiasis [247]. Because allogeneic HSCT recipients are at risk for invasive molds as well as for *Candida* infections, it stands to reason that broader-spectrum antifungal agents, such as late-generation azoles, would provide more effective prophylaxis.

A randomized, double-blind trial compared voriconazole to fluconazole as prophylaxis for allogeneic HSCT recipients until 100 days after transplantation, using a concurrent structured intensive galactomannan screening monitoring program [251]. In a preliminary analysis, each group had a similar rate of fungal infection and fungal-free survival, although there was a trend toward fewer *Aspergillus* infections among patients receiving voriconazole. There were no differences in toxicities. These data suggest that both fluconazole and voriconazole provide long-term antifungal prophylaxis in allogeneic HSCT recipients.

A recent comparative open trial of voriconazole and itraconazole among allogeneic HSCT recipients demonstrated fewer interruptions of study drug and a trend to fewer fungal infections among those who received voriconazole but comparable survival at 100 and 180 days. There were more adverse gastrointestinal events associated with itraconazole but more adverse visual and hepatic events associated with voriconazole [252]. Considerations that may influence the choice of antifungal therapy include prior *Aspergillus* infection, risk for GVHD (which is an important predictor of invasive aspergillosis), and cost.

Additionally, because prolonged durations of neutropenia are associated with the development of invasive aspergillosis, many experts would recommend a mold-active agent for prophylaxis in HSCT recipients with anticipated prolonged neutropenic periods of at least 14 days or those with a lengthy duration of neutropenia immediately prior to HSCT. Finally, in leukaemic patients with prior recent history of invasive mold infection, the administration of mold-active agents appeared to reduce the risk of reactivation during HSCT conditioning [264–265]. Although routine azole drug level monitoring during prophylaxis is not recommended, low levels of the oral mold-active azoles have been noted [260, 266–268]. Therefore, drug level monitoring may aid in decisions about dosing in some patients.

The appropriate duration of anti-mold prophylaxis in high-risk patients is uncertain. Prophylaxis stop-dates for patients with acute leukemia generally coincide with myeloid reconstitution. HSCT allograft transplant recipients should receive prophylaxis through the neutropenic period and beyond, because a survival advantage has been demonstrated for patients who continue antifungal prophylaxis long after engraftment, for at least 75 days after transplant [269], or until cessation of immunosuppressive therapy [270].

IX. What Is the Role of Antiviral Prophylaxis and What Virus Infections Require Antiviral Treatment?

Recommendations

35. HSV-seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis **(A-I).**

36. Antiviral treatment for HSV or VZV is only indicated if there is clinical or laboratory evidence of active viral disease **(C-III).**

37. Respiratory virus testing (including testing for influenza, parainfluenza, adenovirus, RSV, and human metapneumovirus) and chest radiography are indicated for patients with upper respiratory symptoms (eg, coryza) and/or cough **(B-III).**

38. Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer **(A-II).** Optimal timing of vaccination is not established, but serologic responses may be best between chemotherapy cycles (>7 days after the last treatment) or >2 weeks before chemotherapy starts **(B-III).**

39. Influenza virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible **(A-II)**. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically **(C-III).**

40. Routine treatment of RSV infection in neutropenic patients with upper respiratory disease should not be given **(B-III).**

Evidence Summary

Herpes Viruses

Prophylaxis with an HSV-active agent, such as acyclovir, should be offered to all HSV-seropositive autologous or allogeneic HSCT recipients [271] and patients with acute leukemia

undergoing induction or reinduction therapy [272]. Prophylaxis should be given until recovery of the white blood cell count or resolution of mucositis, whichever occurs later. Duration of prophylaxis can be extended for persons with frequent recurrent HSV infections or those with GVHD or can be continued as VZV prophylaxis for up to 1 year [273].

Empirical use of antiviral drugs is generally not indicated in the management of other febrile neutropenic patients with cancer. Treatment of active HSV or VZV infection should be given to all patients.

Other herpesvirus infections occur in the post-HSCT setting, including infections due to cytomegalovirus and human herpesvirus 6. However, neutropenia is not a predisposition to reactivation of either virus; thus, prevention strategies for these 2 herpes viruses are not discussed in this document [274].

Respiratory Viruses

All patients with cancer and their household contacts should be immunized against influenza with inactivated influenza vaccine on a yearly basis. Despite the lack of conclusive data about vaccine efficacy, inactivated influenza vaccine may yield adequate serologic responses in some patients treated for solid tumors [275–276]. Live attenuated formulations of influenza vaccine should be avoided in patients who are receiving chemotherapy cycles or are within 6 months after the end of therapy. However, family members of patients with cancer may receive the live attenuated influenza vaccination. With the advent of new strains of influenza, such as the 2009 H1N1 pandemic strain, it is important that the most-current available vaccines for each season be given promptly [277]. The optimal timing of influenza vaccination in patients who are being actively treated for solid tumor and lymphoma has not been established. It is possible that influenza vaccination responses may be best between chemotherapy cycles (>7 days after the last treatment) or >2 weeks before chemotherapy starts [276, 278–279]. HSCT recipients usually respond best to influenza vaccination if vaccinated at >6 months after transplantation. If an exposure to influenza occurs, 5 days of post-exposure treatment with anti-influenza antivirals (eg, oseltamivir or zanamivir) is recommended for the neutropenic patient regardless of vaccination status [280].

Patients with respiratory complaints, including cough and nasal congestion or a pulmonary infiltrate noted on chest radiograph during the peri-transplant period, should be evaluated by examination of nasopharyngeal swab or washing specimens. The specimen can be tested by PCR, direct antigen assay, or culture for respiratory viruses (including influenza, parainfluenza, adenovirus, RSV, and human metapneumovirus) [281]. Neutropenic patients infected with these respiratory viruses may be afebrile and may lack "classic" systemic symptoms, such as myalgia and fatigue [282]. If influenza is suspected epidemiologically, empirical therapy with an anti-influenza agent (eg, oseltamivir and zanamivir) should be initiated while test results are pending. In the setting of an influenza outbreak, aggressive infection control measures should be instituted to halt further nosocomial spread [283]. Delay in chemotherapy or in the start of the HSCT conditioning regimen should be considered for patients with acute respiratory viral infections until the infection is controlled, if feasible. Some experts believe that documented influenza virus infection should be treated even if the diagnosis is made >48 h after the start of symptoms [284–285].

Although aerosolized and oral administration of ribavirin has been used, there is no antiviral agent proven to be effective against parainfluenza virus [286]. Similarly, there is no clear evidence from randomized trials that aerosolized or oral ribavirin or any other antiviral is effective against RSV pneumonia. No agent been shown to prevent RSV upper respiratory infection from progressing to RSV pneumonia, although a modest effect had been observed in a retrospective analysis [287]. Some experts employ ribavirin for RSV upper respiratory tract infection in patients with profound lymphocytopenia. Monoclonal antibody (palivizumab) and RSV immunoglobulin also do not appear to prevent or attenuate RSV upper respiratory infection or progression to pneumonia [288]. There is no proven effective therapy for adenovirus infection, although some experts would employ cidofovir or ribavirin for clinically significant adenovirus disease [289].

X. What Is the Role of Hematopoietic Growth Factors (G-CSF or GM-CSF) in Managing Fever and Neutropenia?

Recommendations

41. Prophylactic use of myeloid CSFs (also referred to as hematopoietic growth factors) should be considered for patients in whom the anticipated risk of fever and neutropenia is ⩾20% **(A-II).**
42. CSFs are not generally recommended for treatment of established fever and neutropenia (**B-II**).

Evidence Summary Prophylactic use of myeloid CSFs has been shown to reduce the incidence of neutropenic fever in a variety of studies and, in meta-analyses, also was associated with reductions in infection-related mortality and all-cause mortality [290–291]. Authoritative evidence-based guidelines have indicated that clinical benefits from prophylactic CSFs accrue when the risk of neutropenic fever associated with a chemotherapy regimen is ⩾20%, unless the treatment is symptomatic or palliative, in which cases dose reduction is usually appropriate [292–294]. However, because of their high expense, it is not clear that CSF prophylaxis, when given widely to patients who are at the threshold of 20% risk of fever and neutropenia, is cost-effective in all health care markets

[295–297]. If societal costs are considered, the economic impact of fever and neutropenia becomes more apparent, and there may be recognition of greater cost-saving benefits of CSFs [297]. Primary prophylaxis—the use of CSFs for prevention in the first cycle of treatment for many solid tumors—does appear to reduce the incidence of fever and neutropenia and is likely to be most cost-effective. CSF prophylaxis should be especially considered for older patients or if the presence of additional risk factors, including prior fever and neutropenia, poor nutritional or performance status, no antibiotic prophylaxis, comorbid medical conditions, or other modifying disease characteristics, suggests that there is substantial risk of fever and/or severe infection during neutropenia [298–300]. If the risk is $\leqslant$10%, the benefit is low, and CSFs are generally not recommended. If given, CSF treatment should be started immediately after the chemotherapy is completed.

Myeloid CSFs are not recommended as adjuncts to antibiotics for treating established fever and neutropenia. Although days of neutropenia, duration of fever, and length of hospital stay have been minimally (but statistically significantly) decreased in some randomized studies, the actual clinical benefit of these reductions is not convincing [301–304]. None of the studies have demonstrated a survival benefit associated with therapeutic CSFs. Given the cost of and adverse effects associated with the CSFs, as well as the lack of consistent clinical data, addition of G-CSF or GM-CSF at the onset of fever and neutropenia is generally not advocated by the Panel.

XI. How are Catheter-Related Infections Diagnosed and Managed in Neutropenic Patients?

Recommendations

43. DTP >120 min of qualitative blood cultures performed on specimens simultaneously drawn from the CVC and a vein suggests a CLABSI **(A-II).**

44. For CLABSI caused by *S. aureus*, *P. aeruginosa,* fungi, or mycobacteria, catheter removal is recommended in addition to systemic antimicrobial therapy for at least 14 days **(A-II).** Catheter removal is also recommended for tunnel infection or port pocket site infection, septic thrombosis, endocarditis, sepsis with hemodynamic instability, or bloodstream infection that persists despite $\geqslant$ 72 h of therapy with appropriate antibiotics **(A-II)**.

45. For documented CLABSI caused by coagulase-negative staphylococci, the catheter may be retained using systemic therapy with or without antibiotic lock therapy **(B-III).**

46. Prolonged treatment (4–6 weeks) is recommended for complicated CLABSI, defined as the presence of deep tissue infection, endocarditis, septic thrombosis **(A-II),** or persistent bacteremia or fungemia occurring >72 h after catheter removal in a patient who has received appropriate antimicrobials (**A-II** for *S. aureus*, **C-III** for other pathogens).

47. Hand hygiene, maximal sterile barrier precautions, and cutaneous antisepsis with chlorhexidine during CVC insertion are recommended for all CVC insertions **(A-I).**

Evidence Summary In addition to the gastrointestinal tract, the CVC is a major source of bloodstream infections in the neutropenic patient population [7, 305–306]. The hub/lumen of the catheter is the major site of colonization and source of the CLABSI [307]. Accordingly, CLABSI is most commonly caused by colonizers of the skin and mucosa, including coagulase-negative staphylococci, *S. aureus,* and *Candida* species. Less common organisms include *Bacillus* species, *Corynebacterium* JK, enterococci (including VRE), rapidly growing mycobacteria, and non-fermentative gram-negative bacilli [308].

A useful diagnostic tool for diagnosing CLABSI is the DTP of blood cultures performed on specimens drawn simultaneously through the catheter and peripheral vein. The premise of the test is that, when the catheter is the source of bacteremia, the concentration of organisms will be extremely high in the hub/lumen, resulting in a rapidly positive culture. Studies have suggested that a CVC blood culture that becomes positive at least 120 min earlier than a simultaneously drawn peripheral vein blood culture indicates that the catheter is likely to be the source of infection [305, 309–318]. Therefore, during initial assessment of fever and neutropenia and prior to antibiotic administration, specimens for blood culture sets should be drawn simultaneously from each catheter lumen and from a peripheral vein. Once antibiotic therapy has been started, DTP might not be reliable.

Catheter removal is considered in most CLABSIs. The decision rests largely on the organism(s) isolated. For example, although bacteremia with coagulase-negative staphylococci is common among neutropenic patients, the pathogen is of low virulence; management often does not require catheter removal and can usually be achieved with vancomycin given through the infected catheter lumen(s). In contrast, CLABSI with *S. aureus,* gram-negative bacilli (such as *P. aeruginosa*), or *Candida* species typically requires catheter removal along with systemic antimicrobial treatment for optimal outcomes [319–323]. In some patients, catheter removal is not feasible because of thrombocytopenia, the hazards associated with reimplantation during neutropenia, or the absence of other vascular access sites. In cases in which the catheter must be retained, it is prudent to prolong the antimicrobial IV systemic therapy, particularly in the case of *S. aureus* and gram-negative bacillary bacteremia. Anecdotal data suggest that antibiotic lock therapy might be useful in salvaging some of the long-term catheters [324–328]. However, strategies such

as antibiotic lock therapy are currently being studied and cannot be routinely recommended at this time for salvage treatment or for prophylaxis.

The duration of systemic antimicrobial therapy depends on several factors, including whether the catheter was removed or retained, response to antimicrobial therapy within 48–72 h (resolution of fever and bacteremia), and whether complicated infection (deep tissue infection, septic thrombosis, or endocarditis) [308] is present. In general, for organisms other than coagulase-negative staphylococci, a 14-day course of systemic antimicrobial therapy is adequate in the neutropenic patient if the catheter is removed, if the patient responds to antimicrobial therapy within 72 h, and if the CLABSI is uncomplicated by deep-tissue infection [308]. However, a recent study suggests that *S. aureus* CLABSI in patients with cancer (including neutropenic patients) may require longer than 2 weeks of antimicrobial therapy because of an increased incidence of complications associated with shorter courses of treatment [329]. CLABSI due to any pathogen that is complicated by disseminated or deep infection requires 4–6 weeks of antimicrobial therapy [308]. Transthoracic echocardiogram may be the only modality available for assessment of valves, because transesophageal echocardiogram may be delayed until resolution of neutropenia and concurrent thrombocytopenia.

Hand hygiene, maximal sterile barrier precautions, cutaneous antisepsis with chlorhexidine during catheter insertion, and antimicrobial catheters have been shown to be useful in preventing catheter-related bloodstream infections [330]. Further specifics as to the management of the catheter and the duration of antimicrobial therapy for long-term catheter-related bloodstream infections have been outlined in the IDSA guidelines for the management of intravascular catheter–related infections [308].

XII. What Environmental Precautions Should be Taken When Managing Febrile Neutropenic Patients?

Recommendations

48. Hand hygiene is the most effective means of preventing transmission of infection in the hospital **(A-II).**

49. Standard barrier precautions should be followed for all patients, and infection-specific isolation should be used for patients with certain signs or symptoms **(A-III).**

50. HSCT recipients should be placed in private (ie, single-patient) rooms **(B-III).** Allogeneic HSCT recipients should be placed in rooms with >12 air exchanges/h and HEPA filtration **(A-III)**.

51. Plants and dried or fresh flowers should not be allowed in the rooms of hospitalized neutropenic patients **(B-III)**.

52. Hospital work exclusion policies should be designed to encourage HCWs to report their illnesses or exposures **(A-II)**.

♦ *Hand Hygiene*

Hand hygiene is the most effective means of preventing hospital-acquired infections [331]. All persons, including HCWs, must sanitize their hands before entering and after leaving the rooms of neutropenic (and all other) patients.

Isolation and Barrier Precautions

No specific protective gear (eg, gowns, gloves, and masks) is required during the routine care of neutropenic patients. However, as with other hospitalized patients, when contact with body fluids is anticipated, standard barrier precautions should be followed [332]. Patients with neutropenia, other than HSCT recipients, do not need to be placed into a single-patient room. HSCT recipients should be placed in private (ie, single-patient) rooms.

♦ *Food*

A ''neutropenic diet'' typically is given to patients with neutropenia. This usually consists of well-cooked foods. Prepared luncheon meats should be avoided. Well-cleaned, uncooked raw fruits and vegetables are acceptable, as are cooked foods brought from home or restaurants, provided that the freshness of ingredients and the means of preparation can be confirmed [333]. In a small randomized trial, cooked and noncooked food diets were compared; avoidance of raw fruits and vegetables did not prevent major infection or death [189].

♦ *Room Ventilation*

Most patients with neutropenia do not require specific room ventilation. All allogeneic HSCT recipients, however, should be placed in rooms with >12 air exchanges/h [333] and HEPA filtration. The air pressure in the patient rooms should be positive compared with adjoining areas, such as hallways, toilets, and anterooms.

♦ *Patient Skin and Oral Care*

To optimize skin integrity, patients should take daily showers or baths during any hospitalization for cancer therapy or complication. Skin care during neutropenia should also include daily inspection of skin sites likely to be portals of infection (eg, the perineum and intravascular access sites). Patients should maintain good perineal hygiene; to facilitate this, hospitals should develop protocols for perineal care, including recommendations for gentle but thorough perineal cleaning after bowel movement and thorough drying of the perineum after urination. Females should wipe the perineum from front to back after using the toilet to prevent contamination. Menstruating immunocompromised patients should not use tampons, which can be abrasive. Rectal thermometers, enemas, suppositories, and rectal examinations are contraindicated for patients with neutropenia [333].

Patients and their caregivers should be taught how to maintain good oral and dental hygiene during neutropenia. For those with ongoing mucositis, this includes oral rinses 4–6 times/day with sterile water, normal saline, or sodium bicarbonate solutions. Patients should brush their teeth ⩾2 times/day with a soft regular toothbrush. If this cannot be tolerated, an ultrasoft toothbrush or toothette (ie, foam swab on a stick) can be used, but physicians should be aware that toothettes remove less dental debris. Using toothpaste is optional. Daily dental flossing can be done if it can be accomplished without trauma.

To decrease the risk for mechanical trauma and infection of oral mucosa, fixed orthodontic appliances and space maintainers should not be worn during neutropenia until mucositis resolves.

♦ *Plants and Animals*

Plants and dried or fresh flowers should not be allowed in the rooms of hospitalized neutropenic patients, because molds, including *Aspergillus* and *Fusarium* species, have been isolated from the soil of potted ornamental plants (eg, cacti), the surfaces of dried flower arrangements, and fresh flowers [333].

Household pets that might be brought to the hospital for pet therapy should not be allowed onto the ward where patients with neutropenia are housed.

♦ *HCWs and Visitors*

Vaccination of HCWs and visitors, including annual influenza, measles, mumps, rubella, and varicella vaccination (if indicated), are recommended to prevent transmission of vaccine-preventable diseases to patients with cancer [334].

HCWs or visitors who are currently symptomatic with infections transmissible by air, droplet, and direct contact (eg, VZV infection, infectious gastroenteritis, HSV lesions on lips or fingers, and upper respiratory tract infections) should not engage in patient care or visit patients unless appropriate barrier (eg, mask and glove) protection is established. For HCWs, work exclusion policies should be designed to encourage HCWs to report their illnesses or exposures.

♦ *Infection Control Surveillance*

In the absence of epidemiologic clusters of infections, infection control personnel should not perform routine bacterial surveillance cultures of the environment or of equipment or devices. [332].

Cancer centers caring for patients at high-risk for invasive mold infection (such as HSCT recipients or patients with leukemia) should routinely monitor the number of aspergillosis cases. A 2-fold or greater increase in the attack rate of aspergillosis during any 6-month period should prompt an examination of the environment, observation of staff for breaks in infection control technique and procedures, and inspection of the ventilation system.

The role of routine screening for problematic pathogens, such as VRE and MRSA, is still being defined. Many experts recommend this approach for high-risk patients [332, 335].

PERFORMANCE MEASURES

1. All patients with fever and neutropenia should be evaluated for level of risk (high or low), have history and physical examination performed, have cultures and radiological tests performed, and initiate treatment with broad-spectrum empirical antibiotics promptly (ie, within 2 h of presentation). In the absence of effector cells, primarily neutrophils, signs and symptoms of inflammation may be lacking and rapid progression of invasive bacterial infections may occur, so antibiotics are a life-saving measure in this situation. However, the collection of clinical and laboratory data that will locate a potential site or cause of infection is critical prior to the initiation of antibiotics.
2. Antimicrobial changes or additions to the initial empirical antibiotic regimen should be based on clinical, radiographic, or microbiological evidence of infection and not on the persistence of fever alone in a patient whose condition is otherwise stable. An exception is that empirical antifungal therapy should be started after 4–7 days of fever that does not respond to empirical antibiotic therapy.
3. Low-risk patients who are anticipated to have a short duration of neutropenia (<7 days) do not require antibiotic prophylaxis.

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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