

## Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline

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### A B S T R A C T

#### Purpose

To provide guidelines on antimicrobial prophylaxis for adult neutropenic oncology outpatients and on selection and treatment as outpatients of those with fever and neutropenia.

#### Methods

A literature search identified relevant studies published in English. Primary outcomes included: development of fever and/or infections in afebrile neutropenic outpatients and recovery without complications and overall mortality in febrile neutropenic outpatients. Secondary outcomes included: in afebrile neutropenic outpatients, infection-related mortality; in outpatients with fever and neutropenia, defervescence without regimen change, time to defervescence, infectious complications, and recurrent fever; and in both groups, hospital admissions, duration, and adverse effects of antimicrobials. An Expert Panel developed guidelines based on extracted data and informal consensus.

#### Results

Forty-seven articles from 43 studies met selection criteria.

#### Recommendations

Antibacterial and antifungal prophylaxis are only recommended for patients expected to have  $< 100$  neutrophils/ $\mu\text{L}$  for  $> 7$  days, unless other factors increase risks for complications or mortality to similar levels. Inpatient treatment is standard to manage febrile neutropenic episodes, although carefully selected patients may be managed as outpatients after systematic assessment beginning with a validated risk index (eg, Multinational Association for Supportive Care in Cancer [MASCC] score or Talcott's rules). Patients with MASCC scores  $\geq 21$  or in Talcott group 4, and without other risk factors, can be managed safely as outpatients. Febrile neutropenic patients should receive initial doses of empiric antibacterial therapy within an hour of triage and should either be monitored for at least 4 hours to determine suitability for outpatient management or be admitted to the hospital. An oral fluoroquinolone plus amoxicillin/clavulanate (or plus clindamycin, if penicillin allergic) is recommended as empiric therapy, unless fluoroquinolone prophylaxis was used before fever developed.

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### INTRODUCTION

The first guideline<sup>1</sup> published by the American Society of Clinical Oncology (ASCO) provided recommendations on uses of hematopoietic colony-stimulating factors (CSFs), including primary prophylaxis of fever and neutropenia (FN) in patients undergoing chemotherapy for malignancy if their risk was  $\geq 40\%$ . ASCO has updated this guideline periodically, most recently in 2006,<sup>2</sup> when the threshold for primary prophylaxis with a CSF was revised to include patients at  $\geq 20\%$  risk for FN.

Although the CSF guideline is scheduled for another update soon, ASCO has not previously addressed other measures (eg, prophylactic antimicrobial drugs or protective environments) to prevent infection in outpatients who are neutropenic, not yet febrile, and either continue to receive or have recently completed chemotherapy for malignancy. Additionally, a priority-setting exercise of the ASCO Clinical Practice Guidelines Committee (CPGC) selected outpatient management of febrile neutropenia as an important topic for a new guideline.

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Editor's note: This is the complete American Society of Clinical Oncology Clinical Practice Guideline and provides the recommendations with comprehensive discussions of the relevant literature for each. The Executive Summary of the guideline, Data Supplements with evidence tables as well as other tables and figures, and a list of all abbreviations used in the text, tables, and figures are available at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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Managing FN in oncology patients began to change in the late 1960s and early 1970s, when evidence emerged that empiric antibacterial therapy reduced deaths resulting from infection, compared with waiting for results of microbiologic assays.<sup>3-7</sup> The spectrum of bacterial pathogens most commonly isolated from patients with FN during or after treatment for malignancy shifted from mostly Gram-negative species in the 1960s and 1970s to more Gram-positive species in the 1980s and 1990s. Currently, coagulase-negative staphylococci are the most common species identified in blood cultures, but the frequency of antibiotic-resistant Gram-negative bacterial infections is increasing. However, blood cultures and other cultures are negative and the causative organism and site of infection uncertain in many oncology patients with fever. Because infection can progress rapidly and become life threatening if patients are neutropenic, clinical practice guidelines recommend administration of broad-spectrum antibacterials (using monotherapy or a combination regimen) soon (within an hour) after fever is documented in a neutropenic patient.<sup>7-13</sup>

Until the late 1980s and early 1990s, empiric antibacterial therapy was almost invariably administered intravenously (IV) in the hospital if an

oncology patient developed FN. Presently, a wider spectrum of disorders than ever before is being managed on an outpatient basis. Potential advantages of outpatient management include increased convenience for patients and their family members, reduced costs of care, and, particularly for those at risk of infection, decreased exposure to hospital-acquired infections, which often may be resistant to the antibiotics used most frequently. Malignancies currently being treated outside the hospital range from adjuvant systemic therapy for breast cancer to postremission consolidation with high-dose cytarabine for acute myeloid leukemia to reduced-intensity conditioning stem-cell transplantation (SCT). Various approaches have been studied to stratify such patients who develop FN by risk for medical complications or death.<sup>14-21</sup> Several of these approaches have been used to select low-risk patients for early discharge or outpatient therapy, and a number of trials randomly assigning low-risk patients have compared outcomes of inpatient versus outpatient management<sup>14,21-25</sup> or oral versus IV antibacterials as empiric therapy.<sup>14,26,27</sup> In light of the evidence from such studies, the ASCO CPGC assembled a panel of experts to address the following clinical questions.

## THE BOTTOM LINE

### ASCO GUIDELINE

#### Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy

##### Interventions

- Antibacterial and/or antifungal prophylaxis for afebrile outpatients with neutropenia from treatment for malignancy
- Identification of oncology outpatients with fever and neutropenia (FN) at low risk for medical complications
- Initial empiric therapy in the outpatient setting to treat FN in patients at low risk for medical complications

##### Target Audience

- Medical oncologists, primary care physicians, and oncology nurses

##### Key Recommendations

- Only use antibacterial and antifungal prophylaxis if neutrophils are expected to remain  $< 100/\mu\text{L}$  for  $> 7$  days, unless other factors (see text and Table 2) increase risks for complications or mortality
- An oral fluoroquinolone is preferred for antibacterial prophylaxis and an oral triazole for antifungal prophylaxis
- Interventions such as footwear exchange, protected environments, respiratory or surgical masks, neutropenic diet, or nutritional supplements are not recommended because evidence is lacking of clinical benefits to patients from their use
- Assess risk for medical complications in patients with FN using the Multinational Association for Supportive Care in Cancer (MASCC) score (see Table 3) or Talcott's rules; score  $\geq 21$  or Talcott's group 4 with no other risk factors (see text and Table 4) defines low risk
- An oral fluoroquinolone plus amoxicillin/clavulanate (or plus clindamycin for those with penicillin allergy) is recommended for initial empiric therapy, unless fluoroquinolone prophylaxis was used before fever developed (see text for alternatives)

##### Methods

- An Expert Panel was convened to develop clinical practice guideline recommendations based on a review of evidence from a systematic review of the medical literature

##### Additional Information

- An Executive Summary of this guideline has been published in *Journal of Clinical Oncology*

Data Supplements, including evidence tables, and clinical tools and resources can be found at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn).

## GUIDELINE QUESTIONS

- A. What interventions are appropriate to prevent infections in patients with a malignancy who have received chemotherapy in an inpatient or outpatient setting and who are, or are anticipated to become, neutropenic as outpatients?
- A-1. How should risk of developing a febrile neutropenic episode (FNE) be assessed in such patients who are not yet febrile? What clinical characteristics identify patients who should be offered antimicrobial prophylaxis?
  - A-2. What antimicrobial drug classes should be used to prevent infection in afebrile neutropenic outpatients who should be offered prophylaxis?
  - A-3. What additional precautions are appropriate to prevent exposure of neutropenic but afebrile outpatients with a malignancy to infectious agents or organisms?
- B. Which patients with a malignancy and febrile neutropenia are appropriate candidates for outpatient management?
- B-4. What clinical characteristics should be used to select patients for outpatient empiric therapy?
  - B-5. Should outpatients with FN at low risk for medical complications receive their initial dose(s) of empiric antimicrobial(s) in the hospital or clinic and be observed, or can some selected for outpatient management be discharged immediately after evaluation?
  - B-6. What psychosocial and logistic requirements must be met to permit outpatient management of patients with FN?
- C. What interventions are indicated for patients with a malignancy and febrile neutropenia who can be managed as outpatients?
- C-7. What diagnostic procedures are recommended?
  - C-8. What antibacterials are recommended for outpatient empiric therapy?
  - C-9. What additional measures are recommended for outpatient management?
  - C-10. How should persistent neutropenic fever (PNF) syndrome be managed?

## CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, use of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions

9. Criteria for use in credentialing decisions
10. Identification of areas where future research is needed

## METHODS

**Panel Composition**

The ASCO CPGC convened an Expert Panel (hereafter referred to as the Panel) consisting of experts in clinical medicine and research methods relevant to prevention and treatment of infection in patients with neutropenia after therapy for a malignancy and reflecting the perspectives of academic and private practice clinicians. The experts' fields included medical oncology, hematology, infectious diseases, oncology nursing, health services research, epidemiology, public health, and biostatistics. The Panel also included a patient representative. Panel members are listed in Appendix Table A1 (online only).

**Literature Review and Analysis**

*Literature search strategy.* The MEDLINE database was searched using PubMed for relevant evidence published from 1987 through the end of April 2011. The search included terms for malignant diseases linked to terms for neutropenia, fever, or infection and to terms for clinical trials, systematic reviews, meta-analyses, or clinical guidelines. Data Supplement 1 provides the full search strategy (online at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn)). One reviewer selected articles for full-copy retrieval and consulted a Panel cochair when potential relevance was uncertain. Reference lists of articles retrieved in full copy were searched for other relevant reports. Panel members provided additional references from personal files.

*Inclusion and exclusion criteria.* Articles were selected for inclusion in the systematic review if they were fully published English-language reports on: antimicrobials for prophylaxis of infection in oncology outpatients with neutropenia from chemotherapy, development and/or validation of methods to stratify risk of complications in oncology patients with FN, empiric antimicrobial therapy for oncology outpatients with FN, or direct comparisons of outcomes for inpatient versus outpatient management of oncology patients with FN. For clinical questions addressing antimicrobials for prophylaxis of infection or as empiric therapy for FN, study selection criteria limited inclusion to reports from randomized controlled trials (RCTs) of adult human participants, systematic reviews and meta-analyses of RCTs, or evidence-based clinical practice guidelines. Prospective or retrospective cohort studies, case-control studies, and case series were included for questions addressing risk stratification or direct comparison of inpatient versus outpatient management. Meeting abstracts, letters, commentaries, editorials, case reports, and nonsystematic (narrative) reviews were excluded from evidence tables for all questions.

*Data extraction.* For studies on afebrile neutropenic outpatients, primary outcomes included: 1) febrile episodes and 2) infections, whereas secondary outcomes included infection-related mortality. For studies on outpatients with FN, primary outcomes included: 1) empiric treatment success (defined as recovery from FN without medical complications) and 2) overall and infection-related mortality, whereas secondary outcomes included: 1) defervescence without regimen change, 2) time to defervescence, 3) complications from infection, and 4) relapsed or recurrent fever. Additional secondary outcomes relevant to both sets of studies included: 1) hospital admissions, 2) duration of hospital stay, and 3) adverse effects of antimicrobials. Data were extracted directly into evidence tables (see Data Supplement Tables DS-3 to DS-9; online at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn)) by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved by discussion and by consultation with Panel cochairs if necessary.

**Guideline Development Process**

The entire Panel met once to review results of the systematic review; additional work to revise the clinical questions and to draft guideline recommendations and a manuscript was completed by telephone conferences (when necessary) and electronic review of documents. All members of the Panel participated in preparation and revision of the draft guideline document and approved the final version submitted for peer review and publication in *Journal of Clinical Oncology*. Additional feedback was solicited from external

reviewers. The content of the guidelines and manuscript were reviewed and approved by the ASCO CPGC before publication.

### Definition of Terms

For purposes of this guideline, the Panel defined neutropenia as an absolute neutrophil count (ANC)  $< 1,000/\mu\text{L}$  (equivalent to  $< 1.0 \times 10^9/\text{L}$ ), severe neutropenia as ANC  $< 500/\mu\text{L}$  (equivalent to  $< 0.5 \times 10^9/\text{L}$ ), and profound neutropenia as ANC  $< 100/\mu\text{L}$  (equivalent to  $< 0.1 \times 10^9/\text{L}$ ). The Panel defined the state of being febrile as a temperature of  $\geq 38.3^\circ\text{C}$  by oral or tympanic thermometry, but it did not exclude evidence from studies that used slightly different definitions (eg, core temperature  $> 38^\circ\text{C}$ ).

### Guideline Policy

The practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary. The Executive Summary and additional information are available at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn).

### Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines (Procedures; summarized at <http://www.asco.org/guidelinescoi>). Members of the Panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

### Revision Dates

At annual intervals, the Panel coauthors and two Panel members designated by the coauthors will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel or an update committee will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revised guidelines to the ASCO CPGC for review and approval.

## RESULTS

The MEDLINE search identified a total of 4,863 unique records. Review of titles and abstracts eliminated 4,397 as either not relevant to the clinical questions of the guideline or not meeting study selection criteria (Data Supplement 2; online at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn)). Of 466 articles selected for full-text retrieval, 45 met study selection criteria for data extraction. Hand-searching of reference lists from included articles and input from Panel members identified 140 additional articles retrieved in full, of which two met selection criteria.

Of the 47 articles extracted, none addressed guideline Key Question A (preventing infection in neutropenic adult outpatients who are not febrile); 25 addressed Key Question B (selecting adult patients with FN who are eligible for outpatient management; Data Supplement Tables DS-3 to DS-6), and 22 addressed Key Question C (comparing interventions used to manage FN in the outpatient setting). Data extracted from the 47 reports that met selection criteria are listed in Data Supplement Tables DS-3 to DS-9.

### Other Guidelines and Consensus Statements

Other organizations have published guidelines or consensus statements addressing clinical questions also addressed here. These

include guidelines on managing FN in patients with cancer from the Japan Febrile Neutropenia Study Group,<sup>9</sup> the European Society of Medical Oncology (ESMO),<sup>10</sup> and an Australian consensus panel.<sup>13,21,28,29</sup> Additionally, the National Comprehensive Cancer Network (NCCN) has published guidelines on prevention and treatment of cancer-related infections,<sup>11</sup> and the Infectious Disease Society of America (IDSA)<sup>7,12</sup> and the Infectious Diseases Working Party of the German Society of Hematology and Oncology<sup>8</sup> have published guidelines on uses of antimicrobial drugs in neutropenic patients with cancer. The Panel has evaluated the recommendations of these organizations and found them to be generally consistent with recommendations in this ASCO clinical practice guideline. Specific differences are highlighted and discussed in the Literature Review and Analysis sections that follow each recommendation.

## GUIDELINE RECOMMENDATIONS

Each of the 10 recommendations (Table 1) considers issues relevant to one of the guideline key questions. Recommendations A-1 to A-3 address issues relevant to Key Question A on preventing infection in oncology outpatients who have or are expected to develop neutropenia but are without fever or evidence of infection. These include assessing risk for infection and selecting candidates for prophylaxis (Recommendation A-1), choosing prophylactic antimicrobials for appropriate patients (Recommendation A-2), and other precautions to consider (Recommendation A-3). Recommendations B-4 to B-6 address selection of individuals with FN who can remain outpatients (Key Question B), including assessing risk of medical complications (Recommendation B-4), evaluation and observation after initial dose(s) (Recommendation B-5), and psychosocial and logistic requirements for outpatient management (Recommendation B-6). Finally, Recommendations C-7 to C-10 focus on managing oncology patients with FN outside the hospital (Key Question C), including diagnostic procedures (Recommendation C-7), empiric antibacterial therapy (Recommendation C-8), additional measures to be considered (Recommendation C-9), and management of PNF (Recommendation C-10).

### Clinical Key Question A

What interventions are appropriate to prevent infections in patients with a malignancy who have received chemotherapy in an inpatient or outpatient setting and who are, or are anticipated to become, neutropenic as outpatients?

#### Question A-1

How should risk of developing an FNE be assessed in such patients who are not yet febrile? What clinical characteristics identify patients who should be offered antimicrobial prophylaxis?

Because evidence to address Question A-1 was unavailable from trials limited to outpatients, the Panel considered evidence from studies on inpatients or mixed populations. The following recommendations on risk assessment (A-1a) and patient selection for antibacterial (A-1b), antifungal (A-1c), anti-*Pneumocystis* (A-1d), and antiviral (A-1e to A-1g) prophylaxis are based on the evidence summarized here and Panel members' expert opinion.

#### Recommendation A-1a

Risk for developing an FNE should be systematically assessed (in consultation with infectious disease specialists as needed), including

**Table 1.** Summary of 2012 Recommendations  
2012 Recommendations

Clinical Question	
<p>A. What interventions are appropriate to prevent infections in patients with a malignancy who have received chemotherapy in an inpatient or outpatient setting and who are, or are anticipated to become, neutropenic as outpatients?</p>	<p>Recommendation A-1. Because evidence to address this question was unavailable from trials limited to outpatients, the Panel considered evidence from studies on inpatients or mixed populations and recommends the following, based on such evidence and members' expert opinion:</p> <p>A-1a. FNE risk should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors (see Table 2); G-CSF prophylaxis should be used before neutropenia develops for patients who meet criteria specified in the ASCO WBC growth factors guideline</p> <p>A-1b. Clinicians should consider antibacterial prophylaxis only for patients expected to experience profound neutropenia (defined as ANC &lt; 100/<math>\mu</math>L) likely to last for <math>\geq</math> 7 days; the Panel does not recommend routine antibacterial prophylaxis if neutropenia is less severe or of shorter duration, the usual course with current chemotherapy regimens for solid tumors; thus, the Panel does not recommend routine use of antibacterial prophylaxis for patients with solid tumors undergoing conventional chemotherapy with or without biologics (eg, trastuzumab, bevacizumab, or cetuximab)</p> <p>A-1c. Limit antifungal prophylaxis (for decreasing IFIs from opportunistic yeast or mold species) to patients receiving chemotherapy expected to cause profound neutropenia (ANC &lt; 100/<math>\mu</math>L) for <math>\geq</math> 7 days, which confers substantial risk (<math>&gt;</math> 6% to 10%) for IFI; antifungal prophylaxis is not recommended for patients with solid tumors receiving conventional-dose chemotherapy with or without biologics (eg, trastuzumab, bevacizumab, or cetuximab)</p> <p>A-1d. Patients receiving chemotherapy regimens associated with <math>&gt;</math> 3.5% risk for pneumonia from <i>Pneumocystis jirovecii</i> (eg, those with <math>\geq</math> 20 mg of prednisone equivalents daily for <math>\geq</math> 1 month or those based on purine analogs) are eligible for prophylaxis</p> <p>A-1e. Antiviral prophylaxis should be considered for patients known to be at substantial risk for reactivation of HBV infection</p> <p>A-1f. Prophylaxis to prevent reactivation of infection from herpesviruses (HSV or VZV) is recommended for seropositive patients undergoing therapy for certain hematologic malignancies (see details in text)</p> <p>A-1g. Seasonal influenza immunization is recommended for all patients receiving chemotherapy for malignancy and for all family and household contacts</p>
<p>A-2. What antimicrobial drug classes should be used to prevent infection in afebrile neutropenic outpatients who should be offered prophylaxis?</p>	<p>Recommendation A-2. Because evidence to address this question was unavailable from trials limited to outpatients, the Panel considered evidence from studies on inpatients or mixed populations and recommends the following based on such evidence and members' expert opinion:</p> <p>A-2a. Antibacterial prophylaxis should use an orally administered, systemically absorbed fluoroquinolone to prevent invasive infection by Gram-negative bacilli of outpatients with profound neutropenia expected to last for <math>\geq</math> 7 days associated with severe mucositis (eg, from primary or salvage remission-induction therapy for acute leukemia, dose-intensive postremission consolidation for acute leukemia, or HSCT); prophylaxis may be less effective in environments where <math>&gt;</math> 20% of Gram-negative bacilli are resistant to fluoroquinolones</p> <p>A-2b. Use an orally administered triazole antifungal or parenterally administered echinocandin in the outpatient setting as prophylaxis against opportunistic yeast infection in those with profound neutropenia and mucositis expected to last for <math>\geq</math> 7 days in environments with <math>&gt;</math> 10% risk of invasive <i>Candida</i> infection; a mold-active triazole is recommended in environments with a substantial risk (<math>&gt;</math> 6%) for invasive aspergillosis</p> <p>A-2c. Prophylaxis with trimethoprim-sulfamethoxazole should only be used if risk for pneumonia from <i>Pneumocystis jirovecii</i> is <math>&gt;</math> 3.5% (eg, patients administered regimens with <math>\geq</math> 20 mg of prednisone equivalents daily for <math>\geq</math> 1 month or those based on purine analogs); additional details and alternatives for patients with sulfa-based hypersensitivities are provided in the text</p> <p>A-2d. Lamivudine is recommended as prophylaxis in patients at substantial risk for reactivation of HBV infection</p> <p>A-2e. A nucleoside analog is recommended to prevent herpesvirus infection in those at risk</p> <p>A-2f. Influenza immunization should use trivalent inactivated vaccine; in select circumstances after proven exposure of a susceptible patient with cancer, a neuraminidase inhibitor (eg, oseltamivir, zanamivir) may be offered</p>

(continued on following page)

Table 1. Summary of 2012 Recommendations (continued)

Clinical Question	2012 Recommendations
<p>A-3. What additional precautions are appropriate to prevent exposure of neutropenic but afebrile outpatients with a malignancy to infectious agents or organisms?</p>	<p>Recommendation A-3. Because direct evidence was unavailable from randomized trials, the Panel considered evidence from uncontrolled and retrospective studies and based the following recommendations on such evidence and members' expert opinion:</p> <p>A-3a. All health care workers should follow hand hygiene guidelines including handwashing practices to reduce exposure through contact transmission and respiratory hygiene/cough etiquette guidelines to reduce exposure through droplet transmission</p> <p>A-3b. Outpatients with neutropenia from cancer therapy should avoid prolonged contact with environments that have high concentrations of airborne fungal spores (eg, construction and demolition sites)</p> <p>A-3c. None of the following measures are routinely necessary to prevent infection of afebrile outpatients with a malignancy and neutropenia: protected environments (HEPA filters with or without laminar air flow), respiratory or surgical masks (to prevent invasive aspergillosis), footwear exchange at entry and exit, and the neutropenic diet or similar nutritional interventions; gowning and gloving should only be considered in accordance with local infection prevention and control practices for antibiotic-resistant organisms such as methicillin-resistant <i>Staphylococcus aureus</i>, vancomycin-resistant enterococci, or extended-spectrum <math>\beta</math>-lactamase-producing and carbapenemase-producing Gram-negative bacilli</p>
<p>B. Which oncology patients with FN are appropriate candidates for outpatient management?</p>	
<p>B-4. What clinical characteristics should be used to select patients for outpatient empiric therapy?</p>	<p>Recommendation B-4. Because medical complications occurred in up to 11% of patients identified as low risk for medical complications of FN in studies validating risk indices or scoring systems, the Panel considers inpatient treatment the standard approach for managing an FNE; however, outpatient management may be acceptable for carefully selected patients: when considering a patient with an FNE for outpatient management, the Panel recommends beginning the evaluation with a systematic risk assessment using a validated index; the MASCC risk index (see Table 3) has been evaluated most thoroughly of the available risk indices for adults; Talcott's rules have also been validated in prospective studies; however, the FNE should be managed in the hospital if the clinician has any reservations with respect to the accuracy of an index for an individual, even if the patient is classified as low risk (MASCC score <math>\geq</math> 21 or Talcott group 4); Table 4 lists additional factors to take into account when assessing risk for medical complications in the setting of outpatient FNE management; patients meeting any of the criteria listed in Table 4, those with MASCC score <math>&lt;</math> 21, or those in Talcott groups 1 to 3 should not be managed as outpatients; moreover, neither a currently available risk index nor the criteria in Table 4 should substitute for clinical judgment when deciding whether a given patient with an FNE should be admitted to the hospital for inpatient management</p>
<p>B-5. Should outpatients with FN at low risk for medical complications receive their initial dose(s) of empiric antimicrobial(s) in the hospital or clinic and be observed, or can some be selected for outpatient management and be discharged immediately after evaluation?</p>	<p>Recommendation B-5. The duration of observation before outpatients were discharged varied considerably among studies that directly compared inpatient versus outpatient empiric therapy or oral versus IV regimens in outpatients; lacking evidence from direct comparisons, the Panel relied on members' expert opinion to recommend that the first dose of empiric therapy be administered within 1 hour after triage from initial presentation in the clinic, emergency room, or hospital department, after fever has been documented in a neutropenic patient and pretreatment blood samples have been drawn; similarly, the Panel recommends that patients identified as low risk and selected for outpatient management be observed for at least 4 hours before discharge to verify they are stable and can tolerate the regimen they will receive</p>
<p>B-6. What psychosocial and logistic requirements must be met to permit outpatient management of patients with fever and neutropenia?</p>	<p>Recommendation B-6. Because direct comparative evidence was unavailable for any of these factors, the Panel relied on members' expert opinion to recommend that an oncology patient with FN during or after chemotherapy meet each of the following criteria to receive empiric therapy as an outpatient:</p> <ol style="list-style-type: none"> <li>Residence <math>\leq</math> 1 hour or <math>\leq</math> 30 miles (48 km) from clinic or hospital</li> <li>Patient's primary care physician or oncologist agrees to outpatient management</li> <li>Able to comply with logistic requirements, including frequent clinic visits</li> <li>Family member or caregiver at home 24 hours a day</li> <li>Access to a telephone and transportation 24 hours a day</li> <li>No history of noncompliance with treatment protocols</li> </ol> <p>(continued on following page)</p>

**Table 1.** Summary of 2012 Recommendations (continued)

Clinical Question	2012 Recommendations
<p>C. What interventions are indicated for oncology patients with an FNE who can be managed as outpatients?</p> <p>C-7. What diagnostic procedures are recommended?</p>	<p>Recommendation C-7. On the basis of members' expert opinion, the Panel recommends that in the absence of an alternative explanation, fever in a patient with neutropenia from cancer therapy should be assumed to be the result of a bacterial infection; the initial diagnostic approach should maximize the chances of establishing clinical and microbiologic diagnoses that may affect antibacterial choice and prognosis; the Panel also recommends systematically evaluating the patient to identify the infectious agent and anatomic focus (see text for details)</p>
<p>C-8. What antibacterials are recommended for outpatient empiric therapy?</p>	<p>Recommendation C-8. Patients with cancer and FN who are at low risk for medical complications by criteria of Recommendation B-4 may be administered oral empiric therapy with a fluoroquinolone (ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate (or plus clindamycin for those with penicillin allergy); however, a fluoroquinolone is not recommended for initial empiric therapy of neutropenic patients with cancer who develop fever after receiving fluoroquinolone-based antibacterial prophylaxis or in environments where the prevalence of fluoroquinolone resistance is &gt; 20%; for these patients, and if deemed appropriate by the treating physician, IV therapy is recommended with a regimen suitable for outpatient administration, provided they meet clinical and other criteria for outpatient management (see Recommendations B-4 and C-9); hospitalized stable and responding low-risk patients receiving initial IV empiric antibacterial therapy, particularly those classified as having unexplained FN, may be considered for stepdown to an orally administered regimen and early discharge for outpatient follow-up and monitoring; for patients with FN from cancer therapy who are at high risk for medical complications, the Panel recommends hospitalization for IV antimicrobial therapy and endorses the most recent (2010) recommendations from IDSA<sup>12</sup></p>
<p>C-9. What additional measures are recommended for outpatient management?</p>	<p>Recommendation C-9. The literature review did not identify any studies comparing outcomes of outpatient management for patients with FN with or without specific logistic measures or with different frequencies of contact or evaluation; on the basis of members' expert opinion, the following are recommended as prudent and sensible measures for outpatient management:</p> <ol style="list-style-type: none"> <li>Frequent evaluation for at least 3 days in clinic or at home</li> <li>Daily or frequent telephone contact to verify (by home thermometry) that fever resolves</li> <li>Monitoring of ANC and platelet count for myeloid reconstitution</li> <li>Frequent return visits to clinic</li> <li>Patients should be evaluated for admission to the hospital if any of the following occur: PNF syndrome, fever recurrence, new signs or symptoms of infection, use of oral medications is no longer possible or tolerable, change in the empiric regimen or an additional antimicrobial drug becomes necessary, or microbiologic tests identify species not susceptible to initial regimen</li> </ol>
<p>C-10. How should PNF syndrome be managed?</p>	<p>Recommendation C-10. Low-risk patients who do not defervesce after 2 to 3 days of an initial empiric broad-spectrum antibiotic regimen should be re-evaluated to detect and treat a new or progressing anatomic site of infection and considered for hospitalization</p>
<p>Abbreviations: ANC, absolute neutrophil count; ASCO, American Society of Clinical Oncology; FN, fever and neutropenia; FNE, febrile neutropenic episode; G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B virus; HEPA, high-efficiency particulate air; HSCT, hematopoietic stem-cell transplantation; HSV, herpes simplex virus; IDSA, Infectious Disease Society of America; IFI, invasive fungal infection; IV, intravenous; MASCC, Multinational Association for Supportive Care in Cancer; PNF, persistent neutropenic fever; VZV, Varicella-Zoster virus.</p>	

patient-, cancer-, and treatment-related factors. The Panel supports the recommendations in the ASCO guideline on WBC growth factors<sup>2</sup> that granulocyte CSF prophylaxis be considered before the development of neutropenia for appropriate patients as defined in that guideline.

### Literature Review and Analysis

*Risk factors for FNE and FNE complications.* Investigators and reviewers have evaluated risk factors for developing an FNE or for complications or mortality resulting from an FNE in oncology patients undergoing systemic chemotherapy. Table 2 lists variables

**Table 2.** Factors to Consider in Assessing Risk of an FNE in Patients Undergoing Cytotoxic Chemotherapy for Malignancy

Factor	Effect on Risk	Reported FN Rate (%)	95% CI (%)	Reference No.
<b>Patient characteristic</b>				
Advanced age	Risk increases if age $\geq$ 65 years			30-32
ECOG PS	Risk increases if PS $\geq$ 2			33, 34
Nutritional status	Risk increases if albumin $<$ 35 g/L			33, 35
Prior FN episode	Risk in cycles two to six is four-fold greater if FN episode occurs in cycle one			36
Comorbidities	FN odds increase by 27%, 67%, and 125%, respectively, for one, two, or $\geq$ three comorbidities			37
<b>Underlying malignancy</b>				
Cancer diagnosis*				
Acute leukemia/MDS		85-95		38-41
Soft tissue sarcoma		27	19 to 34.5	36, 37, 42, 43
NHL/myeloma		26	22 to 29	36, 37, 42, 43
Germ cell carcinoma		23	16.6 to 29	36, 37, 42, 43
Hodgkin lymphoma		15	6.6 to 24	36, 37, 42, 43
Ovarian carcinoma		12	6.6 to 17.7	36, 37, 42, 43
Lung cancers		10	9.8 to 10.7	36, 37, 42, 43
Colorectal cancers		5.5	5.1 to 5.8	36, 37, 42, 43
Head and neck carcinoma		4.6	1.0 to 8.2	36, 37, 42, 43
Breast cancer		4.4	4.1 to 4.7	36, 37, 42, 43
Prostate cancer		1	0.9 to 1.1	36, 37, 42, 43
Cancer stage	Risk increases for advanced stage ( $\geq$ 2)			33, 37
Remission status	Risk increases if not in remission			38, 44
Treatment response	Risk is lowest if patient has a CR			38
	If patient has a PR, FN risk is greater for acute leukemia than for solid tissue malignancies			
	FN risk is higher if persistent, refractory, or progressive disease despite treatment			45, 46
<b>Treatment for malignancy</b>				
Cytotoxic regimen				
	Risk is higher with regimens that administer:			42
	Anthracyclines at doses $\geq$ 90 mg/m <sup>2</sup>			
	Cisplatin at doses $\geq$ 100 mg/m <sup>2</sup>			
	Ifosfamide at doses $\geq$ 9 g/m <sup>2</sup>			
	Cyclophosphamide at doses $\geq$ 1 g/m <sup>2</sup>			
	Etoposide at doses $\geq$ 500 mg/m <sup>2</sup>			
	Cytarabine at doses $\geq$ 1 g/m <sup>2</sup>			43
	High dose-density (eg, CHOP-14)			
	Anthracycline + taxane $\pm$ cyclophosphamide, or anthracycline + gemcitabine for breast cancer			32, 47
Dose-intensity	Increased risk if $>$ 85% of scheduled doses are administered†			43, 47
Degree and duration of GI and/or oral mucositis	Risk is greatest if NCI mucositis grade $\geq$ 3 (GI) or if peak OMAS score $\geq$ 2			41, 48-50
Degree and duration of:				
Neutropenia	ANC $<$ 500/ $\mu$ L for $\geq$ 7 days			7, 51, 52
Lymphopenia	ALC $<$ 700/ $\mu$ L (ANC surrogate)			42, 53
Monocytopenia	AMC $<$ 150/ $\mu$ L (ANC surrogate)			54
Prophylactic use of WBC growth factors	Reduces risk for patients selected as in ASCO guideline			2, 55, 56

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; ASCO, American Society of Clinical Oncology; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FN, fever and neutropenia; FNE, febrile neutropenic episode; MDS, myelodysplastic syndrome; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; OMAS, Oral Mucositis Assessment Scale; PR, partial response; PS, performance status.

\*Highest to lowest risk.

†Note that the Panel recommends against routine decreases in dose-intensity as a means of preventing FN.



shown to influence these risks in one or more studies, grouped by characteristics of: patients and their health status, their underlying malignancy, and the chemotherapy regimen they are receiving. Most of the studies cited in Table 2 used multivariable regression analysis to identify independent predictors of FNE risk. Studies cited in Table 2<sup>34-37,42,47,53</sup> and others<sup>56,57</sup> have also developed and tested models to predict likelihood of an FNE in the first or a subsequent chemotherapy cycle. However, the literature search found no data from prospective studies on patients receiving conventional-dose regimens that used validated models, checklists, or scores to select or deselect afebrile neutropenic oncology outpatients for prophylaxis with antibacterial drugs and compared outcomes (eg, rates of FNEs or documented infection) with controls. Thus, on the basis of members' expert opinion, the Panel recommends that patients starting a new chemotherapy regimen undergo an individualized but systematic assessment of risk for an FNE to evaluate the factors listed in Table 2, involving consultation with local infectious disease experts as needed.

**CSF prophylaxis.** Table 2 notes that prophylaxis with a WBC growth factor, also termed a CSF, reduces the risk of an FNE in patients undergoing cytotoxic chemotherapy for malignancy. Guidelines from ASCO<sup>2</sup> and other organizations<sup>11,12,55,58-60</sup> recommend primary prophylaxis with a CSF for patients with a high risk of an FNE based on age, medical history, disease characteristics, and myelotoxicity of their chemotherapy regimen (Table 1 in the ASCO CSF guideline<sup>2</sup> lists commonly used regimens by malignancy, with data on incidence of hematologic toxicities including neutropenia and FNEs; available online at [www.asco.org/guidelines/wbcgf](http://www.asco.org/guidelines/wbcgf)). This guideline Panel endorses the recommendations in the ASCO CSF guideline. Readers are referred to this guideline for recommendations on selecting patients likely to benefit from primary prophylaxis and for review and discussion of the evidence supporting this recommendation.<sup>2</sup> Note that antibacterial and antifungal prophylaxis would generally not be indicated when CSF prophylaxis effectively reduces the depth and duration of neutropenia. Prophylaxis combining an antibacterial therapy with a CSF has not been shown to be more effective for preventing fever or documented infection than either strategy alone (termed indifferent interaction). However, it might be appropriate for outpatients receiving myelosuppressive cytotoxic therapy likely to reduce the ANC to  $< 100/\mu\text{L}$  for  $\geq 7$  days (see Literature Review for Recommendation A-1b). Examples include postremission consolidation with high-dose cytarabine for outpatients with acute myeloid leukemia or outpatient conditioning for a peripheral blood stem-cell autograft for myeloma using a regimen based on melphalan at  $200 \text{ mg}/\text{m}^2$ .

### Recommendation A-1b

The Panel suggests that clinicians consider the use of antibacterial prophylaxis only for patients expected to experience profound neutropenia (defined as  $\text{ANC} < 100/\mu\text{L}$ ) likely to last for  $\geq 7$  days. The Panel does not recommend routine antibacterial prophylaxis for patients with neutropenia that is less severe or of shorter duration. Currently, there are no chemotherapy regimens for solid tumors that would routinely be expected to produce profound neutropenia for  $\geq 7$  days. Therefore, the Panel does not recommend routine use of antibacterial prophylaxis for patients with solid tumors undergoing conventional chemotherapy with or without biologics such as trastuzumab, bevacizumab, or cetuximab. However, antibacterial prophylaxis

might be recommended for patients at high risk of mortality if an FNE occurs.

### Literature Review and Analysis

The literature search identified a systematic review<sup>61</sup> of 29 meta-analyses of RCTs testing various aspects of managing febrile neutropenia that were indexed in PubMed or the Cochrane database through December 2006. Five<sup>62-67</sup> of the 29 meta-analyses, including a Cochrane review,<sup>65,66</sup> focused on outcomes of antibacterial prophylaxis in afebrile neutropenic patients with cancer. The search for this guideline also found two updates<sup>68,69</sup> from the Cochrane review group and two other meta-analyses<sup>70,71</sup> not cited in the systematic review,<sup>61</sup> plus a more recent systematic review<sup>72</sup> of RCTs of antibacterial prophylaxis. Early meta-analyses<sup>62-64</sup> reported that antibacterial prophylaxis reduced the incidence of documented infection and/or fever but did not decrease overall or infection-related mortality. Subsequent meta-analyses<sup>65-67,69,70</sup> and systematic reviews<sup>61,72,73</sup> have reported that antibacterial prophylaxis decreased mortality when compared with pooled controls receiving either placebo or no treatment.

However, a majority of patients included in the RCTs pooled for these meta-analyses<sup>61-71</sup> were undergoing either remission induction (or reinduction) for hematologic malignancy (mostly acute leukemia) or hematopoietic SCT (HSCT). Pooled data from the Cochrane review<sup>65</sup> showed high rates of febrile episodes, clinically documented infection, microbiologically documented infection, and bacteremia for patients in the control arms of these trials: 60%, 30%, 30%, and 20%, respectively, across controls from all studies of prophylaxis versus placebo or no intervention, and 53%, 23%, 28%, and 16%, respectively, across controls from RCTs of fluoroquinolone prophylaxis versus placebo or no intervention. Thus, the neutropenic patients enrolled onto nearly all these trials were at relatively high risk for an FNE and infection, and results from the meta-analyses<sup>61-71</sup> may not generalize to low-risk patients undergoing conventional-dose chemotherapy for solid tumors or lymphoma. Although the meta-analyses<sup>61-71</sup> did not report pooled estimates of neutropenia duration among randomly assigned patients, the within-study mean duration ranged from 7 to 32 days across nine RCTs of fluoroquinolone prophylaxis that reported this outcome,<sup>63</sup> and the IDSA guideline panel<sup>12</sup> estimated the duration as typically  $> 7$  days for the majority of patients enrolled across all RCTs of antibacterial prophylaxis.

Few RCTs of antibacterial prophylaxis focused on patients with cancer and neutropenia at low risk for an FNE or infection. The largest ( $N = 1,565$ ) was a double-blind placebo-controlled RCT of levofloxacin prophylaxis in patients with solid tumors or lymphoma at risk for short-term severe neutropenia ( $\text{ANC} < 500/\mu\text{L}$ ) while receiving multiple cycles of standard-dose chemotherapy without CSF prophylaxis.<sup>74</sup> Levofloxacin prophylaxis significantly decreased documented febrile episodes (core temperature  $> 38^\circ\text{C}$ , the primary outcome of the trial) attributed to infection in the first cycle (3.5% *v* 7.9%; relative risk [RR], 0.44; 95% CI, 0.28 to 0.68) and over the full course of chemotherapy (10.8% *v* 15.2%; RR, 0.71; 95% CI, 0.55 to 0.92). Levofloxacin prophylaxis also significantly decreased rates of probable infection and hospitalization for infection, again both in the first cycle and over the full course of chemotherapy. However, levofloxacin prophylaxis did not yield a statistically significant decrease in rates of severe infection (infection-related sepsis syndrome, death, or both) or infection-related mortality. Incidence of FNEs was not listed as a secondary outcome and was not reported.

A subset analysis in one meta-analysis<sup>69</sup> pooled data from the RCT by Cullen et al<sup>74</sup> with three trials<sup>75-77</sup> using other fluoroquinolones as prophylaxis in patients with solid tumors or lymphoma and reported a statistically significant decrease in all-cause mortality during the first month of chemotherapy (1.4% v 2.8%; RR, 0.51; 95% CI, 0.27 to 0.97). However, the absolute difference in 30-day mortality was modest (1.4%), and the relative effect size in the largest (1,565 randomly assigned patients) and most recent trial<sup>74</sup> (RR, 0.67; 95% CI, 0.32 to 1.38) was substantially smaller than in the other three RCTs,<sup>75-77</sup> with RRs of 0.13, 0.24, and 0.33. The effect size in one of the trials<sup>75</sup> may have been smaller than suggested in the meta-analysis,<sup>69</sup> resulting in a smaller absolute difference overall (1.2%). Additionally, levofloxacin prophylaxis did not significantly decrease all-cause mortality by the end of follow-up (4% v 4.6%; RR, 0.86; 95% CI, 0.54 to 1.38),<sup>69</sup> although data on this outcome were available only from the trial by Cullen et al.<sup>74</sup> Given the competing influences on all-cause mortality, including antibacterial therapy administered as treatment for the FNE, and the mortality impact of the underlying cancer, these data are insufficient to support the routine use of prophylactic antibacterial therapy in low-risk patients.

The Cochrane review<sup>65,66</sup> also reported statistically significant increases in adverse effects for patients randomly assigned to antibacterial prophylaxis compared with controls (9.5% v 6%; RR, 1.53; 95% CI, 1.24 to 1.90 for 15 RCTs of fluoroquinolone prophylaxis and 12% v 7%; RR, 1.59; 95% CI, 1.37 to 1.85 for 34 RCTs of any antibacterial prophylaxis, v placebo or no intervention). Antibacterial prophylaxis also significantly increased the proportion of patients who discontinued study drug for adverse effects across 16 RCTs of any antibacterial prophylaxis compared with controls (4.3% v 2.0%; RR, 2.32; 95% CI, 1.39 to 3.88), although the increase was not statistically significant across seven RCTs of fluoroquinolone prophylaxis compared with controls (3.1% v 1.9%; RR, 1.52; 95% CI, 0.79 to 2.92). Although available meta-analyses<sup>61-71</sup> did not report pooled results for specific adverse effects, rash and GI effects were reported most frequently in the largest RCT of levofloxacin prophylaxis for low-risk patients<sup>74</sup>; however, data on grade and severity were not included. Although musculoskeletal events including tendinitis and tendon rupture have been associated with fluoroquinolone administration in settings other than antibacterial prophylaxis for neutropenia resulting from cancer chemotherapy,<sup>78-80</sup> and the US Food and Drug Administration (FDA) added blackbox warnings of these risks to the package inserts for all fluoroquinolones in 2008, few musculoskeletal events occurred in the RCT by Cullen et al<sup>74</sup> (four among those randomly assigned to levofloxacin and one among controls).

Prior reviews<sup>63,65-69,72,73,81</sup> and guidelines<sup>7,11,12,29</sup> have raised and discussed concerns that routine use (or overuse) of antibacterial prophylaxis may increase spread of resistant strains. Patients infected while receiving antibacterial prophylaxis likely harbor strains resistant to the drug they received and possibly to other drugs of the same class. If these organisms spread within the unit (eg, an outpatient infusion clinic) or institution, patients treated there subsequently may be at increased risk for infection by resistant strains, and the antibacterial drug class may become less useful if resistant strains spread across the locality, region, or nation. Although single-institution observational studies<sup>82-85</sup> have reported that patients with cancer administered a prophylactic fluoroquinolone often are colonized subsequently by

fluoroquinolone-resistant bacteria, meta-analysis<sup>69</sup> of eight RCTs (including the two largest<sup>74,86</sup>) did not find that fluoroquinolone prophylaxis increased rates of infection by resistant strains (54 [4%] of 1,358 randomly assigned to a fluoroquinolone v 51 [3.8%] of 1,354 randomly assigned to placebo or no treatment; RR, 1.04; 95% CI, 0.73 to 1.50). Fluoroquinolone prophylaxis also did not have a statistically significant effect on the proportion of patients who then developed fungal infections (14 trials; 6.9% of 535 patients randomly assigned to treatment v 8.2% of 536 patients randomly assigned to placebo or no treatment; RR, 0.83; 95% CI, 0.56 to 1.22).<sup>65,66</sup> However, fluoroquinolone-resistant species were cultured from 54 (35%) of 154 patients with documented infections after fluoroquinolone prophylaxis.<sup>81</sup> Thus, it is probably inadvisable to use a different fluoroquinolone as empiric therapy for neutropenic patients who develop fever while receiving fluoroquinolone prophylaxis.

Because 1) robust evidence is lacking that antibacterial prophylaxis yields a statistically significant decrease in infection-related or all-cause mortality at the completion of chemotherapy in neutropenic patients at low risk for an FNE, 2) most infections in low-risk patients are mild and readily treated with empiric therapy, 3) routine fluoroquinolone prophylaxis might select for Gram-positive bacteria as the predominant pathogens if an infection develops subsequently, and 4) routine prophylaxis can cause adverse effects, spread resistant strains, and require use of more intensive empiric antibacterial therapy for an FNE, the Panel recommends that clinicians limit use of antibacterial prophylaxis to patients at high risk for an FNE associated with prolonged severe neutropenia (ANC < 500/ $\mu$ L). The expected duration and depth of neutropenia are important determinants of such risk, although not the only factors to consider (Table 2). However, because direct evidence is lacking to define risk thresholds for either of the two variables, the Panel reached an informal consensus and recommends that for patients without any of the other high-risk features listed in Table 2, potential benefits of antibacterial prophylaxis are likely to outweigh potential harms only if profound neutropenia (defined as ANC < 100/ $\mu$ L) is likely to last for  $\geq$  7 days. Other guidelines<sup>11,12</sup> agree that patients with an expected duration  $\geq$  7 days are at high risk, whereas risk is low if the expected duration is shorter. However, these guidelines disagree on the depth of neutropenia to define high risk for an FNE. Unless one or more other high-risk features of Table 2 are present, the ASCO Panel agrees with the IDSA guideline<sup>12</sup> that antibacterial prophylaxis should be limited to patients expected to have profound neutropenia (ANC < 100/ $\mu$ L) for at least 7 days, whereas the NCCN guideline<sup>11</sup> recommends antibacterial prophylaxis if the ANC is expected to be < 1000/ $\mu$ L for > 7 days.

### **Recommendation A-1c**

The Panel recommends administering antifungal prophylaxis to decrease invasive fungal infections (IFIs) resulting from opportunistic yeast or mold species to patients receiving chemotherapy expected to cause profound neutropenia (ANC < 100/ $\mu$ L) for  $\geq$  7 days, which confers substantial risk (> 6% to 10%) for IFI. The Panel does not recommend antifungal prophylaxis for patients with solid tumors undergoing conventional-dose chemotherapy with or without biologics such as trastuzumab, bevacizumab, or cetuximab.

### Literature Review and Analysis

The literature search identified multiple systematic reviews<sup>61,81,87,88</sup> and meta-analyses<sup>89-94</sup> of RCTs that enrolled patients with neutropenia or patients expected to develop neutropenia from treatment for malignancy and compared outcomes of systemic antifungal prophylaxis versus controls administered placebo, no treatment, or a nonabsorbable oral antifungal. Three of the meta-analyses are not directly applicable here because they either pooled data from RCTs on antifungal prophylaxis with data from RCTs on empiric therapy<sup>89,91</sup> or focused on RCTs of itraconazole and pooled results across control arms administered placebo, no treatment, nonabsorbable oral polyenes, or fluconazole.<sup>93</sup> The remaining three meta-analyses<sup>90,92,94</sup> reported that when compared with controls, systemic antifungal prophylaxis significantly decreased mortality attributed to fungal infections. Additional meta-analyses in these reviews showed statistically significant decreases in the need for subsequent full-dose parenteral antifungal therapy and in the incidence of systemic, invasive, and/or superficial fungal infections. However, most patients randomly assigned in the RCTs pooled for meta-analysis were at high risk for IFI resulting from HSCT, induction chemotherapy for acute leukemia, or other treatments that caused lengthy durations of profound neutropenia. Furthermore, no trials included in these meta-analyses were limited to patients with solid tumors undergoing conventional-dose chemotherapy with or without biologics.

The first meta-analysis<sup>90</sup> to report a significant effect on fungal infection-related mortality only included trials of oral fluconazole versus control (13 trials; N = 2,688; odds ratio [OR], 0.45; 95% CI, 0.29 to 0.72). Subset analysis showed the effect was not statistically significant across trials without any patients who underwent bone marrow transplantation (five trials; N = 1,323; OR, 0.91; 95% CI, 0.30 to 2.82). Meta-analytic results pooling the other eight trials were not reported; only two of these were limited to patients undergoing transplantation. Although fluconazole had no impact on mold infections, it significantly decreased the incidence of proven systemic opportunistic yeast infections across all trials (16 trials; N = 3,734; OR, 0.42; 95% CI, 0.31 to 0.57) but not across trials without patients receiving marrow transplants (six trials; N = 1,373; OR, 0.85; 95% CI, 0.47 to 1.55). Other analyses showed that fluconazole decreased systemic yeast infections across trials with proven infections in > 15% of controls (OR, 0.23; 95% CI, 0.15 to 0.36) but not across trials with proven infections in < 15% of controls (OR, 0.78; 95% CI, 0.50 to 1.21).

A subsequent review<sup>92</sup> pooled data from 38 RCTs, including 17 trials of fluconazole (58% of randomly assigned patients), five of itraconazole (22% of patients), 10 of ketoconazole (10% of patients), two of miconazole (3% of patients), and four of IV amphotericin B (6% of patients). Systemic antifungal prophylaxis significantly decreased fungal infection-related mortality across RCTs reporting this outcome (30 trials; N = 5,528; OR, 0.58; 95% CI, 0.41 to 0.82) but did not significantly decrease overall mortality (32 trials; N = 6,160; OR, 0.87; 95% CI, 0.74 to 1.02). In subset analyses, the effect of systemic antifungal prophylaxis on fungal infection-related mortality was statistically significant across trials limited to patients undergoing HSCT (OR, 0.48; 95% CI, 0.28 to 0.82) but not across trials without any patients receiving transplants (OR, 0.67; 95% CI, 0.43 to 1.03). Other subset analyses found that systemic antifungal prophylaxis reduced overall mortality across trials with mean neutropenia durations > 15 days (ie, shortest quartile excluded; OR, 0.76; 95% CI, 0.62 to 0.94) but not across trials with mean neutropenia durations < 22 days (ie,

longest quartile excluded; OR, 0.85; 95% CI, 0.71 to 1.01). Metaregression analysis of trial and patient characteristics suggested a statistically significant treatment effect on overall mortality was more likely for RCTs in which most patients underwent HSCT, in trials with a high rate of proven IFIs in the control arm, and in trials with prolonged neutropenia, whereas a statistically significant treatment effect on fungal infection-related mortality was more likely in trials with a high proportion of patients treated for acute leukemia and prolonged neutropenia.

The most recent review<sup>94</sup> pooled data from 33 RCTs and also found a statistically significant decrease in fungal infection-related mortality (2.2% of 2,710 randomly assigned to systemic antifungal prophylaxis v 4.2% of 2,653 randomly assigned to control; RR, 0.55; 95% CI, 0.41 to 0.74). The review also found statistically significant decreases in all-cause mortality at the end of follow-up (31 trials; 12% of 2,963 randomly assigned to systemic antifungal prophylaxis v 14.5% of 2,918 randomly assigned to control; RR, 0.84; 95% CI, 0.74 to 0.95; number needed to treat [NNT], 43; 95% CI, 26 to 138) and at 30 days after treatment (28 trials; RR, 0.79; 95% CI, 0.68 to 0.92). Subset analyses showed systemic antifungal prophylaxis significantly decreased overall mortality across trials limited to patients who underwent allogeneic HSCT (four trials; N = 552; RR, 0.62; 95% CI, 0.45 to 0.85) but not across all trials involving patients who underwent HSCT of any type (six trials; N = 1,090; RR, 0.67; 95% CI, 0.42 to 1.09). Additional subset analyses found statistically significant decreases in documented IFIs and fungal infection-related mortality for trials involving patients undergoing allogeneic HSCT but not for trials involving patients undergoing autologous HSCT (four trials each; N = 553 for allogeneic HSCT; N = 298 for autologous HSCT). Subset analyses of trials with most patients undergoing treatment for acute leukemia (24 trials; N = 4,206, majority undergoing induction) found significant decreases in fungal infection-related mortality and IFI rates, but the decrease in all-cause mortality at the end of follow-up did not reach statistical significance (RR, 0.88; 95% CI, 0.74 to 1.06). Metaregression analysis showed statistically significant associations between the proportion of randomly assigned patients being treated for leukemia with the treatment effects of systemic antifungal prophylaxis in both overall mortality and risk for IFI.

Data from the most recent meta-analysis of RCTs of antifungal prophylaxis<sup>93</sup> also showed that pooled IFI rates (either candidiasis or aspergillosis) among controls were approximately 6% across 24 studies of patients undergoing treatment for acute leukemia and > 10% across four studies of patients undergoing HSCT, each associated with lengthy durations of profound neutropenia. IFI risk is well below this threshold in patients undergoing conventional-dose chemotherapy for lymphoma<sup>95</sup> or solid tumor,<sup>96</sup> including those undergoing autologous HSCT for these malignancies,<sup>97</sup> and thus, antifungal prophylaxis is unlikely to benefit these patients. Therefore, in agreement with other guidelines,<sup>11,12,98</sup> the Panel recommends limiting antifungal prophylaxis to patients at substantial risk for IFI (> 6% to 10%).

Reviewers<sup>96,99</sup> list the following among risk factors for invasive mold infection: prolonged profound neutropenia (ANC < 100 cells/ $\mu$ L for > 7 days) in the context of intensive remission-induction or reinduction therapy for acute leukemia in environments where the risk for invasive aspergillosis exceeds 6%; prolonged (> 21 days) severe neutropenia (ANC < 500/ $\mu$ L), lymphocytopenia (absolute lymphocyte count < 500 cells/ $\mu$ L), or monocytopenia (absolute monocyte count < 150 cells/ $\mu$ L) among allogeneic HSCT recipients

experiencing graft failure; use of purine analogs (eg, fludarabine) to treat malignancy or for pre-HSCT conditioning; use of intensive immunosuppression for treating graft-versus-host disease; reactivation of cytomegalovirus; iron overload states; a previous documented invasive mold infection; and environmental exposures associated with personal habits (eg, cigarette smoking, rural living, and agricultural or construction occupation), outside activities (eg, exposures to dusty environments, construction, or demolition sites), or indoor activities (eg, manipulation of potted plants, being nursed in a non–high-efficiency particulate air-filtered protected environment). If they co-exist, many of these risk factors may interact to enhance the risk for mold infection.

### Recommendation A-1d

Patients receiving chemotherapy regimens associated with a risk > 3.5% for pneumonia resulting from *Pneumocystis jirovecii* (PCP; eg, those with  $\geq 20$  mg of prednisone equivalents daily for  $\geq 1$  month or those based on purine analogs) are eligible for prophylaxis.

### Literature Review and Analysis

Direct evidence from RCTs is lacking to compare outcomes of patients receiving specific chemotherapy regimens for malignancy with versus without prophylaxis for PCP or to establish a PCP risk threshold for benefit from prophylaxis. On the basis of data from retrospective analyses and members' expert opinion, the Panel recommends that prophylaxis be considered if risk for PCP is > 3.5%.

Retrospective analyses<sup>100-102</sup> suggest those at greatest risk are patients undergoing intensive induction (or salvage reinduction) for acute leukemia, allogeneic bone marrow transplantation (particularly if receiving alemtuzumab), or treatment with either high-dose corticosteroids (eg,  $\geq 20$  mg of prednisone equivalents daily for  $\geq 1$  month) or purine analogs that deplete T cells such as fludarabine or cladribine. Additionally, a recent report<sup>103</sup> suggests the regimen combining rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone every 2 weeks (R-CHOP-14) is associated with elevated risk for PCP (10% to 15%), although the regimen with the same drugs every 3 weeks (classical R-CHOP) is not. Another recent retrospective analysis<sup>104</sup> suggests that CD4+ lymphocyte counts  $\leq 200/\mu\text{L}$  predicted a higher risk (approximately 19%) for PCP in patients treated for B-cell non-Hodgkin lymphoma. Finally, PCP has been reported in two of 258 patients with breast cancer administered dose-dense chemotherapy with doxorubicin plus cyclophosphamide followed by paclitaxel.<sup>105</sup>

### Recommendation A-1e

Antiviral prophylaxis should be offered to patients known to be at substantial risk for reactivation of hepatitis B virus (HBV) infection.

### Literature Review and Analysis

Reactivation of HBV infection after treatment for malignancy has been reviewed extensively.<sup>81,106-111</sup> Guidelines from several other organizations suggest that patients at risk for HBV reactivation should be screened for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc).<sup>112-116</sup> Such patients may include, but are not limited to, those born in countries with a prevalence of HBsAg of  $\geq 2\%$ , patients who are intravenous drug users, or those infected with HIV. An ASCO provisional clinical opinion (PCO) addressed the issue of HBV screening for patients receiving cyto-

toxic or immunosuppressive chemotherapy for treatment of malignant diseases.<sup>117</sup> The PCO concluded that available evidence was insufficient to determine the net benefits and harms of routine screening for chronic HBV infection in all individuals with cancer about to receive (or already receiving) cytotoxic or immunosuppressive therapy. The PCO Panel recommended a more targeted approach to HBV testing, using clinical judgment to select patients at risk who are about to receive or already receiving highly immunosuppressive treatments including, but not limited to, HSCT and regimens that include rituximab.

Three groups with a history of prior exposure to HBV are at risk: patients with chronic infection and viremia, chronic inactive carriers (positive for HBsAg for  $\geq 6$  months but with serum HBV DNA < 2,000 IU/mL and normal serum levels of hepatic transaminases), and those with immunity against HBV because of past exposure (resolved hepatitis B; HBsAg negative and undetectable serum HBV DNA but anti-HBc positive alone or with antibodies to the surface antigen).<sup>81,106</sup> Studies have reported reactivation in 24% to 67% of patients with lymphoma or solid tumor who are either HBsAg positive or negative but positive for antibody to the HBV envelope antigen<sup>111</sup>; reactivation is less frequent among those with resolved hepatitis B. In one retrospective study of 524 patients receiving rituximab, 20 (3.8%) were HBsAg positive, and of these, 10 (50%) developed HBV reactivation.<sup>112</sup> Factors that may increase reactivation risk include male sex, younger age, hepatic transaminase levels > the normal range or HBV DNA >  $3 \times 10^5$  copies/mL before cytotoxic therapy begins, dose-intense chemotherapy, and severe immunosuppression.<sup>81,106,110</sup> Treatment regimens for lymphoma or solid tumors that include anti-CD20 antibodies (eg, rituximab), glucocorticoids, or anthracyclines are associated with higher risk of HBV reactivation, as are most regimens for hematologic malignancies or HSCT conditioning.

Patients with active HBV disease (high circulating levels of HBV DNA plus increased serum levels of hepatic transaminases) should be treated for HBV infection before chemotherapy, if possible. Multiple reviews<sup>106-112,118-120</sup> of prospective controlled trials have concluded that prophylaxis with a nucleoside analog decreases HBV reactivation and hepatitis and improves outcomes when compared with therapy deferred until serology shows evidence of reactivation (Recommendation A-2d provides review and analysis of supporting literature). However, the overwhelming majority of patients studied in these trials were HBsAg positive at baseline.<sup>81,106,109,119</sup> For patients with resolved hepatitis B (HBsAg negative and undetectable serum HBV DNA but anti-HBc positive), available evidence is insufficient to determine whether outcomes of HBV prophylaxis are superior to outcomes of frequent monitoring and preemptive therapy when evidence of reactivation is detected (eg, increased levels of ALT).

### Recommendation A-1f

Prophylaxis to prevent reactivation of infection because of herpesviruses (herpes simplex virus [HSV] or Varicella-Zoster virus [VZV]) is recommended for seropositive patients undergoing therapy for certain hematologic malignancies (see Literature Review and Analysis for details).

### Literature Review and Analysis

Evidence summarized in other reviews<sup>11,81,121-123</sup> suggests that most HSV or VZV infections in patients undergoing treatment for malignancy are the result of reactivation of latent virus from prior

exposure; new primary infections are uncommon. Most US adults are seropositive for HSV-1 and/or -2, and much of the morbidity resulting from oral mucositis during treatment for malignancy has been attributed to HSV reactivation.<sup>121-124</sup> In the absence of HSV prophylaxis, reactivation has been reported in 37% to 57% of patients undergoing intensive chemotherapy for hematologic malignancies<sup>81,124</sup> and in 68% to 90% of those undergoing myeloablative allogeneic HSCT.<sup>81,125-127</sup> Reactivation usually occurs soon after chemotherapy, while patients are still severely neutropenic.

A Cochrane review<sup>128</sup> pooled data from 12 placebo-controlled RCTs of persons undergoing cancer treatment and found that nucleoside analogs active against HSV decreased the proportion of patients with oral HSV lesions (nine trials; N = 398; RR, 0.16; 95% CI, 0.08 to 0.31) and with culture-positive viral isolates (nine trials; N = 511; RR, 0.17; 95% CI, 0.07 to 0.37). However, none of the trials reported the effects of HSV prophylaxis on analgesia use or patients' quality of life, secondary outcomes for the review. Note that only one of the RCTs enrolled patients with solid tumors (57 patients with squamous cell head and neck cancer undergoing chemotherapy and radiation therapy).<sup>129</sup> Although HSV prophylaxis modestly decreased the low frequency of viral isolates observed among controls, it had no effect on the frequency or type of oral lesions. Given the low frequency of both outcomes in the placebo group, the investigators concluded that HSV is not a frequent complication of oral mucositis in patients with head and neck cancers. Most patients in the other 11 trials (and in a meta-analysis limited to trials for hematologic malignancies<sup>130</sup>) underwent allogeneic HSCT or received therapy for acute leukemia.

Because there is insufficient evidence of clinical benefit, the Panel does not recommend HSV prophylaxis in low-risk outpatients who are moderately neutropenic from conventional dose regimens for solid tumors or lymphoma. Prophylaxis also is not recommended for patients who are HSV seronegative. The Panel agrees with other guidelines<sup>11,12,118,131-134</sup> and recommends use of HSV prophylaxis for seropositive patients undergoing allogeneic HSCT; patients receiving induction, reinduction, or consolidation chemotherapy for acute leukemia; patients receiving T-cell depleting chemotherapy with alemtuzumab or purine analogs such as fludarabine or chlorodeoxyadenosine; and patients receiving bortezomib.<sup>135</sup> Guidelines from other organizations disagree on whether to offer HSV prophylaxis to all seropositive patients undergoing autologous HSCT while they are neutropenic,<sup>11,12</sup> to those who undergo CD34-selected stem-cell transplantation from the start of conditioning until engraftment,<sup>118</sup> or to those most likely to experience substantial mucositis from the conditioning regimen.<sup>131</sup> Definitive data are lacking to address this uncertainty because there have been no placebo-controlled RCTs of HSV prophylaxis involving patients undergoing autologous HSCT.

Reactivation of latent VZV, present in most adults, results in herpes zoster; complications may include postherpetic neuralgia, zoster ophthalmicus, scarring, or bacterial superinfection.<sup>121,122</sup> T-cell suppression and compromised immune function seem to confer greater risk of VZV reactivation than myelosuppression or neutropenia.<sup>118</sup> The risk is generally deemed insufficient to warrant prophylaxis in patients who are moderately neutropenic after conventional-dose regimens for solid tumors or lymphoma.<sup>11,12,118</sup> Among patients with hematologic malignancies, VZV reactivation is reportedly uncommon after imatinib for chronic myeloid leukemia (CML; 2.6%)<sup>136</sup> but more frequent after fludarabine or alemtuzumab for chronic lymphocytic leukemia (10% to 15%),<sup>121,137,138</sup> treatment for Hodgkin lym-

phoma or autologous HSCT (25%),<sup>121,139,140</sup> and bortezomib for multiple myeloma (11% to 15% in most reports<sup>135,141</sup>); however, one small series<sup>142</sup> reported reactivation in six of 10 refractory and relapsed patients).

VZV reactivation occurs in 30% to 60% of those who undergo allogeneic HSCT but is typically delayed until after engraftment.<sup>81,121,122,143-146</sup> The median time to reactivation among such patients has been reported to be approximately 8 months, and approximately one in five may develop postherpetic neuralgia.<sup>147</sup> Nucleoside analogs used for HSV prophylaxis in neutropenic patients also seem to suppress VZV reactivation. Data from an RCT<sup>148</sup> demonstrated that long-term prophylaxis (from months 1 to 2 through the first year after allogeneic transplantation) significantly decreased the proportion of patients who experienced VZV disease by the end of year 1 (n = 77; hazard ratio [HR], 0.16; 95% CI, 0.035 to 0.74; P = .006); however, it had no statistically significant effect on VZV disease once prophylaxis was discontinued (year 2: HR, 0.52; 95% CI, 0.21 to 1.3; years 2 to 5: HR, 0.76; 95% CI, 0.36 to 1.6). Perhaps because of this, organizations vary with respect to their recommendations on use of long-term VZV prophylaxis in allogeneic transplant recipients. The NCCN<sup>11</sup> recommends use for all seropositive patients during the first year after transplantation, citing additional data from two retrospective cohort studies<sup>149,150</sup> and an uncontrolled prospective study<sup>151</sup> that reported no evidence of rebound VZV disease after prophylaxis ended. In contrast, German<sup>118</sup> and British<sup>132</sup> guidelines recommend against extended anti-VZV prophylaxis for all allogeneic transplant recipients, arguing that most reactivations are easily managed. A recent joint guideline from the IDSA, Association for Medical Microbiology and Infectious Diseases Canada, American Society of Blood and Marrow Transplant, US Centers for Disease Control and Prevention (CDC), European Blood and Marrow Transplant Group, and Society for Healthcare Epidemiology of America recommends that all VZV seropositive patients undergoing allogeneic and autologous SCT receive long-term acyclovir prophylaxis over the first year after transplantation.<sup>134,152</sup> The optimum duration of prophylaxis remains undefined for patients with graft-versus-host disease; however, some investigators advocate continuance until all immunosuppressive therapy has been discontinued, and the circulating CD4-T lymphocyte count has recovered to > 200/ $\mu$ L. Although prophylaxis strategies may be effective for patients receiving other treatments such as bortezomib,<sup>153,154</sup> the optimal duration for prophylaxis remains unknown in these settings as well.

Several guidelines<sup>118,131,134</sup> also recommend vaccinating VZV-seronegative family members and household contacts of allogeneic transplantation candidates at least 4 weeks before conditioning begins. Finally, multiple guidelines recommend offering anti-VZV prophylaxis to all patients undergoing autologous transplantation,<sup>11,12,134</sup> although another<sup>118</sup> recommends against it unless hematopoiesis is reconstituted with stem cells selected for CD34 positivity.

### Recommendation A-1g

Seasonal influenza immunization is recommended for all patients undergoing treatment for malignancy and for all family and household contacts.

## Literature Review and Analysis

Previous reviews<sup>81,121,122,155-159</sup> and guidelines of other organizations<sup>11,12,118</sup> have summarized evidence on the epidemiology of and risks for serious and life-threatening complications (eg, viral pneumonia) from influenza-related upper respiratory tract infections (URTIs) in oncology patients. Mortality among US patients with cancer admitted for treatment of URTIs between 1998 and 2001 was approximately 9%.<sup>157</sup> Systematic reviews<sup>158-160</sup> of available studies (predominantly retrospective cohorts) found that immunologic responses to influenza vaccine were significantly weaker in patients undergoing cancer chemotherapy than in persons not receiving chemotherapy. Nevertheless, most studies reported that a substantial proportion of patients administered cancer chemotherapy mounted protective responses to influenza vaccine, particularly if vaccinated after a chemotherapy-free interval of  $\geq 30$  days.<sup>159</sup> The safety of inactivated influenza vaccines in oncology patients also is well established.<sup>158,159,161-165</sup>

A recent Cochrane review<sup>164</sup> of the safety and effectiveness of viral vaccines in patients with hematologic malignancies identified two RCTs (one of children with acute lymphocytic leukemia or lymphoma and the other of adults with multiple myeloma) comparing inactivated influenza vaccine with no vaccine. Although neither trial reported on incidence of influenza (primary outcome of the Cochrane review), and mortality did not differ significantly between arms in the trial reporting this outcome, pooled analyses showed that vaccination decreased the risks of experiencing  $\geq$  one URTI (RR, 0.56; 95% CI, 0.44 to 0.72;  $P < .001$ ),  $\geq$  one lower respiratory tract infection (RR, 0.39; 95% CI, 0.19 to 0.78;  $P = .008$ ), and hospitalization (RR, 0.17; 95% CI, 0.09 to 0.31;  $P < .001$ ). The frequency of irritability and local adverse effects was significantly greater among vaccine recipients than controls. An earlier Cochrane review<sup>165</sup> of influenza vaccination in children undergoing chemotherapy included one RCT and eight non-randomized controlled trials, but none reported on clinical outcomes of influenza infection. The literature search for this guideline found no reports of RCTs of influenza vaccination in adult patients undergoing chemotherapy for solid tumors. Data are also unavailable comparing outcomes of oncology outpatients with versus without vaccination of family members and household contacts. Nevertheless, given that many patients mount adequately protective immunologic responses to inactivated influenza vaccine<sup>158-160</sup> and the well-documented safety of the vaccine in such patients,<sup>158,159,161-165</sup> the Panel agrees with recommendations from the CDC Advisory Committee on Immunization Practices<sup>166-169</sup> and other organizations<sup>11,12,118</sup> that all patients undergoing treatment for malignancy and all family and household contacts receive the seasonal influenza vaccination.

### Question A-2

What antimicrobial drug classes should be used to prevent infection in afebrile neutropenic outpatients who should be offered prophylaxis?

Because evidence was unavailable from trials limited to outpatients, the Panel considered evidence from studies on inpatients or mixed populations. Recommendations A-2a to A-2f on prophylaxis for neutropenic but afebrile outpatients, evaluated and found likely to benefit from prophylaxis as described in Recommendations A-1a to A-1g, are based on the summarized evidence and Panel members' expert opinion. Similarly, because evidence was unavailable to directly compare different durations and timing (start and stop dates) for

prophylactic therapies, the suggestions of the Panel on timing and duration reflect members' experience and expert opinion.

### Recommendation A-2a

The Panel recommends using antibacterial prophylaxis with an orally administered, systemically absorbed fluoroquinolone to prevent invasive infection resulting from Gram-negative bacilli in outpatients with profound neutropenia expected for  $\geq 7$  days in association with severe mucositis (eg, from primary or salvage remission-induction therapy for acute leukemia, dose-intensive postremission consolidation for acute leukemia, or HSCT). Note that prophylaxis may be less effective in environments where  $> 20\%$  of Gram-negative bacilli are resistant to fluoroquinolones.

## Literature Review and Analysis

The Cochrane review<sup>65,66,69</sup> of antibacterial prophylaxis in afebrile neutropenic patients with cancer identified 13 randomized trials that directly compared outcomes of a quinolone with those of trimethoprim-sulfamethoxazole (TMP-SMX). The review also found nine trials comparing a quinolone plus another drug active against Gram-positive organisms versus the same quinolone alone and additional trials comparing systemic versus nonabsorbable antibiotics. Nearly all of these trials tested a fluoroquinolone in the experimental arm, although meta-analyses did not exclude the few trials with older quinolones (eg, nalidixic acid). As in the RCTs versus placebo or no treatment (see Recommendation A-1b), a majority of randomly assigned patients were hospitalized and treated for hematologic malignancies (eg, remission induction for acute leukemia, CML in blast crisis, lymphoma, or multiple myeloma).

Indirect comparison of meta-analytic results for all-cause mortality in a subset of RCTs that compared fluoroquinolones versus placebo or no treatment (15 trials;  $N = 1,753$ ; fluoroquinolones, 3.1%  $\nu$  control, 4.9%; RR, 0.62; 95% CI, 0.45 to 0.86)<sup>69</sup> with meta-analytic results for a subset of RCTs that compared TMP-SMX versus placebo or no treatment (14 trials;  $N = 870$ ; TMP-SMX, 9.4%  $\nu$  control, 13.1%; RR, 0.71; 95% CI, 0.49 to 1.02)<sup>65,66</sup> suggested that fluoroquinolones might be more efficacious than TMP-SMX as antibacterial prophylaxis. However, meta-analyses of RCTs directly comparing quinolones with TMP-SMX found no statistically significant differences in all-cause mortality (10 trials;  $N = 917$ ; quinolones, 7.1%  $\nu$  TMP, 6.7%; RR, 1.07; 95% CI, 0.66 to 1.72) or infection-related mortality (11 trials;  $N = 1,019$ ; quinolones, 4.5%  $\nu$  TMP-SMX, 5.1%; RR, 0.91; 95% CI, 0.54 to 1.54),<sup>65</sup> and additional meta-analyses<sup>65</sup> found no statistically significant differences between quinolones and TMP-SMX in the number of febrile episodes, clinically documented infections, or bacteremia. Quinolone prophylaxis did significantly decrease microbiologically documented infections (11 trials;  $N = 1,019$ ; 24.7%  $\nu$  34.2%; RR, 0.72; 95% CI, 0.6 to 0.86) in trials that directly compared it with TMP-SMX. Quinolones also caused fewer adverse effects overall (10 trials;  $N = 1,027$ ; 26.7%  $\nu$  36.9%; RR, 0.74; 95% CI, 0.63 to 0.87) and fewer adverse effects leading to discontinuation (seven trials;  $N = 850$ ; 7.7%  $\nu$  18.1%; RR, 0.44; 95% CI, 0.3 to 0.63) than TMP-SMX.<sup>65</sup> Finally, a smaller proportion of patients treated with a quinolone were infected with bacteria resistant to the drug they received for prophylaxis compared with those administered TMP-SMX (six trials;  $N = 366$ ; quinolones, 9.9%  $\nu$  TMP-SMX, 22.7%; RR, 0.45; 95% CI, 0.27 to 0.74).<sup>65,68</sup>

Prophylactic regimens that combined a quinolone with a drug active against Gram-positive organisms did not significantly improve all-cause mortality (nine trials; N = 1,232; quinolone plus other drug, 3.4% *v* quinolone alone, 2.8%; RR, 1.23; 95% CI, 0.66 to 2.30) or infection-related mortality (nine trials; N = 1,232; quinolone plus other drug, 3.9% *v* quinolone alone, 3.4%; RR, 1.11; 95% CI, 0.63 to 1.95) when compared with the same quinolone alone.<sup>65</sup> Similarly, adding a drug with Gram-positive activity did not significantly decrease the number of febrile episodes or clinically or microbiologically documented infections. Although adding a drug with Gram-positive coverage did reduce the number of Gram-positive infections, all bacteremia, and Gram-positive bacteremia, it also increased the number of adverse effects (six trials; N = 516; quinolone plus other drug, 17.1% *v* quinolone alone, 8.9%; RR, 1.94; 95% CI, 1.28 to 2.94) and adverse effects leading to discontinuations (five trials; N = 432; quinolone plus other drug, 7.5% *v* quinolone alone, 0.9%; RR, 4.92; 95% CI, 1.61 to 15.01). Prophylaxis with a nonabsorbable antibacterial significantly increased infection-related mortality (11 trials; N = 1,005; RR, 2.48; 95% CI, 1.65 to 3.73) but not all-cause mortality (eight trials; N = 813; RR, 1.06; 95% CI, 0.74 to 1.50) when compared with a systemically absorbed antibacterial. Use of a nonabsorbable antibacterial also significantly increased the number of microbiologically documented infections, Gram-negative infections, Gram-positive infections, bacteremia, and overall adverse effects.

The Cochrane review<sup>65,69</sup> also found five studies directly comparing different fluoroquinolones (all excluded from meta-analyses). None reported statistically significant differences in all-cause or infection-related mortality. Two trials directly compared ciprofloxacin versus norfloxacin; the other three each compared a different fluoroquinolone pair. Review authors found evidence from these studies inadequate to establish superiority of outcomes from a specific fluoroquinolone.<sup>69</sup>

Taken together, available evidence shows that systemically absorbed fluoroquinolones are more tolerable than other antibacterials investigated for prophylaxis in neutropenic oncology patients and are as efficacious yet more tolerable when used alone as when combined with other antibacterials active against Gram-positive organisms. Thus, in agreement with other guidelines,<sup>11,12</sup> the Panel recommends use of an orally administered, systemically absorbed fluoroquinolone for antibacterial prophylaxis in oncology outpatients with profound neutropenia expected for  $\geq 7$  days. Prophylaxis should be administered from the first day of the cytotoxic antineoplastic regimen until myeloid reconstitution. Readers are reminded that the Panel recommends against routine antibacterial prophylaxis when the expected duration of neutropenia is  $< 7$  days, the severity is less than profound, and none of the risk factors listed in Table 2 are present (see Recommendation A-1b). The Panel acknowledges that the published experience with ciprofloxacin- or levofloxacin-based antibacterial prophylaxis has been similar, despite the theoretic advantages of the former against *Pseudomonas aeruginosa* or the latter against Gram-positive organisms in the setting of oral mucositis. Accordingly, the Panel recommends that the choice of agent be based on local consensus. The Panel also concurs with the IDSA recommendations<sup>12</sup> regarding the need for a strategy to systematically monitor for fluoroquinolone resistance among Gram-negative bacilli in environments where fluoroquinolones are being deployed.

### Recommendation A-2b

The Panel recommends an orally administered triazole antifungal or an echinocandin parenterally administered in the outpatient setting as prophylaxis against infection with opportunistic yeasts, but only for those with profound neutropenia and mucositis expected to last  $\geq 7$  days and in environments with  $> 10\%$  risk of invasive *Candida* infection. A mold-active triazole is recommended in environments with a substantial risk ( $> 6\%$ ) for invasive aspergillosis.

### Literature Review and Analysis

RCTs of antifungal prophylaxis in patients undergoing chemotherapy for malignancy have studied orally administered nonabsorbable drugs (eg, nystatin or other polyenes), orally administered absorbable drugs (including diazoles such as ketoconazole and triazoles such as fluconazole), and IV administered drugs (eg, amphotericin B, the echinocandins). Results from these trials have been summarized in systematic reviews<sup>61,81,87,88,98,170,171</sup> and combined in meta-analyses.<sup>89-94,172-175</sup> The literature search for this guideline also identified several RCTs<sup>176-178</sup> published after these reviews. A majority of randomly assigned patients in studies that reported net benefit from antifungal prophylaxis with orally absorbable or parenteral drugs versus controls receiving placebo, no treatment, or nonabsorbable oral drugs (see Literature Review and Analysis for Recommendation A-1c) were at high risk for invasive *Candida* infection ( $> 10\%$ ) or aspergillosis ( $> 6\%$ ) resulting from long periods ( $\geq 7$  days) of severe to profound neutropenia as a consequence of induction therapy for acute leukemia or HSCT. The same was true of trials that compared different systemically available drugs or regimens for antifungal prophylaxis in oncology patients. Outpatients undergoing less-intensive chemotherapy for other (solid tumor or hematologic) malignancies rarely experience the depth and duration of neutropenia necessary to result in a similar risk level for IFIs. Thus, Recommendation A-1c advises against antifungal prophylaxis in these cases, and the evidence comparing alternatives for prophylaxis of high-risk patients is not reviewed in detail here. When risk level justifies antifungal prophylaxis, the Panel concurs with other guidelines<sup>12,98</sup> and recommends an orally administered triazole (fluconazole, itraconazole, posaconazole, or voriconazole) or an echinocandin administered parenterally in the outpatient setting (micafungin or caspofungin).

Note that more trials of antifungal prophylaxis with more randomly assigned oncology patients at risk for IFIs have investigated fluconazole than any other orally absorbed or parenterally administered antifungal drug. Furthermore, evidence in the reviews cited here also suggests patients administered fluconazole are less likely to discontinue antifungal prophylaxis because of intolerable adverse effects than patients receiving another triazole or an echinocandin. However, fluconazole lacks activity against molds such as *Aspergillus*, and thus a mold-active second-generation azole is recommended if there is a substantial risk ( $> 6\%$ ) for invasive aspergillosis. Other data suggest that if itraconazole is selected (perhaps because it has been tested more than other alternatives to fluconazole), the oral solution seems to be more effective than capsules. Because few trials have studied echinocandins for antifungal prophylaxis of oncology patients, and because they require parenteral administration, their use in this setting might best be limited to patients who cannot tolerate a triazole or cannot take oral drugs.

### Recommendation A-2c

The Panel recommends that prophylaxis with TMP-SMX only be used if the risk for PCP is  $> 3.5\%$  (eg, patients administered regimens with  $\geq 20$  mg of prednisone equivalents daily for  $\geq 1$  month or those based on purine analogs; see Recommendation A-1d). Alternatives for patients with sulfa-based hypersensitivities are provided in the Literature Review and Analysis.

### Literature Review and Analysis

A systematic review and meta-analysis<sup>179,180</sup> compiled evidence from randomized trials of prophylaxis to prevent PCP in immunocompromised patients not infected by HIV. Although first published in 2007, a search update through October 2010 found no new studies to include.<sup>179</sup> The two published versions of the review included 11 (N = 1,155)<sup>179</sup> and 12 (N = 1,245)<sup>180</sup> trials, respectively, with one (a comparison of two TMP-SMX regimens in children with acute lymphoblastic leukemia [ALL]<sup>181</sup>) excluded from the Cochrane review<sup>179</sup> (because it defined PCP diagnosis in a way that did not meet study selection criteria) but included in the other publication.<sup>180</sup> Of the 11 trials included in both publications, five compared daily oral TMP-SMX versus placebo or no treatment (one of which included a third arm administered oral TMP-SMX three times per week), three compared daily oral TMP-SMX versus quinolones (inactive against *Pneumocystis jirovecii*), two compared oral TMP-SMX daily versus three times per week (including the aforementioned three-arm trial), and one trial each compared daily oral TMP-SMX versus either oral pyrimethamine plus sulfadoxine or oral atovaquone. In six of the trials, most or all of the randomly assigned patients were immunosuppressed from treatment for acute leukemia; in one trial, from HSCT; and in four trials, to prevent rejection of solid organ transplants. Ten trials included a mix of inpatients and outpatients, whereas one randomly assigned inpatients only. All patients received chemotherapy or antirejection regimens, including corticosteroids in seven trials; however, steroid monotherapy was not an isolated PCP risk factor for any of the randomly assigned patients.

Meta-analysis found that TMP-SMX decreased the incidence of documented PCP versus controls receiving placebo, no treatment, or an antibacterial drug inactive against *Pneumocystis* (eight trials; N = 821; TMP-SMX, 0% v control, 7.5%; RR, 0.09; 95% CI, 0.02 to 0.32; NNT, 15; 95% CI, 13 to 20).<sup>179,180</sup> In subset analyses, TMP-SMX significantly decreased PCP incidence in the five trials with placebo or no-treatment controls (N = 528; RR, 0.08; 95% CI, 0.02 to 0.38), but the difference in PCP incidence was not statistically significant in the three trials with quinolone controls (N = 293; RR, 0.09; 95% CI, 0.01 to 1.57). The review also reported a significant reduction in PCP incidence for a subset of trials of patients with hematologic malignancies (RR, 0.05; 95% CI, 0.01 to 0.39). Although TMP-SMX did not significantly reduce all-cause mortality (five trials; N = 509; RR, 0.81; 95% CI, 0.27 to 2.37), it did significantly decrease PCP-related mortality (seven trials; N = 701; RR, 0.17; 95% CI, 0.03 to 0.94). Additional meta-analyses showed no statistically significant differences between those randomly assigned to TMP-SMX and those randomly assigned to placebo or no treatment with respect to any adverse events (AEs) or AEs causing patients to discontinue treatment.

The reviews<sup>179,180</sup> noted that no trial comparing TMP-SMX once daily versus three times per week reported differences in PCP incidence or PCP-related mortality; differences between the regimens regarding AEs were not statistically significant. Direct comparative

evidence on timing and duration was unavailable. The Panel recommends using any of the published daily, twice per week, or three times per week schedules during the period of immunodeficiency: from engraftment until day 180 for those undergoing allogeneic HSCT, from initiation of induction therapy in acute lymphoblastic leukemia until completion of all antileukemic therapy, from initiation of alemtuzumab therapy until 2 months after the last dose and circulating CD4 T lymphocytes are  $> 200$  cells/ $\mu$ L, and from initiation of fludarabine-based or T cell–depleting therapy until circulating CD4 T4 lymphocytes are  $> 200$  cells/ $\mu$ L.

The RCT that compared TMP-SMX versus sulfadoxine-pyrimethamine (N = 125; after liver allografts) reported two cases of PCP in the arm administered TMP-SMX (both patients discontinued treatment for intolerability) and none in the other arm. PCP did not occur in any patients in the trial of TMP-SMX versus atovaquone. Few other studies and no RCTs have reported on alternatives to TMP-SMX for PCP prophylaxis in non-HIV patients. Nevertheless, for patients who may be hypersensitive to sulfonamides or unable to tolerate TMP-SMX for other reasons, alternatives may include dapsone, aerosolized pentamidine, or atovaquone. Data from an RCT<sup>182</sup> comparing atovaquone versus dapsone in patients with HIV who could not tolerate TMP-SMX suggest modest differences in PCP incidence and mortality that were not statistically significant but slightly better tolerability for atovaquone. Retrospective analysis of patients receiving bone marrow transplants<sup>183</sup> suggested aerosolized pentamidine may be the least effective alternative.

### Recommendation A-2d

The Panel recommends an antiviral nucleoside analog with demonstrated activity against HBV (eg, lamivudine) as prophylaxis for those at substantial risk for reactivation of HBV infection.

### Literature Review and Analysis

Systematic reviews,<sup>81,109,119</sup> narrative reviews,<sup>106-108,110,111,184</sup> and two guidelines based on narrative reviews<sup>115,118,185,186</sup> have examined evidence on outcomes of nucleoside analogs for HBV prophylaxis of oncology patients at risk of reactivation (see Recommendation A-1e). Although other nucleosides active against HBV have been approved by the FDA to treat active HBV infection (adefovir, entecavir, tenofovir, and telbivudine),<sup>187</sup> only lamivudine has been investigated in RCTs to prevent HBV reactivation in oncology patients at risk.<sup>111,119</sup>

The most recent systematic review<sup>119</sup> found two RCTs comparing rates of HBV reactivation and of HBV-related hepatitis, hepatic failure, or death in patients randomly assigned to lamivudine prophylaxis or to treatment deferred until evidence of reactivation. The review also included data from eight prospective (concurrent controls in three; historical controls in eight) and four retrospective cohort studies (N = 657 for all 12 cohorts; untreated controls in three cohorts; deferred treatment in nine). One RCT studied patients with lymphoma (N = 30), whereas the other studied patients with hepatocellular carcinoma (HCC; N = 73). In seven cohorts, all patients had the same malignancy (lymphoma in three; breast cancer in two; HCC and nasopharyngeal cancer in one each); five included patients with various malignancies. Only one RCT and three cohorts treated all analyzed patients with identical chemotherapy regimens.

The review did not include pooled analyses, either across all 14 studies or across subsets by study design, because of heterogeneity in



study populations, designs, and other methods.<sup>119</sup> Nevertheless, in each RCT and in 11 reporting cohort studies, the RRs for HBV reactivation and for HBV-related hepatitis ranged from 0.00 to 0.21, with 95% CI upper limits  $\leq 0.86$  in all studies but a prospective cohort with a total of 14 patients. Thus, both RCTs and 10 of 11 cohorts reported statistically significant decreases in HBV reactivation and HBV-related hepatitis with lamivudine prophylaxis in patients at risk. Absolute HBV reactivation rates decreased from ranges of 24% to 88% in control groups to 0% to 12.5% in the lamivudine prophylaxis groups. Absolute rates of HBV-related hepatitis decreased from 24% to 88% in control groups to 0% to 12.5% in the lamivudine prophylaxis groups. Furthermore, no patients in lamivudine groups of either the RCT or the five reporting cohort studies experienced HBV-related hepatic failure, whereas hepatic failure occurred in 5% to 33% of control groups. In eight of 10 studies that reported HBV-related deaths (including one RCT; the other did not report mortality), none occurred in lamivudine groups versus 0.8% to 26% in controls. HBV-related mortality despite prophylaxis occurred in only two cohorts (both prospective): one of eight patients receiving lamivudine versus five of eight concurrent controls in one study, and three of 26 receiving lamivudine versus none of 25 historical controls in the other.

Eight studies reported no adverse effects of lamivudine (including one RCT; the other and five cohorts did not report on adverse effects), whereas the proportion of patients who had their chemotherapy regimen disrupted was higher for controls than for those administered lamivudine in six reporting studies (including one RCT). Furthermore, cancer-related (four reporting studies, including one RCT) and all-cause (eight reporting studies, including both RCTs) mortality was also more frequent for controls than for lamivudine groups. Although direct comparative studies have not established the duration of HBV prophylaxis needed to protect patients at risk from reactivation, the Panel agrees with reviewers<sup>81,106,110,111,119</sup> who recommend starting therapy 1 week before chemotherapy begins and continuing for at least 6 months after chemotherapy ends.

### Recommendation A-2e

The Panel recommends using a nucleoside analog to prevent herpesvirus infections in those at risk from the initiation of cytotoxic therapy until myeloid reconstitution.

### Literature Review and Analysis

A Cochrane review<sup>128</sup> summarized and analyzed results from 12 placebo-controlled RCTs of drugs for HSV prophylaxis in oncology patients at risk for reactivation (see Literature Review and Analysis for Recommendation A-1f on evaluating risk and selecting patients). Eight trials compared oral acyclovir versus placebo, three compared IV acyclovir versus placebo, and one compared oral prostaglandin E versus placebo. The review also included one trial each that directly compared active therapies as follows: two doses of oral valacyclovir, oral valacyclovir versus IV acyclovir, and two doses of oral valacyclovir versus oral acyclovir. However, reviewers found no RCTs comparing valacyclovir versus placebo. As noted in Recommendation A-1f, no placebo-controlled trials reported effects of HSV prophylaxis on analgesic use or quality of life. Only one trial<sup>129</sup> enrolled patients with solid tumors, and outcomes of interest (eg, viral isolates, oral HSV lesions) were infrequent among controls. Most patients in the other trials underwent HSCT or therapy for acute leukemia. The review did not include survival or mortality as an outcome of interest.

Meta-analyses showed that acyclovir prophylaxis yielded statistically significant decreases in oral HSV lesions (reported in nine RCTs; N = 398; RR, 0.16; 95% CI, 0.08 to 0.31) and culture-positive viral isolates (reported in nine RCTs; N = 511; RR, 0.17; 95% CI, 0.07 to 0.37).<sup>128</sup> In subgroup meta-analyses, acyclovir significantly reduced oral lesions for both the subset using the oral route and the subset using the IV route. However, the decrease in viral isolates was only significant for the RCT subset using the oral route. Nine trials reported on adverse effects, although the review did not include a pooled analysis or data tables. A brief summary stated that no trials reported a statistically significant difference between experimental and control arms in the presence or number of adverse effects. The trial comparing prostaglandin E versus placebo reported more frequent HSV isolates among patients in the experimental arm than among placebo-treated controls (71% v 38%; RR, 1.87; 95% CI, 1.12 to 3.14).

Two trials compared outcomes of HSV prophylaxis with acyclovir versus valacyclovir.<sup>128</sup> A two-arm trial (N = 30) compared IV acyclovir with oral valacyclovir, and a three-arm trial (N = 181) compared oral acyclovir with two doses of oral valacyclovir. The trial of IV acyclovir observed no HSV oral lesions in either arm, whereas the trial of oral acyclovir observed no statistically significant difference between those randomly assigned to acyclovir or valacyclovir in the proportion of patients with HSV oral lesions. Data on other efficacy outcomes or adverse effects were unavailable for this comparison. Neither of two trials that compared different doses of oral valacyclovir (500 v 1,000 mg, each three times daily in one trial; 250 v 500 mg, each twice daily in the other) reported statistically significant differences between arms in frequency of HSV lesions, viral isolates, or withdrawals because of adverse effects.

The only RCT of VZV prophylaxis identified for this guideline compared acyclovir versus placebo in patients at risk for reactivation undergoing allogeneic HSCT (N = 77).<sup>148</sup> One to 2 months of prophylactic acyclovir significantly reduced active VZV infections at 1 year after transplantation (HR, 0.16; 95% CI, 0.035 to 0.74). However, the difference between arms was no longer statistically significant at 2 and 5 years after treatment. Although data are unavailable from randomized direct comparisons of different prophylaxis durations, a retrospective study<sup>149</sup> compared the incidence of VZV reactivation disease in three sequential cohorts administered either acyclovir or valacyclovir for prophylaxis during and after HSCT. Patients in cohort one (n = 932 HSCTs from 1996 to 1998) were treated until engraftment (as prophylaxis for HSV, but eligibility was limited to VZV seropositive patients), in cohort two (n = 1,117 HSCTs from 1998 to 2002) until 1 year after transplantation, and in cohort three (n = 586 HSCTs from 2002 to 2003) until the later of 1 year after transplantation or 6 months after cessation of all immunosuppressive therapy. In separate analyses, longer prophylactic duration reduced the incidence of post-transplantation VZV disease among seropositive patients undergoing allogeneic (25% of cohort one, 9% of cohort two, and 4% of cohort three) or autologous (21% of cohort one v 7% of cohorts two and three combined) transplantation.

### Recommendation A-2f

Influenza immunization should use the trivalent inactivated vaccine. In select circumstances after proven exposure of a susceptible patient with cancer, a neuraminidase inhibitor (eg, oseltamivir, zanamivir) may be offered.

## Literature Review and Analysis

The literature search found no RCTs or other studies that directly compared clinical outcomes of different preparations or strategies used to vaccinate adult outpatients with solid tumors against influenza virus. Studies of adults with solid tumors included in previous systematic reviews<sup>158,159</sup> were (mostly retrospective) cohorts that reported immunologic but not clinical outcomes. In contrast, a recent Cochrane review of viral vaccines for patients with hematologic malignancies<sup>164</sup> included five RCTs of influenza vaccination. Each trial used inactivated trivalent vaccine in at least one arm, but none reported the incidence of documented influenza (primary outcome of the review). Two RCTs compared outcomes of vaccination versus unvaccinated controls. Separate pooled analyses showed fewer URTIs, lower respiratory tract infections, and hospital admissions among those randomly assigned to the vaccine arms (for summarized results, see Literature Review and Analysis for Recommendation A-1g). However, neither RCT determined whether influenza virus caused the observed respiratory infections and hospitalizations, and mortality resulting from pneumonia did not differ between arms in the one trial that reported this outcome. Irritability and local adverse effects were more common among those randomly assigned to vaccination.

Of the remaining three trials included in the Cochrane review,<sup>164</sup> one compared two doses versus a single dose of the same trivalent inactivated vaccine and reported no significant difference in the proportion of patients who attained prespecified levels of in vitro immune responses to the vaccine. The trial did not report any other outcomes of interest. The second trial compared three different doses of a recombinant vaccine versus the standard trivalent inactivated vaccine. This trial also reported only in vitro immune response outcomes and found no statistically significant differences between the preparations at any dose of the recombinant vaccine. The third RCT (of children with ALL) used two doses of vaccine in each arm; one arm received the first dose with reinduction chemotherapy and the second dose 4 weeks later, and the other arm received the first dose 4 weeks before and the second dose together with reinduction chemotherapy. Again, the only reported outcomes were in vitro immune responses, and there were no significant differences between arms.

Although direct comparative data are lacking, the Panel agrees with other reviews<sup>122,159</sup> and guidelines<sup>11,12,118,166-169,188</sup> and recommends seasonal vaccination with trivalent inactivated influenza vaccine for oncology patients. Although it is generally recommended that vaccines be administered before the initiation of chemotherapy or at least 4 weeks after the discontinuance of chemotherapy, these recommendations may not always be practical for patients already receiving systemic therapy. A guideline from the Association for Medical Microbiology and Infectious Diseases Canada (<http://www.ammi.ca/pdf/GuidelineH1N1.pdf>) and studies cited therein<sup>158,162,189-194</sup> may provide advice on the strategies and the timing of immunization during therapy and additional considerations that need to be made for influenza vaccine, particularly during the flu season or during outbreaks. One systematic review<sup>158</sup> notes that evidence is lacking to confirm that patients immunocompromised because of chemotherapy or HSCT for a malignancy are at risk of influenza infection from the live attenuated (intranasal) vaccine. Nevertheless, the FDA-approved package insert for the intranasal vaccine warns that limited data are available on safety and efficacy in immunocompromised patients. To protect patients from possible exposure, the

Panel also recommends use of the trivalent inactivated vaccine for family and household contacts.

Immunologic responses to influenza vaccine are weaker in patients undergoing cancer chemotherapy than in healthy persons and take longer to reach adequately protective levels.<sup>158-160</sup> Thus, vaccination after exposure to influenza virus is unlikely to protect susceptible oncology patients; chemoprophylaxis should be considered under these circumstances. Two drug classes are active against influenza viruses: the M2 inhibitors (eg, amantadine, rimantadine) and the neuraminidase inhibitors (eg, oseltamivir, zanamivir).<sup>81,121,122,166-169</sup> However, resistance to the M2 inhibitors develops rapidly during influenza treatment, and they are no longer recommended for this indication.<sup>168,169,195</sup> Although data are unavailable on prophylactic use in oncology patients, there is evidence that neuraminidase inhibitors are effective to prevent influenza in persons exposed through household contacts.<sup>168,169,196</sup>

### Question A-3

What additional precautions are appropriate to prevent exposure of neutropenic but afebrile outpatients with a malignancy to infectious agents or organisms?

### Recommendation A-3

Readers are referred to a separate ASCO guideline (Schiffer et al, manuscript submitted for publication) with recommendations on care of central venous catheters (CVCs) in oncology patients. Because direct evidence was unavailable from randomized trials on many of the other measures and precautions discussed in this section, the Panel considered evidence from uncontrolled and retrospective studies. Recommendations A-3a to A-3c are based on evidence summarized in sources cited and Panel members' expert opinion.

### Recommendation A-3a

All health care workers and caregivers (particularly those caring for neutropenic oncology patients) should follow hand hygiene guidelines including handwashing practices to reduce exposure through contact transmission and respiratory hygiene/cough etiquette guidelines to reduce exposure through droplet transmission and should receive annual trivalent split influenza vaccine to protect patients and themselves.

### Literature Review and Analysis

Several reviews<sup>81,121,156</sup> and guidelines<sup>12,168,197,198</sup> discuss physical and environmental measures to reduce infection in oncology patients and others with impaired immunity by preventing exposure through aerosol droplets or direct contact. Although direct evidence is lacking to prove these measures influence outcomes for oncology outpatients with neutropenia from chemotherapy, the Panel endorses recommendations from the CDC<sup>197-199</sup> concerning prudent practices to minimize their exposure to potentially communicable infectious diseases. Recommendations on administrative measures, education and training of personnel, and monitoring and reporting of health care-associated infections are outside the scope of this guideline. Standard precautions include sanitizing hands before entering and after exiting a patient-care area or after touching a patient.<sup>197</sup> Soap and water are recommended if hands are soiled or after care of patients with known or suspected infection; otherwise, an alcohol-based rub is adequate. Use of personal protective equipment (eg, gowns, gloves,

face masks) by caregivers is recommended only when contact with blood or body fluids is anticipated.<sup>12</sup> Safe injection practices and safe handling of potentially contaminated equipment or surfaces are additional components of standard precautions.<sup>199</sup> Finally, respiratory secretions from patients, companions, or clinic personnel with a possible respiratory infection should be contained and properly disposed of to prevent spread of pathogens.<sup>198,199</sup>

### Recommendation A-3b

Outpatients with neutropenia resulting from cancer therapy should avoid prolonged contact with environments that have high concentrations of airborne fungal spores (eg, construction and demolition sites).

### Literature Review and Analysis

Multiple reports<sup>200-204</sup> document that construction, renovation, or demolition of hospitals and other health care facilities is associated with increased exposure of building occupants to *Aspergillus* spores and with elevated risk to neutropenic patients of nosocomial invasive pulmonary aspergillosis (IPA). Retrospective data suggest that masking during room-to-room transport<sup>203</sup> and other protective measures<sup>204</sup> can reduce nosocomial IPA of neutropenic oncology inpatients while construction proceeds. In light of these reports, the Panel believes it prudent to recommend that oncology outpatients with neutropenia from chemotherapy avoid such environments when possible.

### Recommendation A-3c

None of the following measures are routinely necessary to prevent infection of afebrile outpatients with a malignancy and neutropenia: protected environments (high-efficiency particulate air [HEPA] filters with or without laminar air flow), respiratory masks (to prevent invasive aspergillosis), footwear exchange at entry and exit, and the neutropenic diet or similar nutritional interventions. Gowning and gloving should only be considered in accordance with local infection prevention and control practices for antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, or extended-spectrum  $\beta$ -lactamase-producing and carbapenemase-producing Gram-negative bacilli.

### Literature Review and Analysis

The literature search for this guideline identified a systematic review<sup>205</sup> of RCTs and observational studies that reported effects of HEPA filtration on mortality and fungal infection in highly immunosuppressed patients undergoing intensive chemotherapy for hematologic malignancy or HSCT. Six RCTs (N = 774) and three nonrandomized studies (N = 231) were included for separate meta-analyses on mortality, and four RCTs (N = 238) and six nonrandomized studies (N = 759) were included for separate meta-analyses of incidence of fungal infection. Use of HEPA filters with or without laminar air flow did not yield a statistically significant decrease in either outcome, neither among the RCTs nor in the nonrandomized direct comparisons. A more recent review<sup>81</sup> pooled data from 12 RCTs (967 inpatients) that compared the incidence of all-cause pneumonia between those randomly assigned to a protective environment (HEPA filters  $\pm$  laminar air flow) and controls randomly assigned to usual care. Most of these trials randomly assigned patients being treated for

acute leukemia or undergoing HSCT. Meta-analysis showed that use of a protected environment decreased the incidence of pneumonia from 31% to 14% (OR, 0.29; 95% CI; 0.20 to 0.41). However, evidence was unavailable on low-risk patients maintained outside the hospital. Given the absence of a statistically significant effect on mortality for high-risk inpatients, the Panel recommends that use of HEPA filters with or without laminar air flow is not routinely necessary for oncology outpatients with neutropenia.

Studies<sup>206,207</sup> and a systematic review<sup>208</sup> have reported that persons infected with respiratory viruses who wear surgical or respiratory masks are less likely to transmit the virus to household contacts. However, the literature search identified only one RCT<sup>209</sup> (N = 80) that compared standard hygiene procedures with versus without use of well-fitting respiratory masks whenever hospitalized patients undergoing chemotherapy for acute leukemia or allogeneic HSCT left their rooms. The incidence of IFI and mortality from invasive aspergillosis did not differ significantly between arms. Similarly, the literature search identified only one nonrandomized single-center study<sup>210</sup> that compared the incidence of FNEs in patients undergoing chemotherapy for a hematologic malignancy during years (1997 to 1999) when visitors and health care workers were required to change shoes before entering patients' rooms with the frequency of FNEs after footwear exchange was discontinued (2000 to 2003). Reportedly, eliminating the requirement to change shoes had no significant effect on the incidence of FNEs. In light of these studies on high-risk inpatients, the Panel recommends that use of either respiratory masks or footwear exchange is not routinely necessary for low-risk oncology outpatients with neutropenia.

Several studies found in the literature search of this guideline investigated whether specific dietary or nutritional interventions influenced the incidence of FNEs or infectious complications in oncology patients with neutropenia from chemotherapy. A few studies compared diets that excluded raw fruits or vegetables and only permitted cooked foods, pasteurized juices, and so on (often termed the neutropenic diet) with diets that permitted raw foods and fresh juices. An RCT of adult inpatients (N = 153)<sup>39</sup> undergoing remission induction for acute myeloid leukemia reported incidence of and time to major infection, deaths, and episodes of unexplained FN (often termed fever of unknown origin). A pilot RCT (N = 19)<sup>211</sup> of children with solid tumors receiving myelosuppressive chemotherapy as inpatients reported rates of FNEs and infection. Another pilot RCT of adult inpatients receiving induction chemotherapy for acute leukemia (N = 20)<sup>212</sup> compared GI colonization with Gram-negative bacilli or *Candida*, infection rates, days with fever, and use of antimicrobial drugs for patients fed a low-bacterial diet versus the normal hospital diet. Finally, an observational study compared the number of febrile hospital admissions and positive blood cultures among oncology outpatients beginning chemotherapy regimens associated with a high incidence of neutropenia (N = 28)<sup>213</sup> for subgroups who did or did not adhere to the recommended neutropenic diet. None of these studies reported a statistically significant improvement in any of the specified outcomes for the group fed the experimental (neutropenic or low-bacterial) diet. A recent review of published studies on neutropenic diets<sup>214</sup> also concluded there is no clear evidence they benefit patients and recommended standard safe food-handling practices to permit more liberalized diets. This guideline Panel also finds no need for oncology outpatients with neutropenia to routinely adhere to a neutropenic diet, provided they follow safe food-handling practices.

The search also found two studies, each of which investigated the impact of a nutritional supplement on the incidence of FNEs. One was a double-blind RCT<sup>215</sup> that compared the incidence and duration of FNEs and the duration of neutropenia in adults (N = 54) undergoing intensive chemotherapy for acute leukemia while receiving parenteral nutrition supplemented with glycyl-glutamine dipeptide or placebo. Investigators reported a slightly shorter median duration of neutropenia for the dipeptide-supplemented group than for controls, but there was no difference in the incidence or duration of FN. The second was an open-label nonrandomized study<sup>216</sup> in which adding a fermented wheat germ extract to the diet for one member of each pair matched for diagnosis, stage, age, and sex (N = 11) reportedly decreased FNEs in children with solid tumors receiving chemotherapy. In view of the limited available data, the Panel does not recommend routine use of these or other nutritional supplements in oncology outpatients with neutropenia.

### CLINICAL KEY QUESTION B

Which patients with a malignancy and febrile neutropenia are appropriate candidates for outpatient management?

#### Question B-4

What clinical characteristics should be used to select patients for outpatient empiric therapy?

#### Recommendation B-4

Because medical complications occurred in up to 11% of patients identified as low risk for medical complications of FN in studies validating risk indices or scoring systems, the Panel considers inpatient treatment as the standard approach for managing an FNE. However, outpatient management may be acceptable for carefully selected patients. When considering a patient with FN for outpatient management, the Panel recommends that evaluation begin with a systematic assessment of risk for medical complications using a validated index. Of the tools available to estimate risk in adults, the Multinational Association for Supportive Care in Cancer (MASCC) risk index (Table 3) has been evaluated most thoroughly; Talcott's rules have also been validated in prospective studies. However, if the clinician has any reservations with respect to the accuracy of an index for an individual, the FNE should be managed in the hospital even if the patient is classified as low risk (MASCC score  $\geq$  21 or Talcott group 4). Table 4 provides a list of additional factors to take into account when assessing a given patient's risk for medical complications in the setting of outpatient management. Patients meeting any of the criteria listed in Table 4, those with MASCC score  $<$  21, and those in Talcott groups 1 to 3 should not be managed as outpatients. Moreover, neither a currently available risk index nor the criteria in Table 4 should substitute for clinical judgment when deciding whether a given patient with an FNE should be admitted to the hospital for inpatient management.

### Literature Review and Analysis

The Panel evaluated two separate bodies of evidence to develop its recommendation on selecting patients for outpatient management. The first group of studies derived and validated risk assessment tools. However, because an overwhelming majority of patients enrolled onto this first group of studies were managed in the hospital for the full course of their FNEs, the Panel also needed to consider a second group of studies that directly compared outcomes of inpatient versus outpa-

**Table 3.** MASCC Scoring System to Identify Patients With Cancer and Febrile Neutropenia at Low Risk of Medical Complications\*

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

Abbreviation: MASCC, Multinational Association for Supportive Care in Cancer.  
\*Maximum score is 26; scores  $\geq$  21 indicate a low risk for medical complications. Data adapted.<sup>12,217</sup>

†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.

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

§Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

tient management of an FNE in patients deemed at low risk for medical complications. As detailed in the discussion here, the Panel did not find available evidence conclusive to define an optimal method of selecting low-risk patients with an FNE who can be managed safely outside the hospital. Therefore, the recommendation offers the Panel's consensus on a conservative interim strategy to maximize patient safety, pending the future development and validation of improved risk assessment tools.

The first group of studies included 16 reports from 15 studies on stratifying risk for medical complications in adult oncology patients with FN from chemotherapy (see Data Supplement Tables DS-3 for detailed information on the designs, methods, and patients in these studies and DS-4 for their results; online at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn)). Eight studies derived<sup>38</sup> and validated<sup>38,218-225</sup> the MASCC risk score, and the remaining seven either modified the MASCC scoring system for patients in Thailand<sup>226</sup> or derived other models<sup>44,45,227-230</sup> to stratify risk. Each of five studies<sup>226-230</sup> (pooled N = 1,546; range, 40 to 834) developed a unique risk model not tested elsewhere, whereas two derived (N = 184)<sup>44</sup> and validated (N = 444)<sup>45</sup> Talcott's prediction rules, which classify outpatients at FNE onset without either serious comorbidity or uncontrolled cancer (ie, those in group 4) as low risk. Eight studies on the MASCC score included a total of 2,582 patients (range, 53 to 1,139) and 2,758 FNEs (range, 60 to 1,139). Four studies<sup>38,220,222-224</sup> only included each patient's first episode, whereas analyses in the other four<sup>218,219,221,225</sup> included repeat FNEs. Only one<sup>225</sup> of the eight MASCC studies was retrospective; the others were prospective. In contrast, only one<sup>45</sup> of the seven studies on other risk models was prospective; the rest were retrospective.

Of eight studies on the MASCC score, five<sup>38,218,221,223,225</sup> reported the proportion of outpatients versus inpatients at FN onset, which ranged from all outpatients<sup>225</sup> to 50% of inpatients.<sup>38</sup> Six studies<sup>218,219,221-225</sup> admitted all patients and treated the FNEs in the

## Antimicrobial Prophylaxis and Management of Fever and Neutropenia in Outpatients

**Table 4.** Additional Specific Clinical Criteria\* That Exclude Oncology Patients With FN From Initial Outpatient Care Even With a MASCC Score  $\geq$  21

Category	Criteria
Cardiovascular	Presyncope/witnessed syncope Accelerated hypertension New onset or worsening of hypotension Uncontrolled heart failure, arrhythmias, or angina Clinically relevant bleeding Pericardial effusion
Hematologic	Severe thrombocytopenia (platelets $<$ 10,000/ $\mu$ L) Anemia (Hb $<$ 7 g/dL or Hct $<$ 21%) ANC $<$ 100/ $\mu$ L of expected duration $\geq$ 7 days Deep venous thrombosis or pulmonary embolism
GI	Unable to swallow oral medications Intractable nausea and/or vomiting New onset or clinically relevant worsening of diarrhea Melena, hematochezia (nonhemorrhoidal), or hematemesis Abdominal pain Ascites
Hepatic	Impaired hepatic function (aminotransferase values $>$ 5 $\times$ ULN) or clinically relevant worsening of aminotransferase values Bilirubin $>$ 2.0 or clinically relevant increase in bilirubin
Infectious	Presence of a clear anatomic site of infection (eg, symptoms of pneumonia, cellulitis, abdominal infection, positive imaging, or microbial laboratory findings) <sup>†</sup> Any evidence of severe sepsis <sup>‡</sup> Allergies to antimicrobials used for outpatients Antibiotics $\leq$ 72 hours before presentation Intravascular catheter infection
Neurologic	Altered mental status/sensorium or seizures Presence of or concern for CNS infection or noninfectious meningitis Presence of or concern for spinal cord compression New or worsening neurologic deficit
Pulmonary/thorax	Tachypnea or hypopnea Hypoxemia, hypercarbia Pneumothorax or pleural effusion Presence of cavitory lung nodule or imaging findings suggestive of an active intrathoracic process
Renal	Impaired renal function (creatinine clearance $\leq$ 30 mL/min) or oliguria or clinically relevant worsening renal function (as determined by the treating physician) New onset of gross hematuria Urinary obstruction or nephrolithiasis Clinically relevant dehydration Clinically relevant electrolyte abnormalities, acidosis or alkalosis (requiring medical intervention)
Other significant comorbidity	Presence of a major abnormality in regard to: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, laboratory data, or imaging data Any relevant clinical worsening (as determined by the treating physician) of: organ dysfunction, comorbid condition, vital signs, clinical signs or symptoms, laboratory data, or imaging data Pregnant or nursing Need for IV pain control Fractures, injuries, or need for emergent radiation therapy

Abbreviations: ANC, absolute neutrophil count; FN, fever and neutropenia; Hb, hemoglobin; Hct, hematocrit; IV, intravenous; MASCC, Multinational Association for Supportive Care in Cancer; Pa CO<sub>2</sub>, arterial carbon dioxide tension; SIRS, Systemic Inflammatory Response Syndrome; ULN, upper limit of normal.  
\*This is not a comprehensive list. Less-severe clinical conditions or abnormalities may require hospitalizations as suggested in this guideline's text and summary. This list does not replace the need for clinical judgment while making decisions on outpatient versus inpatient management of FN for individual patients.  
<sup>†</sup>New onset of minimal symptoms of urinary tract infection and sinusitis may be excluded from this requirement in most settings with neutropenia  $<$  7 days and absence of fungal infection.  
<sup>‡</sup>Severe sepsis is a syndrome defined by the presence of evidence for SIRS (defined by  $\geq$  two of the following criteria: body temperature  $>$  38°C or  $<$  36°C, heart rate  $>$  90 beats/minute, respiratory rate  $>$  20/minute, Pa CO<sub>2</sub>  $<$  32 mmHg, an alteration in the total leukocyte count to  $>$  12  $\times$  10<sup>9</sup>/L or  $<$  4  $\times$  10<sup>9</sup>/L, or the presence of  $>$  10% band neutrophils in the leukocyte differential) plus evidence of infection, plus evidence of end-organ dysfunction (altered mental status, hypoperfusion [defined by hypotension (systolic blood pressure  $<$  90 mmHg, mean arterial pressure  $<$  70 mmHg, systolic blood pressure decrease of  $>$  40 mmHg, or  $<$  two standard deviations below the mean for age), by an elevated serum lactate  $>$  4 mmol/L, or by oliguria (urine output  $<$  0.5 mL/kg/hour)], and/or hypoxia).

hospital; the other two<sup>38,220</sup> hospitalized most patients. Six studies<sup>38,218,219,221-223</sup> reported the performance characteristics (sensitivity, specificity, positive and negative predictive values, and in some instances misclassification or accuracy rates) of a MASCC score  $\geq$  21 to identify patients with an FNE at low risk for medical complications.

Sensitivity ranged from 71% (validation set of the initial MASCC study<sup>38</sup>) to 95% in two studies,<sup>218,221</sup> and specificity ranged from 58%<sup>219</sup> to 95%.<sup>218,221</sup> Positive predictive values ranged from 84%<sup>219</sup> to 98%,<sup>218,221</sup> whereas negative predictive values ranged from 36%<sup>38</sup> to 86%.<sup>218,221</sup> Four studies<sup>38,219,222,223</sup> reported misclassification or accuracy

rates; 13%<sup>222</sup> to 28%<sup>219</sup> of patients were classified incorrectly. One study<sup>225</sup> reported the sensitivity (52%) and specificity (95%) of a MASCC score < 21 to correctly identify patients with FN at high risk for complications but did not report positive or negative predictive values.

Several studies compared performance of a MASCC score  $\geq 21$  with that of an alternative method to classify patients with FN as low risk for complications (see Data Supplement Table DS-4 for results). Uys et al<sup>221</sup> compared it with various laboratory assays. This study did not find any assay to be a statistically significant predictor of outcome and also reported that performance characteristics of the MASCC score were better than for procalcitonin levels, the assay most strongly correlated with MASCC score. Hui et al<sup>223,224</sup> compared MASCC score  $\geq 21$  with the Talcott prediction rules and with an artificial neural network (ANN) model that this group developed. The ANN model performed approximately as well as the MASCC score, and each performed substantially better than Talcott's rules. A third study<sup>222</sup> modified the MASCC model by reclassifying as high risk those patients ( $n = 6$  of 21 considered low risk by the original model) with score  $\geq 21$  but also diagnosed with a complex infection and compared performance characteristics of the original and modified models. Although specificity and positive predictive value decreased, sensitivity and negative predictive value improved to 100% with the modified model, because no patients it classified as low risk developed complications. However, the sample size in this study was small ( $N = 53$ ), and the modified model has not been independently validated or replicated. A modified scoring system<sup>226</sup> developed for oncology patients with FN in Thailand ( $N = 220$ ) reportedly had better specificity and positive predictive value (albeit with some loss of sensitivity) than either MASCC score  $\geq 21$  or  $\geq 22$  to identify patients with a favorable outcome. These results also have not been independently replicated or validated. Studies on models other than the MASCC score either lacked adequate discriminatory power (to predict risk of bacteremia) based on receiver operating characteristic curves<sup>230</sup> or did not report performance characteristics.<sup>44,45,227-229</sup>

Several conclusions emerge from available studies on stratifying medical complication risks of adult oncology patients with an FNE. First, the MASCC score has been prospectively validated in more studies, patients, and FNEs than alternatives, and Talcott's rules are the only other prospectively validated method. Second, available data do not define an optimal method to select patients with an FNE free of risk for medical complications. Although overall performance characteristics reported for the MASCC score are as good as or better than published modifications or alternatives (with the possible exceptions of one that classifies anyone with a complex infection as high risk<sup>222</sup> and another developed for patients in Thailand<sup>226</sup> and not validated prospectively), the key variables of interest here are rates of medical complications and mortality among patients classified as low risk. The only prospective study (Data Supplement Table DS-4)<sup>223,224</sup> to directly compare outcomes for those classified as low risk by MASCC score versus Talcott's rules (selected from a single patient group) reported similar rates of mortality (2% *v* 1.9%) and poor outcomes (23 of 160; 14.4% *v* 16 of 101; 15.8%) for the two methods. Data pooled from seven studies (Data Supplement Table DS-4)<sup>38,218-220,222-225</sup> showed that 197 (11%) of 1,771 patients classified as low risk by MASCC score  $\geq 21$  had complications or other unfavorable empiric therapy outcomes, and 29 (1.6%) died before FN resolved. Data pooled from three studies (Data Supplement Table DS-4)<sup>44,45,223,224</sup> showed that serious complications occurred in 23 (7.3%) and

death in two (0.6%) of 317 patients classified by Talcott's rules as low risk. Thus, both the MASCC score and Talcott's rules misclassify some patients as low risk. Finally, because nearly all patients in these studies were hospitalized to treat FN, the Panel needed other evidence to evaluate the safety and efficacy of managing low-risk patients at home. Note that although hospitalizing misclassified low-risk patients seems unlikely to cause harms (although it may increase costs, inconvenience, and exposure to antibiotic-resistant strains), at-home treatment of misclassified high-risk patients may prove life threatening.

The second body of evidence resulting in this recommendation included 10 studies that directly compared outcomes of management in versus out of the hospital for adult oncology patients with an FNE deemed at low risk for medical complications (see Data Supplement Tables DS-5 for detailed information on the designs, methods, and patients in these studies and DS-6 for their results; online at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn)). Four of these<sup>231-234</sup> were RCTs, another four<sup>217,219,235,236</sup> were prospective but not randomized, and two<sup>237,238</sup> were retrospective. Patient eligibility criteria varied, both among and between the RCTs and nonrandomized studies. None of the RCTs required a MASCC score  $\geq 21$ , and only one<sup>233</sup> required that patients met Talcott's definition<sup>44,45</sup> of low risk. Although each of the four prospective comparisons<sup>217,219,235,236</sup> required a MASCC score  $\geq 21$  for at-home management, they defined FN somewhat differently and also differed with respect to several other eligibility criteria (Data Supplement Table DS-5). Patients were required to have an expected neutropenia duration of  $\leq 7$  days to be eligible for outpatient management in a retrospective comparison<sup>237</sup> and two RCTs.<sup>232,234</sup>

In two RCTs,<sup>232,233</sup> all doses of empiric FN therapy (including the first) were administered orally for outpatients and IV for inpatients, using different drugs or regimens in the two arms. In one of these trials,<sup>232</sup> patients randomly assigned to outpatient therapy received their first oral doses as inpatients and were discharged at 24 hours if stable and improved; in the other,<sup>233</sup> outpatients were discharged shortly after the first oral dose. In the other two trials, the same empiric therapy was administered to patients in each arm: an IV regimen in one<sup>231</sup> and an oral regimen in the other.<sup>234</sup> The trial with an IV regimen<sup>231</sup> evaluated all patients in the hospital over the first 48 to 72 hours of empiric therapy; only responders were randomly assigned, and those randomly assigned to finish empiric therapy as outpatients were discharged. The trial with an oral regimen<sup>234</sup> randomly assigned patients before the first dose but did not report the timing or requirements for outpatient discharge. Each prospective nonrandomized study observed patients for 24 to 48 hours after the first dose of empiric antibiotics, using orally administered drugs from the first dose in two studies<sup>217,235</sup> and switching from IV to orally administered drugs at discharge in the other two.<sup>219,236</sup> One retrospective study<sup>237</sup> used oral drugs as empiric therapy for most patients (both in and out of the hospital), whereas the other<sup>238</sup> administered IV empiric therapy to all patients. Each observed patients in the clinic or hospital to verify they were clinically stable before discharge.

Success or failure of empiric therapy for FN was the primary outcome in all 10 studies, although their definitions varied. Each RCT and one retrospective study<sup>237</sup> defined success as resolution (of fever and symptoms<sup>231,232,237</sup> or the FNE,<sup>233,234</sup> including ANC > neutropenia threshold) without changing the initial antibiotic regimen or readmission. However, two RCTs<sup>233,234</sup> considered resolution after a

change of empiric regimen or readmission an intermediate category of outcome rather than failure. The prospective nonrandomized studies<sup>217,219,235,236</sup> and one<sup>238</sup> retrospective study defined success as resolution without complications whether or not the empiric regimen changed. Definitions of success also varied (see Data Supplement Table DS-5) with respect to the required duration (after resolution) of time without fever or symptoms (3, 5, or 7 days in different studies). The Panel concluded that differences between studies in patient eligibility, clinical treatment protocols, and outcome definitions precluded meaningful pooled analyses of results.

The four RCTs (N = 451; Data Supplement Table DS-6)<sup>231-234</sup> reported generally high rates of successful empiric therapy (approximately 80% to > 90%), with no statistically significant differences between outpatient and inpatient arms. In each of three RCTs, only one patient died; two were in inpatient arms managed with IV regimens,<sup>232,233</sup> whereas the third was in an outpatient arm also managed with an IV regimen.<sup>231</sup> Three outpatients and two inpatients died in the fourth RCT,<sup>234</sup> all managed with an oral antibiotic. The nonrandomized studies (pooled N = 972 prospective; N = 752 retrospective) also reported generally high rates of successful empiric therapy and few deaths with outpatient management. One RCT<sup>232</sup> reported higher rates of grade 1 to 2 GI toxicities with the oral antibiotic regimen it used for empiric therapy in outpatients with FN; the other studies did not report any differences in adverse effects. The Panel concluded that at best, results of these studies provide evidence for the safety and efficacy of outpatient empiric therapy in carefully and systematically selected adults with FN from cancer chemotherapy who are deemed at low risk for medical complications.

However, the optimal strategy to select low-risk patients for management of an FNE outside the hospital is inadequately informed by available evidence and thus remains somewhat uncertain. As mentioned, pooled data from Data Supplement Table DS-4 show a false-positive rate of approximately 10% with a MASCC score  $\geq 21$  and a false-positive rate of approximately 7% with Talcott's rules as the sole determinants of low-risk patients. Therefore, the Panel recommends managing certain patients in the hospital even if they are classified as low risk by either method. Among these are patients with a major abnormality (or significant clinical worsening since the most recent chemotherapy or onset of neutropenia) with respect to any of the following: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, documented anatomic site of infection (as defined by the Immunocompromised Host Society<sup>239</sup>), laboratory data, or imaging data. The Panel also reviewed clinical criteria excluding patients from studies that compared inpatient versus outpatient management (Data Supplement Tables DS-5 and DS-6) or oral versus IV regimens for outpatient empiric therapy (Data Supplement Tables DS-7 and DS-8; see Recommendation C-8) among oncology patients with low-risk FN. Table 4 compiles these clinical exclusion criteria by organ system and provides additional details on factors that may be considered major abnormalities. The Panel recommends inpatient management with initial IV empiric antibacterial therapy if the patient has evidence of any active comorbid medical conditions such as hemodynamic instability, oral or GI mucositis that prevents oral intake or is associated with severe diarrhea, GI symptoms (such as abdominal pain, nausea, or vomiting), new mental status changes or focal CNS abnormalities, CVC-related infection, new pulmonary infiltrates, or hypoxia. Furthermore, any evidence of organ dysfunction (such as changes in liver or renal function tests) or prolonged (> 7 days)

profound neutropenia (ANC < 100/ $\mu$ L) all help define a patient as not at low risk.<sup>12</sup>

### Question B-5

Should outpatients with FN at low risk for medical complications receive their initial dose(s) of empiric antimicrobial(s) in the hospital or clinic and be observed, or can some selected for outpatient management be discharged immediately after evaluation?

### Recommendation B-5

The duration of observation before outpatients were discharged varied considerably among studies that directly compared inpatient versus outpatient empiric therapy or oral versus IV regimens in outpatients. Lacking evidence from direct comparisons, the Panel members' expert opinion agrees with other groups that physician assessment should occur soon (eg, within 15 minutes) after triage for patients presenting with FN within 6 weeks of having received chemotherapy for a malignancy.<sup>240-242</sup> Although multiple studies report it can be difficult to achieve this target,<sup>243-246</sup> the Panel recommends that the first dose of empiric therapy be administered within 1 hour after triage from initial presentation in the clinic, emergency room, or hospital department, after fever has been documented in a neutropenic patient, and pretreatment blood samples have been drawn. The Panel also recommends that patients identified as low risk and selected for outpatient management be observed for at least 4 hours before discharge to verify they are stable and can tolerate the regimen they will receive.

### Literature Review and Analysis

The literature search did not find any studies that directly compared outcomes of immediate versus delayed discharge or of different observation periods before discharge for outpatient empiric therapy for low-risk FN. As discussed in Recommendation B-4, initial antibacterial doses were administered before discharging outpatients in all studies that compared empiric therapy in versus out of the hospital for patients with low-risk FN. The intervals from first dose to discharge ranged from immediate in one RCT<sup>233</sup> to 48 to 72 hours in another<sup>231</sup> that only randomly assigned patients once they became afebrile. Four<sup>247-250</sup> of nine RCTs (Data Supplement Table DS-7) that compared oral versus IV outpatient empiric therapy of a low-risk FNE also discharged patients after initial doses and observation for 2 to 24 hours. Two others<sup>251,252</sup> observed patients before discharge for up to 72 hours after empiric therapy began, whereas one trial<sup>253</sup> did not report whether or for how long patients were observed. Only two trials<sup>254,255</sup> discharged patients before their first dose and immediately after random assignment. However, each of these RCTs administered at-home IV empiric therapy for the first 24 hours to all patients in both arms and then switched regimens for those randomly assigned to oral therapy. These and other differences between studies with respect to patient characteristics, treatment protocols, and outcome definitions (see Data Supplement Tables DS-5 and DS-7) preclude using a comparison of their outcomes to determine minimal or optimal durations of inpatient observation before discharge for outpatient empiric therapy.

Nevertheless, some consistently or commonly followed procedures are discernible in most methods of the studies, and the Panel recommends these as prudent routine practice. Studies of empiric

therapy for FN typically required that fever be documented and samples (eg, of blood and other fluids) be obtained for culture and microbiologic assays before patients received their first dose. The Panel recommends adherence to this practice outside of clinical trials so that culture and assay results are not altered by initial doses of the empiric regimen, possibly obscuring identification of infecting organisms. A retrospective study on patients who presented with severe sepsis or septic shock<sup>256</sup> reported overall mortality of 19.5% and 33.2%, respectively, in patients who received antibacterial therapy  $\leq 1$  versus  $> 1$  hour ( $P = .02$ ). In light of these data, the Panel agrees with an international guideline panel of the Surviving Sepsis Campaign<sup>257</sup> and recommends that the first dose of empiric initial antibacterial therapy be administered as soon as possible after triage from presentation with FN. In the opinion of the Panel, a triage-to-antibiotic target of  $\leq 1$  hour seems a practical, achievable, and prudent performance standard in most instances. Methods of nearly all studies also specified that treating clinicians verify patients were clinically stable before they were discharged for outpatient management of FN and that those receiving an oral regimen were able to tolerate their oral medications. Lacking evidence from direct comparison of different observation intervals, the Panel recommends as prudent practice observing those who will continue empiric therapy as outpatients for  $\geq 4$  hours before they are discharged from the clinic, emergency room, or hospital department. In circumstances where outpatient monitoring for 4 hours is not practical, the safest strategy for initial management of FN is admission for a brief period ( $< 24$  hours) of inpatient observation.

#### Question B-6

What psychosocial and logistic requirements must be met to permit outpatient management of patients with FN?

#### Recommendation B-6

Direct comparative evidence was unavailable for any of these factors. On the basis of members' expert opinion, the Panel recommends that an oncology patient who develops FN during or after chemotherapy should meet each of the following criteria to receive empiric therapy as an outpatient:

- Residence  $\leq 1$  hour or  $\leq 30$  miles (48 km) from clinic or hospital
- Patient's primary care physician or treating oncologist agrees to outpatient management
- Able to comply with logistic requirements, including frequent clinic visits
- Family member or caregiver at home 24 hours a day
- Access to a telephone and transportation 24 hours a day
- No history of noncompliance with treatment protocols

#### Literature Review and Analysis

As with Question and Recommendation B-5, the literature search did not find any studies that directly compared outcomes of outpatient empiric therapy for an FNE in patients who did versus did not meet any of the psychosocial or logistic requirements in Recommendation B-6. Nevertheless, studies comparing inpatient versus outpatient empiric therapy (Data Supplement Table DS-5) or oral versus IV therapy for outpatients (Data Supplement Table DS-7) limited eligibility to patients with an FNE who met all or most of these criteria. Because the only evidence for safety and efficacy of outpatient therapy is from studies conducted in patients who satisfied these require-

ments, the Panel recommends treatment in the hospital for patients who do not meet one or more of the listed criteria.

#### CLINICAL KEY QUESTION C

What interventions are indicated for patients with a malignancy and febrile neutropenia who can be managed as outpatients?

#### Question C-7

What diagnostic procedures are recommended?

#### Recommendation C-7

On the basis of members' expert opinion, the Panel recommends that in the absence of an alternative explanation, fever in a patient with neutropenia from cancer therapy should be assumed to be the result of a bacterial infection. The initial diagnostic approach should maximize the chances of establishing clinical and microbiologic diagnoses that may affect antibacterial choice and prognosis. The Panel also recommends systematically evaluating the patient to identify the infectious agent and the anatomic focus (see Literature Review and Analysis for specific details).

#### Literature Review and Analysis

The literature search did not find direct comparative evidence on the clinical utility of different diagnostic procedures for oncology patients who present with FN. On the basis of their collective experience and expertise, the Panel considers bacterial infection the most reasonable assumption and likeliest source of such patients' fever if an alternative explanation cannot be documented (unexplained fever). For that reason, the Panel recommends that the diagnostic approach seek to identify infecting organisms and establish a microbiologic diagnosis if at all possible and thoroughly evaluate possible sites of infection to establish a clinical diagnosis. The Panel considers systematic evaluation of oncology patients who present with FN to include the following:

- Complete history and physical examination to identify infectious foci
- Complete blood count with leukocyte differential count, hemoglobin, and platelet count; serum electrolytes; serum creatinine and blood urea nitrogen; and liver function tests including total bilirubin, transaminases, and cholestatic enzymes
- At least two sets of blood cultures from different anatomic sites, including a peripheral site as well as each lumen of a CVC if present
- Cultures from other sites such as urine, lower respiratory tract, CSF, stool, skin, or wounds, as clinically indicated
- Chest imaging study for patients with signs and/or symptoms of lower respiratory tract infection
- Patients with an influenza-like illness (sudden onset of a respiratory illness characterized by fever and cough and  $\geq$  one of malaise, sore throat, coryza, arthralgias, or myalgias) in the setting of seasonal community-acquired respiratory illnesses should have a nasopharyngeal swab obtained for detection of respiratory viruses (influenza, parainfluenza, adenovirus, respiratory syncytial virus, and human metapneumovirus)



These recommendations are generally consistent with guidelines from other organizations including the IDSA,<sup>12</sup> NCCN,<sup>11</sup> Japan Febrile Neutropenia Study Group,<sup>9</sup> ESMO,<sup>10</sup> and an Australian consensus panel.<sup>21,28</sup>

### Question C-8

What antibacterials are recommended for outpatient empiric therapy?

### Recommendation C-8

For patients with cancer, fever, and neutropenia who are at low risk for medical complications by criteria of Recommendation B-4, the Panel recommends oral empiric therapy with a fluoroquinolone (ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate (or plus clindamycin for those with penicillin allergy). However, the Panel cautions against use of a fluoroquinolone as initial empiric therapy for neutropenic patients with cancer who develop fever after receiving fluoroquinolone-based antibacterial prophylaxis and in environments where the prevalence of fluoroquinolone resistance is > 20%. For these patients, and if deemed appropriate by the treating physician, the Panel recommends IV therapy with a regimen suitable for outpatient administration, provided they meet clinical and other criteria for outpatient management (for details, see Literature Review and Analysis for Recommendations B-4 and C-9).

Hospitalized stable and responding low-risk patients receiving initial IV empiric antibacterial therapy, particularly those classified as having unexplained FN, may be considered for stepdown to an oral regimen and early discharge for outpatient follow-up and monitoring.

For patients with FN from cancer therapy who are at high risk for medical complications, the Panel recommends hospitalization for IV antimicrobial therapy and endorses the most recent (2010) recommendations from the IDSA.<sup>12</sup>

### Literature Review and Analysis

Randomized trials of empiric therapy for FN in hospitalized oncology patients not selected or stratified by risk for complications were outside the scope of this systematic review; see other reviews<sup>3-6,14-20,22-27</sup> and guidelines<sup>7-13,21</sup> for summaries of relevant data. Evidence from these RCTs supports the following widely accepted principles of empiric therapy for FN in oncology patients. Early use of broad-spectrum antibacterial drugs decreases mortality and morbidity compared with waiting for culture and assay results to start treatment. Appropriately targeted antibiotics should replace the initial regimen if results identify an infecting organism and determine its susceptibility or if examination reveals a focal infection typically associated with a specific pathogen of known drug susceptibility. If occult infection is suspected in a patient with negative cultures and no discernible focus (unexplained fever; see review by Antoniadou et al<sup>258</sup>), broad-spectrum empiric therapy should continue until either fever resolves and neutropenia improves or a new regimen is required because of persistent or worsening fever or other symptoms. Although no single drug or regimen protects against all pathogens, empiric regimens should be bactericidal to both Gram-positive and Gram-negative bacteria (including *Pseudomonas*) in patients with impaired cellular immunity and should cause few to no adverse effects. Drug or regimen choice is influenced by the patient's risk for complications and recent local epidemiologic and antibiotic susceptibility patterns of infections in oncology patients.

Many RCTs that compared outcomes of different drugs or regimens for empiric therapy also enrolled mostly hospitalized patients not selected or stratified by risk for complications. Although such trials also are outside the scope of this systematic review, results of meta-analyses<sup>26,27,259-269</sup> relevant to both inpatients and outpatients are summarized in Data Supplement Table DS-9. Among these, a meta-analysis of 18 RCTs<sup>26,27</sup> reported similar safety and efficacy with oral or IV antibacterials as initial empiric therapy for FN in oncology patients who were: hemodynamically stable; without organ failure, acute leukemia, severe soft tissue infection, pneumonia, or a CVC; and able to tolerate oral medications. Outcomes compared in this meta-analysis included all-cause mortality (nine trials; pooled N = 1,392; RR, 0.95; 95% CI, 0.54 to 1.68), treatment failure by intention-to-treat analysis (18 trials; pooled N = 2,763; RR, 0.95; 95% CI, 0.85 to 1.07), and AEs leading to discontinued therapy (12 trials; pooled N = 1,577; RR, 1.80; 95% CI, 0.58 to 5.60). Data Supplement Table DS-8 summarizes results from nine RCTs<sup>247-255</sup> that compared oral versus IV empiric therapy for low-risk FN in the outpatient setting. Although only three of these trials<sup>247-249</sup> enrolled adult patients, each reported similar rates of treatment success or response for oral and IV empiric therapy, with no deaths among those randomly assigned to an oral antibacterial. Only one RCT<sup>249</sup> of adult patients reported greater toxicity with an oral regimen; acute renal failure occurred in four of 40 patients administered oral ciprofloxacin plus clindamycin versus none of 43 administered IV aztreonam plus clindamycin. Taken together, these meta-analyses (Data Supplement Table DS-9) and RCTs (Data Supplement Tables DS-7 and DS-8) provide convincing evidence that initial empiric therapy with an oral regimen is safe and effective for oncology patients with low-risk FN, as defined in Recommendation B-4.

Most of the other meta-analyses (Data Supplement Table DS-9) either compared monotherapy versus a combination<sup>263-265,267-269</sup> or analyzed the effects of adding a specific drug class to monotherapy or a combination.<sup>261,262</sup> Results from two independent meta-analyses<sup>263-265</sup> agreed that adding an aminoglycoside to a broad-spectrum  $\beta$ -lactam active against *Pseudomonas* did not improve survival or therapeutic success but increased toxicity. Two other meta-analyses<sup>261,262</sup> agreed that adding a glycopeptide (eg, vancomycin) or other drug<sup>261</sup> targeted against Gram-positive bacteria to  $\beta$ -lactam monotherapy or to the combination of a  $\beta$ -lactam plus an aminoglycoside did not reduce overall or infection-related mortality or shorten the duration of fever. Note, however, that antipseudomonal  $\beta$ -lactams are unavailable in oral dosage forms and thus must be administered parenterally.

Although outpatient IV therapy is widely available, oral drugs are more convenient, less costly, and preferred by many patients and clinicians to treat a low-risk FNE in the outpatient setting.<sup>237,270</sup> The literature search did not identify any trials that directly compared different oral regimens for outpatient empiric therapy of an FNE in oncology patients. Thus, recommendations on choice of an oral regimen must rely on indirect comparison of results from separate RCTs. Except for one,<sup>252</sup> each RCT that compared oral versus IV antibacterials as outpatient empiric therapy for a low-risk FNE (Data Supplement Tables DS-7 and DS-8) used a fluoroquinolone, either alone<sup>247,248,250,251,254,255</sup> or in combination,<sup>249,253</sup> for patients in the oral arm. However, three of the trials of fluoroquinolone monotherapy first administered IV antibacterials to all randomly assigned patients and then switched one arm to ciprofloxacin after 8<sup>250</sup> or 48

hours<sup>251,254</sup>; another<sup>247</sup> used moxifloxacin in the oral therapy arm. Only two trials (one with 183 randomly assigned adults with FNEs<sup>248</sup> and the other with 93 randomly assigned children with FNEs<sup>251</sup>) used ciprofloxacin monotherapy throughout for patients randomly assigned to oral therapy. In three<sup>232-234</sup> of four RCTs and four<sup>217,219,235,237</sup> of six nonrandomized studies on inpatient versus outpatient empiric therapy (Data Supplement Tables DS-5 and DS-6), the outpatient arms received an oral fluoroquinolone. Each of these used ciprofloxacin plus another drug<sup>217,219,232,235,237</sup> or ofloxacin monotherapy<sup>233,234</sup> in the outpatient arms. Additional evidence comes from two large widely cited RCTs (with 163<sup>271</sup> and 312<sup>272</sup> randomly assigned patients) that tested oral ciprofloxacin plus amoxicillin-clavulanate versus an IV regimen as initial empiric therapy for an FNE. Both trials randomly assigned patients with a low-risk FNE; managed all patients in the hospital (which formally excludes them from this systematic review); and, in contrast to the other trials cited here, administered oral and IV placebos, respectively, to patients in the IV and oral arms. Both trials reported similar rates of therapeutic success, mortality, and duration of fever for the oral and IV treatment regimens. Results of these<sup>271,272</sup> and additional smaller trials<sup>232,273</sup> provide a larger body of evidence supporting the safety and efficacy of oral ciprofloxacin plus amoxicillin/clavulanate compared with alternative oral regimens.

RCTs<sup>234,274-277</sup> and other studies<sup>278,279</sup> report that certain fluoroquinolones (eg, ciprofloxacin, ofloxacin) lack adequate activity at standard doses against some Gram-positive species (eg, viridans streptococci) when administered alone as either prophylaxis or empiric therapy for an FNE, although conflicting data exist.<sup>280</sup> Levofloxacin may be more active against such Gram-positive bacteria, but at usual doses, it is less active than ciprofloxacin against *Pseudomonas*.<sup>281,282</sup> Furthermore, levofloxacin and other fluoroquinolones (eg, moxifloxacin<sup>283</sup> and clinafloxacin<sup>284</sup>) have not yet been adequately studied in RCTs (either alone or in combination regimens) as oral empiric therapy for a low-risk FNE. On the basis of the evidence reviewed in this and the preceding paragraph, and in agreement with other guidelines,<sup>11,12</sup> the Panel recommends ciprofloxacin plus amoxicillin-clavulanate as a first-choice oral regimen in empiric therapy for low-risk FN in oncology outpatients. The Panel also agrees with other guidelines<sup>11,12</sup> and advises against use of a fluoroquinolone alone as initial empiric therapy for outpatient management of an FNE.

However, the Panel recognizes that certain circumstances may rule out or argue against selection of ciprofloxacin plus amoxicillin-clavulanate as initial empiric therapy for a low-risk FNE. For example, patients with a known allergy to penicillin should not be treated with amoxicillin. On the basis of its safety and efficacy in an RCT versus IV empiric therapy (N = 96 randomized FNEs in adult patients<sup>249</sup>; see DS Tables 7 and 8), the Panel recommends ciprofloxacin plus clindamycin as an alternative oral regimen for initial empiric therapy of a low-risk FNE in patients allergic to penicillin. Patients with neutropenia who develop fever during or soon after prophylaxis with a fluoroquinolone may be infected with a resistant strain and thus should not be administered a fluoroquinolone-based regimen for empiric therapy. Similar concerns also apply to hospitals, clinics, and communities with > 20% prevalence of fluoroquinolone resistance in bacterial isolates. Also, oral regimens are contraindicated for patients presenting with nausea and/or vomiting or who are otherwise unable to tolerate or absorb oral medications. If any one of these circumstances pertains but all other criteria for outpatient therapy are met (see

Recommendation B-4), the Panel recommends outpatient IV empiric therapy with a broad-spectrum  $\beta$ -lactam active against *Pseudomonas*.

A Cochrane review and meta-analysis<sup>259</sup> updated in 2010<sup>260</sup> summarized evidence from 44 RCTs comparing an antipseudomonal  $\beta$ -lactam versus another  $\beta$ -lactam (either alone or with the same glycopeptide in both arms; see Data Supplement Table DS-9) for initial empiric therapy of oncology patients with FN. Antibacterials investigated (all administered by IV) included ceftazidime (in 21 trials), cefepime (in 22 RCTs), imipenem-cilastatin (in 16 trials), meropenem (in 13 trials), and piperacillin-tazobactam (in 13 trials). Outcomes included all-cause and infection-related mortality, clinical treatment failure, superinfection, change of antibiotic regimen, and AEs. Meta-analysis results suggested less mortality at 30 days with piperacillin-tazobactam than with its comparators (eight RCTs; pooled N = 1,314; RR, 0.56; 95% CI, 0.34 to 0.92) but no statistically significant differences in mortality between ceftazidime and its comparators or between the carbapenems (imipenem-cilastatin and meropenem) and their comparators. However, results suggested cefepime led to more all-cause mortality at 30 days than its comparators (21 RCTs; N = 3,471; RR, 1.39; 95% CI, 1.04 to 1.86), and reviewers cautioned against its use.

The FDA conducted its own meta-analyses of cefepime in 2009 (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm167254.htm>), using both trial- and patient-level data to estimate effects on mortality by the Mantel-Haenszel risk-difference method. The FDA analyses included 38 trials from a 2007 Cochrane review<sup>285</sup> on all published RCTs of cefepime (19 of which involved patients with FN) plus another 50 trials. The 88 trials randomly assigned 9,467 patients to cefepime and 8,288 to comparators. In the trial-level analysis, all-cause mortality at 30 days was 6.2% in patients treated with cefepime and 6.0% in those treated with comparators (adjusted risk difference of 5.38 per 1,000 treated; 95% CI, -1.53 to 12.28). There was also no statistically significant difference in all-cause 30-day mortality in a trial-level subset analysis of 24 RCTs of patients with an FNE (adjusted risk difference of 9.67 per 1,000 treated; 95% CI, -2.87 to 22.2). Finally, the meta-analysis of patient-level data (available from 35 of 88 RCTs, including 5,058 patients treated with cefepime and 3,976 treated with comparators) found 30-day mortality of 5.63% and 5.68%, respectively, in the cefepime and comparator groups (adjusted risk difference of 4.83 per 1,000 treated; 95% CI, -4.7 to 14.4). For comparison, FDA analysts applied the risk-difference method to the data set available to the Cochrane group<sup>285</sup> and found an adjusted risk difference of 19 per 1,000 treated (95% CI, 4.96 to 33.02). On the basis of these analyses, the FDA concluded that the totality of available evidence on safety of cefepime did not show a statistically significant increase of all-cause mortality at 30 days. The ASCO Panel thus agrees with other guidelines<sup>11,12</sup> that cefepime continues to be an acceptable alternative for initial empiric therapy of an FNE and may be used when IV therapy is either preferred or necessary to manage outpatients with a low-risk FNE.

Also note that patients infected by Gram-negative pathogens resistant to both fluoroquinolones and  $\beta$ -lactams should be treated as inpatients with a regimen that likely requires multiple doses per day (eg, meropenem every 8 hours or piperacillin/tazobactam every 6 to 8 hours).<sup>286</sup>

The Panel acknowledges that some patients and clinicians will prefer to begin empiric therapy with an IV regimen administered in the hospital even for a low-risk FNE. RCTs have demonstrated the safety and effectiveness of early discharge and a switch from IV to oral regimens 8<sup>250</sup>, 24,<sup>232</sup> or 48 hours<sup>251,254</sup> after the initial IV infusion if the fever is responding, and the patient remains clinically stable (see Data Supplement Tables DS-5 to DS-8). The regimen used during postdischarge treatment and follow-up was oral ciprofloxacin monotherapy in three of these trials.<sup>250-252</sup>

Management of FN in oncology patients at high risk for medical complications is outside the scope of this systematic review and guideline. For such patients, the Panel recommends hospitalization for IV antimicrobial therapy and endorses the most recent (2010) recommendations from the IDSA.<sup>12</sup>

### Question C-9

What additional measures are recommended for outpatient management?

### Recommendation C-9

On the basis of members' expert opinion, the Panel recommends that prudent and sensible outpatient management include:

- Frequent evaluation for at least 3 days, in clinic or at home
- Daily or frequent telephone contact thereafter to verify resolution of fever as determined by home thermometry
- Monitoring of ANC and platelet count for myeloid reconstitution
- Frequent return visits to clinic
- Patients should be evaluated for admission to the hospital if any of the following occur: PNF syndrome, fever recurrence, new signs or symptoms of infection, use of oral medications is no longer possible or tolerable, change in the empiric regimen or an additional antimicrobial drug becomes necessary, or microbiologic tests identify species not susceptible to initial empiric regimen.

### Literature Review and Analysis

The literature search did not identify any studies directly comparing outcomes for oncology outpatients with FN managed with versus without specific logistic measures or with different frequencies of contact or evaluation. Because relevant evidence was lacking, the Panel examined follow-up and evaluation procedures for outpatients in studies that compared inpatient versus outpatient therapy (Data Supplement Tables DS-5 and DS-6) or oral versus IV regimens in outpatients (Data Supplement Tables DS-7 and DS-8). Panel members relied on their expertise and experience to devise and agree on the list of procedures they judged to be prudent and sensible for follow-up and evaluation of oncology outpatients with an FNE, based on those described in the Methods sections of the studies cited in Data Supplement Tables DS-5 to DS-8.

### Question C-10

How should PNF syndrome be managed?

### Recommendation C-10

The Panel recommends that low-risk patients who do not defer- vance after 2 to 3 days of an initial empiric broad-spectrum antibiotic

regimen be re-evaluated to detect and treat a new or progressing anatomic site of infection and considered for hospitalization.

### Literature Review and Analysis

Evidence on outcomes of alternative strategies to manage PNF syndrome was outside the scope of the systematic review conducted for this guideline. It suffices to say that Panel members agreed unanimously with the need to re-evaluate and possibly hospitalize patients whose fever does not resolve after 2 to 3 days of empiric therapy with a broad-spectrum regimen. The same approaches to evaluation and subsequent treatment of patients with PNF seem appropriate whether patients received initial empiric therapy in the hospital or as outpatients. More detailed recommendations are available in guidelines from other organizations.<sup>11,12</sup>

## PATIENT AND CLINICIAN COMMUNICATION

This section suggests communication practices for patients (as well as their relatives and/or volunteer caregivers) and clinicians while managing FNEs in adult outpatients treated for malignancy. Note that the literature cited here was not identified by the search strategy (Data Supplement 1) but rather through separate literature searches and Panel members' suggestions. The communication strategies described here have not been evaluated in RCTs.

Research has shown that effective patient-clinician communication can influence treatment outcome. A study of communication on cancer treatment and AEs surveyed 508 patients with cancer (of whom 67% had low WBC counts) and found that discussions alone do not seem to provide patients with sufficient understanding or skills to deal with AEs.<sup>287</sup> The findings suggested that efforts to improve cancer care should include development of tools both to improve patients' understanding of AEs and to provide resources to reduce the risks associated with AEs.

The effectiveness of patient-clinician communication can be as important as that of a diagnostic or treatment intervention. Its scope encompasses: patient, caregiver, and clinician roles, responsibilities, and expectations for health care; sharing all necessary information; and tailoring communication to individual patient needs according to health literacy and numeracy, living circumstances, language barriers, and decision-making capacity.<sup>287,288</sup> Communication strategies adapted to health literacy can benefit patients of all literacy levels.<sup>289</sup> Clinicians are encouraged to inform patients of evidenced-based infection control guidelines to minimize unnecessary restrictions.<sup>214,290</sup>

Successful management of FNEs in adult oncology outpatients requires that patients be educated to promptly recognize and act on signs and symptoms of possible infection. Effective education about monitoring body temperature and other symptoms of infection is vital. Additionally, communications should acknowledge and address the reality that many patients are reluctant to seek help outside of office hours. It is essential that patients and caregivers receive clear written instructions on when and how to contact health care practitioners.<sup>291</sup>

In 2008, the National Confidential Enquiry into Patient Outcome and Death studied care delivered to patients who died within 30 days of chemotherapy and identified several significant issues related to management of FN. The report<sup>292</sup> highlighted the need to communicate management guidelines to all concerned, including patients, their relatives, and primary and secondary care staff.

Oncology nurses play a vital role in educating patients about FNEs. Therefore, expanded dissemination and implementation of clinical practice guidelines to nursing professionals will support patient education goals.<sup>293,294</sup>

Although knowledge of how best to manage FNEs in adult oncology outpatients has grown significantly during the last several decades, new challenges to effective communication have arisen. These include the increasing numbers of immunocompromised patients, changing epidemiology of infection, and growing resistance of bacteria to commonly used antimicrobial agents. As new chemotherapy regimens have been developed, and as new antibiotics have been introduced for prophylaxis or therapy, new infection risks have been defined.<sup>295</sup> Coordination of care among primary and specialist settings and emergency departments is essential to ensure a rapid response when an FNE is suspected. Patients should be both encouraged and supported to advocate for their care in emergency situations so they are not put at greater risk. Patients should have access to written and/or electronic copies of their febrile neutropenia management plans so that health care providers making treatment decisions are fully aware of patients' needs.<sup>10,291</sup>

### HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer from some racial or ethnic minority groups and those of lower socioeconomic status suffer disproportionately from comorbidities, experience more-substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.<sup>296-301</sup> Many other patients lack access to care because of their geography and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Limited data are available to support definitive conclusions on how health disparities may affect management of neutropenic patients and outcomes of febrile neutropenia. In a study<sup>302</sup> of 326 women, 251 severe neutropenia events (ANC < 500/ $\mu$ L) occurred among 140 patients (43%), and 24 FNEs occurred among 22 patients (7%). White race (HR, 2.13;  $P = .01$ ) was a predictor of severe neutropenia (ANC < 500 per/ $\mu$ L) in multivariate models, as was treatment on a research protocol (HR, 1.93;  $P < .01$ ). Although considerable evidence<sup>303</sup> has demonstrated that ethnic neutropenia occurs across populations of African descent, data are limited to define the impact this entity may have on the management of neutropenia and FN.<sup>304</sup> Experts

agree that timely assessment and administration of initial empiric antibacterial therapy to febrile neutropenic patients with cancer is important, yet the reported times from initial triage to first antibiotic in this circumstance have ranged from 135 to 254 minutes,<sup>243-246,305,306</sup> despite the benchmark recommendations from the surviving sepsis campaign<sup>257,307</sup> to complete the process from clinical and laboratory assessment to first antibiotic dose in < 60 minutes. Performance standards such as this, although difficult to achieve, are necessary commitments to make to provide high-quality care for all patients.

### LIMITATIONS OF THE RESEARCH AND FUTURE DIRECTIONS

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate. One major limitation of the evidence available to inform this guideline is the absence of data from RCTs that either studied the net effect on health outcomes or compared the efficacy and safety of alternative regimens for antibacterial prophylaxis specifically in afebrile neutropenic outpatients. Another is the lack of well-validated scales or models to assess and stratify risk for complications and mortality and thus identify afebrile outpatients with neutropenia most likely to benefit from prophylactic antibiotics. The Panel sees a need for future research to fill these gaps.

Although the MASSC scale is a validated tool to identify patients at low risk for medical complications among those with FN, the false-positive rate in trials reviewed for this guideline shows there is a definite need for improvement. Future research is needed to develop and validate a modified MASCC score with improved sensitivity and specificity. Also needed are better data to define a minimal observation period in the hospital or clinic before discharging patients to continue empiric therapy for FNEs at home.

### ADDITIONAL RESOURCES

Data Supplements, including evidence tables, and clinical tools and resources can be found at [www.asco.org/guidelines/outpatientfn](http://www.asco.org/guidelines/outpatientfn). Patient information is available there and at [www.cancer.net](http://www.cancer.net).

### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

### AUTHOR CONTRIBUTIONS

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**Appendix**

**Table A1.** Panel Members

Panel Member	Expertise
Christopher R. Flowers, MD, MS; Cochair	Medical oncology and hematology
Scott D. Ramsey, MD, PhD; Cochair	Public health science
Eric J. Bow, MD	Infectious diseases, medical oncology and hematology
Clare Karten, MS	Patient representative
Charise Gleason, ARNP	Oncology nursing
Douglas K. Hawley, MD	Medical oncology and hematology
Nicole M. Kuderer, MD	Epidemiology
Amelia A. Langston, MD	Medical oncology and hematology
Kieren A. Marr, MD	Infectious diseases
Kenneth V.I. Rolston, MD	Infectious diseases