JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

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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See accompanying article in *J Oncol Pract*: 10.1200/JOP.2012.000815

ABSTRACT

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/μL 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 ≥ 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 empirical 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.

J Clin Oncol 31. © 2013 by American Society of Clinical Oncology

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Published online ahead of print at www.jco.org on January 14, 2013.

American Society of Clinical Oncology Clinical Practice Guideline Committee approved: September 5, 2012.

Editor's note: This represents a brief summary overview of the complete American Society of Clinical Oncology Clinical Practice Guideline and provides the recommendations with brief discussions of the relevant literature for each. The complete guideline, which includes comprehensive discussions of the literature, methodology information, and all cited references, plus Data Supplements with evidence tables the committee used to formulate these recommendations and a list of all abbreviations used in the text, tables, and figures are available at 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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0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2012.45.8661

INTRODUCTION

The first guideline[1] 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,[2] 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.

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.[3-7] 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 drug-resistant Gram-negative bacterial infections is increasing. However, blood and other cultures are negative and the causative organism and site of infection remain 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.[7-13]

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.[14-21] 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[14,21-25] or oral versus IV antibacterials as empiric therapy.[14,26,27] 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 $< 100/\mu L$ 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 ≥ 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

The complete guideline along with Data Supplements, including evidence tables, and clinical tools and resources can be found at 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

An Expert Panel with a spectrum of contributors reflecting private practice oncology, academic hematology/oncology practice, infectious diseases, oncology nursing, and interest group societies and 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 as well as a patient representative met once in person to discuss evidence from a systematic review and draft recommendations on outpatient management. The Panel interacted by e-mail and telephone to revise and finalize recommendations and to prepare drafts of the full guideline and additional documents and tools. Panel members and their expertise 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). 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) by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved by discussion and by consultation with Panel cochairs if necessary.

Definition of Terms

For purposes of this guideline, the Panel defined neutropenia as an absolute neutrophil count (ANC) $< 1{,}000/\mu L$ (equivalent to $< 1.0 \times 10^9/L$), severe neutropenia as ANC $< 500/\mu L$ (equivalent to $< 0.5 \times 10^9/L$), and profound neutropenia as ANC $< 100/\mu L$ (equivalent to $< 0.1 \times 10^9/L$). The Panel defined the state of being febrile as a temperature of $\geq 38.3°C$ by oral or tympanic thermometry.

Guideline Policy

This Executive Summary for clinicians is an abridged summary of an ASCO practice guideline. The guideline and this summary are 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 summary does not recommend any particular product or course of medical treatment. Use of the practice guideline and this summary is voluntary. The full practice guideline and additional information are available online at 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.

RESULTS

This clinical practice guideline addresses three overarching questions (Table 1), each subdivided into three or four clinical questions. Recommendations A-1 to A-3 address clinical questions relevant to the first overarching question on preventing infection in oncology outpatients who have or are expected to develop neutropenia but are without fever or evidence of infection. Recommendations B-4 to B-6 address the second overarching question on selecting patients with FN who can safely be managed as outpatients. Recommendations C-7 to C-10 focus on interventions and strategies to safely manage oncology patients with FN outside the hospital.

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,[9] the European Society of Medical Oncology (ESMO),[10] and an Australian consensus panel.[13,21,28,29] Additionally, the National Comprehensive Cancer Network (NCCN) has published guidelines on prevention and treatment of cancer-related infections,[11] and the Infectious Disease Society of America (IDSA)[7,12] and the Infectious Diseases Working Party of the German Society of Hematology and Oncology[8] 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 Discussion sections that follow each recommendation in the full guideline (online at www.asco.org/guidelines/outpatientfn).

GUIDELINE RECOMMENDATIONS

Table 1 lists the 10 clinical questions addressed in this practice guideline and the recommendation of the Panel for each. Below are brief summaries of the literature review and discussion for each recommendation. See the full guideline online for detailed analysis and discussion of the evidence.

Literature Review and Discussion for Clinical Question A-1

Because evidence was unavailable from trials limited to outpatients, Recommendations A-1a to A-1g are based on evidence from studies on inpatients or mixed populations (see the full guideline online) and Panel members' expert opinion. Table 2 lists variables shown to influence 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 studies cited in Table 2 used multivariable regression analysis to identify independent predictors of FNE risk. Some of the cited studies[34-37,42,47,52] and others[55,56] 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 that used validated models, checklists, or scores to select neutropenic but afebrile 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 (A-1a) that patients starting a new chemotherapy regimen undergo an individualized but systematic assessment of risk for an FNE that weighs the factors listed in Table 2 and includes consultation with local infectious disease experts as needed.

Guidelines from ASCO[2] and other organizations[11,12,54,57-59] 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. Readers are referred to these guidelines for review and discussion of the evidence supporting this recommendation and for recommendations on selecting patients likely to benefit from primary prophylaxis. Table 1 in the ASCO guideline[2] also includes a list of commonly used regimens by malignancy, with data on incidence of hematologic toxicities including neutropenia and FNEs (available online at www.asco.org/guidelines/wbcgf). Note that antibacterial and antifungal prophylaxis would generally not be indicated when CSF prophylaxis effectively reduces the depth and duration of neutropenia.

Recommendation A-1b (on patient selection for antibacterial prophylaxis) is based on: a systematic review[60] of meta-analyses of RCTs of interventions for febrile neutropenia, the five[61-66] meta-analyses it reviewed of antibacterial prophylaxis, two updates[67,68] of a Cochrane review, and two other meta-analyses[69,70] and a systematic review.[71] Although the preponderance of data from these meta-analyses and the RCTs they included showed that antibacterial prophylaxis decreased mortality when compared with pooled controls administered either placebo or no treatment, a majority of included patients were undergoing either remission induction (or reinduction) for hematologic malignancy (mostly acute leukemia) or hematopoietic SCT (HSCT) and thus were at relatively high risk for an FNE and infection. Lacking robust evidence that antibacterial prophylaxis improves outcomes for patients with neutropenia at low risk for an FNE, and in light of concerns raised in reviews[62,64-68,71-73] and other guidelines[7,11,12,29] that routine use (or overuse) of antibacterial

Table 1. Summary of 2012 Recommendations

Clinical Question	2012 Recommendations
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 an FNE be assessed in such patients who are not yet febrile? What clinical characteristics identify patients who should be offered antimicrobial prophylaxis?	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: 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 A-1b. Clinicians should consider antibacterial prophylaxis only for patients expected to experience profound neutropenia (defined as ANC $<$ 100/μL) likely to last for $\geq$ 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) A-1c. Limit antifungal prophylaxis (for decreasing IFIs from opportunistic yeast or mold species) to patients receiving chemotherapy expected to cause profound neutropenia (ANC $<$ 100/μL) for $\geq$ 7 days, which confers substantial risk ($>$ 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) A-1d. Patients receiving chemotherapy regimens associated with $>$ 3.5% risk for pneumonia from *Pneumocystis jirovecii* (eg, those with $\geq$ 20 mg of prednisone equivalents daily for $\geq$ 1 month or those based on purine analogs) are eligible for prophylaxis A-1e. Antiviral prophylaxis should be considered for patients known to be at substantial risk for reactivation of HBV infection 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 the full guideline online) A-1g. Seasonal influenza immunization is recommended for all patients receiving chemotherapy for malignancy and for all family and household contacts
A-2. What antimicrobial drug classes should be used to prevent infection in afebrile neutropenic outpatients who should be offered prophylaxis?	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: 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 $\geq$ 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 $>$ 20% of Gram-negative bacilli are resistant to fluoroquinolones 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 $\geq$ 7 days 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 A-2c. Prophylaxis with trimethoprim-sulfamethoxazole should only be used if risk for pneumonia from *Pneumocystis jirovecii* 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); additional details and alternatives for patients with sulfa-based hypersensitivities are provided in the full guideline online A-2d. Lamivudine is recommended as prophylaxis in patients at substantial risk for reactivation of HBV infection A-2e. A nucleoside analog is recommended to prevent herpesvirus infection in those at risk 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

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Table 1. Summary of 2012 Recommendations (continued)

Clinical Question	2012 Recommendations
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. 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: 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 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) 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 *Staphylococcus aureus*, vancomycin-resistant enterococci, or extended-spectrum β-lactamase–producing and carbapenemase-producing Gram-negative bacilli
B. Which oncology patients with FN are appropriate candidates for outpatient management?	
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 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 $\geq$ 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 $<$ 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
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 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
B-6. What psychosocial and logistic requirements must be met to permit outpatient management of patients with fever and neutropenia?	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: a. Residence $\leq$ 1 hour or $\leq$ 30 miles (48 km) from clinic or hospital b. Patient's primary care physician or oncologist agrees to outpatient management c. Able to comply with logistic requirements, including frequent clinic visits d. Family member or caregiver at home 24 hours a day e. Access to a telephone and transportation 24 hours a day f. No history of noncompliance with treatment protocols

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Table 1. Summary of 2012 Recommendations (continued)

Clinical Question	2012 Recommendations
C. What interventions are indicated for oncology patients with an FNE who can be managed as outpatients?	
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 anatomic focus (see the full guideline online for details)
C-8. What antibacterials are recommended for outpatient empiric therapy?	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 $> 20\%$; 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[12]
C-9. What additional measures are recommended for outpatient management?	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: a. Frequent evaluation for at least 3 days in clinic or at home b. Daily or frequent telephone contact to verify (by home thermometry) that fever resolves c. Monitoring of ANC and platelet count for myeloid reconstitution d. Frequent return visits to clinic e. 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
C-10. How should PNF syndrome be managed?	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

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.

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.
Patient characteristic				
Advanced age	Risk increases if age ≥ 65 years			30-32
ECOG PS	Risk increases if PS ≥ 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 ≥ three comorbidities			37
Underlying malignancy				
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 (≥ 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
Treatment for malignancy				
Cytotoxic regimen	Risk is higher with regimens that administer:			42
	Anthracyclines at doses ≥ 90 mg/m^2			
	Cisplatin at doses ≥ 100 mg/m^2			
	Ifosfamide at doses ≥ 9 g/m^2			
	Cyclophosphamide at doses ≥ 1 g/m^2			
	Etoposide at doses ≥ 500 mg/m^2			
	Cytarabine at doses ≥ 1 g/m^2			43
	High dose-density (eg, CHOP-14)			
	Anthracycline + taxane ± 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 ≥ 3 (GI) or if peak OMAS score ≥ 2			41, 48, 49
Degree and duration of:				
Neutropenia	ANC < 500/μL for ≥ 7 days			7, 50, 51
Lymphopenia	ALC < 700/μL (ANC surrogate)			42, 52
Monocytopenia	AMC < 150/μL (ANC surrogate)			53
Prophylactic use of WBC growth factors	Reduces risk for patients selected as in ASCO guideline			2, 54, 55

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.

prophylaxis may increase spread of resistant strains, the Panel recommends that clinicians limit use of antibacterial prophylaxis to patients at high risk for an FNE.

Recommendation A-1c (on antifungal prophylaxis) is based on systematic reviews[60,73-75] and meta-analyses[76-81] of RCTs that enrolled patients with or 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. Although the three most relevant meta-analyses[77,79,81] reported that when compared with controls, systemic antifungal prophylaxis significantly decreased mortality attributed to fungal infections and also improved other outcomes, most

patients randomly assigned in the RCTs pooled for meta-analysis were at ≥ 6% risk for invasive fungal infection (IFI) resulting from HSCT, induction chemotherapy for acute leukemia, or other treatments that caused long durations of profound neutropenia. No trials included in these meta-analyses were limited to patients with solid tumors undergoing conventional-dose chemotherapy with or without biologics. Thus, in agreement with other guidelines,[11,12] the Panel recommends limiting antifungal prophylaxis to patients at substantial risk for IFI (> 6% to 10%) from regimens likely to decrease ANC to < 100/μL for ≥ 7 days.

Lacking evidence from RCTs, Recommendation A-1d is based on retrospective observational studies[82-86] and expert opinion; Panel members agreed that *Pneumocystis* prophylaxis should be limited to patients receiving chemotherapy regimens associated with > 3.5% risk for *Pneumocystis* pneumonia. A systematic review[87] of *Pneumocyctis* in immunocompromised patients not infected with HIV reported that *Pneumocyctis* infection rates without prophylaxis were ≥ 3.5% among patients treated with allogeneic HSCT or induction therapy for acute leukemia or rhabdomyosarcoma but were < 3.5% among other oncology patients (eg, those with Hodgkin lymphoma or CNS tumors or those receiving long-term corticosteroid therapy). Evidence from reviews[73,88-90] of prospective controlled studies supported use of a nucleoside analog to prevent hepatitis B virus (HBV) reactivation in patients at known risk (Recommendation A-1e; primarily chronic inactive carriers; see full guideline online for detailed discussion). On the basis of a Cochrane review[91] and data summarized in other guidelines[11,12,92-96] and elsewhere,[73] there was insufficient evidence of clinical benefit from nucleoside analog prophylaxis against reactivation of latent herpes simplex or herpes zoster virus in patients receiving conventional-dose regimens for solid tumors or lymphoma. Thus, the Panel recommends (Recommendation A-1f) limiting such treatment to those undergoing more-intensive therapies (eg, HSCT or remission induction for acute leukemia). Finally, Recommendation A-1g on seasonal influenza immunization is based on systematic reviews[97-104] summarizing evidence of protective responses to and safety of influenza vaccine in oncology patients.

Literature Review and Discussion for Clinical Question A-2

Evidence for question A-2 also was unavailable from trials limited to outpatients; Recommendations A-2a to A-2f are based on evidence from studies on inpatients or mixed populations 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 (see full guideline online) reflect members' experience and expert opinion.

Recommendation A-2a rests primarily on meta-analyses from a Cochrane review,[64,65,68] which showed that systemically absorbed oral fluoroquinolones are the most tolerable choice for prophylaxis in neutropenic oncology patients and are equally protective whether used alone or combined with other antibacterials active against Gram-positive organisms. As detailed under Recommendation A-1b in the full guideline online, the Panel recommends limiting antibacterial prophylaxis to oncology outpatients anticipated to experience profound neutropenia for ≥ 7 days in association with severe mucositis or with other risk factors listed in Table 2.

Evidence from other meta-analyses[77,79-81,105,106] supported Recommendation A-2b for use of an orally administered triazole antifungal drug (eg, fluconazole) to prevent invasive *Candida* infections in patients with > 10% risk or a mold-active triazole (eg, itraconazole oral solution) if aspergillosis risk is > 6%. Again, risks rarely reach these levels unless patients are receiving regimens likely to cause profound neutropenia (ANC < 100/μL) for ≥ 7 days. A systematic review and meta-analysis of RCTs[87,107] supported Recommendation A-2c on use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis* pneumonia in immunocompromised patients not infected by HIV. The Panel recommends use of lamivudine for HBV prophylaxis (Recommendation A-2d); systematic reviews[73,89,90] suggested it is the only drug available to treat active HBV infection that also has been studied in an RCT to prevent HBV reactivation in oncology patients at risk. A Cochrane review[91] reported that acyclovir was the only nucleoside analog tested in placebo-controlled trials as prophylaxis against reactivation of herpesviruses in oncology patients at risk (Recommendation A-2e); meta-analyses showed acyclovir decreased both oral lesions and viral isolates. Recommendation A-2f on use of inactivated trivalent influenza vaccine is based on a Cochrane review of RCTs of viral vaccines for patients with hematologic malignancies[103] and agrees with other guidelines.[11,12,91,108-12]

Literature Review and Discussion for Clinical Question A-3

Direct evidence from RCTs was lacking for an impact on patient outcomes of certain nonpharmacologic interventions and precautions used to minimize exposure of neutropenic but afebrile oncology patients to infection; Recommendations A-3a and A-3b are based on Panel members' experience and expertise. Recommendation A-3a on handwashing reflects the endorsement by the Panel of practices deemed prudent by a panel of the US Centers for Disease Control.[113-15] The recommendation to avoid environments with high spore counts (Recommendation A-3b) rests on retrospective reports[116-20] of risks associated with such sites and the opinion of the Panel on prudent practice. Evidence from RCTs and other comparative studies suggested no effect on health outcomes from routine use of the interventions considered in Recommendation A-3c. A systematic review[121] reported that routine use of high-efficiency particulate air (HEPA) filters did not decrease mortality or fungal infections. An RCT on well-fitting respiratory masks,[122] a nonrandomized study of footwear exchange,[123] and several RCTs on dietary interventions[39,124-26] also reported no significant effects on outcomes.

Literature Review and Discussion for Clinical Question B-4

The Panel needed to evaluate two separate bodies of evidence to develop its recommendation on selecting patients for outpatient management. The first studied outcomes of empiric therapy for an FNE to derive and validate risk assessment tools but enrolled mostly inpatients. The second directly compared outcomes of inpatient versus outpatient management of an FNE in patients deemed at low risk for medical complications. The first group 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 and DS-4 for extracted data); the Multinational Association for Supportive Care in Cancer (MASCC) risk index (Table 3) was derived[38] and validated[38,128-135] in eight of these studies. Extracted data

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 ≥ 21 indicate a low risk for medical complications. Data adapted.[12,127]

†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.

show that the MASCC index has been studied in more patients (N = 2,582) and FNEs (N = 2,758), with performance characteristics as good as or better than those of alternatives (sensitivity, 71% to 95%; specificity, 58% to 95%; positive predictive value, 84% to 98%; negative predictive value, 36% to 86%). Talcott's rules[44,45] provide the only other prospectively validated stratification tool and classify outpatients at FNE onset without either serious comorbidity or uncontrolled cancer (ie, those in group 4) as low risk.

The second group included 10 studies that directly compared outcomes of management in versus out of the hospital for adult oncology patients with FN considered at low risk for complications (see Data Supplement Tables DS-5 and DS-6 for extracted data). These included four RCTs[136-139] (one used Talcott's rules, whereas none used the MASCC score, to identify low-risk patients), four prospective but nonrandomized studies[127,129,140,141] (each required a MASCC score ≥ 21 for outpatient management), and two retrospective studies.[142,143] Data reported from all 10 studies (pooled N = 1,423) showed generally high rates of successful empiric therapy (approximately 80% to > 90%), with no statistically significant differences between outpatient and inpatient arms and few deaths in the outpatient arms. 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 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 remains somewhat uncertain because each validated method misclassifies some high-risk patients. Pooled data (Data Supplement Table DS-4) showed that serious complications developed in up to 11% of patients classified as low risk by MASCC score ≥ 21 and in 7% of patients in Talcott's group 4. Thus, 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[144]), 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 of empiric therapy for an FNE if any of these factors apply.

Literature Review and Discussion for Clinical Question B-5

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. 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, with intervals from first dose to discharge ranging from immediate to 48 to 72 hours (Data Supplement Table DS-5). Similarly, intervals from first dose to discharge ranged from 2 to 72 hours among most RCTs that compared oral versus IV regimens for outpatient empiric therapy; only two discharged patients before their first dose and immediately after random assignment (Data Supplement Table DS-7).

Nevertheless, on the basis of members' expert opinion, the Panel recommends as prudent routine practice the following procedures that were consistently or commonly followed in most studies. Nearly all studies 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. In agreement with an international guideline panel of the Surviving Sepsis Campaign,[145] the Panel also recommends administering the first dose of empiric initial antibacterial therapy as soon as possible after triage (≤ 1 hour seems an achievable and prudent performance standard) from presentation with FN. Most studies also specified that patients' clinical stability and tolerance of oral medications should be verified before they were discharged for outpatient management of FN. Lacking evidence directly comparing different observation intervals, the Panel recommends observation for ≥ 4 hours after the initial dose as prudent practice before discharge to continue empiric therapy as an outpatient.

Literature Review and Discussion for Clinical Question B-6

The literature search did not find any studies that directly compared outcomes of outpatient empiric therapy for FN in patients who did versus did not meet any of the psychosocial and 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 FN who met all or most of these criteria. On the basis of members' expert opinion, the Panel recommends treatment in the hospital

Table 4. Additional Specific Clinical Criteria* That Exclude Oncology Patients With FN From Initial Outpatient Care Even With a MASCC Score ≥ 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/μL)
	Anemia (Hb < 7 g/dL or Hct < 21%)
	ANC < 100/μL of expected duration ≥ 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× 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)†
	Any evidence of severe sepsis‡
	Allergies to antimicrobials used for outpatients
	Antibiotics ≤ 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 cavitary lung nodule or imaging findings suggestive of an active intrathoracic process
Renal	Impaired renal function (creatinine clearance ≤ 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_2, 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 the text and summary of the full guideline online. This list does not replace the need for clinical judgment while making decisions on outpatient versus inpatient management of FN for individual patients.

†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.

‡Severe sepsis is a syndrome defined by the presence of evidence for SIRS (defined by ≥ two of the following criteria: body temperature > 38°C or < 36°C, heart rate > 90 beats/minute, respiratory rate > 20/minute, Pa CO_2 < 32 mmHg, an alteration in the total leukocyte count to > 12 × 10^9/L or < 4 × 10^9/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).

for patients who do not meet one or more of the listed criteria because the only evidence for safety and efficacy of outpatient therapy is from studies conducted in patients who satisfied these requirements.

Literature Review and Discussion for Clinical Question C-7

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 members' expert opinion and experience, the Panel considers bacterial infection the most reasonable assumption and likeliest source of such patients' fever if an alternative explanation cannot be documented. 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 (see the full guideline online for the list of elements the Panel recommends to include in evaluating oncology patients who present with a new FNE).

Literature Review and Discussion for Clinical Question C-8

Evidence from randomized trials of empiric therapy for FN in hospitalized oncology patients supports early use of broad-spectrum antibacterial drugs to decrease mortality and morbidity (see full guideline online for references to relevant reviews and other guidelines). Most 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. Results from 10 meta-analyses[26,27,146-156] of comparative RCTs relevant to both inpatients and outpatients are summarized in Data Supplement Table DS-9. Important findings from these meta-analyses include: similar safety and efficacy with oral versus IV regimens as initial empiric therapy[26,27]; no better survival or therapeutic success, yet increased toxicity from adding an aminoglycoside to a broad-spectrum β-lactam active against *Pseudomonas*[150-52]; and no decrease in overall or infection-related mortality or fever duration from adding a drug targeted against Gram-positive bacteria (eg, vancomycin) to a β-lactam with or without an aminoglycoside.[148]

Although outpatient IV therapy is widely available, oral drugs are more convenient, less costly, and preferred by many patients and clinicians to treat low-risk FN in the outpatient setting.[142,157] Because the literature search did not identify any trials that directly compared different oral regimens for outpatient empiric therapy, the recommendations of the Panel on choice of an oral regimen relied on indirect comparison of results from separate RCTs. Eight of nine RCTs that compared oral versus IV antibacterials as outpatient empiric therapy for low-risk FN used a fluoroquinolone for patients in the oral arm (Data Supplement Tables DS-7 and DS-8). Similarly, most studies on inpatient versus outpatient empiric therapy (Data Supplement Tables DS-5 and DS-6) used an oral fluoroquinolone for the outpatient arms. However, few studies used fluoroquinolone monotherapy exclusively throughout, and the largest and most convincing body of evidence on the safety and efficacy of oral outpatient empiric therapy for FN is from studies that used ciprofloxacin plus amoxicillin-clavulanate. Thus, the Panel recommends this as a first-choice oral regimen in empiric therapy for low-risk FN in oncology outpatients. Also, in agreement with other guidelines,[11,12] the Panel advises against use of a fluoroquinolone alone as initial empiric therapy for outpatient management of FN. If circumstances rule out or argue against selection of this regimen for initial empiric therapy (eg, penicillin allergy), the Panel recommends ciprofloxacin plus clindamycin[158] as an alternative.

Table 5 summarizes the recommendations of the Panel on initial empiric antibacterial therapy for oncology outpatients with FN under various circumstances but considered at low risk for medical complications. Note also that patients infected by Gram-negative pathogens resistant to both fluoroquinolones and β-lactams should be treated as inpatients with an IV regimen that likely requires multiple doses per day (eg, meropenem every 8 hours or piperacillin plus tazobactam every 6 hours).

Table 5. Antibacterial Recommendations for Initial Empiric Therapy for Oncology Outpatients With FN at Low Risk for Medical Complications

Patients Who Are/Have:	Empiric Therapy Regimen
Cancer and FN but at low risk for medical complications (and no allergy to penicillin)	Oral therapy with a fluoroquinolone (ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate
As above but with penicillin allergy	Oral therapy using a fluoroquinolone (ciprofloxacin or levofloxacin) plus clindamycin
As above but fever developed after fluoroquinolone-based antibacterial prophylaxis or in environments where prevalence of fluoroquinolone resistance is > 20%	Do not use fluoroquinolone as initial empiric therapy (see next row for alternatives)
In situation in row above and meet other criteria for outpatient management*	IV therapy with a regimen suitable for outpatient administration*
Unable to tolerate oral medications but meet all other criteria for outpatient management*	IV therapy with a regimen suitable for outpatient administration*
Infected by fluoroquinolone-resistant Gram-negative pathogens coresistant to β-lactams	Treat as inpatients with a regimen that likely requires multiple doses per day (eg, meropenem every 8 hours or piperacillin/tazobactam every 6 hours)
At low risk, hospitalized, stable, and responding to initial IV empiric antibacterial therapy, particularly those classified as having unexplained neutropenic fever	Eligible for stepdown to an orally administered regimen and early discharge for outpatient follow-up and monitoring
FN from cancer therapy and at high or intermediate risk for medical complications	Hospitalization for IV antimicrobial therapy (guideline endorses the current 2010 recommendations of the Infectious Diseases Society of America)

Abbreviations: FN, fever and neutropenia; IV, intravenous.
*See full guideline for details (online at www.asco.org/guidelines/outpatientfn).

Literature Review and Discussion for Clinical Question C-9

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 expert opinion and experience to devise and agree on the listed 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.

Literature Review and Discussion for Clinical Question C-10

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.[11,12]

PATIENT AND CLINICIAN COMMUNICATION

Successful management of FNEs in adult oncology outpatients requires that patients and their family or volunteer caregivers 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. Patients and their caregivers should be informed of evidence-based infection control guidelines to minimize unnecessary restrictions. Instructions should be tailored to individual needs according to health literacy and numeracy, living circumstances, language barriers, and decision-making capacity. Written and/or electronic copies of FN management plans should be provided so that subsequent care decisions are based on adequate information.

HEALTH DISPARITIES

This guideline provides expert recommendations on the best practices to prevent infection and manage FN in oncology outpatients. It is important to note that many patients in the United States have limited access to medical care, including some members of racial and ethnic minorities, those of lower socioeconomic status, and those living some distance from appropriate treatment facilities. Members of some groups 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. 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. Although experts agree that timely assessment and administration of initial empiric antibacterial therapy to febrile neutropenic patients with cancer is important, the time from initial triage to first antibiotic may be longer for those with disparities in access to care. Note also that ethnic neutropenia occurs across populations of African descent, although the impact this entity may have on the management of neutropenia and FN is uncertain.

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. 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. The Panel sees a need for future research to fill these gaps.

ADDITIONAL RESOURCES

The full guideline, with a comprehensive discussion of the literature, more detail on literature search methodology, a full reference list, evidence tables, and clinical tools and resources are found at www.asco.org/guidelines/outpatientfn. Patient information is available there and at 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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Final approval of manuscript: All authors

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Acknowledgment

The Panel wishes to thank reviewers from *Journal of Clinical Oncology* and the Clinical Practice Guidelines Committee (CPGC) as well as the full CPGC for their thoughtful reviews and discussion of earlier drafts.

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
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