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ASCO SPECIAL ARTICLE

Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update

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Editor's note. This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose
To provide an updated joint ASCO/Infectious Diseases Society of American (IDSA) guideline on outpatient management of fever and neutropenia in patients with cancer.

Methods
ASCO and IDSA convened an Update Expert Panel and conducted a systematic review of relevant studies. The guideline recommendations were based on the review of evidence by the Expert Panel.

Results
Six new or updated meta-analyses and six new primary studies were added to the updated systematic review.

Recommendation
Clinical judgment is recommended when determining which patients are candidates for outpatient management, using clinical criteria or a validated tool such as the Multinational Association of Support Care in Cancer risk index. In addition, psychosocial and logistic considerations are outlined within the guideline. The panel continued to endorse consensus recommendations from the previous version of this guideline that patients with febrile neutropenia receive initial doses of empirical antibacterial therapy within 1 hour of triage and be monitored for ≥ 4 hours before discharge. An oral fluoroquinolone plus amoxicillin/clavulanate (or clindamycin, if penicillin allergic) is recommended as empirical outpatient therapy, unless fluoroquinolone prophylaxis was used before fever developed. Patients who do not defervesce after 2 to 3 days of an initial, empirical, broad-spectrum antibiotic regimen should be re-evaluated and considered as candidates for inpatient treatment.

Additional information is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

Neutropenia, a decrease in the absolute neutrophil count (ANC), occurs frequently in recipients of chemotherapy.[1] Neutrophils are critical in providing host defense against infection, particularly bacterial and fungal infections. The risk of infection increases with the depth and duration of neutropenia, with the greatest risk occurring in patients who experience profound, prolonged neutropenia after chemotherapy, which is most likely to occur in the period prior to engraftment during hematopoietic cell transplantation and after induction chemotherapy for acute leukemia.[2] Fever can be an important indicator and is often the only sign or symptom of infection, although clinicians should also be mindful that severely or profoundly neutropenic patients may present with suspected infection in an afebrile state or even may be hypothermic. Prevention and appropriate management of neutropenic fever syndromes (FN) is important because the rate of major complications (eg, hypotension, acute renal, respiratory, heart failure) in the context of FN is approximately 25% to 30%, and the mortality rate ranges up to 11%.[3,4] In addition, in the setting of severe sepsis or septic shock, hospital mortality

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update

Guideline Question

Which patients with fever and neutropenia can be treated as outpatients, and what are the appropriate interventions for these patients?

Target Population

Patients with cancer who require treatment of fever and neutropenia.

Target Audience

Oncologists, infectious disease specialists, emergency medicine physicians, nurses, and advanced practice providers who may treat patients with neutropenia resulting from cancer treatment.

Methods:

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

Key Recommendations for outpatient management of fever and neutropenia are outlined in Figure 1. Additional details regarding the quality of evidence and strength of recommendations are included with the Recommendations section.

Additional Resources:

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

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.

may be as high as 50%.[5] In 2013, ASCO released a guideline on antimicrobial prophylaxis for FN, as well as recommendations for identifying patients with fever and neutropenia who may be treated as outpatients.[6] The Infectious Diseases Society of America (IDSA) "Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer" was released in 2011.[7] For outpatient identification, validated tools such as the Multinational Association of Support Care in Cancer (MASCC) score or Talcott's rules, as well as clinical judgment, were recommended.[6,7] This update includes new evidence on risk stratification of patients who are seemingly stable and at lower risk for FN, a population that has been difficult to assess accurately in the past.[3] Antimicrobial prophylaxis recommendations are not included in this guideline update; they will be updated in a forthcoming separate ASCO/IDSA guidance document. The decision to address these two topics in separate guidelines was made to make the recommendations clearer and easier to use for clinicians.

This guideline update is being carried out in partnership with the IDSA. ASCO methodology relies on analysis of strength and quality of evidence; IDSA uses the Grading of Recommendations Assessment Recommendations and Evaluation (GRADE) system for rating the quality of evidence and determining the strength of the recommendations. This guideline uses ASCO methodology and grading system. A summary of the key recommendations contained within this guideline can be found in the Bottom Line Box.

Guideline Questions

1. What is the recommended initial diagnostic approach for patients with fever who are seeking emergency medical care within 6 weeks of receiving chemotherapy?
2. Which patients with FN are at low risk of medical complications and are, therefore, candidates for outpatient management?
3. What psychosocial and logistic recommendations must be met for patients to be eligible for outpatient management?
4. Should patients with FN who are appropriate candidates for outpatient management receive their initial dose(s) of empirical antimicrobial(s) in the hospital or clinic and be observed, or can they be discharged immediately after evaluation?
5. What antimicrobials are recommended for outpatient empirical therapy in patients with FN?
6. If low-risk outpatients with FN do not defervesce after 2 to 3 days of an initial, empirical, broad-spectrum antibiotic regimen, should they be considered for hospitalization or continue to be treated on an outpatient basis?

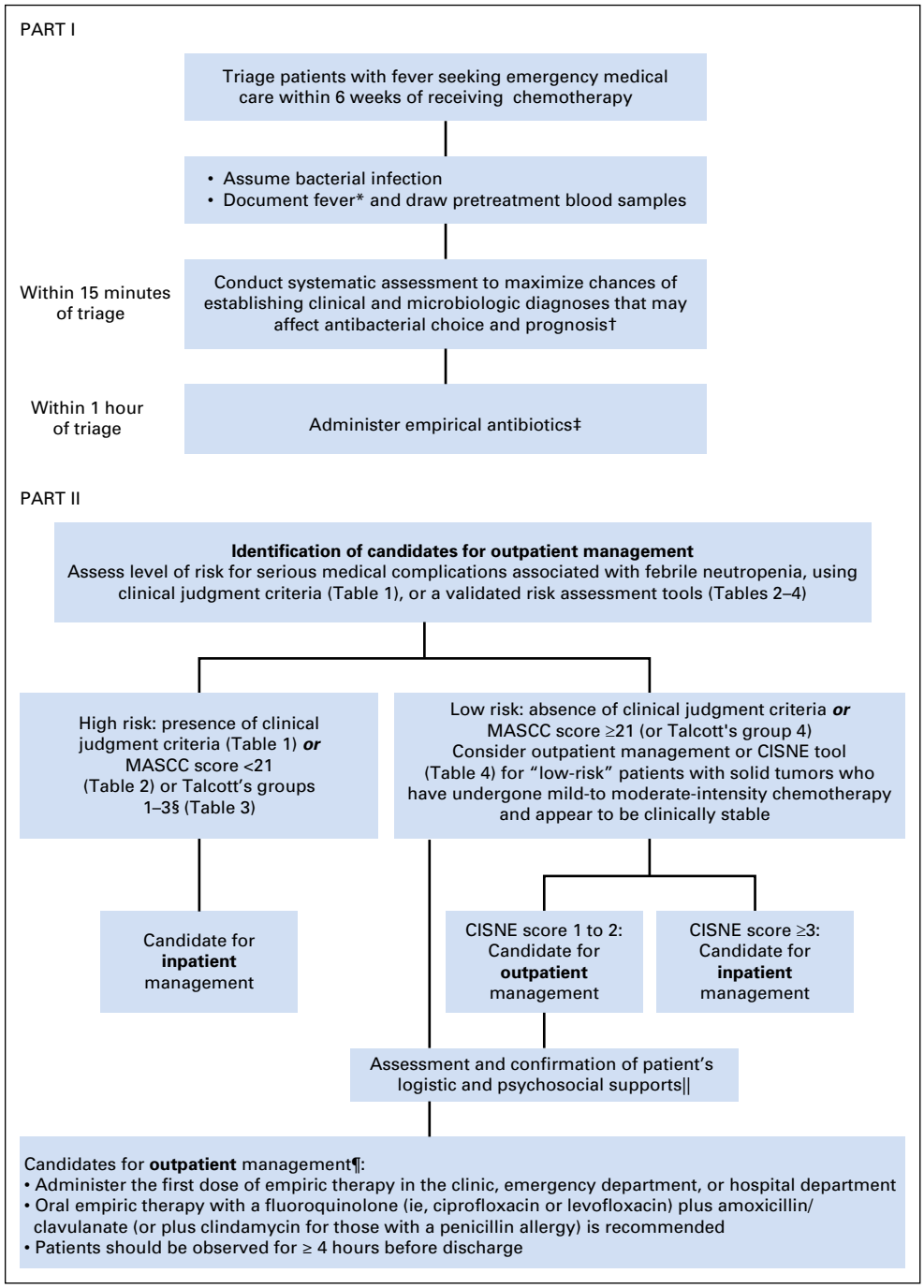

Fig 1. Summary of key recommendations for outpatient management of fever and neutropenia in adults treated for malignancy. (*)See Guideline Update Development Process in Methods for definition of fever. (†)See Recommendation 1.1 for systematic assessment. (‡)See Recommendation 1.1h regarding administration of empirical antibiotics. (§)See Recommendation 5.1, Qualifying statements, regarding settings with high prevalence of resistant pathogens. (||)See Recommendation 3.1 regarding identification of candidate patients for outpatient treatment. (¶)See Recommendation 3.1 regarding evaluation of patients for hospital admission. CISNE, Clinical Index of Stable Febrile Neutropenia; MASCC, Multinational Association for Supportive Care in Cancer.

METHODS

Guideline Update Development Process

This systematic review–based guideline product was developed by an Expert Panel with multidisciplinary expertise (Appendix Table A1, online only). A patient representative and an ASCO guidelines staff member with health research methodology experience were also included. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee prior to publication. In addition, the guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee and Board of Directors. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by an Expert Panel with multidisciplinary representation, including expertise in medical oncology, hematology, infectious diseases, and nursing, and based on a systematic

review of Medline conducted with the PubMed search engine (May 2011 through November 2016). Articles were selected for inclusion in the systematic review if they were randomized trials and observational studies related to outpatient identification and management. Tools designed to identify potential candidates for outpatient management must have been validated by published studies to be considered eligible for inclusion in the evidence base.

Neutropenia was defined by the Panel as an 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 $< 100/\mu L$ (equivalent to $< 0.1 \times 10^9/L$). Fever in neutropenic patients is defined as a single oral temperature of $\geq 38.3°C$ (101°F) or a temperature of $\geq 38.0°C$ (100.4°F) sustained over 1 hour.[7]

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; or (3) published in a non-English language.

The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software (Yale University, New Haven, CT).[8] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation. See the Methodology Supplement for more information about the ASCO grading system.

Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/supportive-care-guidelines, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The Methodology Supplement (available at www.asco.org/supportive-care-guidelines) provides additional information about the "Signals" approach.[9]

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

Clinical Question 1

What is the recommended initial diagnostic approach for patients with fever who are seeking emergency medical care within 6 weeks of receiving chemotherapy?

Recommendation 1.1. In the absence of an alternative explanation, clinicians should assume that fever in a patient with neutropenia from cancer therapy is the result of an infection. The initial diagnostic approach should maximize the chances of establishing clinical and microbiologic diagnoses that may affect antibacterial choice and prognosis. A systematic evaluation should include the following:

a. Complete history and physical examination to identify infectious foci
b. Complete blood count with leukocyte differential count, hemoglobin and platelet count; serum electrolytes; serum creatinine, blood urea nitrogen, and serum lactate concentrations; and liver function tests, including total bilirubin, alkaline phosphatase, and transaminase concentrations
c. At least two sets of blood cultures from different anatomic sites, including a peripheral site as well as one line lumen of a central venous catheter, if present, although the Expert Panel recognizes that that some centers may modify this practice and use only peripheral cultures, given the potential for false-positive results with blood cultures from the line lumen of a central venous catheter
d. Cultures from other sites, such as urine, lower respiratory tract, CSF, stool, or wounds, as clinically indicated
e. Chest imaging study for patients with signs and/or symptoms of lower respiratory tract infection
f. Patients with an influenza-like illness (ie, sudden onset of a respiratory illness characterized by fever and cough and at least one of the following: 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 influenza. In some settings, such as patients with such symptoms in the setting of hematologic malignancy and hematopoietic stem-cell transplantation (HSCT), strong consideration should be given to obtaining expanded viral panels for detection of additional respiratory viruses (influenza virus, parainfluenza virus, adenovirus, coronavirus, respiratory syncytial virus, human metapneumovirus, enteroviruses, and rhinovirus).

(Type of recommendation: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

g. Assessment should occur soon (ie, within 15 minutes) after triage for patients presenting with FN within 6 weeks of receiving chemotherapy.

This assessment is intended to be a sensitive test with low specificity, emphasizing inclusivity rather than exclusivity.

h. The first dose of empirical therapy should be administered within 1 hour after triage from initial presentation. In addition, the following recommendations from the 2010 IDSA guidelines are endorsed:
   - Patients who are seen in clinic or the emergency department for FN and whose degree of risk has not yet been determined to be high or low within 1 hour should receive an initial intravenous (IV) dose of therapy while undergoing evaluation.[7]
   - Monotherapy with an antipseudomonal β-lactam agent, such as cefepime, a carbapenem (eg, meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended. Other antimicrobials (eg, aminoglycosides, fluoroquinolones, vancomycin) may be added to the initial regimen for management of complications (eg, hypotension, pneumonia) or if antimicrobial resistance is suspected or proven.[7]
   - Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.[7]
   - Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood-culture results suspicious for resistant bacteria: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum β-lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.[7]
     - MRSA: Consider early addition of vancomycin, linezolid, or, in the absence of evidence for pneumonia, daptomycin.
     - VRE: Consider early addition of linezolid or daptomycin.
     - ESBLs: Consider early use of a carbapenem.
     - KPCs: Consider early use of polymyxin-colistin or tigecycline,[10] or a newer β-lactam with activity against resistant gram-negative organisms as a less toxic and potentially more effective alternative.

(Type of recommendation: consensus-based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong)

Literature review and analysis. The previous version of this guideline indicated no studies had been found that compared different diagnostic procedures for oncology patients with FN, thus the Panel issued a consensus recommendation that a systematic evaluation should be conducted, which would include the steps outlined in Recommendation 1.1.

The limitations of the rapidity and sensitivity of blood cultures have generated interest in serum markers of inflammation, such as C-reactive protein, interleukins-6 and -8, and procalcitonin, as potential markers to guide decisions about antimicrobial use. In the 2011 IDSA guideline,[7] current data at that time were not sufficient to recommend routine use of these serum markers. For this update, a systematic review with meta-analysis that reported diagnostic accuracy estimates for the biomarker procalcitonin for the diagnosis of bacteremia was included.[11] Bacteremia was identified as the primary outcome rather than sepsis syndrome, because the latter may be too sensitive and nonspecific. In a subgroup analysis of 320 immunocompromised/neutropenic patients, the area under the receiver operating characteristic curve was 0.71 (0.70 to 0.80 is considered a fair level of diagnostic accuracy for predicting bacteremia). Pooled sensitivity was 66% (95% CI, 54% to 76%) and pooled specificity was 78% (95% CI ,71% to 83%), with a high level of statistical heterogeneity (I^2 = 76%).[11] The studies scored highly on the Quality Assessment of Diagnostic Accuracy Studies instrument, a validated tool designed to assess the quality of diagnostic accuracy studies that are included in systematic reviews,[12] although scores for individual studies or for the subset used in the analysis of immunocompromised/neutropenic patients were not available. An additional study found that lipopolysaccharide-binding protein (LBP) had a similar diagnostic accuracy to procalcitonin or IL-6 for the diagnosis of infection.[13] The update panel concluded that more research is needed before options such as procalcitonin or LBP can be recommended as effective tools to determine if antibiotics should be initiated.

Data on time to antibiotic administration are sparse, although two relevant studies[14,15] were found during preparation for this update. Perron et al[14] found a significant association on multivariate analysis between time to administration (TTA) and length of hospital stay, but not mortality or ICU monitoring. Rosa et al[15] found a significant relationship between TTA and 28-day mortality, and a significant difference in 28-day mortality with a TTA of ≤ 30 minutes compared with 31 to 60 minutes for an inpatient population (log-rank P = .0002).

The update panel also endorses the recommendation from the previous version of the guideline[6] for prompt assessment by a physician after initial presentation and administration of the first dose of empirical therapy within 1 hour of triage.

Clinical Question 2

Which patients with FN are at low risk of medical complications and are, therefore, candidates for outpatient management?

Recommendation 2.1.

a. Clinical judgment should be used when selecting candidates for outpatient management. Factors to consider when assessing risk for medical complications in the setting of outpatient management of FN are outlined in Table 1. (Type of recommendation: consensus-based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

b. The MASCC index (Table 2) or Talcott's rules (Table 3) are recommended tools for identifying patients who may be candidates for outpatient management. (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Qualifying statements.

- Patients with FN who are infected by fluoroquinolone-resistant, gram-negative pathogens that are also coresistant to β-lactams/cephalosporins should be treated as inpatients with a carbapenem-based regimen that likely requires multiple doses per day.
- Patients colonized with or suspected of having MRSA, VRE, or *Stenotrophomonas maltophilia* infection should be considered as candidates for inpatient management. Patients undergoing HSCT or induction therapy for acute leukemia are unlikely to be appropriate candidates for outpatient therapy.

Recommendation 2.2. The Clinical Index of Stable Febrile Neutropenia (CISNE; Table 4) may be used as an additional tool to determine the risk of major complications among the group of patients with solid tumors who have undergone mild- to moderate-intensity chemotherapy and who appear to be clinically stable, assuming close proximity to an appropriate medical facility that can provide 24-hour access. (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Literature review and analysis. The previous version of this guideline[6] included several studies on stratifying risk for medical complications in adult oncology patients with FN from chemotherapy. The majority of these studies were validations of the MASCC score, which classifies patients as at low or high risk of medical complications and has been recommended as a method for identifying which patients are candidates for inpatient versus outpatient management of FN. One additional MASCC score validation study was found during preparation of this update that presented findings were consistent with previous results (Data Supplement).[16]

In addition to an assessment of the validity of the MASCC score, as well as Talcott's rules, the previous version of this guideline[6] presented a list of exclusion criteria used in studies of inpatient versus outpatient

Table 1. Additional Specific Clinical Criteria That May Be Used to Exclude Patients With Cancer Who Have Fever and Neutropenia From Initial Outpatient Care Even With a MASCC Score ≥ 21[6]

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
Gastrointestinal	Unable to swallow oral medications
	New-onset or clinically relevant worsening of diarrhea
	Melena, hematochezia (hemorrhoid unrelated), or hematemesis
	Abdominal pain
	Ascites
Hepatic	Impaired hepatic function (aminotransferase values greater than five times ULN) or clinically relevant worsening of aminotransferase values
	Bilirubin > 2.0 mg/dL or clinically relevant increase in bilirubin level
Infectious	Presence of a clear anatomic site of infection (eg, symptoms of pneumonia, cellulitis, abdominal infection, abnormal imaging or microbial laboratory cultures)*
	Any evidence of severe sepsis†
	Allergies to antimicrobials used for outpatient treatment
	Antibiotics ≤ 72 hours before presentation
	Intravascular catheter infection
Neurologic	Altered mental status/sensorium or seizures
	Presence or concern for CNS infection or noninfectious meningitis
	Presence 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, or laboratory or imaging data
	Any relevant clinical worsening (as determined by the treating physician) of organ dysfunction, comorbid condition, vital signs, clinical signs or symptoms, or laboratory or imaging data
	Physically or medically frail (as determined by the treating physician)
	Pregnant or nursing
	Need for intravenous pain control
	Fractures, injuries, or the need for emergent radiation therapy

NOTE. This is not a comprehensive list and does not replace the need for clinical judgment while making decisions on outpatient versus inpatient management of FN for individual patients.

Abbreviations: ANC, absolute neutrophil count; FN, febrile neutropenia; Hct, hematocrit; Hb, hemoglobin; ULN, upper limit of normal.

*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. Recent clinical trials have included patients with more than one site of infection (eg, Kern et al[19]).

†Severe sepsis is a syndrome defined by the presence of evidence for systemic inflammatory response syndrome (defined by two or more of the following criteria: body temperature > 38°C or < 36°C; heart rate > 90 beats/min; respiratory rate > 20/min; partial pressure of CO_2 < 32 mmHg; or 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 (ie, altered mental status, hypoperfusion [itself defined by hypotension (ie, systolic blood pressure < 90 mmHg, mean arterial pressure < 70 mmHg, systolic blood pressure decrease of > 40 mmHg, or < 2 standard deviations below the mean for age)], by an elevated serum lactate > 4 mmol/L, or oliguria (urine output < 0.5 mL/kg/h) and/or hypoxia.

management that were used to provide additional guidance on when inpatient management would be advised even in the event of a "low risk" MASCC score. These criteria are endorsed for this updated version of the guideline.

MASCC score and Talcott's rules have been found to misclassify some patients as being at low risk; pooled analysis found that serious complications developed in ≤ 11% of patients classified as low risk by MASCC score ≥ 21 and in 7% of patients in Talcott's group 4. Furthermore, the MASCC score and Talcott's classification were derived and validated in heterogeneous samples; patient has solid tumors, acute leukemia, or had undergone bone marrow transplant.[17] This update of the guideline identified a more recently validated tool, the CISNE, for predicting major complications, including the occurrence of hypotension; acute renal, respiratory or heart failure; arrhythmia; major bleeding; delirium; acute abdomen; disseminated intravascular coagulation; and other events considered severe according to the study protocol[3] in the lower-risk subpopulation of patients with solid tumors

Table 2. MASCC Scoring System to Identify Patients With Cancer and FN at Low Risk of Medical Complications

Characteristic	Score
Burden of FN with no or mild symptoms*	5
No hypotension (ie, 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 FN with moderate symptoms*	3
Outpatient status	3
Age < 60 years	2

NOTE. Maximum score is 26; scores ≥ 21 indicate a low risk for medical complications.[7]

Abbreviations: FN, febrile neutropenia; MASCC, Multinational Association for Supportive Care in Cancer.

*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, 5), moderate symptoms (score, 3), and severe symptoms or moribund (score, 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.

who appear to be stable and who had been treated with mild- to moderate-intensity chemotherapy. Patients with acute leukemia, bone marrow transplant, and lymphomas treated with therapies other than cyclophosphamide, doxorubicin, vincristine, and prednisone were not included in the study population.

The CISNE tool was validated in a multicenter population of 1,133 patients with seemingly stable FN.[3] A quality assessment of the CISNE validation study was conducted using the Quality in Prognostic Studies tool. According to this tool, the CISNE study appeared to be at low risk of bias for all domains, although the original risk prediction model was limited to clinical variables routinely available at the time of first assessment, and the model may not be generalizable to patients with lymphoma, because they were not highly represented in the sample (n = 22).

The net reclassification improvement of CISNE over MASCC was 32% in the overall validation sample. CISNE demonstrated better performance characteristics than the MASCC index and Talcott's rules (Table 5).

CISNE researchers also conducted an unplanned subgroup analysis that demonstrated the homogeneity of the odds ratios across all subgroups of cancer and infection type within their study population.

Clinical Question 3

What psychosocial and logistic conditions must be met for patients to be eligible for outpatient management?

Recommendation 3.1. Patients with FN who are eligible for discharge and outpatient management must also meet the following psychosocial and logistic requirements:

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

- The following additional measures are recommended:
  - Frequent evaluation for at least 3 days in clinic or at home
  - Daily or frequent telephone contact to verify (by home thermometry) that fever resolves
  - 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: patients do not defervesce after 2 to 3 days of an initial, empirical, broad-spectrum antibiotic regimen, fever recurrence after a period of defervescence, new signs or symptoms of infection, use of oral medications is no longer possible or tolerable, change in the empirical regimen or an additional antimicrobial drug becomes necessary, or microbiologic tests identify species not susceptible to the initial regimen.

(Type of recommendation: consensus-based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Literature analysis and clinical interpretation. These recommendations were based on the expert opinion of the Expert Panel members and on exclusion criteria used in studies of the safety and efficacy of outpatient therapy.

Clinical Question 4

Should patients with fever and neutropenia who are appropriate candidates for outpatient management receive their initial dose(s) of empirical antimicrobial(s) in the hospital or clinic and be observed, or can they be discharged immediately after evaluation?

Recommendation 4.1. In patients with fever and neutropenia who are appropriate candidates for outpatient management, the first dose of empirical therapy should be administered in the clinic, emergency department, or hospital department after fever has been documented and pretreatment blood samples drawn. (Type of recommendation: consensus-based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Qualifying statements.

a. Patients should be observed for ≥ 4 hours before discharge.
b. Patients with FN and a low risk of medical complications, in whom fever is responding to inpatient IV empirical antibiotic treatment and the patient remains clinically stable, are considered eligible for transition to an outpatient regimen.

Literature review and analysis. No studies directly compared outcomes of immediate versus delayed discharge or different observation periods before discharge for outpatient empirical therapy for low-risk FN. In all studies of inpatient versus outpatient management, the initial antibacterial doses were administered before patients were discharged. One new study comparing inpatient versus outpatient management included administration of empirical antibiotics in hospital, as well as a waiting period of 24 hours before early discharge (Data Supplement). The findings of this study were consistent with a failure rate of 3% to 15% with the ambulatory strategy.[18]

Clinical interpretation. Given the lack of evidence for a waiting period prior to discharge for low-risk patients, the Expert Panel endorses consensus-based recommendations from the previous version of this guideline[6] to administer the first dose of empirical therapy in the clinic, emergency department, or hospital department to verify the patient is stable and can tolerate the selected treatment regimen. The update panel also endorses the recommendation from the previous version of the guideline[6] for observation of patients for ≥ 4 hours before discharge.

Where some patients and clinicians have preferred to begin empirical therapy with an IV regimen administered in the hospital, even for a low-risk FN, results of randomized clinical trials have demonstrated the safety and effectiveness of early discharge and a switch from IV to oral regimens 8, 24, or 48 hours after the initial IV infusion if the fever is responding and the patient remains clinically stable.[6]

Table 3. Classification

Group	Characteristic
I	Inpatients (at the time of fever onset)
II	Outpatients with acute comorbidity requiring, by itself, hospitalization
III	Outpatients without comorbidity but with uncontrolled cancer
IV*	Outpatients with cancer controlled and without comorbidity

*Group IV is considered to be low risk.[6]

Clinical Question 5

What antimicrobials are recommended for outpatient empirical therapy in patients with FN?

Recommendation 5.1. For patients with FN who are undergoing outpatient antibiotic treatment, oral empirical therapy with a fluoroquinolone (ie, ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate (or plus clindamycin for those with a penicillin allergy) is recommended. (Type of recommendation: evidence and consensus-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Qualifying statements:

- The use of a fluoroquinolone alone as initial empirical therapy for outpatient management of FN is not recommended; however, some studies have shown that monotherapy may be effective in low-risk outpatients.[19,20]
- In the setting of a high prevalence of ESBL-producing gram-negative bacilli or fluoroquinolone resistance, hospital admission and initial empirical antibacterial treatment with a carbapenem should be considered.[21] Similarly, in a setting of high prevalence of other resistant organisms such as MRSA and VRE and concern for specific, active infection with entities such as pneumonia-causing pathogens or central line–associated bloodstream infection, hospital admission and targeted therapy should be considered.

Literature review and analysis. The previous version of this guideline[6] included 10 meta-analyses with the following main findings:

- A similar level of safety and efficacy with oral versus IV regimens as initial empirical therapy;
- No better survival or therapeutic success, yet increased toxicity from adding an aminoglycoside to a broad-spectrum β-lactam active against *Pseudomonas aeruginosa*; and
- No decrease in overall or infection-related mortality or fever duration from adding a drug targeted against gram-positive bacteria to a β-lactam with or without an aminoglycoside.
- 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.

Table 4. The Clinical Index of Stable Febrile Neutropenia

Explanatory Variable*	No. of Points
Eastern Cooperative Oncology Group performance status ≥ 2	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2	1
Monocytes < 200/μL	1
Stress-induced hyperglycemia	2

*The six variables are integrated into a score ranging from 0 to 8, which classifies patients into three prognostic classes: low risk (0 points), intermediate risk (1 to 2 points), and high risk (≥ 3 points).

An update of the meta-analysis that examined empirical antibiotics targeting gram-positive bacteria for the treatment of patients with cancer who had FN included no new studies.[22] An update of the meta-analysis that assessed adding an aminoglycoside to a broad-spectrum β-lactam active against *P. aeruginosa* included three new studies but reaffirmed the finding that adding an aminoglycoside is not beneficial.[23]

Clinical interpretation. The panel chose to recommend a fluoroquinolone plus amoxicillin-clavulanate (with qualifiers) because the largest and most convincing body of evidence for the safety and efficacy of oral, outpatient, empirical therapy for FN is from studies that used this combination. Based on the updated meta-analyses included in this review, the revised guideline confirms that routine empirical addition of targeted antibiotics for treatment of gram-positive organisms does not improve outcomes for patients with cancer and FN,[22] and that adding an aminoglycoside to a broad-spectrum β-lactam active against *P. aeruginosa* is not beneficial.[23,24] The recommendations of the previous version of the guideline remain unchanged.[6]

Clinical Question 6

Should low-risk outpatients with FN who do not defervesce after 2 to 3 days of an initial empirical broad-spectrum antibiotic regimen (ie, patients who are experiencing persistent neutropenic fever) be considered for hospitalization or continue to be treated on an outpatient basis?

Recommendation 6.1. Low-risk outpatients with FN who do not defervesce after 2 to 3 days of an initial, empirical, broad-spectrum antibiotic regimen should be re-evaluated to detect and treat a new or progressing anatomic site of infection and be considered for hospitalization.

Patients should also be evaluated for admission to the hospital if any of the following occur: fever recurrence after a period of defervescence, new signs or symptoms of infection, use of oral medications is no longer possible or tolerable, change in the empirical regimen or an additional antimicrobial drug becomes necessary, blood cultures drawn on presentation become positive, or microbiologic tests identify species not susceptible to the initial regimen.

(Type of recommendation: consensus-based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Literature review and analysis. The update panel endorses this consensus-based recommendation from the original guideline. A full evidence review of alternative strategies to manage persistent neutropenic fever was outside the scope of this guideline.

DISCUSSION

This updated guideline includes the latest evidence on outpatient management of fever and neutropenia in adult patients undergoing treatment of malignancy. Guidance is provided to assist clinicians in identifying patients who may be candidates for outpatient management of fever and neutropenia, based on clinical criteria and/or validated scoring systems. A newly validated tool is recommended as an option for this update of the guideline; the CISNE can be used in the population of patients with FN who appear to be stable after chemotherapy for treatment of solid tumors. The CISNE can improve classification of this low-risk group of patients, relative to tools that have been previously endorsed.

With the addition of few new studies to the evidence base, the update Expert Panel continued to endorse previous recommendations related to the treatment of patients with fever and neutropenia, including timing and type of antibiotic administration, and other related recommendations. Limited new data continue to support administration of antibiotics as soon as possible; the Expert Panel has continued to endorse a strong

Table 5. Test Performance Characteristics for CISNE, MASCC Index, and Talcott's Rules in a Population of Seemingly Stable Patients With Solid Tumors.[3]

Scale	Sensitivity	Specificity	PPV	NPV	pLR	nLR	AUC-ROC (95% CI)
CISNE (cutoff ≥ 3)	77.7	78.4	36.1	95.7	3.6	0.28	0.868 (0.827 to 0.903)
MASCC (< 21 points)	34.8	86.9	29.3	89.6	2.67	0.75	0.721 (0.669 to 0.768)
MASCC (< 24 points)	64.4	68.6	24.1	92.6	2.05	0.52	
Talcott (high risk)	NR	NR	NR	NR	NR	NR	0.652 (0.598 to 0.703)

Abbreviations: AUC, area under the curve; CISNE, Clinical Index of Stable Febrile Neutropenia; MASCC, Multinational Association for Supportive Care in Cancer; nLR, negative likelihood ratio; NPV, negative predictive value; NR, not reported; pLR, positive likelihood ratio; PPV, positive predictive value; ROC, receiver operator characteristic.

recommendation to administer antibiotics within 1 hour of presentation with fever. Additionally, a new meta-analysis of data regarding the serum biomarker of infection procalcitonin demonstrated that this biomarker had a fair level of diagnostic accuracy; however, the Expert Panel concluded that more research would be needed before serum biomarkers can be used as diagnostic tools to help determine if antibiotics are indicated. ASCO will continue to monitor the literature for new information and update this guideline at regular intervals. This update of the guideline focused on outpatient management of fever and neutropenia, whereas the previous version of this guideline[6] also included recommendations for antimicrobial prophylaxis. ASCO and IDSA plan to update the guideline on antimicrobial prophylaxis in a separate, forthcoming publication.

PATIENT AND CLINICIAN COMMUNICATION

Recommendations throughout this document are aimed at a target audience of oncologists, infectious disease specialists, emergency medicine physicians, nurses, and advanced practice providers. The patient representative included in our Expert Panel highlighted the importance of communication between these clinicians and inpatients and outpatients regarding education about safety practices, what patients need to be aware of to communicate with clinicians, and expectations of patient and/or caregiver responsibility once the patient is discharged. Across the recommendations contained within this guideline, the patient representative highlighted that psychosocial and logistic requirements for outpatient management should be provided to patients and caregivers.

Furthermore, it is important to have specific take-home guidelines for patients and/or caregivers to follow in the event that fever has responded to the initial IV infusion and the patient is clinically stable for discharge. This could be in the form of a basic chart that could be used by clinicians and modified, as necessary, for individual patients.

Finally, patient input also identified the importance of providing talking points to patients and their caregivers in the event of a febrile patient's visit to the emergency department of clinic, so that clinicians will be alerted immediately, avoiding potentially long wait times for triage.

For additional information and strategies for patient and clinician communication, please see ASCO's consensus guideline regarding this topic.[25]

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 who are members of racial or ethnic minorities 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 are others in the United States.[26-29] Many other patients lack access to care because of their geographic location 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.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Many patients for whom guideline recommendations apply present with MCC; therefore, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

The burden of a cancer diagnosis extends beyond the physical and psychological effects of the disease, and the social and financial effects of cancer, cancer treatment, and supportive care on the patient and family can be profound for patients worldwide.[30] The out-of-pocket expenses incurred by patients for accessing care can range widely and can affect patients' financial well-being significantly.[31] In particular, patients with cancer who experience extreme financial toxicity such as bankruptcy, these financial effects can be associated with increased mortality.[32] The financial consequences associated with diagnostic and treatment choices for patients with cancer who have FN rarely are associated with significant costs. However, the cost implications of mismanagement of a patient with cancer who has FN and who subsequently requires intensive care or prolonged hospital stays can be substantial. While discussions about the costs of cancer supportive care commonly focus on balancing the potential to save and extend lives against the costs to society or payers, the low cost of most interventions discussed in this guideline and their potential effect on infectious complications suggest that they have a favorable cost-benefit ratio even without formal evaluations.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. A reviewer of this guideline noted that implementation of some of these recommendations, such the initiation of a health care provider assessment within 15 minutes of triage, will be difficult given insufficient resources in busy emergency departments. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *JCO* and the *Journal of Oncology Practice*.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

Related ASCO Guidelines

- Integration of Palliative Care into Standard Oncology Practice[33] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Recommendations for the use of WBC growth factors update[34] (http://ascopubs.org/doi/10.1200/JCO.2015.62.3488)
- Central venous catheter care for the patient with cancer[35] (http://ascopubs.org/doi/10.1200/JCO.2012.45.5733)
- Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy[6](http://ascopubs.org/doi/10.1200/JCO.2012.45.8661)
- Patient-Clinician Communication[25] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update

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Appendix

Table A1. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: ASCO and Infectious Diseases Society of America Clinical Practice Guideline Update Expert Panel Membership

Name (and designation)	Affiliation/Institution	Role/Area of Expertise
Eric J. Bow, MD	CancerCare Manitoba and the University of Manitoba, Winnipeg, Canada	Infectious diseases, hematology/oncology, blood and marrow transplant
Jennie Crews, PGIN Representative	Seattle Cancer Care Alliance, Seattle, WA	PGIN representative
Christopher R. Flowers, MD, Co-Chair	Emory University School of Medicine, Atlanta, GA	Medical oncology and hematology
Charise Gleason, MSN, NP-C	Winship Cancer Institute, Atlanta, GA	Oncology nursing
Douglas K. Hawley, MD	University of Cincinnati Veterans Affairs Medical Center, Cincinnati, OH	Medical oncology and hematology
Amelia A. Langston, MD	Emory University School of Medicine, Atlanta, GA	Medical oncology and hematology
Erin B. Kennedy	ASCO	ASCO staff/health research methodologist
Loretta J. Nastoupil, MD	MD Anderson Cancer Center, Houston, TX	Medical oncology and hematology
Michelle Rajotte, LMSW	The Leukemia and Lymphoma Society, Rye Brook, NY	Patient representative
Kenneth Rolston, MD	MD Anderson Cancer Center, Houston, TX	Infectious diseases
Lynne Strasfeld, MD	Oregon Health and Science University, Portland, OR	Infectious diseases
Randy A. Taplitz, MD, Co-Chair	UC San Diego Health, La Jolla, CA	Infectious diseases

Abbreviation: PGIN, Practice Guidelines Implementation Network.