

# ASCO | GUIDELINES

Clinical Tools and Resources

## **Antimicrobial Prophylaxis in Neutropenic Adult Oncology Outpatients**

ASCO Clinical Practice Guideline

# Introduction & Context

- ASCO's guideline on hematopoietic colony-stimulating factors recommends primary prophylaxis for patients receiving chemotherapy regimens associated with  $\geq 20\%$  risk for fever & neutropenia (FN) (last updated 2006)
- ASCO guidelines previously did not address other measures to prevent infectious complications in outpatients who are undergoing chemotherapy and are neutropenic

# Guideline Methodology & Systematic Review Results

- An Expert Panel reviewed relevant medical literature
  - Databases searched: MEDLINE; Dates: 1987-April 2011
- Evidence on patient selection and drug choice for antimicrobial prophylaxis was unavailable from trials limited to outpatients
  - Panel recommendations are based on inpatient studies and expert opinion.
- Limited RCT evidence on physical precautions and non-drug interventions

# Clinical Questions

A) What interventions are appropriate to prevent infections in patients with a malignancy who have received chemotherapy as inpatients or outpatients, 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? What clinical characteristics identify patients who should be offered antimicrobial prophylaxis?

A-2) What antimicrobial drug classes should be used to prevent infection?

A-3) What additional precautions are appropriate to prevent exposure to infectious agents or organisms?

Recommendations A-1 and A-2: assessing risk of infection, selecting candidates for prophylaxis, and choosing antimicrobials for prophylaxis of infection

***FOR AFEBRILE PATIENTS WITH  
CANCER & WITH (OR EXPECTED  
TO DEVELOP) NEUTROPENIA:***

Follow recommendations in ASCO's guideline on white blood cell growth factors with respect to appropriate use of primary prophylaxis to prevent FNEs.

Assess risk systematically (see Table 2 & text in online full guideline for risk factors to evaluate; consult with infectious disease specialists as needed)

<i>To protect against :</i>	<i>Appropriate patient population(s)/limitation(s) (Recommendation A-1)</i>	<i>Prophylaxis Choice (Recommendation A-2)</i>
<b>Bacterial infection (specifically invasive infection by Gram-negative bacilli)</b>	<p>Prophylaxis appropriate for patients expected to experience profound neutropenia (ANC &lt;100/<math>\mu</math>L) likely to last for <math>\geq</math>7 days, or with other significant high risk features (see <b>Table 2 in published guideline</b>).</p> <p>Not if neutropenia is less severe or of shorter duration (as is true for nearly all patients with solid tumors undergoing conventional chemotherapy <math>\pm</math> a targeted or biologic drug).</p>	<p>Orally administered, systemically absorbed fluoroquinolone.</p> <p>Note: less effective in clinical settings where &gt;20% of Gram-negative bacilli are resistant to fluoroquinolones.</p>
<b>Fungal infection</b>	<p>Prophylaxis appropriate for patients expected to have profound neutropenia (ANC &lt;100/<math>\mu</math>L) for <math>\geq</math>7 days (thus at &gt;6-10% risk for IFI).</p> <p>Not for patients with solid tumors undergoing conventional chemotherapy <math>\pm</math> biologics</p>	<p>Orally-administered triazole antifungal or an echinocandin parenterally-administered in the outpatient setting; use mold-active triazole, if there is a substantial risk (&gt;6%) for invasive aspergillosis.</p>
<b>Pneumocystis pneumonia (PCP)</b>	<p>Prophylaxis appropriate for patients receiving chemotherapy regimens associated with &gt;3.5% risk (e.g., those with <math>\geq</math>20 mg of prednisone equivalents daily for <math>\geq</math>1 month, or those based on purine analogs).</p>	<p>Trimethoprim-sulfamethoxazole.</p> <p><i>See guideline online for alternatives if patient is hypersensitive to sulfonamides</i></p>
<b>Hepatitis B virus (HBV) infection</b>	<p>Only for patients known to be at substantial risk for reactivation</p>	<p>Lamivudine</p>
<b>Herpesviruses (Herpes simplex virus or Herpes zoster virus)</b>	<p>Only for seropositive patients undergoing therapy for certain hematologic malignancies (see details in full guideline online)</p>	<p>Nucleoside analog active versus HSV and/or VZV</p>
<b>Seasonal influenza</b>	<p>All patients undergoing treatment for malignancy, all family and household contacts.</p>	<p>Influenza immunization utilizing trivalent inactivated vaccine</p>
	<p>Patients at risk with proven exposure</p>	<p>Neuraminidase inhibitor such as oseltamivir</p>

# Recommendation A-3

*Additional precautions for neutropenic but afebrile outpatients*

## Healthcare workers

- Handwashing practices as in CDC recommendations
- Respiratory hygiene/cough etiquette guidelines

## Patients

- Avoid prolonged contact with environments that have high concentrations of airborne fungal spores (e.g., construction and demolition sites).

# Recommendation A-3, continued

## Not recommended for routine use:

- 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

## Only Consider

- Gowning and gloving for antibiotic-resistant organisms e.g., methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, or extended-spectrum  $\beta$ -lactamase-producing and carbapenemase-producing Gram-negative bacilli.



# Bottom Line

- ***Interventions***

- Antibacterial &/or antifungal prophylaxis and physical precautions to prevent infection of afebrile oncology outpatients with neutropenia;

- ***Target Audience***

- Oncologists, primary care physicians, and oncology nurses

- ***Key Recommendations***

- Only use antibacterial and antifungal prophylaxis if ANC is expected to remain  $<100$  per  $\mu\text{L}$  for  $>7$  days, unless other factors (see Table 2 in text) increase risks for complications or mortality.
- If indicated, an oral fluoroquinolone is preferred for antibacterial prophylaxis and an oral triazole for antifungal prophylaxis.
- Interventions such as such as footwear exchange, protected environments, respiratory or surgical masks, a “neutropenic” diet, or nutritional supplements are not recommended since evidence is lacking of clinical benefits to patients from their use.

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

ASCO Clinical Practice Guideline

# Background

## Oncology patients with fever and neutropenia

- Previous evidence showed that empiric antibacterial therapy reduces deaths from infection, compared with waiting for results of microbiological assays
- The most common species found in blood cultures are coagulase-negative staphylococci, but the frequency of antibiotic-resistant gram-negative species is increasing
- Blood and other cultures often are negative, and the causative organism and site of infection remain uncertain in many oncology patients with fever
- No previous ASCO recommendations on
  - identifying oncology outpatients with fever and neutropenia at low risk for medical complications
  - strategies to manage their empiric therapy in the outpatient setting

# Definitions

For this guideline, the Panel defined:

- Neutropenia: absolute neutrophil count (ANC)  $<1000$  per  $\mu\text{L}$
- Severe neutropenia: ANC  $<500$  per  $\mu\text{L}$
- Profound neutropenia: ANC  $<100$  per  $\mu\text{L}$
- Febrile: temperature of  $\geq 38.3^{\circ}\text{C}$  by oral or tympanic thermometry

# Clinical Questions

B) Among patients with a malignancy and febrile neutropenia:

B-4) What clinical characteristics should be used to select patients for outpatient empiric therapy?

B-5) Should outpatients with fever and neutropenia 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 logistical requirements must be met to permit outpatient management of patients with fever and neutropenia?

# Clinical Questions

C) What interventions for patients with a malignancy and febrile neutropenia who are managed as outpatients?:

C-7) Diagnostic procedures

C-8) Antibacterial drugs for outpatient empiric therapy

C-9) Additional measures

C-10) How should the persistent neutropenic fever syndrome be managed?

# Recommendation B-4

- Inpatient management is considered the standard approach. However, carefully selected patients may be managed as outpatients.
- Systematic risk assessment should begin with a validated risk assessment tool (see next two slides, 16 & 17).
  - The MASCC index has been evaluated most thoroughly
  - Talcott's Groups has been prospectively validated.
- Oncology patients with FN may be considered low risk if either the MASCC Score is  $\geq 21$  or they are in Talcott's Group 4.
- FN should be managed in the hospital if the clinician has any reservations with respect to an assessment tool's accuracy for an individual, even if the patient is classified as low risk.

## Table 1. Multinational Association for Supportive Care in Cancer (MASCC) Scoring System – To Identify Patients with Cancer and Febrile Neutropenia at Low Risk of Medical Complications<sup>a</sup>

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

<sup>a</sup> Maximum score is 26; scores  $\geq 21$  indicate a low risk for medical complications. Adapted from Klastersky et al. 2006 + Freifeld et al. 2011.

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

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

<sup>d</sup> Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.



# Talcott's Groups for Stratifying Risk of Medical Complications from FN

- **Group 1:** inpatients at onset of FN
- **Group 2:** outpatients with a serious acute comorbidity (defined as a medical condition other than FN requiring inpatient observation or therapy)
- **Group 3:** outpatients with uncontrolled cancer (defined as leukemia not in CR or, for other malignancies, progressive disease despite chemotherapy or other evidence of treatment failure)
- **Group 4:** outpatients without serious comorbidity or uncontrolled cancer (thus at low risk for medical complications from FN)

# Recommendation B-5

*Immediate discharge versus observation after initial dose of empiric therapy– bottom line*

- Administer the first dose of empiric therapy within 1 hr after triage from initial presentation after fever has been documented in a patient with neutropenia and pre-treatment blood samples have been drawn.
- Observe patients identified as low risk and selected for outpatient management for at least 4 hours to verify they are stable and can tolerate the regimen they will receive

# Recommendation B-6

*Psychosocial and logistical requirements for outpatient management of fever and neutropenia– bottom line*

All of the following should apply for patients with cancer to receive empiric therapy for fever and neutropenia as outpatients:

- a. residence  $\leq 1$  hour or  $\leq 30$  miles (48 km) from clinic or hospital;
- b. patient's primary care physician agrees to outpatient management;
- c. able to comply with logistical requirements, including frequent clinic visits;
- d. family member or other care giver at home 24 hours each day;
- e. 24-hour a day access to a telephone and transportation;
- f. no prior history of non-compliance with treatment protocols.

Note: Direct comparative evidence was unavailable; based on informal panel consensus. See full guideline.

# Recommendation C-7: Diagnosis

- If no evidence for an alternative explanation, assume a bacterial infection is the cause of fever in a patient with neutropenia from cancer therapy.
- Initial diagnostic approach should maximize possibility of establishing a clinical and microbiologic diagnosis that may affect antibacterial choice and prognosis.
- Systematically evaluate the patient, seeking to identify the infectious agent and the anatomic focus (see the full guideline online for details).

# Recommendation C-8: Antibacterials for outpatient empiric therapy

<i>Patients who are/have</i>	<i>Empiric therapy regimen</i>
cancer, fever, and neutropenia but at low-risk for medical complications (& 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 the prevalence of fluoroquinolone resistance is >20%.	Do not use fluoroquinolone in initial empiric therapy regimen (see next row).
If either situation in row above holds, but other criteria met for outpatient management*	intravenous therapy with a regimen suitable for outpatient administration; consider admission for inpatient treatment
unable to tolerate oral medications but meet all other criteria for outpatient management*	intravenous therapy with a regimen suitable for outpatient administration; consider admission for inpatient treatment
infected by fluoroquinolone-resistant gram-negative pathogens co-resistant to $\beta$ -lactams	Treat as inpatients with a regimen that likely requires multiple doses per day (e.g. meropenem every 8 hours or piperacillin/tazobactam every 6 hours)
at low risk, hospitalized, stable and responding to intravenously administered initial empirical antibacterial therapy, particularly those classified as having unexplained neutropenic fevers	Eligible for stepdown to an orally administered regimen and early discharge for out-patient follow-up and monitoring.
fever and neutropenia from cancer therapy and at high or intermediate risk for medical complications	Hospitalization for intravenous antimicrobial therapy (guideline endorses the current 2010 recommendations of the Infectious Diseases Society of America.)

\* see full guideline text online for details

# Recommendation C-9

## *additional measures*

Prudent and sensible outpatient management should include:

- 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:
  - persistent neutropenic fever syndrome
  - fever recurs
  - new signs or symptoms of infection appear
  - oral medications are no longer possible or tolerable
  - change in the empiric regimen or an additional antimicrobial drug becomes necessary;
  - microbiologic tests identify species not susceptible to initial regimen

# Recommendation C-10

*Managing the persistent neutropenic fever syndrome—  
bottom line*

Re-evaluate low-risk patients who fail to defervesce after 2-3 days of an initial empirical broad-spectrum antibiotic regimen, to detect and treat a new or progressing anatomical site of infection and consider for hospitalization.

# Bottom Line

- ***Interventions***

- Identifying oncology outpatients with FN at low risk for medical complications; and
- Initial empiric therapy for FN in the outpatient setting for patients at low risk of medical complications.

- ***Target Audience***

- Oncologists, primary care physicians, and oncology nurses

- ***Key Recommendations***

- Assess risk for medical complications in patients with FN using the MASCC score or Talcott's Groups;
  - scores  $\geq 21$  or Talcott's Group 4 with no other risk factors (slides 16-17) define 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.



# Patient and Clinician Communication

- Educate patients & family members or other caregivers to recognize and act on signs or symptoms of possible infection, including instructions on:
  - monitoring body temperature (how & how often);
  - contacting clinicians outside of office hours (when & how).
- Tailor instructions to individual needs according to health literacy and numeracy, living circumstances, language barriers, and decision-making capacity.
- Inform patients of evidenced-based infection control guidelines to minimize unnecessary restrictions.
- Provide written and/or electronic copies of plans for managing FN

# Guideline Methodology: Panel Members

Panel Members	Affiliation/Institution	Expertise
Christopher R. Flowers, MD, MS; Co-Chair	Winship Cancer Institute; Emory Univ School of Medicine	Medical Oncology and Hematology
Scott D. Ramsey, MD, PhD; Co-Chair	Fred Hutchinson Cancer Research Center	Public Health Science
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Charisse Gleason, ARNP	Winship Cancer Institute; Emory Univ School of Medicine	Oncology Nursing
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# Additional ASCO Resources

- The guideline executive summary, full guideline, and data supplements are available at <http://www.asco.org/guidelines/outpatientfn>
- A patient guide on neutropenia and a podcast for patients on this guideline are also available at <http://www.cancer.net>
- A guideline endorsement on the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem Cell Transplantation can be found at <http://www.asco.org/endorsements/pedfn>

# ASCO Guidelines

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