NCCN Prevention and Treatment of Cancer-Related Infections Panel Members

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漈 Internal medicine
 EXTI Pulmonary medicine
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∑ Pharmacology

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Print the Prevention and Treatment of Cancer-Related Infections Guideline

For help using these documents, please click here

This manuscript is being updated to correspond with the newly updated algorithm.

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus:
All recommendations are Category 2A unless otherwise specified.
See NCCN Categories of Consensus

Summary of Guidelines Updates

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. © 2007.
SUMMARY OF GUIDELINES UPDATES

Prior NCCN guidelines on infections in patients with cancer focused primarily on the management of fever and neutropenia. Reflecting the heterogeneity of immunocompromised conditions in patients with cancer and the spectrum of pathogens to which they are susceptible, the NCCN expanded the scope of our panel to create guidelines on “Prevention and Treatment of Cancer-Related Infections” to expand the “Fever and Neutropenia” guidelines. Although neutropenia remains a key risk factor for infections, other immunocompromised states pose at least equal risk. Allogeneic hematopoietic stem cell transplant (HSCT) recipients with neutrophil recovery who require intensive immunosuppressive therapy for graft-versus-host disease (GVHD) are an example of non-neutropenic patients at great risk for common bacterial and opportunistic infections. We also make new recommendations on other highly immunocompromised patients with cancer such as those receiving high-dose corticosteroids, purine analogues, and alemtuzumab. Indeed, prior NCCN guidelines on fever and neutropenia have addressed infections in the non-neutropenic setting. In the current guidelines, the subject of infections in neutropenic and immunocompromised non-neutropenic patients with cancer are given equal weight.

We expanded the definitions applied to assessment of risk of infections. In patients with neutropenia, the risk of infections is related to the degree and duration of neutropenia. In non-neutropenic, immunocompromised patients, the level of risk may be more difficult to define. For example, in non-neutropenic allogeneic HSCT recipients, the risk of opportunistic fungal and viral infections is strongly related to the degree of GVHD and intensity of immunosuppressive therapy. Therapy with purine analogues and alemtuzumab leads to prolonged suppression of cellular immunity. Host factors were used to stratify the risk for specific infectious complications and were incorporated into new algorithms for prophylaxis, diagnosis, and early therapy in specific patient groups.

We also made modifications related to prophylaxis and early treatment of specific infectious diseases. These modifications were based on the availability of newer antibiotic agents and diagnostics and recent clinical trial data. The new guidelines address the benefits and trade-offs of quinolone prophylaxis in neutropenic patients in light of new data from randomized studies. In addition, the availability of newer broad spectrum antifungal agents with a good safety profile raise the possibility of using mold-active prophylaxis in patients at high risk for invasive fungal infections without the need to empirically modify antifungal therapy solely on persistent neutropenic fever of unknown etiology. Algorithms that include chest CT scans and laboratory surrogates for invasive fungal infections are discussed.

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### OVERALL INFECTION RISK IN CANCER PATIENTS

#### DISEASE / THERAPY EXAMPLES

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard chemotherapy regimens for most solid tumors</td>
<td>Autologous HSCT</td>
<td>Allogeneic HSCT</td>
</tr>
<tr>
<td>Anticipated neutropenia less than 7 d</td>
<td>Lymphoma</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>▶ Induction</td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td>▶ Consolidation</td>
</tr>
<tr>
<td></td>
<td>Purine analog therapy (ie, Fludarabine, 2-CdA)</td>
<td>▶ Alemtuzumab (CAMPATH) therapy</td>
</tr>
<tr>
<td></td>
<td>Anticipated neutropenia 7 to 10 d</td>
<td>▶ GVHD treated with high dose steroids</td>
</tr>
</tbody>
</table>

#### FEVER & NEUTROPENIA RISK CATEGORY (See FEV-3)

- **Low**
- **Intermediate** Usually HIGH, but some experts suggest modifications depending on patient status
- **High**

#### ANTIMICROBIAL PROPHYLAXIS

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bacterial - None</td>
<td>• Bacterial - Consider fluoroquinolone prophylaxis</td>
<td>• Bacterial - Consider fluoroquinolone prophylaxis</td>
</tr>
<tr>
<td>• Fungal - None</td>
<td>• Fungal - Consider anti-mold agent</td>
<td>• Fungal - Consider anti-mold agent</td>
</tr>
<tr>
<td>• Viral - None unless prior HSV episode</td>
<td>• Viral - During neutropenia and at least 30 d after HSCT</td>
<td>• Viral - during neutropenia and at least 30 d after HSCT</td>
</tr>
</tbody>
</table>

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**KEY:** 2-CdA = chlorodeoxyadenosine (cladribine), CLL = chronic lymphocytic leukemia, GVHD = graft versus host disease, HSCT = hematopoietic stem cell transplant, HSV = herpes simplex virus, TMP/SMX = trimethoprim/sulfamethoxazole

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*a General categories based on observational studies, duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies.

*b Pneumocytis prophylaxis will be addressed separately.

*c See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.

*d See Antifungal Agents (FEV-B) for dosing, spectrum and specific comments/cautions.

*e See Antiviral Agents (FEV-C) for spectrum and specific comments/cautions.
OVERALL INFECTION RISK IN CANCER PATIENTS

**Low**
- Standard chemotherapy regimens for most solid tumors
- Anticipated neutropenia less than 7 d

**Intermediate**
- Autotransplants
- Lymphoma
- CLL
- Multiple myeloma
- Purine analog therapy
- Anticipated neutropenia 7 to 10 d

**High**
- Allogeneic HSCT (neutropenic)
- Acute leukemia (neutropenic)
- MDS (neutropenic)
- Anticipated neutropenia greater than 10 d
- GVHD
- Alemtuzumab

ANTIBACTERIAL PROPHYLAXIS

**DURATION**

- **Low**
  - None

- **Intermediate**
  - Consider fluoroquinolone prophylaxis or None

- **High**
  - Penicillin and TMP/SMX
  - For a minimum of 2 mo after alemtuzumab and until CD4 ≥ 200 cells/mcL

*General categories based on observational studies, duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies.*

*See Antibacterial Tables (FEV-A) for dosing, spectrum, and specific comments/cautions.*

*Although there are data to support levofloxacin prophylaxis for low and intermediate risk patients, the panel discourages this practice in low-risk patients (because of concerns about antimicrobial resistance); however, it can be considered in intermediate-risk patients.*

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OVERALL INFECTION RISK IN CANCER PATIENTS\(^a\)

**Low**
- Standard chemotherapy for most solid tumors
  - **DISEASE/THERAPY EXAMPLES**
  - **ANTIFUNGAL PROPHYLAXIS\(^d\)**
  - **DURATION**
    - None
    - Until resolution of neutropenia

**Intermediate to High**
- **ALL**
- MDS (neutropenic)
- AML (neutropenic)
- Autologous HSCT
  - With mucositis\(^i\)
  - Without mucositis
- Allogeneic HSCT (neutropenic)
- Significant GVHD\(^h\)

**DISEASE/THERAPY EXAMPLES**
- **ANTIFUNGAL PROPHYLAXIS\(^d\)**
- **DURATION**

- Fluconazole\(^j\)
- Posaconazole (category 1)
- Voriconazole (category 2B)
- Fluconazole (category 1)
- Micafungin (category 1)
- Fluconazole (category 1)
- Itraconazole (category 1)
- Micafungin (category 1)
- Voriconazole (category 2B)
- Posaconazole (category 2B)
- Fluconazole (category 1)
- Itraconazole (category 1)
- Micafungin (category 1)
- Voriconazole (category 2B)
- Posaconazole (category 2B)
- Echinocandin (category 2B)

\(^a\) General categories based on duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies.

\(^d\) See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.

\(^h\) Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy.

\(^i\) Severe mucositis is a risk factor for candidemia in patients with hematologic malignancies and stem cell transplant recipients not receiving antifungal prophylaxis.

\(^j\) Itraconazole, voriconazole, and posaconazole are potent inhibitors of cytochrome P450 A enzymes and may significantly decrease the clearance of vinca alkaloids.

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### OVERALL INFECTION RISK IN CANCER PATIENTS

<table>
<thead>
<tr>
<th>OVERALL INFECTION RISK IN CANCER PATIENTS</th>
<th>DISEASE / THERAPY EXAMPLES</th>
<th>VIRUSES</th>
<th>ANTIVIRAL PROPHYLAXIS</th>
<th>DURATION OF ANTIVIRAL PROPHYLAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Standard chemotherapy regimens for solid tumors</td>
<td>HSV</td>
<td>None unless prior HSV episode</td>
<td>During neutropenia</td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Autologous HSCT</td>
<td>HSV</td>
<td>Acyclovir Famciclovir Valacyclovir</td>
<td>During neutropenia and at least 30 d after HSCT</td>
</tr>
<tr>
<td></td>
<td>• Lymphoma</td>
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<td>High</td>
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<td></td>
<td>&gt; Induction</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>&gt; Consolidation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|                                          | Alemtuzumab (Campath) therapy | HSV VZV CMV | Acyclovir Famciclovir or Valacyclovir as HSV prophylaxis (See INF-6) for CMV | HSV prophylaxis
  • Minimum of 2 mo after alemtuzumab and until CD4 ≥ 200 cells/mL
  • During neutropenia and at least 30 d after HSCT
  Pre-emptive therapy for CMV (See INF-6) |

**KEY:** 2-CdA = chlorodeoxyadenosine (cladribine), CLL = chronic lymphocytic leukemia, GVHD = graft versus host disease, HSCT = hematopoietic stem cell transplant, HSV = herpes simplex virus, TMP/SMX = trimethoprim/sulfamethoxazole

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*a General categories based on observational studies, duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies.

*See Antiviral Agents (FEV-C) for spectrum and specific comments/cautions.

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Prevention and Treatment of Cancer-Related Infections

INFECTION RISK IN CANCER PATIENTS

DISEASE / THERAPY EXAMPLES

DURATION OF PROPHYLAXIS

ANTIPNEUMOCYSTIS PROPHYLAXIS

General categories based on duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies.

*See Antiviral Agents (FEV-C)* for spectrum and specific comments/cautions.

If prednisone equivalent less than 20 mg daily.

Consider trimethoprim/sulfamethoxazole desensitization or atovaquone, dapsone, aerosolized pentamidine when *Pneumocystis jirovecii* pneumonia prophylaxis is required, and patients are trimethoprim/sulfamethoxazole intolerant.

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## Prevention of Cytomegalovirus Disease

### Infection Risk in Cancer Patients

<table>
<thead>
<tr>
<th>High risk for Cytomegalovirus disease</th>
<th>Disease / Therapy Examples</th>
<th>Surveillance Period[^m]</th>
<th>Pre-emptive Therapy[^e,n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic stem cell transplant recipients</td>
<td>Cytomegalovirus infection / therapy examples</td>
<td>1 to 6 months after transplant, GVHD, CD4 &lt; 100/mcL</td>
<td>Ganciclovir, Foscarnet, or Valganciclovir</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>For a minimum of 2 mo after alemtuzumab and until CD4 ≥ 100 cells/mcL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^a]: General categories based on duration of neutropenia, underlying disease, intensity of chemotherapy, and other immunomodulatory therapies.

[^e]: See Antiviral Agents (FEV-C) for spectrum, and specific comments/cautions.

[^m]: CMV surveillance consists of weekly monitoring of CMV PCR.

[^n]: Duration of prophylaxis antiviral therapy generally is for at least 2 weeks and until CMV is no longer detected.

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**initial evaluation of fever and neutropenia**

- **fever:**
  - single temperature ≥ 38.3°C orally or ≥ 38.0°C over 1 h

- **neutropenia:**
  - < 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 h

**site specific H&P including:**

- intravascular access device
- skin
- lungs and sinus
- alimentary canal (mouth, pharynx, esophagus, bowel, rectum)
- perivaginal/perirectal

**supplementary historical information:**

- major comorbid illness
- time since last chemotherapy administration
- history of prior documented infections
- recent antibiotic therapy/prophylaxis
- medications
- HIV status
- exposures:
  - others at home with similar symptoms
  - pets
  - travel
  - tuberculosis exposure
  - recent blood product administration

**laboratory/radiology assessment:**

- CBC including differential, platelets, BUN, electrolytes, creatinine, and LFTs
- consider chest x-ray, urinalysis, pulse oximetry
- chest x-ray for all patients with respiratory symptoms

**primary cultures**

- blood culture x 2 sets (one set consists of 2 bottles). Options include:
  - one peripheral + one catheter or
  - both peripheral or
  - both catheter
- urine (if symptoms, urinary catheter, abnormal urinalysis)
- site-specific culture:
  - diarrhea (Clostridium difficile assay, enteric pathogen screen)
  - skin (aspirate/biopsy of skin lesions)
  - vascular access cutaneous site with inflammation (consider routine/fungal/mycobacteria)
- viral cultures:
  - vesicular ulcerated lesions on skin or mucosa
  - throat or nasopharynx for respiratory virus symptoms, especially during seasonal outbreaks

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INITIAL THERAPY FOR FEVER AND NEUTROPENIA

Initial antibiotic therapy should be based on:
- Infection risk assessment (See FEV-3)
- Potential infecting organisms include vancomycin-resistant enterococcus (VRE) and extended spectrum beta-lactamase (ESBL)
- Colonization with or prior infection with methicillin-resistant S. aureus (MRSA)
- Site of infection
- Local antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Broad spectrum of activity
- Previous antibiotic therapy
- Antipseudomonal coverage
- Bactericidal

...continued...

Site-Specific Evaluation and Therapy:

Mouth, Esophagus and Sinus/Nasal (FEV-4)

Abdominal Pain, Perirectal Pain, Diarrhea, Vascular Access Devices (FEV-5)

Lung Infiltrates (FEV-6)

Cellulitis, Wound, Vesicular Lesions, Disseminated Papules or other lesions, Urinary Tract Symptoms, Central Nervous System Symptoms (FEV-7)

OR

Follow-up (FEV-8)

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See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.

Weak Gram-positive coverage and increased breakthrough infections limit utility.

Some authorities recommend avoidance of aminoglycosides because of potential nephrotoxicity, which may be diminished by once-daily administration. Once-a-day aminoglycoside therapy should be avoided for treatment of meningitis or endocarditis.

Although there are published studies recommending use of these agents; the NCCN panel strongly recommends that these agents should not be used routinely because of concerns about resistance and breakthrough infections.

See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).
INITIAL RISK ASSESSMENT FOR FEBRILE NEUTROPENIC PATIENTS

High risk (any factor listed below):
- Inpatient status at time of development of fever
- Significant medical comorbidity or clinically unstable
- Anticipated prolonged severe neutropenia: ≤ 100/mcL and ≥ 7 d
- Hepatic insufficiency (5 times ULN for aminotransferases)
- Renal insufficiency (a creatinine clearance of less than 30 mL/min)
- Uncontrolled/progressive cancer
- Pneumonia or other complex infections at clinical presentation
- Alemtuzumab
- Mucositis grade 3-4
- OR
- A score of 21 or greater on the MASCC Risk Index

Low risk (none of the above factors and most of the following):
- Outpatient status at time of development of fever
- No associated acute comorbid illness, independently indicating inpatient treatment or close observation
- Anticipated short duration of severe neutropenia
  (≤ 100 cells/mcL for < 7 d)
- Good performance status (ECOG 0-1)
- No hepatic insufficiency
- No renal insufficiency
- OR
- A score of 21 or greater on the MASCC Risk Index

SITE OF CARE 

Hospital → IV therapy
Hospital or Sequential IV/oral therapy
Consider ambulatory clinic
Home for selected low-risk patients with adequate outpatient infrastructure established

TREATMENT OPTIONS

Risk categorization can predict outcome during the febrile episode, including complications/mortality. See Risk Assessment Resources (FEV-E).

Uncontrolled/progressive cancer is defined as any leukemic patient not in complete remission, or non-leukemic patients with evidence of disease progression after more than 2 courses of chemotherapy.

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INITIAL CLINICAL PRESENTATION

FINDING

EVALUATION

Additions to initial empiric regimen

Mouth/mucosal membrane

Necrotizing ulceration

• Culture and gram stains
  ▶ Viral - Herpes simplex virus (HSV)
  ▶ Fungal
  ▶ Biopsy for lesions suspicious for mold

• Ensure adequate anaerobic activity
• Consider anti-HSV therapy
• Consider systemic antifungal therapy

Add vancomycin if periorbital cellulitis noted
Add lipid amphotericin B preparation to cover possible aspergillosis and mucormycosis in high risk patients with suspicious CT/MRI findings
Infectious disease consult

Thrush

• Viral cultures or PCR or other diagnostics and direct fluorescent antibody test for HSV and Varicella-zoster virus (VZV)

• Antifungal therapy
  ▶ Fluconazole first-line therapy
  ▶ Voriconazole, posaconazole, or echinocandin if refractory to fluconazole

Vesicular lesions

• Viral cultures or PCR or other diagnostics and direct fluorescent antibody test for HSV and Varicella-zoster virus (VZV)

• Anti-HSV therapy (category 1)

Esophagus

• Retrosternal burning
• Dysphagia/odynophagia

• Culture suspicious oral lesions
  ▶ HSV
  ▶ Fungal
  ▶ Endoscopy once ANC recovers, if no response to therapy

• Initial therapy guided by clinical findings (eg, thrush or perioral HSV)
• Antifungal therapy
  ▶ Fluconazole, first-line therapy
  ▶ Voriconazole, posaconazole, or echinocandin if refractory to fluconazole
• Acyclovir
• If at high risk for invasive CMV, consider ganciclovir or foscarnet

Sinus/nasal

• Sinus tenderness
• Periorbital cellulitis
• Nasal ulceration
• Unilateral eye tearing

• High resolution sinus CT/orbit MRI
• ENT/ophthalmological urgent evaluation
• Culture and stains/biopsy

• Add vancomycin if periorbital cellulitis noted
• Add lipid amphotericin B preparation to cover possible aspergillosis and mucormycosis in high risk patients with suspicious CT/MRI findings
• Infectious disease consult

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b See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
See Antibacterial Agents (FEV-A)

j See Antifungal Agents (FEV-B) for dosing, spectrum and specific comments/cautions.
See Antifungal Agents (FEV-B)

k See Antiviral Agents (FEV-C) for spectrum and specific comments/cautions.
See Antiviral Agents (FEV-C)
## Initial Clinical Presentation (Day 0)

### Finding

<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>Perirectal pain</th>
<th>Diarrhea</th>
<th>Vascular access devices (VAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVALUATION^m</strong></td>
<td><strong>EVALUATION^m</strong></td>
<td><strong>EVALUATION^m</strong></td>
<td><strong>EVALUATION^m</strong></td>
</tr>
<tr>
<td>Abdominal CT (preferred) or ultrasound</td>
<td>Perirectal inspection</td>
<td>Consider abdominal/pelvic CT</td>
<td>Entry or exit site inflammation</td>
</tr>
<tr>
<td>Alkaline phosphatase, transaminases, bilirubin, amylase, lipase</td>
<td></td>
<td></td>
<td>Tunnel infection/ port pocket infection</td>
</tr>
</tbody>
</table>

### Additions to Initial Empiric Regimen^b,j,k

- All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-2).

#### Entry or exit site inflammation

- Swab exit site drainage (if present) for culture
- Blood culture from each port of VAD

#### Vascular access devices (VAD)

- Remove catheter and culture surgical wound
- Add vancomycin^g

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^b See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
^g See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).
^j See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
^k See Antiviral Agents (FEV-C) for spectrum and specific comments/cautions.
^l Surgical and other subspecialty (e.g., gastroenterology, interventional radiology) consultations should be considered for these situations as clinically indicated.
^m Lab studies include CMV antigens/PCR and abdominal/pelvic CT.
^n Enterococcal colonization must be differentiated from infection. Vancomycin use must be minimized because of the risk of vancomycin resistance.

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### Prevention and Treatment of Cancer-Related Infections

#### RISK CATEGORY

- **Low risk**

- **Intermediate to High risk**

#### EVALUATION\(^o,p\)

- Blood and sputum cultures
- Nasal wash for respiratory viruses, rapid tests (during season)
- Legionella urine Ag test
- Consider BAL, particularly if no response to initial therapy or if diffuse infiltrates present

#### ADDITIONS TO INITIAL EMPIRIC REGIMEN\(^b,j,k\)

- Azithromycin or fluoroquinolone added to cover atypical bacteria
- Consider adding:
  - Oseltamivir during influenza outbreaks
  - Vancomycin or linezolid if MRSA suspected
  - G- or GM-CSF

---

\(^b\) See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.

\(^j\) See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.

\(^k\) See Antiviral Agents (FEV-C) for spectrum and specific comments/cautions.

\(^o\) Other diagnoses to consider include pulmonary edema, hemorrhage and drug toxicities.

\(^p\) Assess for healthcare acquired pneumonia and/or resistant pathogens.

\(^q\) See Adjunctive Therapies (FEV-E).

---

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### Evaluation

<table>
<thead>
<tr>
<th>Initial Clinical Presentation (Day 0)</th>
<th>Evaluation</th>
<th>Additions to Initial Empiric Regimen $^b,j,k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>Consider aspirate or biopsy for culture</td>
<td>Consider vancomycin $^g$</td>
</tr>
<tr>
<td>Wound</td>
<td>Culture</td>
<td>Consider vancomycin $^g$</td>
</tr>
<tr>
<td>Vesicular lesions</td>
<td>Aspiration or scraping for VZV or HSV direct fluorescent antibody (DFA)/herpes virus cultures</td>
<td>Consider acyclovir, famciclovir, or valacyclovir</td>
</tr>
</tbody>
</table>
| Disseminated papules or other lesions| Aspiration or biopsy for bacterial, fungal, mycobacterial cultures and histopathology | • Consider vancomycin $^g$  
• Consider mold-active antifungal therapy in high-risk patients |
| Urinary tract symptoms               | • Urine culture  
• Urinalysis | No additional therapy until specific pathogen identified |
| Central nervous system symptoms      | • Infectious disease (ID) consult  
• CT and/or MRI  
• Lumbar puncture (if possible)  
• Neurology consult | • Empiric therapy for presumed meningitis must include a beta-lactam agent that readily enters CSF (eg, cefepime, ceftazidime, meropenem) plus vancomycin $^g$, plus ampicillin (category 1)  
• For encephalitis add high-dose acyclovir (10-12 mg/kg/dose 3x/d), with hydration and monitor renal function |

$^b$ See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
$^g$ See Appropriate Use Of Vancomycin And Other Agents For Gram-positive Resistant Infections (FEV-D).
$^j$ See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
$^k$ See Antiviral Agents (FEV-C) for spectrum and specific comments/cautions.

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PRINCIPLES OF DAILY FOLLOW-UP

- Daily site-specific H&P
- Daily review of laboratory tests and cultures: document clearance of bacteremia, fungemia with repeat blood cultures
- Evaluate for response to therapy and drug toxicity:
  - Fever trends
  - Signs and symptoms of infection
- Evaluation of drug toxicity including end-organ toxicity (LFTs and renal function tests at least 2x/wk)

Evaluate overall response to empiric therapy in 3-5 d⁷ (72-120 h)

RESPONDING
- Decreasing fever trend
- Signs and symptoms of infection are stable or improving
- Patient is hemodynamically stable

NONRESPONDING
- Persistently or intermittently febrile
- Signs and symptoms of infection are not improving
- Patient may be hemodynamically unstable
- Persistent positive blood cultures

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See Adjunctive Therapies (FEV-E).

See Follow-up Therapy (FEV-9)

See Follow-up Therapy (FEV-12)
FOLLOW-UP THERAPY FOR RESPONDING PATIENTS

- No change in initial empiric regimen
- If patients started on “appropriate” initial vancomycin, continue course of therapy
- Initial antibiotic regimen should be continued at least until neutrophil count is ≥ 500 cells/mcL and increasing

Documented infection
- Bacteremia
  - Simple (no tissue site)
  - Complex (tissue infection with bacteremia)
- Pneumonia
- Skin/soft tissue
- Sinus
- Fungal
- Viral

See Suggested Duration of Therapy for Documented Infection (FEV-10)

See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).

Fever of unknown origin

See Suggested Duration of Therapy for Fever of Unknown Origin (FEV-11)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Documented infection**

- Initial antibiotic regimen should generally be continued until neutrophil count is ≥ 500 cells/mcL and increasing
- Duration of antimicrobial therapy may be individualized based upon:
  - Neutrophil recovery
  - Rapidity of defervescence
  - Specific site of infection
  - Infecting pathogen
  - Patient's underlying illness

**SUGGESTED DURATION OF THERAPY FOR DOCUMENTED INFECTION**

- Skin/soft tissue: 7-14 d
- Bloodstream infection (uncomplicated):
  - Gram-negative: 10-14 d
  - Gram-positive: 7-14 d
  - *S. aureus*: at least 2 weeks after first negative blood culture and normal transesophageal echocardiogram (TEE)^r
  - Yeast: ≥ 2 wks after first negative blood culture
  - Consider catheter removal for *Candida, S. aureus, Pseudomonas aeruginosa, Corynebacterium jeikeium, Acinetobacter, and Stenotrophomonas maltophilia* (category 2B)
- Sinusitis: 10-21 d
- Bacterial pneumonia: 10-21 d
- Fungal (mold and yeast):
  - *Candida*: minimum of 2 wks after first negative blood culture
  - Mold (ie, *Aspergillus*): minimum of 12 wks
- Viral:
  - HSV/VZV: 7-10 d (category 1); acyclovir, valacyclovir, or famciclovir (uncomplicated, localized disease to the skin)
  - Influenza: Oseltamivir is approved by FDA for 5 d based on data from ambulatory otherwise healthy individuals with intact immune systems.

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^b [See Antibacterial Agents (FEV-A)] for dosing, spectrum, and specific comments/cautions.

^i [See Antifungal Agents (FEV-B)] for dosing, spectrum and specific comments/cautions.

^k [See Antiviral Agents (FEV-C)] for spectrum and specific comments/cautions.

^r A TEE should be considered in all cases of *S. aureus* bacteremia. In patients with conditions that may increase the likelihood of complications (eg, neutropenia, thrombocytopenia, mucositis), a transthoracic echocardiogram (TTE) may be performed initially and, if negative, a TEE should be performed when safe. A TEE is more sensitive and preferred when compared with TTE.
**FOLLOW-UP THERAPY FOR RESPONDING PATIENTS**

- **Neutrophils**
  - \( \geq 500 \text{ cells/mcL} \) → **Discontinue therapy**

- **Neutrophils**
  - < 500 \( \text{cells/mcL} \)

- **SUGGESTED DURATION OF THERAPY FOR FEVER OF UNKNOWN ORIGIN**

  - \( ^{s} \text{Use clindamycin for penicillin-allergic patients.} \)

  - **Note:** All recommendations are category 2A unless otherwise indicated.

  - Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SUGGESTED DURATION OF THERAPY

**FOLLOW-UP THERAPY FOR NONRESPONDING PATIENTS**

**Stable**
- Continue current antibacterial therapy: modification of antibacterial therapy solely on the basis of neutropenic fever not required

**Unstable**
- Broaden coverage to include anaerobes, resistant Gram-negative rods, and resistant Gram-positive organisms, as clinically indicated
- Consider adding G-CSF or GM-CSF (category 2B)
- Ensure coverage for *Candida*
- Infectious disease consult

**Documented infection**
- Assess appropriateness of antibiotics for pathogens isolated (susceptibility testing, dosing)
- Consider adding G-CSF or GM-CSF (category 2B)
- Consider granulocyte transfusions for life-threatening refractory bacterial or fungal infections (category 2B)

**FEVER OF UNKNOWN ORIGIN**
- Assess appropriateness of antibiotics for pathogens isolated (susceptibility testing, dosing)
- Consider adding G-CSF or GM-CSF (category 2B)
- Consider granulocyte transfusions for life-threatening refractory bacterial or fungal infections (category 2B)

1 The timing to add empirical antifungal therapy varies with the risk of invasive mold infection but generally ranges between 4-7 d of neutropenic fever. In patients at high risk for mold infection (neutropenia > 10 d, allogeneic stem cell transplant recipients, high-dose corticosteroids), the panel recommends adding empirical antifungal therapy after 4 d unless patient is receiving prophylaxis directed against molds. See text for discussion of antifungal prophylaxis versus empirical antifungal therapy.

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## OUTPATIENT THERAPY FOR LOW RISK PATIENTS

### INDICATION

- Patient determined to be in low risk category on presentation with fever and neutropenia
  - Outpatient status at time of development of fever
  - No associated acute comorbid illness, independently indicating inpatient treatment or close observation
  - Anticipated short duration of severe neutropenia (<7 days)
  - Good performance status (ECOG 0-1)
  - Serum creatinine ≤ 2.0 mg/dL, liver functions ≤ 3x normal OR
  - A score of 21 or greater on the MASCC Risk Index<sup>h</sup>

### ASSESSMENT

- Careful exam
- Review lab results: no critical values
- Review social criteria for home therapy
  - Patient consents to home care
  - 24 h home caregiver available
  - Home telephone
  - Access to emergency facilities
  - Adequate home environment
  - Distance within approximately one hour of a medical center or treating physician's office
- Assess for oral antibiotic therapy
  - No nausea and vomiting
  - Able to tolerate oral medications
  - Not on prior fluoroquinolone prophylaxis

### MANAGEMENT

- Observation period (2-12 h) (category 2B) in order to:
  - Confirm low-risk status and ensure stability of patient
  - Observe and administer first dose of antibiotics and monitor for reaction
  - Organize discharge plans to home and follow-up
  - Patient education
  - Telephone follow-up within 12-24 h

<sup>h</sup>Risk categorization can predict outcome during the febrile episode, including complications/mortality. See Risk Assessment Resources (FEV-E).

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OUTPATIENT THERAPY FOR LOW RISK PATIENTS

TREATMENT OPTIONS

- IV antibiotics at home
- Daily long-acting intravenous agent ± oral therapy
  - Home or office
- Oral therapy only:¹
  - 500 mg every 8 h ciprofloxacin⁵ plus 500 mg every 8 h amoxicillin/clavulanate⁵ (category 1)
  - Other oral regimens are less well-validated (eg, levofloxacin)

FOLLOW-UP

- Patient should be monitored dailyʷ
- Daily examination (clinic or home visit) for the first 72 h to assess response, toxicity, and compliance; if responding, then telephone follow-up daily thereafter.
- Specific reasons to return to clinic:
  - Any positive culture
  - New signs/symptoms reported by the patient
  - Persistent or recurrent fever at days 3-5
  - Inability to continue prescribed antibiotic regimen (ie, oral intolerance)
  - Office visit for infusion of IV antibiotics

⁵Use clindamycin for penicillin-allergic patients.
¹Criteria for oral antibiotics: no nausea or vomiting, patient able to tolerate oral medications, and patient not on prior fluoroquinolone prophylaxis.
⁵The fluoroquinolone chosen should be based on reliable Gram-negative bacillary activity, local antibacterial susceptibilities, and the use of quinolone prophylaxis of fever and neutropenia.
ʷProvider should be individual (eg, MD, RN, PA, NP) who has expertise in the management of patients with neutropenia and fever.
<table>
<thead>
<tr>
<th>GRAM-POSITIVE AGENTS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DOSE</th>
<th>SPECTRUM</th>
<th>COMMENTS/CAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg IV every 12 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Gram-positive organisms with exception of VRE and a number of rare Gram-positive organisms</td>
<td>• Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present (See FEV-D)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg PO/IV every 12 h</td>
<td>Gram-positive organisms including VRE</td>
<td>• Hematologic toxicity may occur, thrombocytopenia most common (0.3% to 10%) &lt;br&gt;• Serotonin syndrome rare, use cautiously with SSRI’s&lt;sup&gt;1&lt;/sup&gt; &lt;br&gt;• Not for routine use in fever and neutropenia although does not impair neutrophil recovery &lt;br&gt;• Treatment option for VRE and MRSA &lt;br&gt;• Peripheral/optic neuropathy with long-term use</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>4-6 mg/kg d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Gram-positive organisms &lt;br&gt;• Has in vitro activity against VRE but is not FDA-approved for this indication</td>
<td>• Equivalent to standard antistaphylococcal agents for <em>Staphylococcus aureus</em> bacteremia at 6 mg/kg dose in non-neutropenic patients&lt;sup&gt;2&lt;/sup&gt; &lt;br&gt;• Weekly CPK to monitor for rhabdomyolysis &lt;br&gt;• Not indicated for pneumonia due to inactivation by pulmonary surfactant &lt;br&gt;• Not studied in patients with fever and neutropenia &lt;br&gt;• Myositis is a potential toxicity</td>
</tr>
<tr>
<td>Quinupristin/ Dalfopristin</td>
<td>7.5 mg/kg every 8 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Gram-positive organisms including most VRE (does not have activity against <em>Enterococcus faecalis</em>) or intolerance to vancomycin</td>
<td>• Use limited by myalgias/arthritis (up to 47%) &lt;br&gt;• Requires central venous access delivery &lt;br&gt;• Avoid use due to toxicity although coverage is good &lt;br&gt;• Musculoskeletal pain syndrome is a potential toxicity</td>
</tr>
</tbody>
</table>

<sup>a</sup> These drugs are not recommended as monotherapy for fever in the setting of neutropenia and should only be added for documented infection with resistant Gram-positive organisms if certain risk factors are present. (See FEV-D)

<sup>b</sup> Requires adjustment in patients with renal insufficiency

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Continued on next page
**BROAD SPECTRUM AGENTS AND COMBINATION THERAPY AGENTS**

<table>
<thead>
<tr>
<th>ANTIBACTERIAL AGENTS</th>
<th>DOSE</th>
<th>SPECTRUM</th>
<th>COMMENTS/CAUTIONS</th>
</tr>
</thead>
</table>
| Cefepime            | 2 grams every 8 h<sup>b</sup> | • Broad spectrum activity against most Gram-positive and Gram-negative organisms  
• Not active against most anaerobes, MRSA, and *Enterococcus spp.* | • Use for suspected/proven CNS infection with susceptible organism  
• Increased frequency of resistance among Gram-negative rod isolates at some centers  
• Empiric therapy for neutropenic fever |
| Ceftazidime         | 2 grams every 8 h<sup>b</sup> | • Relatively poor Gram-positive activity  
• Breakthrough streptococcal infections reported  
• Not active against most anaerobes, MRSA and *Enterococcus spp.* | • Use for suspected/proven CNS infection with susceptible organism  
• Category 2B recommendation by panel due to weaknesses in antimicrobial spectrum  
• Increased frequency of resistance among Gram-negative rod isolates at some centers  
• Empiric therapy for neutropenic fever |
| Imipenem/cilastin   | 500 mg every 6 h | • Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms | • Use for suspected intra-abdominal source  
• Meropenem is preferred over imipenem for suspected/proven CNS infection  
• Imipenem may lower seizure threshold in patients with CNS malignancies or infection  
• Empiric therapy for neutropenic fever |
| Meropenem           | 1 gram every 8 h<sup>b</sup> (2 g every 8 h for meningitis) | • Not active against MRSA or VRE  
• Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms | |
| Piperacillin/Tazobactam | 4.5 grams every 6 h<sup>b</sup> | • Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms  
• Not active against MRSA or VRE | • Use for suspected intra-abdominal source  
• Not recommended for meningitis  
• May result in false positive galactomannan<sup>3</sup>  
• Empiric therapy for neutropenic fever |

<sup>b</sup>Requires adjustment in patients with renal insufficiency

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**BROAD SPECTRUM AGENTS AND COMBINATION THERAPY AGENTS**

| ANTIBACTERIAL AGENTS (References are on page 4) |
|---------------------------------|-----------------|-----------------|-----------------|
| **Tigecycline**                | 100 mg load then 50 mg every 12 h | • Broad spectrum including many Gram-negative organisms, anaerobes, VRE, MRSA  
• Poor activity against *Pseudomonas aeruginosa*, and some strains of *Proteus, Providencia, and Morganella* | • Not recommended for treatment of bloodstream infections due to poor serum levels  
• Nausea common  
• Not studied in patients with fever and neutropenia  
• Does not cover pneumonia  
• Selected patients intolerant of other agents with non-pseudomonal infections |
| **Ciprofloxacin**              | 500-750 mg PO every 12 hours or 400 mg IV every 12 h<sup>b</sup> | • Good activity against Gram-negative and atypical (e.g., *Legionella spp.* ) organisms  
• Less active than “respiratory” fluoroquinolones against Gram-positive organisms  
• No activity against anaerobic organisms | • Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis  
• Increasing Gram-negative resistance in many centers  
• Oral antibiotic combination therapy in low risk patients (with amoxicillin/clavulanate or clindamycin)  
• In combination with antipseudomonal penicillin in higher risk patients |
| **Levofloxacin**               | 500-750 mg oral or IV daily<sup>b</sup> | • Good activity against Gram-negative and atypical (e.g., *Legionella spp.* ) organisms  
• Improved Gram-positive activity compared to ciprofloxacin  
• Limited activity against anaerobes  
• Prophylaxis in neutropenic patients<sup>5,6</sup> | • Prophylaxis may increase bacterial resistance and superinfection<sup>7</sup>  
• Limited studies as empirical therapy in patients with fever and neutropenia |

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Continued on next page
### ANTIBACTERIAL AGENTS

<table>
<thead>
<tr>
<th>BROAD SPECTRUM AGENTS AND COMBINATION THERAPY AGENTS</th>
<th>DOSE</th>
<th>SPECTRUM</th>
<th>COMMENTS/CAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gentamicin</td>
<td></td>
<td>• Activity primarily against Gram-negative organisms</td>
<td>• Nephrotoxicity and ototoxicity limit use</td>
</tr>
<tr>
<td>• Tobramycin</td>
<td></td>
<td>• Synergy with beta-lactams against susceptible <em>S. aureus</em> and <em>Enterococcus</em> infections</td>
<td>• Combination therapy with anti-pseudomonal penicillin or extended spectrum cephalosporin</td>
</tr>
<tr>
<td>• Amikacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole (TMP/SMX)</td>
<td></td>
<td></td>
<td>• Highly effective as prophylaxis against <em>P. jiroveci</em> in high risk patients (see INF-5)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>REFERENCES</th>
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## ANTIFUNGAL AGENTS (References are on page 4)

<table>
<thead>
<tr>
<th>AZOLES&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DOSE</th>
<th>SPECTRUM</th>
<th>COMMENTS/CAUTIONS</th>
</tr>
</thead>
</table>
| **Fluconazole** | In adults with normal renal function: 400 mg daily | • Active against *Candida* species  
• Active against dimorphic fungi (eg histoplasmosis, coccidioidomycosis) and *C. neoformans* | • *Candida glabrata* is associated with variable resistance in vitro and *Candida krusei* is always resistant  
• Inactive against molds (eg, *Aspergillus* species, Zygomycetes) |
| **Itraconazole** | IV 200 mg every 12 h x 4 doses, followed by 200 mg daily; oral 400 mg daily (aim for trough of at least 0.5 mcg/ml after 7 d of therapy) | • Active against *Candida*, *Aspergillus* species and some of the rarer molds  
• Active against dimorphic fungi and *C. neoformans* | • Itraconazoloe has negative inotropic properties and is contraindicated in patients with significant cardiac systolic dysfunction  
• IV formulation should be used with caution in patients with significant pre-existing renal dysfunction based on potential to worsen azotemia |
| **Voriconazole** | IV 6 mg/kg every 12 h x 4 doses, then 4 mg/kg every 12 h; oral 200 mg PO BID | • Active against *Candida*, *Aspergillus* species and some of the rarer molds  
• Standard of care as primary therapy for invasive aspergillosis<sup>1</sup>  
• Effective in candidemia in non-neutropenic patients<sup>2</sup> | • Poor activity against Zygomycetes  
• IV formulation should be used with caution in patients with significant pre-existing renal dysfunction based on potential to worsen azotemia |
| **Posaconazole** | • Prophylaxis: 200 mg PO TID as prophylaxis  
• Salvage therapy: 200 mg PO QID followed by 400 mg PO BID once disease has stabilized have been evaluated | • Effective as prophylaxis in neutropenic patients with myelodysplastic syndrome and acute myelogenous leukemia<sup>3</sup>, and in HSCT recipients with significant GVHD<sup>4</sup>  
• Active against *Candida*, *Aspergillus* sp, some Zygomycete sp, and some of the rarer molds  
• Active against dimorphic fungi and *C. neoformans* | • Evaluated as salvage therapy (but not FDA-approved) against a broad spectrum of invasive fungal infections.  
• Has not been evaluated as primary therapy for invasive fungal infections  
• Should be administered with a full meal or liquid nutritional supplement. For patients who can not eat a full meal or tolerate an oral nutritional supplement alternative antifungal therapy should be considered. |

<sup>a</sup>Azoles inhibit fungal cell membrane synthesis and inhibit cytochrome P450 isoenzymes that may lead to impaired clearance of other drugs metabolized by this pathway. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details). Reversible liver enzyme abnormalities are observed.

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Continued on next page
### AMPHOTERICIN B FORMULATIONS

<table>
<thead>
<tr>
<th>AMPHOTERICIN B FORMULATIONS</th>
<th>DOSE</th>
<th>SPECTRUM</th>
<th>COMMENTS/CAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate (AmB-D)</td>
<td>Varies on indication, generally 0.5 to 1.5 mg/kg/d</td>
<td>Broad spectrum of antifungal activity including <em>Candida</em>, <em>Aspergillus</em> sp (excluding <em>Aspergillus terreus</em>), <em>Zygomycetes</em>, <em>rarer molds</em>, <em>Cryptococcus neoformans</em>, and dimorphic fungi</td>
<td>• Substantial infusional and renal toxicity including electrolyte wasting</td>
</tr>
<tr>
<td>Liposomal amphotericin B (L-AMB)</td>
<td>3 mg/kg/d was as effective as, but less toxic than, 10 mg/kg/d as initial therapy for invasive mold infections</td>
<td></td>
<td>• Saline loading may reduce nephrotoxicity</td>
</tr>
<tr>
<td>Amphotericin B lipid complex (ABLC)</td>
<td>5 mg/kg/d for invasive mold infections</td>
<td></td>
<td>• Infusional toxicity may be managed with anti-pyretics, an anti-histamine, and meperidine (for rigors)</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion (ABCD)</td>
<td>5 mg/kg/d for invasive mold infections</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Broad spectrum of antifungal activity. Significant infusional and renal toxicity, less so with lipid formulations.**

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## ANTIFUNGAL AGENTS (References are on page 4)

<table>
<thead>
<tr>
<th>ECHINOCANDINS&lt;sup&gt;c&lt;/sup&gt;</th>
<th>DOSE</th>
<th>SPECTRUM</th>
<th>COMMENTS/CAUTIONS</th>
</tr>
</thead>
</table>
| Caspofungin               | • 70 mg x 1 dose, then 50 mg daily; some investigators use 70 mg daily as therapy for aspergillosis  
  • Dose reduction may be considered in severe liver disease | Active against *Candida* and *Aspergillus* sp. Not reliable or effective against other fungal pathogens. | • Primary therapy for candidemia and invasive candidiasis  
  • Salvage therapy for aspergillosis. Similar efficacy compared to AmB-D as primary therapy for candidemia and invasive candidiasis, but significantly less toxic<sup>6</sup>  
  • 45% success rate as salvage therapy for invasive aspergillosis<sup>7</sup>  
  • Similar efficacy, but less toxic compared with L-AMB as empirical therapy for persistent neutropenic fever<sup>8</sup>  
  • Excellent safety profile. |
| Micafungin                | 100 mg/d for candidemia and 50 mg/d as prophylaxis | | • Primary therapy for candidemia and invasive candidiasis  
  • Similar efficacy compared to caspofungin<sup>9</sup> and compared to L-AMB<sup>10</sup> as primary therapy for candidemia and invasive candidiasis  
  • Superior efficacy compared to fluconazole as prophylaxis during neutropenia in HSCT recipients<sup>11</sup>  
  • Excellent safety profile. |
| Anidulafungin            | 200 mg x 1 dose, then 100 mg/d | | • Primary therapy for candidemia and invasive candidiasis  
  • Superior efficacy compared to fluconazole as primary therapy for candidemia and invasive candidiasis<sup>12</sup>  
  • Excellent safety profile. |

<sup>c</sup>A number of centers use combination therapy consisting of voriconazole plus an echinocandin based on in vitro and limited data.

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
REFERENCES FOR ANTIFUNGAL AGENTS (page 4 of 4)


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### Antiviral Agents

<table>
<thead>
<tr>
<th>Agents</th>
<th>Spectrum</th>
<th>Comments/Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>HSV, VZV</td>
<td>Hydration to avoid crystal nephropathy with high doses</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>HSV, VZV</td>
<td></td>
</tr>
<tr>
<td>Foscarnet</td>
<td>HSV(^1), VZV(^1), CMV</td>
<td>Drug of choice for acyclovir-resistant HSV and VZV and ganciclovir-resistant CMV; nephrotoxic; monitor electrolytes closely</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>CMV</td>
<td>May cause marrow suppression</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>CMV</td>
<td>May cause marrow suppression</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>CMV(^1), HSV(^1), VZV(^1), Adenovirus, BK</td>
<td>Nephrotoxicity, ocular toxicity, bone marrow toxicity; hydration and probenecid required to reduce nephrotoxicity</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Influenza A &amp; B</td>
<td>May cause nausea (improved when taken with food)</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Influenza A &amp; B</td>
<td>May cause bronchospasm</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Influenza A</td>
<td>Not currently recommended for use because of resistance</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>Influenza A</td>
<td>Not currently recommended for use because of resistance</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>RSV, HCV</td>
<td>Inhaled ribavirin is used for RSV and requires special aerosol generator; highly teratogenic, oral ribavirin may cause anemia</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>Pegylated Interferon-alpha</td>
<td>HCV</td>
<td></td>
</tr>
<tr>
<td>Intravenous Immunoglobulin</td>
<td>RSV, Parvovirus B19, CMV</td>
<td></td>
</tr>
<tr>
<td>Palivizumab</td>
<td>RSV</td>
<td>Humanized monoclonal anti-RSV antibody; inadequate database to judge efficacy in RSV disease in patients with hematologic malignancies and stem cell transplant recipients</td>
</tr>
</tbody>
</table>

HSV=herpes simplex virus; VZV=varicella zoster virus; CMV=cytomegalovirus; RSV=respiratory syncitial virus; HCV=hepatitis C virus; HBV=hepatitis B virus

\(^1\)Typically only used in cases of intolerance or resistance to preferred agent(s).

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Vancomycin should not be considered as a routine component of initial therapy for fever and neutropenia. Because of the emergence of vancomycin-resistant organisms, empiric vancomycin should be avoided except for serious infections associated with the following clinical situations:

- Clinically apparent, serious, catheter-related infection
- Blood culture positive for Gram-positive bacterium prior to final identification and susceptibility testing
- Known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*
- Hypotension or septic shock without an identified pathogen (ie, clinically unstable)
- Soft tissue infection
- Risk factors for viridans group streptococcal, bacteremia (category 2B): severe mucositis (eg, associated with high-dose cytarabine) and prophylaxis with quinolones or TMP-SMX (see text)¹
- Colonization with MRSA

Vancomycin should be discontinued in 2-3 days if a resistant Gram-positive infection (eg, MRSA) is not identified and if clinically appropriate.

Linezolid, quinupristin/dalfopristin, and daptomycin may be used specifically for infections caused by documented vancomycin-resistant organisms (eg, VRE) or in patients for whom vancomycin is not an option. Linezolid should be considered for ventilator associated MRSA pneumonia.

¹Recent studies have shown that addition of vancomycin is likely to be unnecessary solely on the basis of neutropenic fever and mucositis when broad spectrum beta-lactam agents with activity against oral flora (eg, piperacillin/tazobactam or imipenem) are used.
**RISK ASSESSMENT RESOURCES**

### USING THE MASCC-RISK SCORE
- Using the visual analogue score, estimate the patient's burden of illness at the time of initial clinical evaluation. No signs or symptoms or mild signs or symptoms are scored as 5 points, moderate signs or symptoms are scored as 3 points. These are mutually exclusive. No points are scored for severe signs or symptoms or moribund.
- Based upon the patient's age, past medical history, present clinical features and site of care (inpt/outpt when febrile episode occurred), score the other factors in the model and sum them.

### BURDEN OF ILLNESS

<table>
<thead>
<tr>
<th>How sick is the patient at presentation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signs</td>
</tr>
<tr>
<td>or signs or symptoms</td>
</tr>
</tbody>
</table>

Estimate the burden of illness considering all comorbid conditions

### MASCC RISK-SCORE/MODEL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of illness</td>
<td></td>
</tr>
<tr>
<td>No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No COPD</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or hematologic malignancy with no previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt;60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

### TALCOTT RISK ASSESSMENT

**High Risk:**
- Group 1 - Patients hospitalized at onset of fever and neutropenia
- Group 2 - Outpatients with a concurrent comorbidity at presentation (hemodynamic instability, clinical bleeding, respiratory failure, altered mental status or new neurologic symptoms, dehydration)
- Group 3 - Outpatients with uncontrolled cancer at presentation (newly treated tumors, newly relapsed, refractory or persistent leukemia, or progressive disease)

**Low Risk:**
- Group 4 - Outpatients without comorbidity or uncontrolled cancer at presentation

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Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ADJUNCTIVE THERAPIES

Limited or anecdotal data are available to suggest that these interventions may be beneficial:

- G-CSF/GM-CSF (category 2B) may be considered in the following clinical settings:
  - Pneumonia
  - Invasive fungal infection
  - Progressive infection (any type)
- Granulocyte transfusions (category 2B)
  - Invasive fungal infection
  - Gram-negative rod infection unresponsive to appropriate antimicrobial therapy
- Intravenous immunoglobulin
  - Should be used in combination with ganciclovir for CMV pneumonia
  - Consider IV IgG for patients with profound hypogammaglobulinemia (category 2B)

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
The guidelines should be applied in conjunction with careful, individual patient evaluation and with an understanding of the variations in types of infection, treatment settings, antimicrobial susceptibility patterns, the underlying causes of neutropenia, and the expected time of neutrophil recovery. Managing infections in neutropenic patients remains a dynamic process, supported by the appearance of new pathogens, the emergence of antibiotic-resistant organisms, and the improved stratification of patients’ infection risk.

Increasingly, however, it is clear that infectious complications are also common and often serious in nonneutropenic cancer patients, and clinicians must be prepared to identify and treat them promptly. Accordingly, these NCCN guidelines include current management approaches for fever and neutropenia, as well as for a variety of specific infections that are common in patients who are treated for cancer, whether or not they have neutropenia.

**Scope of the Problem**

The absence of granulocytes; the disruption of the integumentary, mucosal, and mucociliary barriers; and inherent microbial flora shifts that accompany severe illness and antimicrobial usage predispose the neutropenic patient to infection. The signs and symptoms of infection are often absent or muted in the presence of neutropenia, but fever remains an early, although nonspecific, sign.\(^1\) Approximately 48% to 60% or more of the patients who become febrile have an established or occult infection.\(^2\) Roughly 10% to 20% or more of patients with neutrophil counts less than 100/mm\(^3\) will develop a bloodstream infection.\(^3\) Primary sites of infection are the alimentary tract (ie, mouth, pharynx, esophagus, large and small bowel, and rectum), sinuses, lungs, and skin.
The pathogens responsible for initial infections early in the course of fever and neutropenia are primarily bacteria, whereas antibiotic-resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections. Coagulase-negative staphylococci, *Staphylococcus aureus*, viridans group streptococci, and enterococci are now the major Gram-positive pathogens. *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa* are the most common Gram-negative pathogens causing initial fever. Herpes simplex virus (HSV), respiratory syncytial virus, parainfluenza, and influenza A and B are also occasionally initial pathogens. Infections due to *Candida* sp. may occur later in the course of neutropenia, particularly as a consequence of gastrointestinal mucositis. *Aspergillus* sp. and other filamentous fungi are an important cause of morbidity and mortality in patients with prolonged neutropenia or in the setting of graft versus host disease treated with steroids. Deaths resulting from infections identified at the onset of fever during neutropenia remain uncommon, and most infection-associated deaths result from subsequent infections during the course of neutropenia.

**Definitions**

The precise definitions of fever and neutropenia vary slightly from center to center. In general, however, the definitions incorporated into these clinical guidelines are consistent with those previously developed by the Infectious Disease Society of America and U.S. Food and Drug Administration (FDA) for evaluating antimicrobial therapy for fever and neutropenia. A single temperature >38.3°C orally or ≥ 38.0°C over 1 hour in the absence of an obvious cause, is defined as a fever. Although uncommon, a patient with neutropenia and signs or symptoms of infection (ie, abdominal pain, severe mucositis, perirectal pain) without fever should be considered to have an active infection. The concomitant administration of corticosteroids may also blunt the fever response as well as any localizing signs of infection.

Studies from more than four decades ago have shown that as the neutrophil count decreases below 500/mm$^3$ (which is defined as neutropenia), the susceptibility to infection increases. The frequency and severity of infection are inversely proportional to the neutrophil count; the risks of severe infection and bloodstream infection are greatest when the neutrophil count is less than 100/mm$^3$. The rate of decline of the neutrophil count and the duration of neutropenia are also critical factors. These latter two aspects are a measure of bone marrow reserve and are highly correlated with severity of infection and clinical outcome.

**Initial Evaluation**

The initial evaluation should focus on determining the potential sites and causative organisms of infection and on assessing the patient's risk of developing an infection-related complication. A site-specific history and physical examination should be performed promptly, cultures should be obtained and empiric antibiotics started soon after the time of presentation. The common sites of infection for patients with fever and neutropenia (such as the alimentary tract, groin, skin, lungs, sinus, ears, perivagina, perirectum, and intravascular access device sites) should be thoroughly assessed. Other important historical features to consider include major comorbid illness, medications, time since last chemotherapy administration, recent antibiotic therapy, and exposure to infections from household members.
Initial laboratory/radiology evaluation should include a complete blood count with differential analysis, platelets, blood urea nitrogen, creatinine, electrolytes, total serum bilirubin, liver-associated enzymes, and renal function tests. Oxygen saturation and urinalysis should be considered, depending on symptoms. Chest radiographs should be done for all patients with respiratory signs or symptoms, but radiographic findings may be absent in neutropenic patients with pulmonary infection. This baseline laboratory information is critical for developing a supportive care plan, assessing the patient's risk of infection, and monitoring for future treatment and infection-associated toxicity.

Cultures

Culture specimens should be collected during or immediately after completing the examination. Two blood samples or at least 20 to 40 mL of blood should be cultured. All experts agree that the volume of blood for culture is critical, but the recommendation for obtaining blood from both peripheral veins and venous access devices (VADs) remains controversial. Some experts recommend that blood cultures be obtained from both a peripheral vein and the VAD. This approach may help determine whether the VAD is the source of infection. The differential time to positivity of blood cultures drawn from the catheter and from the vein may be useful in identifying catheter-associated bloodstream infection. Quantitative blood cultures are not routinely recommended for economic reasons but may be helpful in assessing the role of the VAD as the cause of the bloodstream infection. However, some experts recommend that only blood from the VAD needs to be obtained for culture, without the requirement for a peripheral vein blood culture. The meta-analysis has shown little clinical use for two-site culturing in patients with cancer who have a VAD and poor patient acceptance of peripheral venipunctures when a VAD is in place. The panel consensus is that the volume of blood for culture is the most important aspect of blood culturing, but the need for the performance of cultures from both peripheral and central sites remains unclear.

In the absence of lesions or clinical signs and symptoms, routine cultures of the anterior nares, oropharynx, urine, stool, and rectum are rarely helpful. Diarrheal stools felt to be infectious should be tested for the presence of Clostridium difficile. Symptoms of urinary tract infection should be evaluated with a urinalysis and culture. Vascular access site inflammation should be cultured, and biopsy with microbiologic and pathologic evaluation should be considered for new or undiagnosed skin lesions. Viral cultures of mucosal or cutaneous lesions may identify HSV infections. In patients with symptoms of respiratory viral infection, viral cultures and rapid viral antigen testing of the nasopharyngeal secretions can be useful in winter months and during local outbreaks of such infections.

Initial Empiric Antibiotic Therapy

The foundation of infection management is to administer empiric antibiotics in patients with fever and neutropenia. This is necessary because currently available diagnostic tests are not sufficiently rapid, sensitive, or specific to identify or exclude microbial causes of fever from other noninfectious causes. All neutropenic patients should be treated empirically with broad-spectrum antibiotics promptly at the first sign of infection (ie, fever). This is done to avoid the mortality associated with a delay in treatment in those patients who have a serious infection. Many highly effective antibiotic regimens are available and those that are recommended are generally supported by randomized clinical trial evidence.
The selection of initial therapy should take into consideration the following factors:

- The most common potentially infecting organism
- The potential sites of infection
- The antimicrobial susceptibilities of pathogens isolated locally
- The patient's infection risk assessment
- The importance of broad-spectrum antibacterial activity
- Evidence of clinical instability (eg, hypotension)
- Patient medication allergy
- Organ dysfunction
- Previous antibiotic therapy

Although many antibiotic regimens are effective in managing these infections, careful selection of the initial antibiotic regimen may enhance efficacy and minimize adverse effects.

**Recommended Approaches**

The panel considers each of the following approaches to initial management of febrile neutropenia to be appropriate based on the results of large, randomized controlled clinical trials. The first approach is intravenous monotherapy (category 1) with either a carbapenem (imipenem-cilastatin), meropenem, an extended-spectrum antipseudomonal cephalosporin (ceftazidime [category 2B] or cefepime [category 1]). There is some evidence that piperacillin/tazobactam may be effective monotherapy, but the level of evidence to date is insufficient to warrant a category 1 recommendation, however, there is enough clinical experience to recommend it. If piperacillin/tazobactam is used for initial therapy in intravenous monotherapy, it may interfere with galactomannan measurement. Before initiating monotherapy, local institutional bacterial susceptibilities should be determined because of emerging changes in antibiotic sensitivities. Recent studies suggest that certain Gram-negative organisms (eg, *P.aeruginosa*) are developing resistance to cefepime and ceftazidime, highlighting the need to know local susceptibility patterns before prescribing monotherapy.

The second approach is intravenous dual therapy (category 1) with (1) an aminoglycoside plus an antipseudomonal penicillin (with or without a beta-lactamase inhibitor) or an extended-spectrum antipseudomonal cephalosporin, or (2) ciprofloxacin plus an antipseudomonal penicillin. Aminoglycoside use carries the inherent risk of renal and otic toxicity. These toxicities require careful monitoring and necessitate frequent reassessment, but once-daily aminoglycoside dosing may diminish renal toxicity. For patients at high risk for infections (ie, history of prior *Pseudomonas* infections or presence of ecthyma gangrenosum), initial dual therapy with the most active antipseudomonal agents available in the local setting may be considered.

The third recommended approach is the combination of monotherapy or dual therapy with the addition of intravenous vancomycin for specific indications (see section on “Empiric Vancomycin therapy”). Support for the judicious use of vancomycin has developed because of the increased frequency of beta-lactam-resistant Gram-positive infections caused by methicillin-resistant *S.aureus*, most coagulase-negative staphylococci, penicillin-
resistant viridans group streptococci and enterococci, and Corynebacterium jeikeium.

For patients who are considered to be at low risk for developing infection-related complications during the course of neutropenia, the oral combination of ciprofloxacin plus amoxicillin/clavulanate (category 1) is an effective alternative to intravenous monotherapy. Oral ciprofloxacin plus clindamycin is appropriate for low-risk patients who are allergic to penicillin. Low risk has been variably defined by different groups (see section on "Risk Assessment"). Several small studies have investigated the efficacy of high-dose ciprofloxacin or ofloxacin (of which levofloxacin is an isomer) for empiric oral monotherapy. However, the evidence does not currently support the routine use of these fluoroquinolones for monotherapy in low-risk patients with fever and neutropenia. The panel recognizes that oral fluoroquinolone monotherapy is used widely, but they are concerned that ciprofloxacin may not provide adequate coverage for certain Gram-positive organisms (eg, S. aureus, viridans group streptococci) and that levofloxacin may not adequately cover pseudomonas.

Empiric Vancomycin Therapy

There is considerable debate about the use of empiric vancomycin in patients with fever and neutropenia. The clinical concern has been that a small portion of infections caused by Gram-positive pathogens can be fulminating and lead to rapid death in patients who are not treated promptly with appropriate antibiotics. However, a large, prospective, randomized trial from the European Organization for Research and Treatment of Cancer failed to show true clinical advantages for empiric vancomycin in adults. This study reported that empiric vancomycin decreased the number of days the patients had fever but did not improve survival. The study also showed empiric vancomycin to be associated with an increased incidence of nephrotoxicity and hepatotoxicity. However, a prospective randomized trial of fever and neutropenia in children has reported benefit for empiric vancomycin.

The major concern surrounding the uncontrolled use of vancomycin has been the emergence of vancomycin-resistant organisms, especially enterococci. Recent reports of vancomycin-resistant S. aureus, rarely occurring in certain clinical settings, are of key concern and underscore the need for judicious vancomycin use. The increase in vancomycin resistance generally has been associated with excessive use of vancomycin among hospitalized patients. The guidelines panel advises practitioners to adopt the recommendation of the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention for preventing the spread of vancomycin resistance. Because of the increased risk of vancomycin-resistant organisms, empiric vancomycin use should be considered only in patients at high risk for serious Gram-positive infection. Vancomycin should not be considered as a routine component of initial therapy for fever and neutropenia.

The following clinical situations may justify initial vancomycin therapy:

- Serious, clinically apparent, catheter-related infections are present in the patient. Many of these infections are caused by coagulase-negative staphylococcal isolates, which have high-level beta-lactam antibiotic resistance.
- The patient’s blood cultures are positive for Gram-positive bacteria before final identification and susceptibility testing.
• Known colonization with beta-lactam-resistant pneumococci or methicillin-resistant *S. aureus*.

• The patient received previous prophylaxis with ciprofloxacin or trimethoprim/sulfamethoxazole. Both of these agents have been associated with an increased risk of Gram-positive infections. The broad-spectrum, Gram-negative, bacillary coverage, and limited Gram-positive pathogen activity of these drugs allows gastrointestinal colonization and subsequent infection with such organisms. It is not certain, however, that the newer fluoroquinolones with enhanced Gram-positive activity (e.g., moxifloxacin, gatifloxacin) will allow for such colonization if given prophylactically. Therefore, there can be no statement made about the use of vancomycin in the setting of newer fluoroquinolone prophylaxis.

• Hypotension or septic shock develops in the patient without an identified pathogen.

Empiric vancomycin could be considered in any of these situations, but the therapy should be reassessed within 2 to 3 days of initiation. If a resistant Gram-positive pathogen cannot be identified and if clinically appropriate, empiric vancomycin therapy should then be discontinued. While the presence of severe mucositis may present a risk for viridans streptococcal sepsis in neutropenic patients, currently recommended monotherapy (such as cefepime, imipenem, and piperacillin-tazobactam) possesses excellent Gram-positive coverage and appear, to obviate the need to add vancomycin in the setting of mucositis.

**Linezolid, Daptomycin, and Quinupristin/Dalfopristin**

Quinupristin/dalfopristin, linezolid and daptomycin have efficacy against many Gram-positive organisms and against vancomycin-resistant pathogens. The panel recommends that the use of these three drugs be limited to specific situations involving infections caused by vancomycin-resistant organisms or in patients for whom vancomycin is not an option. Currently, there are no data to support the use of these three agents in the routine empiric therapy for fever and neutropenia.

Linezolid has become a mainstay treatment for vancomycin-resistant enterococcal infections. However, there are only limited data about its efficacy in neutropenic patients. Resistance to linezolid is infrequent, but this agent needs to be used cautiously in patients with compromised bone marrow function because of the marrow toxicity associated with long-term use of linezolid. Linezolid can be used for treatment of methicillin-resistant *S. aureus* pneumonia in ventilated patients.

Daptomycin is effective against most Gram-positive pathogens, but it should not be used for treatment of pneumonia due to poor penetration into lung tissue. Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of certain Gram-positive microorganisms.

Use of quinupristin/dalfopristin has been limited by the emergence of resistance and the musculoskeletal symptoms associated with this agent.

**Initial Empiric Therapy for Patients Who Are Clinically Unstable**

Because of the high mortality rate in patients with fever and neutropenia who present with the clinical instability, the panel recommends initial therapy with a broad-spectrum combination such as a carbapenem, an aminoglycoside, and vancomycin.
However, the components of this broad antibiotic cocktail should take into account local susceptibility patterns. Some experts also suggest that patients who have a history of *P. aeruginosa* colonization or invasive disease should receive dual therapy with an antipseudomonal beta-lactam (cephalosporin or penicillin) plus an aminoglycoside or ciprofloxacin.

**Risk Assessment**

Patients may be categorized into either a high- or low-risk group using criteria that are derived either from validated clinical prediction rules based on risk models or from clinical trials eligibility criteria. Risk assessment attempts to predict the probability that a neutropenic patient will experience serious complications during a febrile episode; risk assessment also helps determine whether the patient who is at low risk for serious complications could safely receive treatment outside of the traditional hospital setting and receive initial empiric therapy with oral antibiotics.

Risk assessment should be performed as part of the initial evaluation. Clinical prediction rules include the classification systems developed by Talcott and colleagues, which used patients mainly from Dana-Farber/Partners Cancer Care, and the international study conducted by the Multinational Association of Supportive Care in Cancer (MASCC).

Although neither of the two clinical prediction rules previously discussed considers the duration of neutropenia, the panel acknowledges that the duration of neutropenia is an important factor that influences risk of complications during the febrile episode and should be considered in risk assessment.

**Duration of Neutropenia and Risk**

For decades clinicians have regarded depth and duration of neutropenia as critical determinants of a patient’s risk. Once the relationship between the absolute neutrophil count (ANC) and incidence of infections was demonstrated, the importance of increased neutrophil counts on outcomes was evident. In Bodey’s original work, the fatality rate was highest (80%) in patients who initially started with neutrophil counts less than 100/mm³ that did not change during the first week of infection compared to those patients who started out with neutrophil counts less than 1000/mm³, which then rose to greater than 1000/mm³ (27%). Many clinical trials since then have reported that response rates to antibiotic regimens are highly influenced by trends in the neutrophil count during febrile episodes. In one study, the overall response rate was 73% if the initial neutrophil count increased compared to 43% if it decreased or remained unchanged (P<.00001). The response rate in patients who were initially profoundly neutropenic (ie, ANC<100/mm³) but recovered from neutropenia was 67%, compared to only 32% in patients who remained profoundly neutropenic (P<.0001). In 1988, Rubin and colleagues published a study from the National Cancer Institute examining the influence of the duration of neutropenia on the response to empiric antimicrobial therapy and other important clinical outcomes in patients with fever of undetermined origin. Patients with less than 7 days of neutropenia had response rates to initial antimicrobial therapy of 95%, compared to only 32% in patients with more than 14 days of neutropenia (P<.001); however patients with intermediate durations of neutropenia between 7 and 14 days had response rates of 79%.

Clearly bone marrow recovery is a very important factor that influences outcome during the febrile neutropenic episode. Delayed
bone marrow recovery might be anticipated in certain patient subsets (e.g., those who have received multiple cycles of myelosuppressive chemotherapy; patients with known bone marrow metastases; or patients who have received radiation therapy to the pelvis, spine, or long bones). Most patients with solid tumors have neutropenia lasting less than 7 to 10 days and are at much lower risk. Several studies have demonstrated the ability of clinicians to predict, with good accuracy, anticipated duration of neutropenia. In prospective randomized trials of oral versus intravenous antibiotics for patients at low risk, the predicted expected further duration of neutropenia was used as an eligibility criteria and clinicians were accurate more than 80% of the time.1-3,4,5

Prognostic Factors in Patients with Bacteremia

Elting and colleagues have developed a classification system for bacteremias in febrile neutropenic patients based on size and presence of associated tissue involvement.6 Complex bacteremias are associated with the lung, liver and spleen, kidney, colon, bone and joints, veins and heart, meninges, soft tissues with necrosis, or skin/soft tissue/wound cellulitis greater than 5 cm. Simple bacteremias are associated with less tissue involvement (bacteruria, otitis, pharyngitis, soft tissue <5 cm). The prognostic significance of complex infection associated with bacteremia on survival was dramatic. At 21 days, 20% of patients with complex infections were dead compared to only 5% of patients with simple bacteremias (P<.0001). Profoundly neutropenic patients with simple bacteremias had a much higher response rate to antibiotics (94% versus 70%, P<.0001) compared to patients with complex bacteremias. Response to the initial antibiotic regimen and ultimate outcome were lower in leukemia patients (those who presented with shock or patients with serum albumin <3.5g/dL). The median time to defervescence for patients with simple bacteremias was 50% that observed for patients with complex bacteremias (2.5 days versus 5.3 days, P<.0001).6 Based on these and other studies, clinical criteria can be used to stratify patients with bacteremia into high- and low-risk strata shortly after the onset of the febrile neutropenic episode. These criteria in one combination or another have been used to select patients for risk-adjusted clinical trials of empiric antibiotic therapy.5-8,10,40,41,68,70-73

Early, prospective trials have suggested such patients can be initially evaluated in the hospital, ambulatory clinic, or home and then treated effectively with broad-spectrum intravenous, sequential intravenous/oral, or oral therapy. The panel recognizes that at least two alternative validated tools are available for defining a low-risk patient. However, the best evidence for safe and effective management of low-risk patients only comes from published randomized clinical trials.5,40,41,71 Only centers with the necessary infrastructure should treat low-risk patients in an outpatient setting, preferably in an investigational context.

Antifungal Agents for Treatment of Invasive Fungal Infections

Invasive Candidiasis

Because most invasive fungal infections observed in patients with cancer are caused by Candida spp or Aspergillus spp, the panel restricts its recommendations to treatment of these pathogens. Candida spp are the fourth most common cause of nosocomial bloodstream infections in the United States.74 The crude mortality of candidemia is estimated to range from 30% to 60% and its attributable mortality at 30%.
*Candida albicans* is the most common Candida spp isolated from the blood. The proportion of non-albicans Candida species varies among different centers but appears to be rising and can account for approximately 50% of blood stream isolates at several medical centers. *Candida krusei* is virtually always resistant to fluconazole, and Candida glabrata isolates often have decreased susceptibility to fluconazole.

Several studies comparing intravenous fluconazole with amphotericin B as therapy for candidemia in both neutropenic and nonneutropenic patients found both regimens equally effective, but fluconazole had less toxicity.\(^{75-77}\) Voriconazole, had similar efficacy but reduced nephrotoxicity compared to a strategy of amphotericin B followed by fluconazole in nonneutropenic patients with candidemia.\(^{78}\) Voriconazole is also an acceptable alternative in the treatment of candidemia.

Echinocandins (such as caspofungin and micafungin) are cidal against Candida species, including azole-resistant isolates.\(^{79}\) Caspofungin was compared with conventional amphotericin B in adult patients with invasive candidiasis.\(^{80}\) A modified intention-to-treat analysis revealed that the efficacy of caspofungin was similar to that of amphotericin B, with successful outcomes in 73.4% of the patients treated with caspofungin and in 61.7% of those treated with amphotericin B. Caspofungin recipients had significantly fewer clinical adverse experiences, nephrotoxicity, and premature discontinuation from drug-related toxicity.

For serious infections caused by Candida species in neutropenic patients, the panel recommends caspofungin (70 mg loading dose followed by 50 mg every day) due to comparable efficacy to amphotericin B and excellent safety profile. Caspofungin is recommended for patients with candidemia including those who are clinically unstable, bloodstream infections caused by *C. glabrata* and *C. krusei*, and breakthrough candidal infections in patients receiving azole prophylaxis.

Amphotericin B deoxycholate is infrequently used as primary therapy for candidemia since equally effective and less toxic alternative agents are available. If conventional amphotericin B is used (0.7 mg/kg IV daily is a common dose for invasive candidiasis), we suggest prehydration with normal saline (0.5 to 1L in an average size adult) to decrease the likelihood of azotemia. Saline hydration may not be feasible in patients with significant cardiac or renal dysfunction. Premedication with acetaminophen, diphenhydramine, meperidine, and/or an antiemetic should be considered in patients with infusional toxicity. Infusional and renal toxicity may be decreased by administering amphotericin B as a continuous 24-hour infusion versus standard 2- to 4-hour daily infusions.\(^{81}\) Electrolyte wasting is expected and may persist for prolonged periods after cessation of amphotericin B; therefore, appropriate electrolyte monitoring and replacement is required. Many of the renal toxicity and electrolyte imbalance problems may be alleviated with the use of lipid formulations of amphotericin B.\(^{82,83}\)

**Invasive Aspergillosis**

Prolonged and persistent neutropenia is a critical factor for aspergillosis.\(^{84}\) However, the predominance of invasive aspergillosis cases now occur in the post-engraftment rather than the neutropenic period in allogeneic hematopoietic stem cell transplant (HSCT) recipients, with immunosuppressive therapy for GVHD being a principal risk factor.\(^{85-91}\)

Voriconazole was compared with conventional amphotericin B as initial therapy in an open-label, randomized trial of patients with...
invasive aspergillosis.\textsuperscript{91} Among 277 evaluable patients, voriconazole was more effective than amphotericin B (51% versus 32% of subjects had a successful outcome, respectively) and was associated with improved survival at 12 weeks (71% versus 58%, respectively). This study strongly supports the use of voriconazole as first-line therapy for proven or probable invasive aspergillosis.

Caspofungin has been evaluated as salvage therapy in patients with invasive aspergillosis who are refractory to standard antifungal therapy and in patients intolerant of standard therapy. Most patients had a hematologic malignancy or were allogeneic HSCT recipients. A favorable response to caspofungin therapy was observed in 37 (45%) of 83 patients, including 32 (50%) of 64 with pulmonary aspergillosis and 3 (23%) of 13 with disseminated aspergillosis.\textsuperscript{92} Echinocandins have not been evaluated as initial monotherapy for invasive aspergillosis and are therefore not recommended in this setting.

There has been significant interest in combination antifungal therapy, such as pairing an echinocandin with either an amphotericin B preparation or an azole with activity against \textit{Aspergillus} species based on in vitro and animal studies and on limited clinical data. In a very small retrospective analysis of salvage therapy for invasive aspergillosis in allogeneic HSCT recipients, Marr et al reported a survival advantage of voriconazole plus caspofungin compared to voriconazole alone.\textsuperscript{93} Though several centers use combination regimens as either initial or salvage therapy for invasive aspergillosis, the panel considers the database on combination therapy for invasive aspergillosis preliminary, but promising (category 2B). A randomized study comparing combination with monotherapy is required to definitively demonstrate the value of combination therapy for invasive aspergillosis.

In patients with suspected (but not confirmed) invasive mold infection, pre-emptive antifungal therapy is warranted before confirmation of the diagnosis; for example, a patient with prolonged neutropenia (≥10 days), fever, and a new pulmonary lesion on CT scan requires pre-emptive therapy. \textit{Aspergillus} species account for most of the invasive mold infections in immunocompromised patients with cancer. An important recent trend has been the frequency of invasive zygomycosis noted at some centers in setting of more frequent voriconazole usage.\textsuperscript{94-96} The possibility of zygomycosis should be suspected in histologic samples showing broad aseptate hyphae that are often more clearly visualized with H&E rather than silver staining. Because voriconazole has poor activity against zygomycetes, a lipid formulation of amphotericin B (at least 5 mg/kg/day) should be used for suspected or confirmed zygomycosis. Posaconazole, an investigational second generation azole, has shown promise as salvage therapy for zygomycosis.\textsuperscript{97}

Less common mold infections include \textit{Fusarium sp.}, \textit{Scedosporium sp.}, and dark-walled molds that are either variably or fully resistant to amphotericin B. In addition, \textit{Aspergillus ferreus} has become a rare cause of invasive aspergillosis in patients with cancer, and it is notably resistant to amphotericin B.\textsuperscript{98} The broad spectrum of opportunistic molds and their different sensitivities to antifungal agents emphasize the need to establish a culture diagnosis when feasible.

**Empiric Antifungal Therapy in Persistent Neutropenic Fever**

Empiric antifungal therapy for persistent febrile neutropenia unresponsive to broad-spectrum antibacterial agents is used because neutropenic patients have traditionally been known to be at
risk for invasive fungal infections, and clinical examination and collection of cultures are not sufficiently sensitive for early detection of those infections. The concept of using empirical antifungal therapy was established in the 1970s and 1980s and was principally geared toward early treatment of occult invasive candidiasis with conventional amphotericin B, since fluconazole prophylaxis had not been developed. Because of its toxicity, amphotericin B was used as empiric therapy for refractory neutropenic fever rather than as universal prophylaxis. With the widespread use of fluconazole in the 1990s as prophylaxis in high-risk patients with acute leukemia and in HSCT recipients, empiric antifungal therapy for neutropenic fever principally involved switching from fluconazole to amphotericin B, to broaden the antifungal spectrum to include molds, but at the expense of greater toxicity. The availability of lipid formulations of amphotericin B, newer azoles, and echinocandins that are active against Candida and Aspergillus species (and have significantly less toxicity than conventional amphotericin B) have prompted many centers to use these agents prophylactically (see section on antifungal prophylaxis). It is not clear whether modification of the antifungal regimen is required empirically solely on the basis of persistent neutropenic fever in patients receiving a mold-active drug as prophylaxis. At present, there are no data to support the complete omission of empiric antifungal therapy although this will be an area of research and debate over the next few years.

Voriconazole was compared with liposomal amphotericin B (L-AMB) in an open, randomized study of empiric antifungal therapy (n=837 patients, 72% with hematologic malignancies). The overall success rates were 26% with voriconazole and 31% with L-AMB. Empiric voriconazole was associated with fewer breakthrough fungal infections (1.9% versus 5.0%), with the greatest protective benefit occurring in pre-specified high-risk patients (relapsed acute leukemia and allogeneic HSCT). Because the noninferiority of voriconazole versus L-AMB was not demonstrated in this study, voriconazole did not receive FDA approval for use as empiric therapy. However, some panel members consider voriconazole to be an acceptable option as empiric therapy in patients at high risk for invasive mold infection.

Caspofungin is active against Candida and Aspergillus species but has unreliable activity against most other opportunistic fungi. Caspofungin was recently compared with L-AMB as empiric therapy for fungal infections in a randomized double-blind study of 1095 patients. The overall success rates were 34% in caspofungin and 33.7% in L-AMB recipients. The proportion of patients who survived at least seven days after therapy was greater in the caspofungin group (92.6% vs. 89.2%, P=0.05). The rates of breakthrough fungal infections and resolution of fever during neutropenia were similar in the two groups. In patients with a baseline invasive fungal infection, mortality was 11% in caspofungin and 44% in L-AMB recipients, respectively (P<.01). Drug-related toxicities and premature withdrawals because of drug-related adverse events were significantly lower in caspofungin recipients. This study strongly supports caspofungin as an option for empiric antifungal therapy.

Fluconazole has been used successfully as empiric therapy for neutropenic fever but is limited by lack of activity against molds. Intravenous followed by oral itraconazole solution was as effective as but less toxic than conventional amphotericin B when used as empiric therapy in an open, randomized study; these results led to FDA approval of itraconazole solution for this indication. Itraconazole in the capsule formulation has erratic oral bioavailability and is therefore not suitable as empiric antifungal therapy. Itraconazole has negative inotropic effects and is contraindicated in patients with compromised cardiac function.
Early Diagnosis of Invasive Fungal Infections

Invasive fungal pathogens have increased and remain a major concern. CT scanning of the chest may facilitate early detection of aspergillosis and other filamentous fungi. A CT scan may show peripheral or subpleural nodules inapparent on plain chest radiographs. The “halo sign” is a characteristic early chest CT feature of angioinvasive organisms. The hazy alveolar infiltrates appear to correspond to regions of ischemia and are highly suggestive of invasive aspergillosis. The panel recommends a chest CT scan in patients with 10 to 14 days of neutropenia and persistent or recurrent fever of unknown origin unresponsive to empiric antibacterial agents. A chest CT scan may be considered earlier in patients with multiple prior cycles of potently cytotoxic chemotherapy and in those receiving systemic corticosteroid therapy. Diagnostic and therapeutic modalities for fungal infections remain limited, but careful clinical investigation of new approaches will be needed to define the proper use of these likely expensive new therapeutic additions.

Galactomannan is a fungal cell wall constituent for which a sensitive double-sandwich ELISA has been developed to facilitate early diagnosis of invasive aspergillosis. Maertens and colleagues obtained serial serum galactomannan levels from neutropenic and HSCT patients at high risk for aspergillosis. The positive and negative predictive values were 88% and 98%, respectively. The sensitivity of the galactomannan assay, however, is variable ranging from 65% to greater than 90% with better sensitivity occurring in serial tests.

Several variables can affect the performance of the galactomannan assay including host factors and concomitant medications that may account for the variability of the sensitivity and specificity in these and other series. The assay is likely more sensitive in patients with neutropenia than in the late HSCT period. Use of mold-active drugs prophylactically or empirically reduces the sensitivity of the assay. Concomitant piperacillin/tazobactam causes false-positive results. In patients at high risk for invasive mold infection and compatible radiologic findings (eg, a nodule or infiltrate on chest CT), a positive galactomannan assay establishes the diagnosis of “probable aspergillosis,” and may obviate the need for an invasive diagnostic procedure.

Odagashi et al evaluated the (1-->3)-beta-D-glucan (BG) detection assay (Glucatell assay, Associates of Cape Cod) as an early diagnostic marker for invasive fungal infections in patients with acute leukemia or myelodysplastic syndrome receiving antifungal prophylaxis. At least one serum sample was positive at a median of 10 days before the clinical diagnosis in all patients with a proven or probable invasive fungal infection, including candidiasis, fusariosis, trichosporonosis, and aspergillosis. The negative predictive value was 100%, and the specificity of the test was 90% for a single positive test result and at least 96% for 2 or more sequential positive results. Polymerase chain reaction (PCR) applied to blood and bronchoalveolar lavage is another promising diagnostic adjunct for invasive fungal infections, although standardized techniques are not yet commercially available. A positive galactomannan assay should prompt the physician to order a chest CT scan.

Further studies are required to delineate the performance of these early detection methods among different host groups and to more clearly delineate variables that affect performance. At this point, it is premature to recommend any of these methods as a surveillance tool for neutropenic fever in the absence of symptoms, signs, or radiologic findings suggestive of an invasive fungal infection.
Empiric Antiviral Therapy

Most patients at high risk for HSV activation, especially those undergoing leukemia induction therapy or stem cell transplant, should receive prophylactic antiviral agents to prevent HSV reactivation. Empiric antiviral agents are generally not indicated in the treatment of fever and neutropenia. In patients with cutaneous or mucosal lesions consistent with or suspected to be caused by herpes viruses (HSV, VZV), treatment with acyclovir is recommended, before a specific diagnosis has been made. Oral mucosal lesions caused by HSV provide portals of entry for bacteria, such as viridans group streptococci, into the bloodstream during febrile neutropenic episodes; antiviral therapy in this setting might promote mucosal healing and decrease the chances of such bacteremic infections. If oral therapy is feasible, newer agents such as valacyclovir and famciclovir, which are better absorbed and have a longer dosing interval than acyclovir, should be considered. Consider empiric therapy directed against CMV (ganciclovir or foscarit) in patients at high risk for CMV during influenza season (category 2B). Agents commonly used in the treatment of CMV disease include ganciclovir, foscarit, and, to a lesser extent, cidofovir. Valganciclovir, a prodrug of ganciclovir, is better absorbed than ganciclovir and may be useful in certain settings.

Recent studies have shown that community respiratory viruses (influenza virus, parainfluenza viruses, respiratory syncytial virus) can cause substantial morbidity and some mortality in neutropenic HSCT recipients and in patients with hematologic malignancies. In patients with upper respiratory symptoms, such as rhinorrhea, who are suspected to have community viral infections, nasopharyngeal wash for rapid detection of these viruses should be obtained. If influenza or RSV is identified, antiviral therapy should be considered because progression from an upper respiratory infection to pneumonia is associated with increased mortality for these viruses. Influenza A viral infections may be treated with amantadine or rimantadine. Zanamivir and oseltamivir provide coverage against both influenza A and B virus; oseltamivir is preferred due to the ease of oral administration. Ribavirin is used to treat RSV infections, although there is no consensus about its utility.

Site-Specific Evaluation and Therapy for Infections

The NCCN guidelines provide recommendations for site-specific evaluation and therapy for infections of the mouth and esophagus, sinuses, liver, abdomen, rectum, vascular access sites, lungs, skin/soft tissue, urinary tract, and central nervous system.

Mouth and Esophageal Infections

The mouth and esophagus are common sites of infection in patients with fever and neutropenia. This site predilection occurs because of the propensity of the mouth and alimentary tract mucosa to be disrupted by cytotoxic therapy (mucositis). Unfortunately, the characteristics of this disruption are not etiology specific, and important viral and fungal pathogens often can be distinguished only by microbiologic culture. Empiric antibiotic therapy must consider the endogenous anaerobic flora and the shift in oral flora, which occurs with serious illness or antibiotic use. The increased frequency of HSV reactivation and severity of these infections in cancer patients are well known and preventable. The incidence of HSV reactivation in immunocompromised patients may approach 50% to 75%, but it is nearly zero in those who receive prophylaxis with appropriate antiviral agents. HSV infections are associated
with more extensive mucosal damage, increased secondary infections, and significantly prolonged healing time. Baglin and associates reported that patients with fever and neutropenia who experienced concomitant HSV reactivation and were treated with appropriate antiviral therapy had a significant decrease in the number of days with fever.128 If thrush is present, the patient should receive topical or systemic antifungal therapy.

The predilection of the esophagus for infection is similar to the mouth but is potentially greater because of gastric acid reflux and therapy-induced vomiting. Although the classic symptoms of esophagitis consist of retrosternal burning pain or dysphagia, many experts believe that chronic nausea is the most common symptom of infectious and noninfectious esophagitis. The oral cavity should be inspected for thrush and/or oral lesions; oral lesions should be cultured. Presumed esophagitis is often treated empirically. Fluconazole is a common first-line agent to treat oral mucosal or esophageal candidiasis. Voriconazole or caspofungin is a reasonable option if the patient was previously exposed to an azole or if resistance is suspected.

If HSV esophagitis is strongly suspected (ie, if symptoms are refractory to antifungal therapy) intravenous acyclovir should be instituted (category 1). CMV esophagitis is a rare complication of chemotherapy-induced neutropenia and is most commonly observed in allogeneic HSCT recipients after neutrophil recovery and in the setting of GVHD. If CMV is suspected, upper endoscopy with biopsy should be performed, if possible; institution of ganciclovir or foscarin is appropriate for confirmed cases.

For patients with esophagitis who do not respond to empiric therapy with these agents, careful upper endoscopy with platelet support may be considered to obtain cultures. Tissue biopsies are the gold standard of diagnosis of invasive esophageal infections. However, there may be substantial morbidity associated with endoscopy and biopsy in patients who are profoundly neutropenic and/or thrombocytopenic; therefore, the procedure should be done cautiously. Radiographic procedures, such as barium studies, are insensitive and add little clinically significant information; therefore, these procedures are not recommended.

**Sinus or Nasal Infections**

The sinuses are a common site of bacterial infection. Neutropenic and certain high-risk patients are particularly predisposed to invasive mold infections. Cytotoxic therapy disrupts the natural cleansing mechanisms in the nasal passages and increases colonization. A preceding chronic infection may also become active in the setting of neutropenia. Sinusitis during the early neutropenic period (<7 days) is principally caused by respiratory and Gram-negative bacterial pathogens. In patients with longer duration neutropenia or those receiving concomitant high-dose corticosteroid therapy, invasive mold infections are an important concern.

Initial symptoms of sinusitis may be mild. A high-resolution computed tomographic (CT) scan of the sinuses or orbit MRI is the radiographic procedure of choice to evaluate patients with sinus tenderness, nasal stuffiness, nasal erosions, unilateral eye tearing, headache, or epistaxis. Bony erosion on CT scan suggests invasive fungal disease. ENT and ophthalmologic examination should be performed for symptomatic patients with abnormalities on CT scan, with biopsy and culture of any abnormal tissues. Broad-spectrum coverage for aerobes and anaerobes is appropriate for patients with sinus infections.

Sinus endoscopy with biopsy and culture are often required to definitively establish the diagnosis and should be pursued...
aggressively in patients at high risk for mold infection. Invasive fungal sinusitis in patients with hematologic malignancies and prolonged neutropenia is principally caused by *Aspergillus* species (*A. flavus* and *A. fumigatus*) and zygomycetes. Among patients with leukemia and allogeneic HSCT recipients, noted that prior voriconazole prophylaxis and sinusitis each increased the likelihood of zygomycosis. Voriconazole is the drug of choice for invasive aspergillosis. A lipid formulation of amphotericin B (at least 5 mg/kg/d) should be used for suspected or confirmed zygomycosis. Consider combination therapy (ie, amphotericin B, voriconazole, caspofungin) (category 2B) for resistant mold infection. Vancomycin (or other potent anti-Gram-positive agent) should be added for periorbital cellulitis.

Abdominal, Rectal, and Liver Infections

Most infections in the abdomen, rectum, or liver are discovered because of a combination of clinical signs and symptoms (eg, abdominal pain, perirectal pain, and diarrhea) as well as biochemical abnormalities (eg, abnormal liver function tests). These infections are usually diagnosed and managed based on the radiologic, gastrointestinal, and surgical expertise of the treating oncology center. Improved imaging techniques (including ultrasonography, CT scans, magnetic resonance imaging [MRI], and radionuclide and endoscopic procedures) have decreased the need for surgical intervention. The choice of diagnostic studies should be based on the clinical presentation and relative clinical benefit.

Antimicrobial therapy for gastrointestinal infections must take into account the high likelihood of polymicrobial pathogens and the presence of the endogenous anaerobic gastrointestinal flora. Acceptable therapeutic options in this setting include monotherapy with imipenem, meropenem, or zosyn or cephalosporin (ceftazidime or cefepime) plus an agent with anaerobic activity (eg, flagyl). The importance of enterococci in abdominal infections continues to be debated. The panel believes that enterococcal colonization must be differentiated from true infection. Notably, cephalosporins are inactive against enterococci, and carbapenems are not reliably active against these organisms. Also, because of the risk of vancomycin-resistant organisms, the use of vancomycin for this indication should be minimized.

It is also important to recognize that the gastrointestinal tract is a common origin of systemic yeast infections. Yeast is a component of the colonic flora in 30% to 60% of normal adults. The mucosal damage induced with cytotoxic therapy and the administration of broad-spectrum antibacterial therapy allows the yeast to proliferate to pathogenic levels, with potential bloodstream invasion. *Clostridium difficile* is a common complication of neutropenia, occurring in about 7% of patients. Diarrhea should be evaluated with at least two stool *C. difficile* toxin screens and treated with oral metronidazole if a positive result is obtained.

Neutropenic enterocolitis is a serious, potentially life-threatening syndrome characterized by fever, diarrhea, and abdominal pain. When it occurs in the cecum, it is commonly referred to as typhilitis. The cecum is more vulnerable because of its size and shape, but any or all of the colon may be involved. CT scanning is the diagnostic study of choice and usually demonstrates thickening of the bowel wall. This illness has frequently been associated with acute leukemia, neutropenia, and intensive cytotoxic therapy. The differential diagnosis for this syndrome includes *C. difficile* colitis, CMV enteritis (most common in allogeneic HSCT recipients), and gastrointestinal tract graft-versus-host disease (GVHD).
Bloodstream infections and sepsis (frequently polymicrobial), bowel perforation, and hemorrhage may occur. The natural history of typhlitis is quite variable, but all patients should be assessed for *C. difficile* infection and should be treated with bowel rest and broad-spectrum antibiotics including coverage for *C. difficile* and aerobic as well as anaerobic pathogens. Parenteral nutrition should be considered if clinical signs and symptoms do not resolve promptly. Approximately 5% of patients with typhlitis develop complications requiring surgical intervention (e.g., perforation). Consequently, the panel recommends that surgical and other subspecialty consultations be obtained early in the course of treatment.

**Vascular Access Device Infections**

VAD infections are common as a consequence of the ubiquity of VADs in patients undergoing intensive or cyclic chemotherapy. The risk of infection varies with the device used (long-term implanted catheters versus short-term central catheters), duration of placement, and extent of the patient's immunosuppression. Short-term central catheters impregnated with antibiotics or silver-chlorhexidine appear to be associated with fewer device-related bacterial infections. However, no studies show the value of these coatings for preventing infections in long-term, indwelling devices. VAD infections are categorized as entry or exit site infections, tunnel or pocket infections, or catheter-associated bloodstream infections. More than 66% of these infections are caused by Gram-positive pathogens, with coagulase-negative staphylococci recovered most frequently. Accordingly, intravenous vancomycin is recommended for those infections that are serious and clinically obvious. Although some data suggest that vancomycin prophylaxis may prevent Gram-positive VAD infections, the panel does not currently endorse this practice because of concerns about the emergence of bacterial resistance.

Most VAD entry or exit site infections can be treated effectively with appropriate antimicrobial therapy without the need for catheter removal. Skin swab and culture analysis should be performed from each port to determine site of infection. Empiric coverage with the regimens recommended for fever and neutropenia is appropriate initially in most cases of mild VAD site infection. Vancomycin should be added if the site has not responded after 48 hours of empiric therapy. If there is a clinically apparent, serious, catheter-related infection (such as a tunnel or pocket infection), catheter removal and culture are required and vancomycin should be initiated immediately.

Determining the role of the catheter in bloodstream infections is frequently difficult if there is no evidence of local catheter inflammation. Differential time to positivity method (DTP) is a useful diagnostic tool for detecting VAD infections. Early positivity of central venous blood cultures predicts catheter-related bacteremia and may be used to avoid unnecessary catheter removal in critically ill patients. It was shown that DTP between centrally and peripherally drawn blood cultures of 120 minutes or more is highly sensitive and specific for diagnosing catheter-related bacteremia. It should be noted that these studies were only performed in patients with removable catheters, not implanted catheters (Hickman, etc) that are frequently used in patients undergoing cancer treatment.

Most catheter-associated bloodstream infections will respond to antimicrobial therapy alone without catheter removal, but immediate catheter removal is advisable for patients with bloodstream infections caused by fungi (yeasts or molds) or nontuberculosis mycobacteria (*Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium abscessus*). Bloodstream infections caused by *Bacillus* organisms,
C. jejuni, S. aureus, P. aeruginosa, Stenotrophomonas maltophilia, and vancomycin-resistant enterococci may be difficult to eradicate with antimicrobial therapy alone. For all bloodstream infections, the panel recommends that pathogen-specific antimicrobial therapy should be initiated. Catheter removal is advised if the bloodstream infection is still present after 48 hours of appropriate antibiotic therapy (i.e., continued positive blood cultures at 48 hours). If patient is clinically unstable in the absence of another site of infection, removal of the infected catheter is essential.

For patients with bloodstream infections (regardless of whether they are associated with a catheter) caused by S. aureus, the value of transesophageal echocardiography (TEE) in identifying endocarditis is well demonstrated. In populations in whom the prevalence of endocarditis is between 2% and 38%, therapy based on TEE results is cost effective compared with empiric administration of short-course or long-course antibiotic therapy. The panel recommends that, unless contraindicated (such as in the setting of mucositis and neutropenia), TEE be performed in patients with catheter-associated bloodstream infections caused by S. aureus to rule out the presence of otherwise unidentified endocarditis.

Administering antibiotics through each lumen of the involved catheter has been suggested to avoid treatment failure caused by microbial sequestration. Some experts believe supplemental urokinase infusions can be helpful in patients with catheter-related infections. However, the panel believes data are insufficient to recommend either of these approaches.

**Lung Infections**

The lungs are the infection site with the greatest associated morbidity and mortality, even when a specific pathogen is not identified. These infections are often complex, and early consultation with infectious disease and pulmonary subspecialists is recommended. Noninfectious causes of pulmonary infiltration, including diffuse alveolar hemorrhage (DAH) and drug toxicity, also need to be considered.

Lung infections are usually detected based on a combination of clinical signs and symptoms (i.e., dyspnea, tachypnea, low pulse oximetry readings) and on the discovery of a pulmonary infiltrate on the chest radiograph. Sputum culture for bacterial and fungal pathogens is also a valuable tool for detection of a lung infiltrate. CT of the chest is useful to further define the pulmonary process. An alveolar infiltrate is most suggestive of a bacterial process, while a diffuse interstitial picture is more compatible with a viral or noninfectious etiology. A pulmonary nodule is the most common early (though nonspecific) sign of invasive mold infection in a high-risk patient. A nodule with the “halo sign” in patients with prolonged neutropenia is a highly suggestive early sign of invasive Aspergillosis. Bronchoalveolar lavage (BAL) is recommended as the primary investigation for patients with pneumonia. It is usually well tolerated and can be done safely in patients with relatively low platelet counts. The diagnostic yields are very high for viruses (e.g., CMV), bacteria, and Pneumocystis carinii (recently renamed as P. jirovecii). The yield for molds, such as Aspergillus, is lower (only 50% to 65%). If the BAL is nondiagnostic or the pneumonia is progressive, the panel recommends that a thoracoscopic lung biopsy with adequate platelet support be considered. This invasive procedure may identify the causative pathogen or the presence of a noninfectious etiology (e.g., treatment-associated lung toxicity, hemorrhage). The latter information may allow one to consider the elimination of potentially toxic or unnecessary antimicrobial therapies. In patients at risk for mold infections, the serum
galactomannan (a cell wall component of *Aspergillus*) assay is also a useful adjunct to early diagnosis if performed serially over time (see section on “Invasive Aspergillosis”).

The empiric antimicrobial regimen for patients presenting with pneumonia should be designed based on the patient’s clinical condition, chest radiograph, recent antimicrobial use, and CT appearance. Regimens used for empiric treatment of neutropenic fever are generally appropriate in neutropenic patients with bacterial pneumonia. A newer generation quinolone or azithromycin should be added in patients with community-acquired pneumonia to treat atypical pathogens, including *Legionella* species. Blood and sputum cultures should be obtained; and a urine *Legionella* antigen test should be sent. Addition of voriconazole is appropriate in patients at high risk for mold infection who have suggestive pulmonary lesions on a CT scan of the chest while a diagnosis is pursued. Atypical pneumonias (eg, *Legionella, Mycoplasma, Chlamydia*) may present with focal or diffuse infiltrates, and empiric coverage can be accomplished with a fluoroquinolone (excluding ciprofloxacin), macrolide (eg, clarithromycin, azithromycin), or doxycycline.

Certain infections (such as *Pneumocystis jerovicii, M. tuberculosis* or cytomegalovirus pneumonia) are unlikely to occur in patients who are neutropenic due to cytotoxic chemotherapy, but these infections are not uncommon in patients with severely impaired cellular immunity due to allogeneic HSCT, fludarabine therapy, or prolonged corticosteroid therapy. PCP typically presents with significant hypoxemia and a diffuse interstitial pulmonary infiltrate. Addition of high-dose trimethoprim/sulfamethoxazole (or pentamidine in sulfalergic patients) should be considered until the results of *Pneumocystis* stains are available. Cytomegalovirus pneumonia can also cause diffuse infiltrates, and antiviral agents with activity against CMV (ganciclovir or foscarnet) should be considered in those predisposed patients in whom the disease is suspected. Intravenous immunoglobulin should be considered as adjunctive treatment of documented CMV pneumonia.

During influenza season (November through March), patients with upper respiratory symptoms should be evaluated with a nasal wash specimen to detect respiratory viruses (eg, influenza, parainfluenza, respiratory syncytial virus, adenovirus). The rapid test for influenza A and B may be performed on a throat or nasopharyngeal swab. Consideration should be given to administering oseltamivir or zanamivir (effective against both influenza A and B) or rimantadine or amantadine (only effective against influenza A) (category 2B) empirically to patients within 48 hours after the development of symptoms suggestive of influenza (such as high fever, coryza, myalgia, and dry cough).

Skin/Soft Tissue, Urinary Tract, and Central Nervous System Infections

The evaluation and recommended empiric therapy for skin/soft tissue, urinary tract, and central nervous system infections are discussed in the algorithm. When evaluating the potential for a skin/soft tissue infection, careful examination of all line sites and perineal areas are essential. Antimicrobial therapy should be tailored to the probable organism(s): Staphylococci and streptococci for catheter-associated processes and Gram-negative and anaerobic organisms for perineal processes respectively. Vancomycin may be considered for cellulitis, disseminated papules/lesions, and wound infections. Acyclovir, famciclovir, or valacyclovir should be considered for vesicular lesions after appropriate diagnostic tests (scraping base of vesicle for HSV or...
VZV, direct fluorescent antibody tests, herpes virus culture) have been done.

For suspected CNS infections, CT and/or MRI as well as lumbar puncture (if possible) are recommended; infectious disease and neurology consults are necessary. Empiric therapy must include a beta-lactam agent that readily enters the CNS (ie, cefepime, ceftazidime, imipenem, meropenem). However, some experts feel imipenem should be avoided in patients with known or suspected CNS infection because it lowers the seizure threshold. If Listeria is suspected, then ampicillin should be added. Consider adding vancomycin or high-dose acyclovir (10-12 mg/kg/dose 3 times a day with hydration and monitor renal function) when appropriate.

**Follow-Up**

Daily evaluation by a health care professional who is experienced in treating patients with fever and neutropenia is essential. The daily examination should focus on a site-specific assessment, and an infectious disease consultation should be considered for all complicated cases or progressive infections. Time to defervescence ranges from 2 to 7 days (median, 5 days) for febrile cancer patients with neutropenia who receive appropriate initial antibiotic therapy. This rate of fever response should be considered when assessing the need to adjust initial antibiotics, and random additions or changes for persistent fever are discouraged in the absence of additional clinical or microbiologic evidence. The expected slow defervescence of fever also complicates decisions regarding the need for repeat blood cultures. Although some experts recommend daily blood cultures until the patient becomes afebrile, there is increasing evidence that daily blood cultures are unnecessary in neutropenic patients with persistent fever.

Current bacterial blood culture systems, such as the BACTEC continuous-monitoring culture system, can detect 90% to 100% of bacterial bloodstream pathogens within 48 hours of culture. For this reason, ordering additional cultures before obtaining the results from the initial series is discouraged. Daily review of previously obtained cultures is critical, and the panel recommends documenting clearance of bloodstream bacterial or fungal infections with repeat blood cultures.

**Evaluation of Response and Duration of Therapy**

The duration of antimicrobial therapy, in general, is dictated by the underlying site of infection, causative organism(s), the patient’s clinical condition along with response to treatment and recovery of neutrophils. It is generally recommended that antibiotics be continued until the ANC is above 500 cells/mm³ in cases of fever of unknown etiology. Documented infections are usually treated according to the site, pathogen, and at least until ANC recovery. The panel is limited by a lack of recent high-level evidence to formulate consensus about duration of treatment for all situations; however, general recommendations are given.

**Patients with Documented Infection Sites or Pathogens**

Most experts recommend continuing antimicrobial therapy for documented infections at least until a patient’s ANC recovers to 500/mm³ or greater but also using a defined course of therapy appropriate for the specific infection. Thus, the duration of antimicrobial therapy may be longer than the duration of neutropenia in these patients. For example, most uncomplicated skin and alimentary tract mucosal infections can be treated with 7 to 14 days of therapy. For most bacterial bloodstream infections, 7 to 14 days
of therapy is usually adequate, with longer durations (10-14 days) recommended for Gram-negative bacteremias. A longer duration (14-21 days) of treatment is also usually indicated for infections of the lungs, sinuses, and bacteremias complicated by major organ infection. Complex intra-abdominal infections, such as typhlitis, should be treated until all evidence of infection has resolved, and there has been recovery from neutropenia. For *S. aureus* bloodstream infections, a TEE is recommended to help define the duration of therapy as short (2 weeks after first negative blood culture) or long (4 to 6 weeks). The duration of treatment for HSV (uncomplicated, localized disease to the skin) and VZV (uncomplicated, localized disease to a single dermatome) infections has become standardized at 7 to 10 days (category 1). Life-threatening infections, such as invasive fungi or CMV, require individualized courses of therapy that are often prolonged. It is important to note that the duration of therapy may need to be extended if further chemotherapy is required during the course of treating a significant infection. This may occur with infections that complicate leukemia or lymphoma treatments in which multiple cycles of intensive chemotherapy are required.

Patients with documented infection sites or pathogens who do not respond to initial antimicrobial therapy pose a difficult management challenge and are at increased risk of infection-associated morbidity and mortality. The panel strongly recommends that an infectious disease expert be consulted for all such patients. The lack of response may suggest an infection with a pathogen resistant to the antimicrobial therapy being used, inadequate serum or tissue levels of the antibiotic(s), infection at a vascular site (ie, catheter or “closed space” infection), or emergence of a second infection. Some documented infections fail to respond to appropriate therapy because of associated profound neutropenia. If possible, treatment should be optimized using broad-spectrum antibiotic combinations that minimize other organ toxicity. Adjunctive therapy, including the addition of growth factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) or corticosteroid- or growth factor-mobilized granulocytes for transfusion (category 2B) may be considered.

Patients with documented infections who become afebrile after the initiation of the empiric antibiotic regimen and who are at low risk for complications associated with infection may be candidates for oral antibiotic therapy with ciprofloxacin and amoxicillin/potassium clavulanate.

**Patients with Fever of Unknown Etiology**

A critical component of treating patients with fever of unknown etiology is the daily clinical evaluation. Careful, daily, site-specific examinations should be performed by a health care professional who has experience and expertise in managing neutropenia and fever. Reassessment should include a review of all previous cultures and radiographs. If patients receive vancomycin as part of their initial empiric therapy but they do not have a pathogen recovered or a site of infection identified justifying such treatment or if they are stable, then vancomycin should be discontinued.

Patients with fever of unknown origin who become afebrile soon after starting empiric therapy may have empiric antibiotics discontinued with ANC recovery (≥500 neutrophils/mm³) as long as the neutrophil count is likely to continue to increase (patients are often on a growth factor). This recommendation assumes that the patient is clinically well and afebrile for at least 24 hours before antibiotic discontinuation. Patients who become afebrile but remain...
Persistently neutropenic (<500 neutrophils/mm³) should receive a more prolonged course of antibiotic therapy until the neutropenia resolves. In patients who fail to have neutrophil count recovery, have no documented focus of infection, and have been afebrile for more than 7 to 14 days, some panel members support discontinuing empiric antimicrobial therapy (category 2B). Patients can also be switched to oral antibiotics until their neutropenia resolves (ie, 500 mg ciprofloxacin every 8 hours plus 500 mg of amoxicillin/potassium clavulanate every 8 hours). Patients with recurrent fever should be reassessed promptly to determine the need for a change in their antibiotic regimen or for addition of antifungal therapy.

**Patients with Persistent Fever**

Patients with a fever persisting beyond 4 days of initial antimicrobial therapy and with an unidentified source of infection should undergo reassessment of their antimicrobial therapy. The need for a change in therapy should be based on the patient's clinical status and likelihood of early bone marrow recovery.

The clinically stable patient with persistent fever of unknown etiology may be safely watched without altering the initial antimicrobial therapy. Modifications of initial empirical antibiotic therapy should be based on specific new clinical findings and/or new microbiologic results; fever alone should not prompt changes in antimicrobial therapy. The major exception is the initiation of empiric antifungal therapy in patients who have persistent or recurrent fever after 4 days of empiric antibiotics and who are at high risk for mold infection (ie, neutropenia >7 days, allogeneic stem cell transplant recipients, high-dose corticosteroids). Some specialists have recommended the discontinuation of antimicrobial therapy for a highly select group of clinically stable patients with neutropenia and no identified infectious cause of fever; however, this approach is controversial. If this step is taken, it must be combined with skilled evaluation and a very low threshold to reinitiate empiric antimicrobial therapy. Most experts advise continuing empiric antibiotic therapy throughout the period of fever and neutropenia.

Although fever resolution may be slow during neutropenia, persistent fever may suggest a noninfectious etiology, such as engraftment syndrome, acute graft vs host disease, or drug fever. Persistent fever may also represent an inadequately treated infectious process, such as a nonbacterial infection (fungal or viral) or a bacterial infection that is resistant to empiric antibiotics, a venous access or closed space infection, or inadequate antimicrobial serum levels. It is important to recognize that documented deep tissue infections may take longer than fever of unknown etiology to respond to antimicrobial therapy. In these cases, daily assessment of clinical improvement or failure depends on radiographic, culture, and clinical examination data, as well as on the fever trends.

The panel strongly recommends an infectious disease consultation for these patients. For the patient who is persistently febrile and clinically unstable, a change in antibacterial therapy may be needed. Certain high-risk patients should be evaluated for toxoplasmosis. For example, the addition of vancomycin should be considered if clinical and microbiologic data support its use according to CDC guidelines and if the patient's clinical situation justifies its use based on clinical and microbiologic data.

Alternatively, a change in Gram-negative coverage may be indicated if there is suspected sepsis or deep infection due to a resistant organism. Local sensitivity patterns of Gram-negative pathogens are useful in guiding empiric changes of this type.
If fever persists or is recrudescent beyond 4 to 7 days of empiric antibiotic therapy, antifungal therapy should be initiated empirically because the risk of invasive fungal disease increases with prolonged neutropenia. Please see the section on Empirical Antifungal Therapy above for detailed discussion.

Outpatient Therapy

Outpatient therapy has become a common practice in the community setting for low-risk patients. There is considerable disagreement among panel members about this shift in the standard of care. Some members believe that the clinical data to support this strategy are limited to case series and single-center clinical trials, and that a large, multi-centered randomized trial has not been performed to establish the safety of outpatient therapy. Other panel members believe that the numerous clinical trials support the shift in care for low-risk patients to the outpatient setting and believe that it has never been established that the hospital is a safer place for low-risk patients, given the hazards of hospitalization that have been recently documented by the Institute of Medicine. Despite this fundamental disagreement, the panel believes that not all centers are equipped to attempt such outpatient treatment, nor are all patients with fever appropriate candidates. Early success with this type of therapy has been predicated on the ability to accurately determine an individual patient's risk of developing complications associated with infection and on the presence of an adequate center infrastructure for the treatment and monitoring of such patients.

Once a patient's level of risk has been identified, it can then be used to determine the appropriate site of care and route of administration of broad-spectrum antibiotics. The panel recommends all high-risk patients receive hospital care with broad-spectrum intravenous therapy. Low-risk patients may be treated in the hospital with oral or intravenous antibiotics, in an ambulatory clinic, or at home if adequate follow-up care can be provided 24 hours per day, 7 days per week. Outpatient therapy should be considered only for low-risk patients who consent to home care, have a telephone, can access emergency facilities, have an adequate and supportive home environment, and are within 1 hour's travel time of a medical center or physician's office. Outpatient therapy requires a period of early monitored assessment and an observation period of 2 to 12 hours (category 2B). The assessment requires a careful examination, review of laboratory results, review of social criteria for home therapy (as previously described), and assessment of whether oral antibiotics are feasible. The observation period is used to confirm the patient is low risk, observe and administer the first dose of antibiotics as well as monitor for reaction, ensure the stability of the patient, organize discharge plans to home and follow-up, educate the patient, and perform telephone follow-up within 12 to 24 hours. This assessment and observation can be performed during a short hospital stay or in an ambulatory facility or office staffed with qualified health care professionals. Health care professionals who perform the early assessment and follow-up should be well trained (eg, a physician, nurse, physician assistant, and/or nurse practitioner) as well as have experience and expertise in managing neutropenia and fever.

Outpatient Regimens

Outpatient antimicrobial treatment may consist of broad-spectrum antibiotics given at home or in the clinic, or an oral regimen for carefully selected patients. For low-risk patients who are considered appropriate for oral therapy, the combination of ciprofloxacin with amoxicillin/clavulanate is considered the regimen of choice based
on multiple, well-designed randomized trials (category 1). Although some of these trials were performed in an inpatient setting, they provide evidence of the efficacy of the oral combination compared with standard intravenous therapy in the low-risk population.\(^5,40\) Ciprofloxacin plus clindamycin is an acceptable alternative for penicillin-allergic patients.\(^9\) However, ciprofloxacin monotherapy is not currently considered by the panel to be an adequate broad-spectrum agent because of the potential for serious breakthrough infections caused by alpha streptococci.\(^155\) Nonetheless, several small studies have used high-dose oral ciprofloxacin alone in low-risk patients with fever and neutropenia.\(^9,43,156\)

Oral ofloxacin has been demonstrated to be safe as an oral regimen in several smaller studies. Presumably, levofloxacin (which is the L-isomer of ofloxacin), may be used as well. The newer fluoroquinolones, gatifloxacin and moxifloxacin, have not been studied as agents for empiric therapy for low-risk fever and neutropenia and notably, they lack potent activity against \textit{P. aeruginosa}. The panel feels that outpatient therapy with a fluoroquinolone should be based on reliable Gram-negative bacillary activity of the antibiotic, local antibacterial susceptibilities, and inherent activity against \textit{P. aeruginosa}. Fluoroquinolones should not be used as initial outpatient therapy for patients who have received prophylaxis with a fluoroquinolone; until better levels of evidence are available, the panel cannot recommend oral monotherapy with a fluoroquinolone for low-risk patients considering the strength of the evidence for dual therapy with ciprofloxacin plus amoxicillin/clavulanate. Intravenous therapy may also be used for outpatient treatment of low-risk patients with fever and neutropenia. Several intravenous outpatient regimens for low-risk patients have been studied in nonrandomized or small open trials, including intravenous ceftazidime, imipenem, and aztreonam plus clindamycin.\(^6,41,71\)

Once-daily ceftriaxone has been used for empiric antibiotic therapy in a few noncomparative studies in centers where pseudomonas is not a common pathogen.\(^73\) Ceftriaxone does not possess adequate antipseudomonal activity. Therefore, the panel recommends caution if this agent is used. In addition to antimicrobial spectrum, other factors to consider in the choice of an outpatient regimen include stability of the reconstituted drugs, ability to manage intravenous infusions, and vascular access devices.

**Follow-Up of Outpatients with Fever and Neutropenia**

Follow-up management can be performed at the patient's home or in the physician's office or clinic. The panel recommends that patients be assessed daily while febrile, although some experts feel that less frequent follow-up may be appropriate after fever defervesce. Admission to the hospital should be considered if the patient's clinical status deteriorates; fever persists; serious subsequent infections or adverse events develop, or if the patient is unable to continue the prescribed antibiotic regimen (ie, oral intolerance).

**Prevention of Infection**

Infection prophylaxis in cancer patients generally involves broad-spectrum antimicrobial therapy directed against the most common infecting pathogens, including bacterial, viral and fungal, in the highest risk patients.

**Antibacterial Prophylaxis**

Absorbable and nonabsorbable antibiotic combinations to prevent bacterial infections have been administered to patients in a variety of settings, with variable results. Cost, patient compliance, emerging...
resistant organisms, and drug-associated toxicity have plagued most of these approaches.\textsuperscript{15}

Oral fluoroquinolones are currently the most frequently used agents for antibacterial prophylaxis in high-risk cancer.\textsuperscript{157} These agents have been shown to decrease the frequency of documented Gram-negative bacillary infections. However, their use is controversial because of the lack of consistent efficacy of these drugs (1) in decreasing febrile episodes or days of antibiotic therapy, or (2) in improving overall survival. There is greater consensus, however, that patients anticipated to have prolonged and profound neutropenia (ie, leukemia induction, allogeneic HSCT) may benefit from antibiotic prophylaxis. Prophylactic oral fluoroquinolones have frequently been associated with the emergence of antibiotic-resistant bacteria and fungal overgrowth with subsequent infections. If such prophylaxis is considered, the panel recommends that it be limited to patients expected to experience profound neutropenia (fewer than 100 neutrophils/mm\textsuperscript{3}) for more than 7 days; patients should receive therapy until the onset of fever or the resolution of neutropenia (greater than 100 neutrophils/mm\textsuperscript{3}). Such prophylactic antibiotic therapy is not recommended for patients with short-term neutropenia. If fluoroquinolones are used as prophylaxis, then they should not be utilized as empiric antibacterial coverage if febrile neutropenia subsequently occurs.

**Antifungal Prophylaxis**

The rationale for antifungal prophylaxis is to prevent fungal infections in a targeted group of high-risk patients; antifungal prophylaxis should not be used routinely in all patients with neutropenia. In allogeneic HSCT recipients, two double-blinded, placebo-controlled trials have shown that prophylactic fluconazole controlled yeast colonization as well as decreased the rate of mucosal candidiasis and invasive *Candida* infections.\textsuperscript{158,159} A decrease in mortality was noted in the study by Slavin and colleagues,\textsuperscript{159} in which most of the patients were allograft recipients. This effect of fluconazole conferred significant long-term improvement in survival, possibly by decreasing *Candida* antigen-induced gastrointestinal tract GVHD.\textsuperscript{160}

Fluconazole prophylaxis (category 1) decreased fungal colonization, invasive infection, and fungal infection-related mortality in nontransplant patients with leukemia and in autologous transplant recipients in a placebo-controlled trial.\textsuperscript{161} However, only 30\% of the patients received growth factors, and the median duration of neutropenia was 14 to 16 days.\textsuperscript{161} The benefit of fluconazole prophylaxis was greatest in autologous transplant recipients not receiving colony-stimulating growth factor support and in patients receiving mucotoxic regimens consisting of cytarabine plus anthracycline. Most autologous transplant patients now receive growth factors and generally neutropenia for only about 10 days; therefore, fluconazole is not routinely used for autologous transplantation (category 2B) or for standard solid tumor chemotherapy. Other studies of nontransplant patients with acute leukemia showed no significant benefit of fluconazole.\textsuperscript{162,163} Fluconazole prophylaxis is associated with colonization by azole-resistant *Candida* strains.\textsuperscript{164}

The panel recognizes that there is strong evidence for the use of fluconazole as prophylaxis in allogeneic HSCT recipients (category 1). However, low-dose amphotericin B product or itraconazole has also been studied in high-risk patients and shown to provide protection against invasive molds, although they have provided no survival benefit in randomized studies with fluconazole.\textsuperscript{165,166} Itraconazole, however, may be associated with hepatic toxicity and gastrointestinal...
nal intolerance. Itraconazole is contraindicated in persons with a decreased cardiac ejection fraction based on its negative inotropic properties. It can also increase cyclophosphamide metabolites, which in turn are associated with hyperbilirubinemia and nephrotoxicity during the early transplant period. This finding reinforces a note of caution about itraconazole and newer second-generation triazoles, which are potent inhibitors of cytochrome P450 isoenzymes, with regard to the potential for drug-drug interactions. Conventional amphotericin B is associated with infusional toxicity and nephrotoxicity, and should be avoided as primary prophylaxis.

The echinocandin, micafungin, was recently approved by the U.S. FDA as prophylaxis in HSCT recipients with neutropenia. In a randomized, double-blind trial of autologous and allogeneic HSCT recipients, micafungin was superior to fluconazole based on pre-specified criteria that included absence of a breakthrough fungal infection and the absence of modifying the antifungal regimen empirically due to neutropenic fever. The duration of study drug encompassed the neutropenic period, but not the period after neutrophil recovery where GVHD would be expected to occur. The frequency of breakthrough candidemia was similar in both arms, but there was a trend to fewer episodes of invasive aspergillosis in allogeneic HSCT recipients receiving micafungin. Survival and drug-related toxicity were similar in both arms.

Voriconazole (compared with fluconazole) is being evaluated in an ongoing randomized study, but its potent anti-mold activity and good tolerability have promoted its widespread use. The panel recognizes that the multicenter randomized trial has not yet been completed but cautiously considers voriconazole an untested option for prophylaxis based on its efficacy in treatment trials for invasive aspergillosis.

Antifungal prophylaxis should be administered until at least engraftment in allogeneic HSCT recipients and should be considered in patients with GVHD requiring corticosteroid therapy. Many experts suggest continuing antifungal prophylaxis through day 75 after allogeneic transplant or through induction therapy for leukemia. Antifungal prophylaxis should be considered in nontransplant patients with acute leukemia and in autologous HSCT recipients receiving mucotoxic regimens (but is not endorsed in autologous HSCT patients undergoing routine therapy). Prophylaxis should be administered until neutrophil recovery.

The panel recommends secondary prophylaxis with an appropriate antifungal agent in patients with prior chronic disseminated candidiasis or with invasive filamentous fungal infection during subsequent cycles of chemotherapy or HSCT. Secondary prophylaxis is generally administered for the duration of immunosuppression.

Antiviral Prophylaxis

HSV. HSV is an important pathogen in patients who develop neutropenia and mucositis. These HSV infections are primarily reactivation of latent virus. The presence of latent HSV can be determined by pretreatment HSV serology. HSV reactivation and infection occur in 60% to 80% of HSCT recipients and patients with acute leukemia undergoing induction or re-induction therapy who are seropositive for HSV. Although disseminated HSV infection is uncommon, the reactivation infection is frequently associated with increased mucosal damage, resulting in increased pain, limitation of the patient's ability to maintain oral hydration and nutrition, and an increased risk of bacterial and fungal superinfections.

The panel recommends the use of HSV prophylaxis for bone marrow transplant recipients for the first month after transplantation and for patients with acute leukemia during periods of neutropenia.
Acyclovir and valacyclovir appear to be equally efficacious for this indication, and the choice of agent should be determined by cost and availability. Famciclovir is also an option but has not been evaluated in clinical trials. Herpes virus prophylaxis for other oncology patients should be individualized. Once a patient has had an HSV reactivation infection requiring treatment, the panel recommends HSV prophylaxis for that patient during all future episodes of neutropenia induced by cytotoxic therapy.

Influenza Vaccination. Influenza infections cause significant morbidity and mortality in cancer patients. Among bone marrow transplant recipients, influenza accounts for 11% to 42% of all community-acquired viral respiratory infections. An increased incidence and duration of influenza infections also have been observed in immunosuppressed cancer patients when compared to healthy controls and, during community outbreaks, may represent a significant proportion of episodes of febrile neutropenia. Influenza infections in severely immunocompromised cancer patients are often associated with hospitalizations, delays in potentially life-saving chemotherapy, and occasionally, death.

As a result, annual vaccination against influenza with the inactivated influenza virus is currently recommended for all individuals at increased risk from immunosuppressive disease in several countries, including the United States, Canada, and England. The United States and Canadian guidelines go a step further and also include in their target group for annual immunization the individuals who can transmit influenza to high-risk patients (ie, health care workers and household contacts). Despite these recommendations, influenza immunization among children and adults with cancer remains low. The low rates of influenza vaccination among cancer patients may be explained in part by the controversy surrounding the effectiveness of the vaccine in this population. The primary concern is that cancer patients will be unable to mount an adequate immune response to the vaccine because of their underlying disease and/or the immunosuppressive effects of cancer therapy. Several studies in patients with cancer have demonstrated response rates to inactivated influenza vaccine comparable to those in healthy individuals, even when the vaccine is administered during chemotherapy; however, others have failed to confirm these findings. Nonetheless, evidence suggests that even though cancer patients’ immune response to influenza vaccination might be attenuated, it can still provide protection against clinical infections caused by influenza. Furthermore, inactivated influenza vaccine is generally well tolerated in cancer patients, with side effects comparable to those observed in healthy individuals. Taken together, these findings support the existing recommendations that all patients with cancer and their household contacts should be encouraged to receive annual immunization against influenza with the inactivated influenza vaccine.

The recently approved intranasal attenuated influenza vaccine (FluMist) should be avoided in patients with immunosuppression because FluMist contains live attenuated influenza viruses still capable of replication, which could theoretically lead to infection in immunocompromised individuals. As a result, the CDC has recommended that persons with known or suspected immunodeficiency diseases or those who are receiving immunosuppressive therapies should not be immunized with the live influenza vaccine. In addition, because no data are available assessing the risk for person-to-person transmission of FluMist from vaccine recipients to immunosuppressed contacts, the CDC also...
recommends that inactivated influenza vaccine should be used in household contacts, health-care workers, and others who have close contact with immunocompromised patients.\textsuperscript{193}

**Prophylaxis for Pneumocystis jirovecii Infections**

Trimethoprim/sulfamethoxazole prophylaxis for *P.carinii* (which has been recently renamed as *P.jirovecii*) infections is highly effective.\textsuperscript{64} Studies have documented the efficacy of this prophylactic therapy in patients with acute lymphocytic leukemia and similar results have been found in bone marrow transplant recipients. Prophylactic regimens should be designed to maintain efficacy while enhancing patient compliance. The more difficult questions include: (1) What prophylactic regimen should be used in patients who are truly intolerant of trimethoprim/sulfamethoxazole? and (2) Besides acute leukemia patients, which other patients warrant *P.jirovecii* prophylaxis? Daily dapsone and aerosolized pentamidine are thought to be effective alternatives, although data suggest aerosolized pentamidine may be inferior when used prophylactically in allogeneic transplant recipients.\textsuperscript{194} Atovaquone appears to be equivalent to dapsone in HIV patients who cannot tolerate trimethoprim/sulfamethoxazole. Thus, atovaquone may be a third alternative for oncology patients who require prophylaxis.\textsuperscript{195}

*P.jirovecii* prophylaxis should be considered for allogeneic transplant recipients and patients with acute lymphocytic leukemia (category 1). Some panel members believe that, patients receiving fludarabine therapy and other T-cell depleting agents, autologous hematopoietic cell transplant recipients, and patients with neoplastic diseases receiving prolonged corticosteroid treatment (\( \geq 20 \) mg of prednisone daily) could also be considered (category 2B) for *P.carinii* (*P.jirovecii*) prophylaxis.

**Protected Environments**

Although, well-designed clinical trials have not validated the use of high-efficiency particulate air (HEPA) filtration, the Centers for Disease Control and Prevention (CDC) recommend that allogeneic HSCT recipients be placed in rooms with HEPA filters.\textsuperscript{196} It is reasonable to use HEPA filtration in nontransplant patients with prolonged neutropenia. The principal benefit of HEPA filtration is likely to be related to prevention of mold infections. In a retrospective analysis, HEPA filters were protective in highly immunocompromised patients with hematologic malignancies in the setting of an outbreak of aspergillosis.\textsuperscript{197} The value of laminar air flow in preventing infections is unclear and is not generally recommended.

**Summary**

Significant progress has been made in managing fever and neutropenia in patients with cancer. Although initial empiric antimicrobial treatment remains the foundation of therapy for such patients, improved diagnostic modalities, models of risk assessment, and an understanding of the various clinical situations in which infections occur have required that treatment approaches and options evolve. The development of broad-spectrum antibiotics with decreased toxicity has improved patient outcomes. Nevertheless, the increasing prevalence of antibiotic-resistant pathogens has challenged the clinician to use antimicrobial therapy wisely. Infection control should not rely exclusively on antimicrobial prophylaxis but, rather, should continue to incorporate standard infection control measures and demand careful hand-washing by all health care professionals who come into contact with immunocompromised patients.
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