Febrile Neutropenia

- Febrile neutropenia is defined as a single oral temperature ≥ 38.0°C (100.4°F) and ANC ≤ 500 cells/µL, or < 1000 cells/µL with an expected decline to < 500 cells/µL.
- Patients presenting to the ED should be given the highest priority for treatment.
- High-risk patients should be initially admitted to the hospital for empirical therapy if they are not already inpatients.
- Low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy.
- Calculate a Multinational Association for Supportive Care in Cancer (MASCC) score.

Note: See page 2 for recommendations on patient risk stratification.

- Physical examination.
- Blood culture x 2, 1 set from line (if present).
  - 1 from each lumen.
- U/A and urine for culture.
- Respiratory culture and evaluation.
- Chem 7.
- Liver function panel.
- CBC with differential and platelets.
- CXR (PA and lateral preferred).
- If pulmonary symptoms, urinary antigen for Legionella.

Is patient suffering from severe sepsis or in septic shock? (see page 3 for criteria)

- Consider transferring the patient to ICU if institutional criteria have been met.
- Consider Infectious Disease (ID) consult.
- Add tobramycin and vancomycin.
- Consider caspofungin if patient has mucositis or central line and no evidence of pneumonia.
- Consider amphotericin B liposome or voriconazole if pneumonia is suspected.
- Consider additional antifungal therapy for patients with:
  - Persistent or recurrent fungal infections.
  - Persistent or recurrent fever after 4-7 days of antibiotics whose overall duration of neutropenia is expected to be > 7 days.

Does patient have any of the following conditions:
- Pneumonia.
- Blood culture positive for Gram-positive bacteria prior to final identification and susceptibility testing.
- Suspected catheter-related infection.
- Skin or soft-tissue infection at any site.
- Colonization with MRSA, VRE, or penicillin-resistant Streptococcus pneumoniae.
- Severe mucositis.

At 72 hrs, does patient have persistent fever, neutropenia, and negative cultures?

- Add vancomycin.
- If history of VRE, use daptomycin or linezolid.

If patient afebrile and clinically stable within 48 hours of treatment:
- If CX negative for Gram-positive organisms, continue same regimen, but stop vancomycin.
- If CX positive for Gram-positive organisms, adjust to most appropriate therapy.

- Liver function panel.
- CBC with differential and platelets.
- CXR (PA and lateral preferred).
- If pulmonary symptoms, urinary antigen for Legionella.

- Consider transferring the patient to ICU if institutional criteria have been met.
- Consider Infectious Disease (ID) consult.
- Add tobramycin and vancomycin.
- Consider caspofungin if patient has mucositis or central line and no evidence of pneumonia.
- Consider amphotericin B liposome or voriconazole if pneumonia is suspected.
- Consider additional antifungal therapy for patients with:
  - Persistent or recurrent fungal infections.
  - Persistent or recurrent fever after 4-7 days of antibiotics whose overall duration of neutropenia is expected to be > 7 days.

Note: Antibiotic regimens and recommendations for duration of antibiotics are provided in Appendix A on page 4.
Patient Risk Stratification

Identify high-risk patients based on a Multinational Association for Supportive Care in Cancer (MASCC) score.

**High-Risk Patients**
- Includes patients with:
  - MASCC score < 21.
  - Anticipated prolonged hospital stay (> 7 days).
  - Profound neutropenia defined as:
    - Absolute neutrophil count [ANC] ≤ 100 cells/µL following cytotoxic chemotherapy.
  - Significant medical comorbid conditions, including:
    - Hypotension.
    - Pneumonia.
    - New-onset abdominal pain.
    - Neurological changes.
- High-risk patients should be initially admitted to the hospital for empirical therapy if they are not already inpatients.

**Low-Risk Patients**
- Includes patients with an MASCC score ≥ 21.
- May be candidates for oral and/or outpatient empirical antibiotic therapy.
  - Outpatient therapy should be considered only for low-risk patients who are able to comply with outpatient follow-up plans.
  - Outpatient status should only be accepted after discussion with an attending oncologist.
    - Preferably the patient’s primary oncologist, if available.
  - A complete plan should be developed including:
    - Antibiotic selection.
    - Cautions to return.
    - Follow-up plans.

**Criteria for Severe Sepsis and Septic Shock**

**Severe Sepsis**
Patients with severe sepsis should be evaluated for the presence of acute organ dysfunction. This includes the following:

- **Respiratory dysfunction:**
  - Chest radiograph.
  - Assessment of oxygenation:
    - Pulse oximetry.
    - Arterial blood gas.
  - Hypoxemia:
    - PaO₂/FiO₂ ratio < 300.
    - See OSUWMC Refractory Hypoxemia guideline.

- **Renal dysfunction:**
  - Decreased urine output:
    - < 0.5 ml/kg body weight for at least 1 hour.
  - Serum creatinine:
    - Increase by > 0.5 mg/dL over baseline or > 1.2 mg/dL if no baseline available.

- **Coagulation system dysfunction:**
  - INR (> 1.5).
  - PTT (> 60 seconds).
  - Thrombocytopenia:
    - < 150,000/µL or 50% drop below baseline.

- **Neurologic dysfunction:**
  - Glasgow coma scale (< 13).
  - Presence of delirium:
    - Confusion Assessment Method for the ICU positive.
    - See OSUWMC Management of Delirium in the ICU guideline.

- **Hepatic dysfunction:**
  - Bilirubin (> 1.2 mg/dL).

- **Signs of hypoperfusion:**
  - Elevated lactate (> 2 mmol/L).
  - Delayed capillary refill.
  - Skin mottling.

- **Signs of hypotension:**
  - Arterial hypotension:
    - Systolic blood pressure < 90 mmHg.
    - Mean arterial pressure < 70 mmHg.
    - Need for vasopressor therapy.

**Septic Shock**
Patients with septic shock should be evaluated for signs and symptoms of hypoperfusion or hypotension despite adequate volume resuscitation.

**Note:** See OSUWMC Sepsis and Septic Shock guideline for additional recommendations.

**References**
• Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. CID. 2011:52 (15 February).

Order Sets

- OSU IP ED: Febrile Neutropenia
- OSU IP HEM: Admission Febrile Neutropenia
- OSU IP INF: Febrile Neutropenia Antibiotic Management

Quality Measures

- Order set use
- Appropriate antibiotics administered
- Initial antibiotic administered within 2 hours of ED arrival or presentation

Guideline Authors

- Kurt Stevenson, MD, MPH
- Eric Adkins, MD
- Rebecca Klisovic, MD
- Julianna Roddy, PharmD, BCOP
- Erica Reed, PharmD, BCPS-AQ

Guideline Approved


Disclaimer: Clinical practice guidelines and algorithms at The Ohio State University Wexner Medical Center (OSUWMC) are standards that are intended to provide general guidance to clinicians. Patient choice and clinician judgment must remain central to the selection of diagnostic tests and therapy. OSUWMC’s guidelines and algorithms are reviewed periodically for consistency with new evidence; however, new developments may not be represented.

Copyright © 2016. The Ohio State University Wexner Medical Center. All rights reserved. No part of this document may be reproduced, displayed, modified, or distributed in any form without the express written permission of The Ohio State University Wexner Medical Center.
# Appendix A. Antibiotic Regimens

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Usual Dose</th>
<th>CrCl &lt; 60–30 mL/min</th>
<th>CrCl &lt; 30–10 mL/min</th>
<th>ESRD</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime IV (Maxipime®) Administered over 4 hours</td>
<td>2 g Q8–12h</td>
<td>2 g Q12h</td>
<td>2 g Q24h</td>
<td>2 g Q24h</td>
<td>2 g Q8-12h</td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td><strong>Usual Dose</strong></td>
<td><strong>CrCl &lt; 30–10 mL/min</strong></td>
<td><strong>CrCl &lt; 10 mL/min or ESRD</strong></td>
<td><strong>CVVHD</strong></td>
<td></td>
</tr>
<tr>
<td>Aztreonam IV (Azactam®)</td>
<td>2 g Q8h</td>
<td>2 g Q12h</td>
<td>1 g Q12h</td>
<td></td>
<td>2 g Q12h</td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td><strong>Usual Dose</strong></td>
<td><strong>CrCl &lt; 60–30 mL/min</strong></td>
<td><strong>CrCl &lt; 30 mL/min</strong></td>
<td><strong>CrCl &lt; 10 mL/min or ESRD</strong></td>
<td><strong>CRRT</strong></td>
</tr>
<tr>
<td>Vancomycin IV (Vancocin®) All patients should receive a loading dose of 20-25 mg/kg</td>
<td>15-20 mg/kg Q12h</td>
<td>15-20 mg/kg Q24h</td>
<td>15-20 mg/kg Q48h</td>
<td>15-20 mg/kg Q72–96</td>
<td>15-20 mg/kg Q48h</td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td><strong>Usual Dose</strong></td>
<td><strong>CrCl &lt; 60–40 mL/min</strong></td>
<td><strong>CrCl &lt; 40–20 mL/min</strong></td>
<td><strong>CrCl &lt; 20 mL/min or ESRD</strong></td>
<td><strong>CRRT</strong></td>
</tr>
<tr>
<td>Tobramycin IV (Nebcin®)</td>
<td>7 mg/kg Q24h</td>
<td>7 mg/kg Q36h</td>
<td>7 mg/kg Q48h</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td><strong>Usual Dose</strong></td>
<td><strong>No renal adjustment necessary</strong></td>
<td><strong>Hepatic Insufficiency</strong></td>
<td><strong>Load:</strong> 70 mg 50 mg Q24h</td>
<td><strong>Load:</strong> 70 mg 35 mg Q24h</td>
</tr>
<tr>
<td>Caspofungin IV (Cancidas®)</td>
<td>Load: 70 mg 50 mg Q24h</td>
<td>No renal adjustment necessary</td>
<td></td>
<td><strong>Load:</strong> 70 mg 35 mg Q24h</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B Liposome IV (AmBisome®)</td>
<td>5 mg/kg Q24h</td>
<td>No renal adjustment necessary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotic</strong></td>
<td><strong>Usual Dose</strong></td>
<td><strong>CrCl &lt; 50–30 mL/min</strong></td>
<td><strong>CrCl &lt; 30–10 mL/min</strong></td>
<td><strong>CrCl &lt; 10 mL/min</strong></td>
<td><strong>Hepatic Insufficiency</strong></td>
</tr>
<tr>
<td>Voriconazole IV (Vfend®)</td>
<td>6 mg/kg Q12h x 2 doses, then 4 mg/kg Q12h</td>
<td>Avoid IV Use PO</td>
<td>Avoid IV Use PO</td>
<td>Avoid IV Use PO</td>
<td>6 mg/kg Q12h x 2 doses, then 2 mg/kg Q12h</td>
</tr>
</tbody>
</table>

*Hepatic insufficiency defined as Child Pugh A-C or cirrhosis for voriconazole; Child Pugh B-C or cirrhosis for caspofungin.

## Recommendations for Duration of Antibiotics

- Adjust antibiotics based on culture and sensitivities.
- Consider switching to oral therapy when ANC ≥ 500 cells/µL and mucositis is resolved.
- Consider discontinuing vancomycin after 48 hours if cultures are negative for coagulase negative *Staphylococci*, methicillin-resistant *S. aureus*, or *Corynebacterium jeikeium*.
- If documented bacteremia in the setting of a central venous catheter or implanted venous access device, strongly consider removal of catheter or device.
- Continue antibiotics until ANC ≥ 500 cells/µL and afebrile for at least 24 hours.
- If fever and neutropenia persist, continue antibiotics for 10-14 days and reassess.
  - Consider continuation of antibiotics for duration of neutropenia.
- Consider consultation with an infectious disease specialist.