GUIDELINES FOR THE TREATMENT OF NEUTROPHIC FEVER IN ADULT HIGH-RISK HEMATOLOGY/ONCOLOGY PATIENTS

Fever: Single oral temp $\geq 38.3^\circ C$ (101$^\circ F$) or $\geq 38.0^\circ C$ (100.4$^\circ F$) for $\geq 1$ hour
Neutropenia: ANC $\leq 500/mm^3$ or $< 1000/mm^3$ with a predicted drop to $\leq 500/mm^3$

Assessment:
Blood cultures – two sources including central venous catheter and peripheral vein
Chest x-ray
Urinalysis and urine culture
Throat, sputum, stool, wound cultures when appropriate

Recommended Therapy:
1. The initial empiric treatment regimen should be ordered STAT for:
   1.1. Standard patient: piperacillin-tazobactam (Zosyn) 4.5 g IV q8h
       1.1.1. Patient with penicillin allergy (non-anaphylactic): cefepime 2 g IV q8h
       1.1.2. Patient with penicillin (anaphylactic) and/or cephalosporin allergy: aztreonam 2 g IV q8h + vancomycin IV (see nomogram, AUC goal 400-600)
   1.2. Patient with septic physiology: empiric beta-lactam antibiotic (as per above pathway) + vancomycin IV (see nomogram, AUC goal 400-600) + tobramycin 5 mg/kg/day IV q24h (if GNR suspected). (Consult pharmacy if elderly patient or renal insufficiency. Use ideal body weight for kg dose of tobramycin). Reassess need for double gram-negative coverage and vancomycin after patient stabilized and cultures return.
   1.3. Patient with indwelling catheter that appears infected or cultures positive for GPCs: empiric beta-lactam antibiotic (as per above pathway) + vancomycin IV (see nomogram, AUC goal 400-600). Other scenarios where the addition of vancomycin may be appropriate:
       1.3.1. Hypotension or septic shock without an identified pathogen (i.e., clinically unstable, see Section 1.2 above)
       1.3.2. Soft tissue infection
       1.3.3. Severe mucositis
   1.4. Patient with neutropenic fever AND suspicion for meningitis: cefepime 2 g IV q8h + vancomycin IV (see nomogram, AUC goal 400-600) + ampicillin 2 g IV q4h and consideration of acyclovir 10 mg/kg IV q8h. Consult Infectious Disease (ID) service. 
   1.5. Patient with known or suspected Pseudomonas aeruginosa infection: piperacillin-tazobactam (Zosyn) 4.5 g IV q6h + tobramycin 5 mg/kg/day IV q24h (Consult pharmacy if elderly patient or renal insufficiency. Use ideal body weight for kg dose of tobramycin). Can discontinue tobramycin if organism is sensitive to beta-lactam or carbapenem.
   1.6. If patient has proven C. difficile toxin, add metronidazole 500 mg PO q8h. Patient should receive vancomycin 125 mg PO q6h for severe disease (severe abdominal pain, ileus/toxic megacolon, with sepsis and anticipated ICU transfer, or SCR $\geq 1.5$ times premorbid level)
   1.7. If patient has systemic HSV or VZV increase acyclovir to treatment dose: Acyclovir 5-10 mg/kg IV q8h.
   1.8. If patient remains febrile and clinically unstable without localizing signs of infection, consult ID.

2. If fever continues for 5 - 7 days without defined etiology and NOT currently on posaconazole prophylaxis, start antifungal therapy:
   2.1. Patient with normal liver function: Voriconazole 6 mg/kg PO q12h x 2 doses, then 3 mg/kg PO q12h x 4 doses, then 200 mg PO q12h. Use IV if poor absorption, severe mucositis or clinically unstable.
   2.2. Patient with liver dysfunction prohibiting voriconazole use: Micafungin 100 mg IV q24h.
   2.3. Patient with proven or probable non-candidal infection (via chest CT, micro data, etc.): Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h, then 200 mg PO q12h (once stable). Adjust dose based on goal voriconazole trough of 2.0 to 5.5 micrograms/ml. See UMHS guidelines for antifungal monitoring. Consult ID service if patient clinically unstable or not improving on current therapy.
   2.4. Patient with proven mucor infection: Liposomal amphotericin (Ambisome) 5 mg/kg IV q24h. Premedicate with acetaminophen/diphenhydramine/0.9% sodium chloride. Consult ID.

3. If fever continues for 5 - 7 days without defined etiology AND patient is on posaconazole prophylaxis:
   3.1. Strongly recommend CT scan of the chest
3.2. Strongly discourage any additional antifungal agent or change in antifungal therapy unless high clinical suspicion of invasive fungal infection (encourage ID consult)
3.3. Double antifungal coverage is restricted unless recommended by ID.

4. **In patients with hematologic malignancies other than AML:**
   4.1. If patient remains febrile and clinically stable without localizing signs of infection, continue antibiotics until ANC >500/mm$^3$ (except vancomycin, see below) and consider non-infectious causes of fever (drug reaction, tumor related).
   4.2. Vancomycin should be discontinued if no signs of catheter infection or cultures are negative 72 hours after initiation of vancomycin if causative organism identified, adjust antibiotic coverage to most appropriate treatment (maintain broad-spectrum activity).
   4.3. Continue antibiotic treatment for a minimum of 7 days or until ANC >500/mm$^3$, if patient is afebrile & cultures are negative. Once patient is afebrile, ANC >500/mm$^3$ and no infectious source has been identified, antibiotics may all be discontinued.

5. **See Appendix A for de-escalation recommendations in AML patients.**

GUIDELINES FOR THE TREATMENT OF NEUTROPENIC FEVER IN ADULT HIGH-RISK HEMATOLOGY/ONCOLOGY PATIENTS

Appendix A: Antibiotic De-escalation in Clinically Stable and Afebrile Adult AML patients

Initial Presentation of Febrile Neutropenia in AML Patients following Chemotherapy:
Start broad spectrum IV antibiotics per protocol, obtain cultures, and perform appropriate work-up for source of infection.

Evaluate for De-escalation at Day 5:

Low Suspicion for Bacterial Infection:
- All bacterial cultures are negative
- No suggestion of bacterial infection on imaging studies or physical exam

Suspected Bacterial Infection:
- All bacterial cultures are negative
- Imaging studies or physical exam suggest possible bacterial infection

Documented Bacterial Infection:
- Positive bacterial cultures, plus imaging or physical exam finding consistent with infection

Treatment Recommendations:

- Clinically stable and afebrile x 48 hours, then de-escalate therapy as below

- Newly diagnosed AML patients:
  Discontinue antibiotic therapy including anti-pseudomonal β-lactam, with daily assessment for potential infection

- Relapsed/Refractory AML patients:
  De-escalate to levofloxacin 500 mg QD

- Newly diagnosed AML patients:
  Discontinue antibiotic therapy when appropriate, according to duration of therapy recommendations with daily assessment for potential infection

- Relapsed/Refractory AML patients:
  De-escalate to levofloxacin 500 mg QD

- Newly diagnosed AML patients:
  Discontinue antibiotic therapy according to duration of therapy recommendations, with daily assessment for potential infection

- Relapsed/Refractory AML patients:
  De-escalate to levofloxacin 500 mg QD

Daily monitoring for signs and symptoms of infection

Re-initiate IV anti-pseudomonal β-lactam therapy if:
- Fever (temperature ≥38.3 once or ≥38.0 sustained for 1 hour)
- Positive cultures, physical exam or radiographic imaging with probable or documented bacterial infection
<table>
<thead>
<tr>
<th>Infection*</th>
<th>Pneumonia</th>
<th>Blood Steam Infection</th>
<th>Cellulitis</th>
<th>UTI</th>
<th>Intra-abdominal</th>
<th>Typhilitis</th>
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<tr>
<td>Suggested duration of therapy</td>
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<tr>
<td>• 7-14 days for patients with rapid clinical improvement and without complications</td>
<td>• Duration dependent on whether infection is uncomplicated or complicated and the causative organism*</td>
<td>• 7-14 days of cellitis-directed therapy (e.g., vancomycin)</td>
<td>• 7 days of therapy</td>
<td>• 7-14 days of therapy, if adequate source control is achieved</td>
<td>• 7-14 days of therapy, if persistent symptoms or repeat imaging consistent with infection</td>
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<td>• 14+ days for patients with complications or for patients clinically unstable</td>
<td>• Continue therapy if cellulitis is unresolved by day 14</td>
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*Antibiotics may be discontinued prior to the Day 5 evaluation at the discretion of the primary hematology team if fever is thought to be due to non-infectious causes (i.e. platelet transfusions, fever from active AML, etc.)

**Antibiotic therapy should NOT be de-escalated or discontinued in patients persistent fevers, hemodynamic instability, or clinical instability, thought to be secondary to bacterial infection.

**Blood Stream Infectious Line Removal Recommendations for short-term central venous catheter or arterial catheter related bloodstream infections:

- **Uncomplicated Infections**: fever resolves within 72 hours, patient has no intravascular hardware, no evidence of endocarditis or suppurative thrombophlebitis, and for S. aureus is without active malignancy or immunosuppression
  - Coagulase-negative *Staphylococi*: Remove catheter and treat with antibiotics for 5-7 days; if catheter is retained, treat for 10-14 days (with added lock therapy)
  - *Staphylococcus aureus*: Remove catheter and treat with antibiotics for 4-6 weeks of therapy (AML patients qualify as having complicated *S. aureus* bacteremia)
  - *Enterococcus*: Remove catheter and treat with antibiotics for 7-14 days
  - Gram-negative bacilli: Remove catheter and treat with antibiotics for 7-14 days
  - *Candida spp.*: Remove catheter and treat with antifungal therapy for 14 days

- **Complicated Infections**: those with suppurative thrombophlebitis, endocarditis or osteomyelitis
  - Remove catheter and treat with antibiotics for 4-6 weeks, and 6-8 weeks for osteomyelitis

For further recommendations regarding catheter-related bloodstream infections, please reference IDSA Guidelines for Management of Intravascular Catheter-Related Infections

**Patients with suspected fungal infection: consider Infectious Diseases consult. Antibiotics may be continued at the discretion of the primary hematology team or Infectious Diseases**

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Revision History:

03/21: Updated vancomycin dosing & hyperlinks

The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider’s professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

If obtained from a source other than med.umich.edu/asp, please visit the webpage for the most up-to-date document.

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