Neutropenic Fever\(^1\) Inpatient Pediatric Treatment
(Hematologic Cancers and Stem Cell Patients)

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Note: This algorithm should not be used for patients receiving CAR cell therapy.

Patient presents with fever or develops fever at MD Anderson

PEWS\(^2\) 6 or greater?

Yes

- Complete physical exam and history of recent chemotherapy
- Start IV fluids at maintenance (or less if clinically indicated)
- CBC with differential, CMP, lactic acid
- Blood cultures\(^3\) (with a set collected from each lumen simultaneously if CVAD present and consider one peripheral site); urinalysis with culture
- Other site specific cultures (e.g., stool studies, respiratory viral PCR panel) only if clinically indicated
- Chest\(^4\)/abdominal x-ray or other tests as clinically indicated

See Pediatric Sepsis Management algorithm for stabilization information

See Pages 2-3 for antimicrobial therapy recommendations

No

See Pages 2-3 for antimicrobial therapy recommendations

\(^1\) ANC less than 1 K/microliter and either temperature of at least 38.3°C once or 38.0°C twice separated by at least 1 hour

\(^2\) See Appendix A for Modified PEWS Tool; full details available in the Detecting Pediatric Patient Deterioration Using PEWS algorithm

\(^3\) Do not delay antibiotic administration for blood cultures; antibiotics should be given within one hour

\(^4\) Obtain chest x-ray for all stem cell transplant patients
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Consider the following when selecting antibiotics (antibiotics should be given within 1 hour):
- Recent culture and sensitivity results
- History of MDRO infection or colonization
- Suspected line infection
- Antibiotic history and prophylaxis
- Source of infection if identified
- Antibiotic allergies
- Organ dysfunction
- Mucositis

Yes

Documented beta-lactam allergy (i.e., hives or anaphylaxis)?

- Neutropenic fever:
  - Cefepime or piperacillin and tazobactam or meropenem
  - If clinically suspected line infection, bacteremia, skin/soft tissue infection, MRSA colonization, and/or SCT patient:
    - Add vancomycin
    - If relative contraindication exists to vancomycin use, consider linezolid instead
  - If indicated for double gram negative coverage, add either:
    - Tobramycin or
    - Amikacin or
    - Ciprofloxacin (only if no quinolone prophylaxis)
  - If mucositis (at least Grade 2), suspected intra-abdominal infection, or other indication for anaerobic coverage:
    - Add metronidazole to cefepime
  - If history of MDRO infection:
    - Consider Infectious Disease consult

No

- Neutropenic fever, clinically suspected line infection, bacteremia, skin/soft tissue infection, MRSA colonization, and/or SCT patient:
  - Aztreonam
  - Plus:
    - Tobramycin or amikacin or ciprofloxacin (only if no quinolone prophylaxis)
  - Plus:
    - Vancomycin
    - If relative contraindication exists to vancomycin use, consider linezolid instead
  - If mucositis of at least Grade 2, suspected intra-abdominal infection, or other indication for anaerobic coverage:
    - Add metronidazole
  - If history of MDRO infection:
    - Consider Infectious Disease consult

ANTIMICROBIAL THERAPY RECOMMENDATIONS
See Page 6 for Dosing Information
Gram negative coverage antibiotics should be given first

1 Chills, rigors with infusion through catheter, cellulitis or discharge around the line entry site
2 Consider meropenem if patient has any of the following:
- Non-IgE-mediated allergy to alternative agents
- Failed treatment with cefepime or piperacillin/tazobactam
- Infection with ESBL organism
- Infection with organism only susceptible to carbapenem
3 Confirm use with Pediatric Stem Cell Transplant service prior to starting in transplant patients
4 Double gram negative coverage should be considered with complicated tissue-based infections, neutropenic enterocolitis, and perirectal infections
5 Metronidazole is not necessary if meropenem is used
6 Double gram negative coverage recommended due to reduced aztreonam activity against gram negative organisms according to local MD Anderson antibiogram

ESBL = extended spectrum beta-lactamase
MRSA = methicillin-resistant *staphylococcus aureus*
SCT = stem cell transplant

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Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 10/15/2019
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FINDINGS

VRE colonization or infected patients

- Consider Infectious Disease consult
- Consider using linezolid\(^1\), in place of vancomycin (if prior known sensitivities), with one of the regimens listed on Page 2

Stenotrophomonas maltophilia

- Consider Infectious Diseases consult, especially with patients who have a sulfa allergy

MDRO

- Consider Infectious Disease consult

See Page 4 for re-assessment

VRE = vancomycin-resistant enterococci

\(^1\) Confirm use with Pediatric Stem Cell Transplant service prior to starting in transplant patients

ANTIMICROBIAL THERAPY RECOMMENDATIONS
See Page 6 for Dosing Information

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RE-ASSESSMENT

Patient afebrile

72-hour evaluation

Patient febrile

Identified source of fever?

Yes

Treat for appropriate duration based on nature of infection and ANC (e.g., urinary tract infection, cellulitis)

No

Continue treatment for at least 2 days after ANC is greater than 0.5 K/microliter and rising

Identified source of fever?

Yes

• Check susceptibilities
• Make necessary changes in antibiotic regimen
• CT scans, serology and other diagnostic work-up as clinically indicated
• Consider or re-evaluate antifungals and/or antivirals

No

Repeat cultures
• CT - sinuses and chest, aspergillus antigen, other diagnostic work-up as clinically indicated
• Re-evaluate antibiotics for need to broaden coverage
• Consider antifungals (see Appendix B) and/or antivirals

Fever persists?

Yes

Disposition based on Infectious Disease consult recommendations and/or diagnostic test results

No

Complete antibiotic regimen and disposition per MD

If still inpatient, reassess at Day 5

Fever persists?

Yes

Consider Infectious Disease consult, as well as CT chest (if not already performed) and/or other diagnostic tests if clinically indicated

No

Observe

Monitor counts

• Chest x-ray and cultures and sensitivity results negative

Consider adding or changing antifungal therapy (see Appendix B)

1 Consider narrowing therapy based on cultures and sensitivities (e.g., discontinue anti-MRSA or anti-VRE agents if no gram positive organisms are identified and patient does not have cellulitis or pneumonia)

2 For stem cell patients, refer to the Stem Cell Transplantation and Cellular Therapy Guideline of Care GC14.2 for Febrile Neutropenia

3 Cytomegalovirus (CMV) PCR for SCT patients if not already performed

4 Consider transition to antimicrobial prophylaxis if otherwise indicated and no clear infectious source of fever was identified

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## APPENDIX A: Modified PEWS Tool

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavior</strong></td>
<td>Playing</td>
<td>Irritable, but consolable</td>
<td>Irritated, but not consolable</td>
<td>Lethargic</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Within normal parameters for age</td>
<td>Tachycardia less than 20 above normal for age</td>
<td>Tachycardia 20-29 above normal for age</td>
<td>Tachycardia at least 30 above or bradycardia at least 10 below normal for age</td>
</tr>
<tr>
<td>Color</td>
<td>Pink</td>
<td>Pale or dusky</td>
<td>Mottled</td>
<td>Gray</td>
</tr>
<tr>
<td>Perfusion</td>
<td>Capillary refill 1-2 seconds</td>
<td>Capillary refill 3 seconds</td>
<td>Capillary refill 4 seconds</td>
<td>Capillary refill at least 5 seconds</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td>Within normal parameters for age</td>
<td>Tachypnea 10-19 above normal parameters for age</td>
<td>Tachypnea at least 20 above normal parameters for age with retractions</td>
<td>Bradypnea at least 5 below normal parameters for age with retractions</td>
</tr>
<tr>
<td>Rate</td>
<td>No retractions</td>
<td>Mild retractions/accessory muscle use</td>
<td>Moderate retractions/accessory muscle use (including tracheal tugging)</td>
<td>Severe retractions/accessory muscle use (including tracheal tugging) and grunting</td>
</tr>
<tr>
<td>Effort</td>
<td>Oxygen required to maintain normal(^2) SpO(_2)</td>
<td>Oxygen required to maintain normal(^2) SpO(_2): 24-40% 2 L/minute O(_2)</td>
<td>Oxygen required to maintain normal(^2) SpO(_2): 40-49% At least 3 L/minute O(_2)</td>
<td>Oxygen required to maintain normal(^2) SpO(_2): 50%</td>
</tr>
<tr>
<td>Oxygen</td>
<td>N/A</td>
<td>Any assisted ventilation(^3) or initiation of O(_2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Add 2 extra points if patient requires frequent interventions (e.g., suctioning, positioning, change in O\(_2\) needs, multiple IV attempts required, or every 15-minute or continuous nebulized treatments) or has persistent post-op vomiting.
2. As defined in patient’s orders.
3. Includes home bilevel positive airway pressure (BiPAP)/continuous positive airway pressure (CPAP) or home ventilator at baseline settings.
### Antibiotic agents:
- **Amikacin**
  - 15 mg/kg IV once and then repeat per pharmacokinetic data
- **Aztreonam**
  - 30 mg/kg (maximum 2 g) IV every 8 hours
- **Cefepime**
  - 50 mg/kg (maximum 2 g) IV every 8 hours
- **Ciprofloxacin**
  - 10 mg/kg (maximum 400 mg) IV every 8 hours
- **Linezolid**
  - Less than 12 years old: 10 mg/kg (maximum 600 mg) IV every 8 hours
  - Greater than or equal to 12 years old: 600 mg IV every 12 hours
- **Meropenem**
  - 20 mg/kg (maximum 1 gram) IV every 8 hours
- **Metronidazole**
  - 7.5 mg/kg (maximum 500 mg) IV every 6 hours
- **Piperacillin and tazobactam**
  - 100 mg/kg piperacillin (maximum 4 grams) IV every 8 hours
- **Sulfamethoxazole and trimethoprim (TMP)**
  - 15 mg/kg IV or oral every 8 hours
- **Tobramycin**
  - 7 mg/kg IV once and then repeat per pharmacokinetic data
- **Vancomycin**
  - Less than 6 years old: 20 mg/kg IV every 6 hours
  - 6-11 years old: 15 mg/kg IV every 6 hours
  - Greater than or equal to 11 years old: 15 mg/kg IV every 8 hours

### Antifungal agents:
- **Caspofungin** - load 70 mg/m² (maximum 70 mg) IV once, then 50 mg/m² (maximum 50 mg) IV daily
- **Liposomal Amphotericin** 3-5 mg/kg IV daily
- **Voriconazole**
  - Patients 2 to 11 years old:
    - Loading dose: 9 mg/kg/dose IV every 12 hours x 2 doses
    - Maintenance dose: 8 mg/kg/dose IV every 12 hours
  - Patients greater than or equal to 12 years old:
    - Loading dose: 6 mg/kg/dose IV every 12 hours x 2 doses
    - Maintenance dose: 4 mg/kg/dose IV every 12 hours

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1 Confirm use with Pediatric Stem Cell Transplant service prior to starting

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**APPENDIX B: Antimicrobial Dosing Information**

Note: Adjust dose for patients with renal/hepatic dysfunction. Therapeutic drug monitoring should be performed to ensure safety and efficacy, as appropriate.
SUGGESTED READINGS


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DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Pediatric Neutropenic Fever work group at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

Patricia Amado, BSN, RN (Nursing G9)
Natalie J.M. Dailey Garnes, MD (Infectious Disease)\textsuperscript{T}
Jessica Foglesong, MD (Pediatrics – Patient Care)
Suzanne Gettys, PharmD (Pharmacy Clinical Programs)
Kris Mahadeo, MD (Pediatrics – Patient Care)
Victor Mulanovich, MD (Infectious Disease)
Demetrios Petropoulos, MD (Pediatrics – Patient Care)
Shehla Razvi, MD (Pediatrics – Patient Care)\textsuperscript{T}
Milena Zhang, PharmD\textsuperscript{*}

\textsuperscript{T} Core Development Team Lead
\textsuperscript{*} Clinical Effectiveness Development Team