Neutropenic Fever\textsuperscript{1} Inpatient Pediatric Treatment
(Hematologic Cancers and Stem Cell Patients)

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics. This algorithm should not be used to treat pregnant women.

\textbf{Note:} This algorithm should not be used for patients receiving CAR cell therapy.

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Patient presents with fever or develops fever at MD Anderson

\begin{itemize}
  \item PEWS\textsuperscript{2} 6 or greater?
\end{itemize}

\begin{itemize}
  \item Yes
    \begin{itemize}
      \item See Pediatric Sepsis Management Algorithm for stabilization information
      \item See Antimicrobial Therapy Recommendations (Pages 2-3)
    \end{itemize}
  \item No
    \begin{itemize}
      \item Complete physical exam and history of recent chemotherapy
      \item Start IV fluids at maintenance (or less if clinically indicated)
      \item CBC with differential and platelets, CMP, lactic acid
      \item Blood cultures\textsuperscript{3} (with a set collected from each lumen simultaneously if CVAD present and consider one peripheral site); urinalysis with culture
      \item Other site specific cultures (e.g., stool studies, respiratory viral PCR panel) only if clinically indicated
      \item Chest/abdominal x-ray or other tests as clinically indicated
    \end{itemize}
\end{itemize}

\textbf{See Antimicrobial Therapy Recommendations (Pages 2-3)}

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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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ANTIMICROBIAL THERAPY RECOMMENDATIONS

See Dosing Information (Page 6)
Gram negative coverage antibiotics should be given first

Neutropenic fever:
- Cefepime or piperacillin and tazobactam or meropenem

If clinically suspected line infection¹, 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 coverage², 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 ID consult

Neutropenic fever, clinically suspected line infection¹, bacteremia, skin/soft tissue infection, MRSA colonization, and/or SCT patient:
- Aztreonam³

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 ID consult

SCT = stem cell transplant

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. Double gram negative coverage recommended due to reduced aztreonam activity against gram negative organisms according to local antibiograms

ANTIMICROBIAL THERAPY RECOMMENDATIONS

See additional findings and antibiotic options (Page 3)
See Re-assessment (Page 4)
**FINDINGS**

**ANTIMICROBIAL THERAPY RECOMMENDATIONS**

See Page 6 for Dosing Information

- **Stenotrophomonas maltophilia**
  - Consider adding sulfamethoxazole and trimethoprim to one of the regimens listed on Page 2
  - Consider Infectious Diseases consult, especially with patients who have a sulfa allergy

- **MDRO**
  - Consider Infectious Disease consult

- **VRE colonization or infected patients**
  - Consider Infectious Disease consult
  - Consider using linezolid, in place of vancomycin (if prior known sensitivities), with one of the regimens listed on Page 2

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1 Confirm use with Pediatric Stem Cell Transplant service prior to starting in transplant patients.
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RE-ASSESSMENT

Patient afibrile

72-hour evaluation

Yes

Identified source of fever?

No

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

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

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

Consider adding or changing antifungal therapy (see Appendix B)

Disposition based on ID consult recommendations and/or diagnostic test results

Complete antibiotic regimen and disposition per MD

Yes

Reassess at Day 5

Fever persists?

No

Observe

Monitor counts

Chest x-ray and cultures and sensitivity results negative

Yes

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)

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

3 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
## APPENDIX A: Modified PEWS Tool

<table>
<thead>
<tr>
<th>Behavior</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</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>
</tbody>
</table>

| Respiratory System | | | | |
| Rate | • Within normal parameters for age | • Tachypnea 10-19 above normal parameters for age | • Tachypnea at least 20 above normal parameters for age with retractions | • Bradypnea at least 5 below normal parameters for age with retractions |
| Effort | • No retractions | • Mild retractions/accessory muscle use | • Moderate retractions/accessory muscle use (including tracheal tugging) | • Severe retractions/accessory muscle use (including tracheal tugging) and grunting |
| Oxygen | • N/A | • Oxygen required to maintain normal$^2$ $SpO_2$ | • Oxygen required to maintain normal$^2$ $SpO_2$ and $FiO_2$ of at least 50% | • Oxygen required to maintain normal$^2$ $SpO_2$ and $FiO_2$ of at least 40-49% |

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 BiPAP/CPAP or home ventilator at baseline settings

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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 TMP 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 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

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

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 when possible
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:

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