Neutropenic Fever[1] Inpatient Pediatric Treatment (Hematologic Cancers and Stem Cell Patients)

Note: This algorithm may also be used for patients receiving immune effector cell (IEC) therapy.

PRESENTATION

Patient with neutropenia **and** fever[1]

ASSESSMENT

PEWS[2] ≥ 6?

Yes → See Sepsis Management - Pediatric algorithm and use sepsis ordering tools

No →
- Physical exam and review medical history for recent chemotherapy
- Maintenance IV hydration (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)
- Other cultures (*e.g.,* sputum culture, respiratory viral PCR panel, urinalysis with reflex culture, MRSA nasal swab), only if clinically indicated
- Chest x-ray[4] and/or abdominal x-ray as clinically indicated
- Other tests as clinically indicated

→
- See Page 2 for antibacterial recommendations
- See Page 3 for antibacterial recommendations for patients with serious documented beta-lactam allergy

CMP = comprehensive metabolic panel
CVAD = central vascular access device
MRSA = methicillin-resistant *staphylococcus aureus*
PEWS = Pediatric Early Warning Score

[1] Criteria:
- Absolute neutrophil count (ANC) ≤ 0.5 K/microliter **and** oral temperature either ≥ 38.3°C or equal to 38°C for 1 hour or longer **or**
- ANC ≤ 1 K/microliter and an expected decline to ≤ 0.5 K/microliter over 48 hours **and** oral temperature either ≥ 38.3°C or equal to 38°C for 1 hour or longer

[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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Neutropenic Fever Inpatient Pediatric Treatment
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ANTIBACTERIAL RECOMMENDATIONS

See Appendix B for Dosing Information

Gram negative coverage antibiotics should be given first. Antibiotics should be given within 1 hour of patient presentation.

- **For serious documented beta-lactam allergy, see Page 3**
- **Consider the following when selecting antibacterial therapy:**
  - Recent culture and sensitivity results
  - History of resistant gram negative organism[1] infection or colonization
  - Suspected line infection[2]
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Mucositis ≥ grade 2
  - Drug interactions
  - Local/institutional antibiogram[3]
- Consider the use of therapeutic G-CSF in patients with high risk of infectious complications and in consultation with pediatric leukemia physician for leukemia patients

Neutropenic fever:
- Cefepime
  - Add metronidazole[4] if suspected intra-abdominal infection or other indication for anaerobic coverage
- Piperacillin and tazobactam
- Meropenem[5]

If septic shock with vasopressor use, complicated tissue-based infections, neutropenic enterocolitis, perirectal infections or other indication for double gram negative coverage consider <u>adding:</u>
- Amikacin

Is expanded gram positive coverage needed?

Yes

If suspected line infection[2], bacteremia, skin/soft tissue infection, MRSA colonization, mucositis ≥ grade 2 or AML or SCT patients <u>add</u>:
- Vancomycin[6] **<u>or</u>**
- Linezolid[6,7] (use if relative contraindication exists to vancomycin or in the case of VRE colonization)

<u>or</u>
- Daptomycin[6] (if no evidence of pneumonia and ages ≥ 1 year)

See Page 4 for re-assessment

No

See Page 4 for re-assessment

AML = acute myeloid leukemia
G-CSF = granulocyte colony stimulating factor
SCT = stem cell transplant
VRE = vancomycin-resistant enterococci

[1] Resistant gram negative organisms include:
- *Stenotrophomonas maltophilia*
- Any extended spectrum beta-lactamase (ESBL) producing gram negative bacilli
- Any carbapenem resistant gram negative bacilli
- All other gram negative bacilli that are resistant to usual recommended first-line agents

[2] Chills, rigors with infusion through catheter, cellulitis or discharge around the catheter line entry site
[3] Refer to gram negative and gram positive antibiograms (internal only)
[4] Metronidazole is not necessary if meropenem is used
[5] Consider meropenem if patient has any of the following:
- Non-IgE-mediated allergy to alternative agents
- Infection with ESBL organism
- Failed treatment with cefepime or piperacillin/tazobactam
- Infection with organism only susceptible to carbapenem

[6] For AML patients, discontinue after 48 hours if cultures are negative
[7] Confirm use with Pediatric Stem Cell Transplant service prior to starting in transplant patients

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Neutropenic Fever Inpatient Pediatric Treatment
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SERIOUS DOCUMENTED BETA-LACTAM ALLERGY
(anaphylaxis, hives, or serious non-IgE mediated drug reactions[1])

ASSESSMENT

- **Consider the following when selecting antibacterial therapy:**
  - Recent culture and sensitivity results
  - History of resistant gram negative organism[2] infection or colonization
  - Suspected line infection[3]
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Mucositis ≥ grade 2
- Consider the use of therapeutic G-CSF in patients with high risk of infectious complications and in consultation with pediatric leukemia physician for leukemia patients

ANTIBACTERIAL RECOMMENDATIONS

(Adjust dose for patients with renal/hepatic dysfunction)

Gram negative coverage antibiotics should be given first. Antibiotics should be given within 1 hour of patient presentation.

Neutropenic fever, clinically suspected line infection[3], bacteremia, skin/soft tissue infection, MRSA colonization or SCT patient:

- **For gram negative coverage select:**
  - Aztreonam[4]

  Plus:
  - Amikacin **or**
  - Tobramycin

For anaerobic coverage in the setting of neutropenic enterocolitis, perirectal infections or mucositis ≥ grade 2 add:

- Metronidazole

- **For gram positive coverage select from the following:**
  - Vancomycin **or**
  - Linezolid[5] (use if relative contraindication exists to vancomycin or in the case of VRE colonization. Not preferred for MRSA blood stream infection.)

    or
  - Daptomycin (if no evidence of pneumonia and ages ≥ 1 year)

See Page 4 for re-assessment

[1] Examples of non-IgE mediated drug reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS)

[2] Resistant gram negative organisms include:
- *Stenotrophomonas maltophilia*
- Any extended spectrum beta-lactamase (ESBL) producing gram negative bacilli
- Any carbapenem resistant gram negative bacilli
- All other gram negative bacilli that are resistant to usual recommended first-line agents

[3] Chills, rigors with infusion through catheter, cellulitis or discharge around the catheter line entry site

[4] Double gram negative coverage should be considered with complicated tissue-based infections, neutropenic enterocolitis, and perirectal infections

[5] Confirm use with Pediatric Stem Cell Transplant service prior to starting in transplant patients

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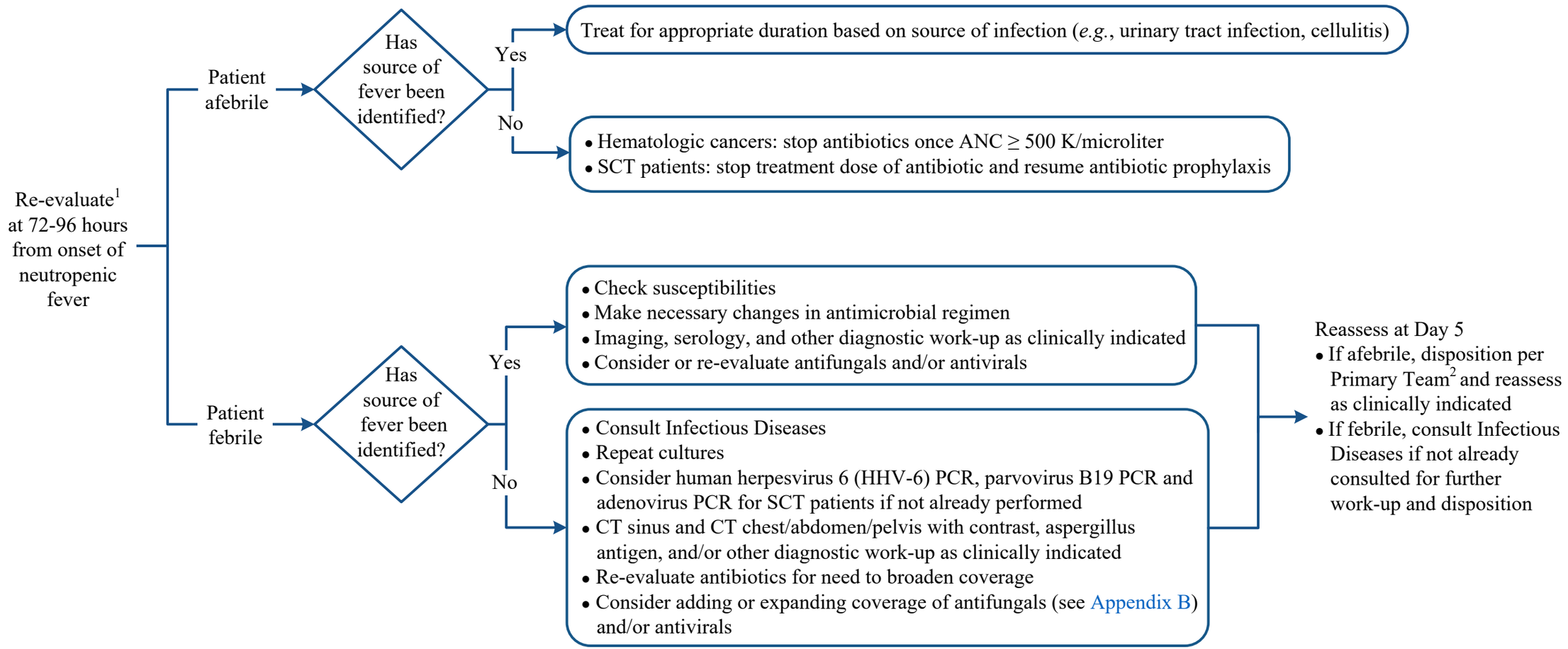
RE-ASSESSMENT **TREATMENT**



[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] 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

	Score[1]			
	0	**1**	**2**	**3**
Behavior	• Playing • Appropriate	• Irritable, but consolable	• Irritated, but not consolable	• Lethargic • Confused • Reduced response to pain
Cardiovascular System				
Rate	• Within normal parameters for age	• Tachycardia less than 20 above normal for age	• Tachycardia 20-29 above normal for age	• Tachycardia at least 30 above **or** bradycardia at least 10 below normal for age
Color	• Pink	• Pale **or** dusky	• Mottled	• Gray
Perfusion	• Capillary refill 1-2 seconds	• Capillary refill 3 seconds	• Capillary refill 4 seconds	• Capillary refill at least 5 seconds
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 ◦ FiO_2 24-39% ◦ O_2 2 L/minute • Any assisted ventilation[3] or initiation of O_2	• Oxygen required to maintain normal[2] SpO_2 ◦ FiO_2 40-49% ◦ O_2 at least 3 L/minute	• Oxygen required to maintain normal[2] SpO_2 ◦ FiO_2 of at least 50%

FiO_2 = fraction of inspired oxygen; O_2 = oxygen; SpO_2 = oxygen saturation

[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

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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.

Antibiotic agents:

- Amikacin 15 mg/kg IV once and then repeat per pharmacokinetic data
- Aztreonam 30 mg/kg (maximum 2 grams) IV every 8 hours
- Cefepime 50 mg/kg (maximum 2 grams) IV every 8 hours
- Daptomycin 8 mg/kg IV every 24 hours
- Linezolid[1]
  - < 12 years old: 10 mg/kg (maximum 600 mg) IV every 8 hours
  - ≥ 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
- Vancomycin: Initial dosing, adjustments per pharmacokinetic data
  - < 6 years old: 20 mg/kg IV every 6 hours
  - 6-11 years old: 15 mg/kg IV every 6 hours
  - > 11 years old: 15 mg/kg IV every 8 hours

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

Antifungal agents:

- Caspofungin - load 70 mg/m^2 (maximum 70 mg) IV once, then 50 mg/m^2 (maximum 50 mg) IV daily
- Liposomal Amphotericin 3-5 mg/kg IV daily
- Voriconazole: Initial dosing, adjustments per pharmacokinetic data
  - Patients < 12 years old:
    - Loading dose: 9 mg/kg/dose IV every 12 hours for 2 doses
    - Maintenance dose: 8 mg/kg/dose IV every 12 hours
  - Patients ≥ 12 years old:
    - Loading dose: 6 mg/kg/dose IV every 12 hours for 2 doses
    - Maintenance dose: 4 mg/kg/dose IV every 12 hours
- Posaconazole: Initial dosing, adjustments per pharmacokinetic data
  - Patients ages 13 years and older:
    - Loading dose: 300 mg IV/PO (delayed release (DR) tab) every 12 hours for 2 doses
    - Maintenance dose: 300 mg IV/PO (DR tab) every 24 hours
  - Patients ages 12 years and younger:
    - Loading dose: 7-10 mg/kg IV/PO (DR tab) every 12 hours for 2 doses
    - Maintenance dose: 7-10 mg/kg IV/PO (DR tab) every 24 hours

SUGGESTED READINGS

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