



TREATMENT OF FEVER AND NEUTROPENIA IN HEMATOLOGY/ONCOLOGY AND HEMATOPOIETIC CELL TRANSPLANT PATIENTS

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| Purpose | Scope | Definitions |
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- I. **PURPOSE:** This algorithm describes the evidence-based approach for the management of high-risk hematology/oncology and hematopoietic cell transplant (HCT) patients with fever and neutropenia.

- II. **SCOPE:** This guideline outlines the antibiotic management of the first neutropenic fever and persistent fever.

- III. **DEFINITIONS:**
 - A. Neutropenia: Absolute neutrophil count (ANC) <500 cells/mm³ or <1000 cells/mm³ with a predicted decline to <500/mm³ based on recent chemotherapy administration
 - B. Fever: Single temperature (oral or axillary) ≥38.3°C (101°F) or two temperatures (oral or axillary) of 38.0°C (100.4°F) at least 1 hour apart
 - *NOTE: Oral temperatures are preferred for increased accuracy. Additional degrees should not be added to axillary temperatures. Rectal temperature should not be obtained in neutropenic patients.

- IV. **GOALS:**
 - A. To ensure febrile neutropenia patients receive appropriate empiric antibiotics and appropriate cultures are obtained
 - B. To ensure all patients have their first dose of antibiotics initiated within 30 minutes of fever or upon arrival to the emergency department (ED)

- V. **INITIAL ASSESSMENT**
 - A. Optimally obtain both aerobic and anaerobic blood cultures from all lumens of ALL central venous catheters and peripheral blood culture before initiation of antimicrobials. In pediatric patients with central access, peripheral cultures are not required (aerobic blood cultures only can be obtained for follow up cultures).
 - B. Optimally, obtain urine culture for those patients who can provide a clean catch prior to antibiotic administration. Neutropenic patients generally should not be catheterized.
 - C. Chest X-ray in patients with signs or symptoms of a respiratory tract abnormality.
 - D. Throat, sputum, viral swabs, stool and wound cultures at the discretion of the evaluating/treating physician.
 - E. Initiate the first dose of antibiotics within 30 minutes of fever or arrival to the ED. The first dose of antibiotics should NOT be delayed if difficulty obtaining blood or urine cultures.
 - F. History of travel outside of United States or Canada, or history of resistant organisms on previous cultures? Consider Infectious Diseases discussion regarding empiric antibiotic therapy plan.

VI. RECOMMENDED TREATMENT

- A. Refer to FIGURE 1 for initial treatment
 - i. Adjunctive treatment: G-CSF and/or GM-CSF are NOT routinely recommended for the treatment of febrile neutropenia
 - B. For blood culture results, refer to [Treatment Guideline of Adult Patients with Bacteremia](#) or [Treatment Guideline for Pediatric Patients with Bacteremia](#) for addition of other antimicrobials
 - i. Please note important difference from general population for patients growing gram positive cocci in chains
 - a. Adult Hematology and Oncology Patient (irrespective of ANC); or Adult HCT recipient with ANC >1000 cells/mm³: start **linezolid** 600 mg every 12 hours PO/IV
 - b. Adult HCT Recipient with ANC <1000 cells/mm³: start **daptomycin** 8-10 mg/kg every 24 hours IV
 - c. Pediatric Hematology and Oncology Patient or HCT recipient: Start **vancomycin** per institutional dosing (same as general pediatric population)
 - C. Bloodstream Infection Duration
 - i. For catheter-related infections, refer to the [Central Vascular Catheter \(CVC\) Infections Guideline](#). See additional organism-specific recommendations below, regardless of infection source.
 - a. *Staphylococcus aureus*
 - Obtain Infectious Diseases (ID) consult
 - See [S. aureus Bacteremia Institutional Guideline](#) for adult patients
 - b. *Candida spp.*
 - Obtain ID consult
 - Remove catheter and obtain Ophthalmology consult
 - See Candidemia guidelines ([adult](#) | [peds](#))
 - c. Coagulase-negative staphylococci
 - Consider echo for persistent bacteremia or other risk factors for endocarditis (i.e., prosthetic valve, cardiac device, congenital heart disease)
 - Consult ID for bacteremia thought secondary to a source other than CVC, (e.g., endocarditis, endovascular infection, prosthetic joint infection).
 - d. *Streptococcus* and *Enterococcus spp.*
 - Consider echo for persistent bacteremia or other risk factors for endocarditis (i.e., prosthetic valve, cardiac device, congenital heart disease)
 - Consult ID for endocarditis or other complicated infections
 - Duration for non-CVC-related infection: 7-14 days¹
 1. Shorter course (7 days) can be considered if no longer neutropenic, rapid clinical resolution, no cardiac devices (pacemaker, prosthetic valve, no endocarditis), and rapid clearance of blood culture (within 48 hours)
 - e. Gram-negative bacilli
 - Consult ID for endocarditis or other complicated infections
 - Duration for non-CVC-related infection:
 1. Enterobacteriaceae: 7-14 days¹
 - a. Shorter courses (7 days) can be considered if single positive blood culture, afebrile and significant clinical improvement within 72 hours, and adequate source control
 2. Other GNRs including *Pseudomonas spp.*: 10-14 days
 - a. Shorter courses (10 days) can be considered if no longer neutropenic, single positive blood culture, afebrile and significant clinical improvement within 72 hours, and adequate source control
- D. Continue daily blood cultures until two cultures are negative for 24-48 hours

VII. MANAGEMENT OF PERSISTENT FEVER

- A. Obtain up to 1 set of repeat aerobic blood cultures every 24 hours while febrile (one set per day while febrile); rotate lumens of central venous catheter for repeat cultures (if applicable).
 - 1. If fevers persist but patient is clinically stable with negative blood cultures, may discontinue daily cultures after 3 days of cultures
 - 2. Obtain new blood cultures if new clinical instability develops
- B. Obtain repeat urine, throat, sputum, stool, wound, etc. cultures as appropriate and repeat imaging as clinically indicated.
- C. If fever curve not improving* for >96 hours without defined etiology:
 - 1. Evaluate for venous thromboembolism, drug fevers, other sources of fever
 - 2. High risk for invasive fungal infection (IFI) (defined as patients with an anticipated duration of neutropenia > 7 days and allogeneic HCT recipients with persistent fever despite prolonged (96 hours) broad spectrum antibiotic therapy).
 - i. Obtain CT of chest (abdomen/pelvis CT if symptoms)
 - a. Consider abdominal US for pediatric patients without localizing symptoms
 - ii. Check azole [antifungal drug level](#) (if applicable)
 - iii. In multiply refractory patients with prolonged neutropenia (>30 days) or allogeneic HCT recipients on prolonged course of high dose steroids, or in any patient symptomatic of sinus disease, consider CT sinus and ENT consult
 - iv. Consider obtaining CMV, HHV-6, and EBV viral PCRs in alloHCT patients
 - v. If HSV/Ab+ with severe esophagitis, consider addition of treatment dose acyclovir
 - 3. Discourage any changes or additions of antibacterial and antifungal therapy unless clinical signs/symptoms indicate a change is needed or if clinically worsening (encourage ID consult if modification to antimicrobial therapy is felt warranted).

*improving fever curve is defined as gradually lower and less frequent fever spikes. Patients who demonstrate a gradual improvement in fever curve do not require extensive work-up or change in antimicrobials despite continuous fevers

- D. If recurrent fever
 - 1. Obtain new blood cultures, and obtain other cultures and imaging as appropriate
 - 2. If not on treatment, re-escalate to initial therapy following [FIGURE 1](#)
 - 3. If currently on treatment (e.g., cefepime), no modifications are needed unless clinical instability.
 - 4. Fever, whether initial or recurrent, is NOT an indication for vancomycin

VIII. DURATION OF THERAPY

- A. Patients who initiated vancomycin or an aminoglycoside for hemodynamic instability should have these therapies discontinued after 48 hours if clinically stable and cultures do not identify organisms requiring vancomycin or aminoglycosides (maintain broad-spectrum anti-pseudomonal), or if an alternative source of infection is identified that does not require continued vancomycin or aminoglycoside therapy.
 - 1. Patients initiated on vancomycin or an aminoglycoside without an indication (per [FIGURE 1](#)) can have these therapies immediately discontinued (48 hour rule out is not warranted unless hemodynamic instability)
- B. No minimum duration of antibiotics is required when patient has count recovery (ANC >200 cells/mm³ and rising) unless a source is identified in which case the duration is dictated by the identified source.
- C. Refer to [FIGURE 2](#) for de-escalation and treatment duration
- D. Refer to [adult vancomycin nomogram](#) or [pediatric vancomycin nomogram](#) for dosing and monitoring.

FIGURE 1: Initial Empiric Treatment of Febrile Neutropenia in High-Risk Hematology/Oncology and Hematopoietic Cell Transplant Patients

ASSESSMENT

- Physical exam of all possible infection sites
- Access and obtain blood cultures from all lumens of CVC (also peripheral blood cultures for adults)
- Chest X-ray and sputum culture (if respiratory symptoms)
- Urinalysis
- Urine culture
- Site specific cultures as appropriate (catheter, wound, stool)

Initial Empiric Treatment

Ordered STAT
Cefepime 2 g/dose (<40 kg: 50 mg/kg/dose extended infusion) IV q8h

Beta-Lactam Allergy?

Low¹/Medium²-Risk Cephalosporin Allergy
Piperacillin/tazobactam 4.5 g/dose (<50 kg: 80 mg piperacillin/kg dose extended infusion) IV q6h ordered STAT

High-Risk³ Allergy or Contraindication⁴ to Beta-Lactams⁵
Aztreonam 2 g/dose (<40 kg: 50 mg/kg/dose) IV q8h ordered STAT + Vancomycin dosing per institutional guidelines ([adult](#) | [peds](#))

If Fluid Refractory Hypotension

- Double cover gram negatives by adding tobramycin 5 mg/kg (<18 years: 7.5 mg/kg) IV once daily ordered STAT to beta-lactam antibiotic
 - Consider amikacin 15 mg/kg (<18 years: 20 mg/kg) IV once daily (instead of tobramycin) ordered STAT for those who have been on broad spectrum antibiotics for ≥10 days (*consider infectious diseases consult*)

AND

- Add vancomycin dosing per institutional guidelines ([adult](#) | [peds](#)) STAT

Indications for Addition of Empiric Vancomycin

- Clinically apparent central catheter-associated infection
- Skin or soft-tissue infection
- No routine use for pneumonia unless symptoms/signs of **severe pneumonia***
- Fluid refractory hypotension
- Recent hospitalization in previous 90 days for a MRSA infection

*obtain MRSA nasal culture, if negative and patient is clinically stable can discontinue vancomycin for above criteria unless positive cultures require vancomycin

Vancomycin dosing per institutional guidelines ([adult](#) | [peds](#))

Suspicion for Meningitis

Cefepime 2 g/dose (<40 kg: 50 mg/kg/dose extended infusion) IV q8h ordered STAT
AND
Vancomycin dosing per institutional guidelines ([adult](#) | [peds](#))
AND
Ampicillin 2 g/dose (<20 kg: 100 mg/kg/dose) IV q6h

- Obtain lumbar puncture
- Consider adding HSV coverage, acyclovir 10 mg/kg/dose IV q8h

Consult Infectious Diseases

Concern for GI Infection

Add metronidazole 500 mg/dose (<38 kg: 13 mg/kg/dose) PO/IV q8h to cefepime
OR
Switch cefepime to piperacillin/tazobactam 4.5 g/dose (<50 kg: 80 mg piperacillin/kg/dose extended infusion) IV q6h

¹Low-risk: pruritus without rash, remote (>10 years) unknown reaction, mild rash (self-resolves without additional medical intervention) with no other symptoms, patient denies allergy but is on record

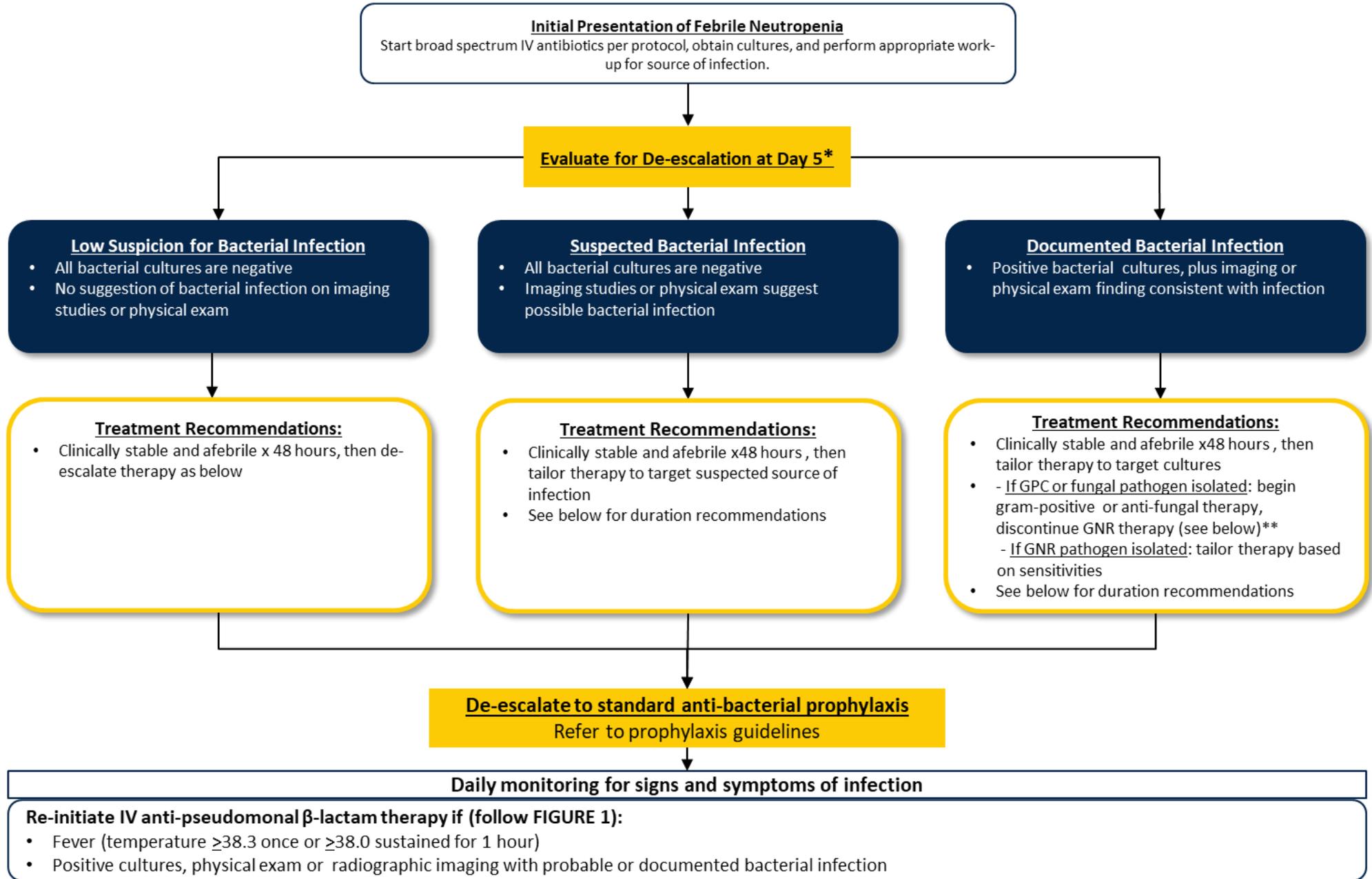
²Medium-risk: Urticaria/hives with no other symptoms, severe rash with no other symptoms (requires medical intervention and/or requires ER visit/hospitalization). Severe rash defined as: rash that requires medical intervention (corticosteroids, anti-histamines) and/or requires ER visit or hospitalization

³High-risk: Any of the following – respiratory symptoms, angioedema, cardiovascular symptoms, anaphylaxis

⁴Contraindication: organ damage, drug-induced immune-mediated anemia/thrombocytopenia/leukopenia, Stevens Johnson Syndrome/Toxic Epidermal Necrosis, acute generalized exanthematous pustulosis, drug rash eosinophilia and systemic symptoms (DRESS), serum sickness

⁵Beta-Lactams: penicillins, cephalosporins, carbapenems, aztreonam; patients with high risk allergy/contraindication to ceftazidime or aztreonam should not receive aztreonam

FIGURE 2: Febrile Neutropenia Antibiotic De-escalation in Clinically Stable and Afebrile Patients



| Infection [^] | Pneumonia | Blood Stream Infection | Cellulitis | UTI | Intra-abdominal | Typhlitis |
|--------------------------------------|--|---|---|--|--|---|
| Suggested duration of therapy | <ul style="list-style-type: none"> 7-14 days for patients with rapid clinical improvement and without complications 14+ days for patients with complications or for patients clinically unstable | <ul style="list-style-type: none"> Duration dependent on whether infection is uncomplicated or complicated and the causative organism (refer to VI. c. bloodstream infection duration) | <ul style="list-style-type: none"> 7-14 days of cellulitis-directed therapy (e.g., vancomycin) Continue therapy if cellulitis is unresolved by day 14 | <ul style="list-style-type: none"> 7 days of therapy 7-14+ days if patient develops bacteremia, pyelonephritis, perinephric abscess or other complications | <ul style="list-style-type: none"> 5-7 days of therapy, if adequate source control is achieved May require longer durations of therapy for patients with inadequate source control | <ul style="list-style-type: none"> 14 days of therapy Continue therapy if persistent symptoms or repeat imaging consistent with infection |

* Antibacterials may be discontinued prior to Day 5 evaluation at the discretion of the primary hematology/oncology/bone marrow transplant team if fever is thought to be due to non-infectious cases (i.e., platelet transfusions, fever from active malignancy/tumor fevers, etc).

** Patients with suspected fungal infections: consider Infectious Diseases and Pulmonary consult. Antibiotics may be continued at the discretion of the primary team

[^] Antibiotic therapy should NOT be de-escalated or discontinued in patients with persistent fevers, hemodynamic instability, or clinical instability, thought to be secondary to bacterial infection

Appendix 1. Pediatric Oncology Triage

I. TRIAGE, TRANSPORTATION, INITIAL ASSESSMENT AND TREATMENT

A. Triage/Initial Parental Transportation: For patients who are not acutely decompensating at home (and thus do not necessitate 911 services), parents may transport the patient by personal vehicle to the University of Michigan Emergency Department as long as they are not traveling for more than 30 minutes.

*If the patient lives more than 30 minutes from the University of Michigan Emergency Department, then they must be recommended to drive to their local Emergency Department for initial assessment, antibiotics and upfront care. (See appendix A for further information regarding regional hospital locations.)

B. Transportation following OSH Evaluation: For patients that are evaluated at OSH and determined to require transfer to the University of Michigan for admission, it is strongly encouraged that they be transferred with ACLS ambulance/helicopter transport. Parents will be discouraged from transporting their child from the OSH ED to the University of Michigan ED by personal vehicle. Exceptions will be made at the discretion of the Children’s Emergency Services (CES) Attending.

Ideally, all patients evaluated at an OSH should preferentially be considered for a direct admission to 7Mott with an ED Triage. Arrangements for the direct admission should be coordinated by the Pediatric Hematology/Oncology Fellow On-Call in conjunction with Bed Management/Mott Admissions. The Pediatric Hematology/Oncology Fellow On-Call should also notify the CES Attending of the expected patient for ED Triage. The final patient disposition – floor admission, PICU admission, or emergent additional ED care – will be at the discretion of the CES Attending at the time of ED Triage.

C. Initial Assessment recommendations for OSH refer to Section V above.

References:

1. NCCN Guidelines Version 2.2016. Prevention and Treatment of Cancer-related Infections. [J Natl Compr Canc Netw. 2016 Jul;14\(7\):882-913.](#)

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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.

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