Neutropenic Fever\(^1\) Inpatient Adult Treatment
(Hematologic Cancers including Lymphoma/Myeloma)

**Disclaimer:** This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. Local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics. This algorithm should not be used to treat pregnant women.

---

**Note:** This algorithm should also be used for patients receiving chimeric antigen receptor (CAR) T-cell therapy.

### PRESENTATION
- Patient with neutropenia **and** fever

### ASSESSMENT

- **Yes**
  - See Inpatient Sepsis Management - Adult algorithm and use sepsis ordering tools

- **No**
  - Physical exam
  - IV hydration
  - CBC with differential, basic metabolic panel, lactic acid
  - Blood cultures (with a set collected from each lumen simultaneously if CVAD present and 1 peripheral site)
  - Other cultures (e.g., sputum culture, respiratory viral PCR panel, urinalysis/urine culture), only if clinically indicated
  - MRSA nasal swab (if pneumonia suspected or confirmed)
  - Chest x-ray
  - Other tests as clinically indicated

---

\(^1\) CVAD = central venous access device
\(^1\) PCR = polymerase chain reaction
\(^1\) MRSA = methicillin-resistant *Staphylococcus aureus*

---

\(^2\) Criteria:
- Absolute neutrophil count (ANC) \(\leq 0.5\) K/microliter **and** temperature either \(\geq 38.3^\circ C\) or equal to \(38^\circ C\) for 1 hour or longer **or**
- ANC \(\leq 1\) K/microliter and an expected decline to \(\leq 0.5\) K/microliter over 48 hours **and** temperature either \(\geq 38.3^\circ C\) or equal to \(38^\circ C\) for 1 hour or longer

\(^2\) See Inpatient Sepsis Management - Adult algorithm for sepsis screening criteria
Neutropenic Fever Inpatient Adult Treatment
(Hematologic Cancers including Lymphoma/Myeloma)

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. Local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics. This algorithm should not be used to treat pregnant women.

ASSESSMENT

- For serious documented beta-lactam allergy, see Page 3
- For selecting antibiotic therapy consider the following:
  - Recent culture and sensitivity results
  - History of resistant gram negative organisms\(^1\) infection or colonization
  - Suspected line infection\(^3\)
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Mucositis \(\geq\) grade 2
  - Consider the use of therapeutic G-CSF if risk factors are present (see Appendix A)

G-CSF = granulocyte colony stimulating factor

VRE = vancomycin-resistant enterococcus

\(^1\)Refer to institutional renal dosing guide (internal only) or tertiary dosing references (e.g., Lexicomp) for dosing recommendations

\(^2\)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 entry site

\(^4\)Consider meropenem if patient has any of the following: • Non-IgE-mediated allergy to alternative agents • Recent treatment (\(\geq 3\) days duration) with cefepime or piperacillin-tazobactam within past 30 days • Infection with ESBL organism • Infection with organism only susceptible to carbapenem

\(^5\)If patient was not previously on levofloxacin prophylaxis, consider adding a fluoroquinolone, azithromycin, or doxycycline for atypical pathogen coverage

\(^6\)Consider expanded gram positive coverage if mucositis \(\geq\) grade 2 and on fluoroquinolone prophylaxis and on ceftazidime as empirical therapy. Isolated mucositis is not an indication for expanded gram positive coverage.

ANTIBACTERIAL RECOMMENDATIONS\(^1\)
(Adjust dose for patients with renal/hepatic dysfunction)

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

Select one:
- Cefepime
  - Add metronidazole if suspected intra-abdominal infection or other indication for anaerobic coverage
- Piperacillin-tazobactam
- Meropenem\(^4\)

If complicated tissue-based infections, neutropenic enterocolitis, perirectal infections or other indication for double gram negative coverage consider adding:
- Amikacin

Is expanded gram positive coverage needed?

If suspected line infection\(^3\) and/or bacteremia add:
- Vancomycin or
- Daptomycin (if no evidence of pneumonia)

If MRSA colonization or skin and soft tissue infection or pneumonia\(^5\) or mucositis\(^6\) \(\geq\) grade 2 add:
- Vancomycin or
- Linezolid (not preferred for MRSA blood stream infection) or
- Daptomycin (if no evidence of pneumonia)

If VRE colonization or infection add:
- Linezolid or
- Daptomycin (if no evidence of pneumonia)

Department of Clinical Effectiveness V4
Approved by the Executive Committee of the Medical Staff on 06/21/2022
Neutropenic Fever Inpatient Adult Treatment (Hematologic Cancers including Lymphoma/Myeloma)

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. Local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics. This algorithm should not be used to treat pregnant women.

SERIOUS DOCUMENTED BETA-LACTAM ALLERGY
(anaphylaxis, hives, or serious non-IgE mediated drug reactions)

**ASSESSMENT**

- For selecting antibacterial therapy consider the following
  - Recent culture and sensitivity results
  - History of resistant gram negative organism infection or colonization
  - Suspected line infection
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Mucositis ≥ grade 2
  - Consider the use of therapeutic G-CSF if risk factors are present (see Appendix A)

**ANTIBACTERIAL RECOMMENDATIONS**
(Adjust dose for patients with renal/hepatic dysfunction)

For gram negative coverage antibiotics should be given first. Antibiotics should be given within 1 hour.

- **For gram negative coverage select:**
  - Aztreonam
  - **Plus:**
    - Amikacin or Ciprofloxacin (only if no quinolone prophylaxis)

  **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 findings**
  - If suspected line infection and/or bacteremia select one of the following:
    - Vancomycin or Daptomycin (if no evidence of pneumonia)

  - If MRSA colonization or skin and soft tissue infection select one of the following:
    - Vancomycin or Linezolid (not preferred for MRSA blood stream infections) or Daptomycin (if no evidence of pneumonia)

  - If none of the above, select one of the following:
    - Vancomycin or Linezolid

---

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 Refer to institutional renal dosing guide (internal only) or tertiary dosing references (e.g., Lexicomp) for dosing recommendations
3 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
4 Chills, rigors with infusion through catheter, cellulitis or discharge around the catheter entry site
5 Double gram negative coverage recommended due to reduced gram negative pathogen susceptibility to aztreonam according to local antibiograms

See Page 4 for re-assessment
Neutropenic Fever Inpatient Adult Treatment (Hematologic Cancers including Lymphoma/Myeloma)

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. Local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics. This algorithm should not be used to treat pregnant women.

RE-ASSESSMENT

 Patient febrile

 Has source of fever been identified?

 Yes

Re-evaluate at 72-96 hours from onset of neutropenic fever

TREATMENT

 Has source of fever been identified?

 Yes

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

 If all of the following criteria are met for 48-72 consecutive hours, consider short (≤ 5 days) course of antimicrobial therapy and resume antimicrobial prophylaxis if neutropenia not resolved

 Resolution of signs and symptoms of infection and

 Normal vital signs and

 Apyrexia

 Has source of fever been identified?

 No

Check susceptibilities

Make necessary changes in antimicrobial regimen

Imaging, serology, and other diagnostic work-up as clinically indicated

Consider or re-evaluate antifungals and/or antivirals

Patient afebrile

Re-evaluate2 at 72-96 hours from onset of neutropenic fever

If all of the following criteria are met for 48-72 consecutive hours, consider short (≤ 5 days) course of antimicrobial therapy and resume antimicrobial prophylaxis if neutropenia not resolved

Resolution of signs and symptoms of infection and

Normal vital signs and

Apyrexia

Check susceptibilities

Make necessary changes in antimicrobial regimen

Imaging, serology, and other diagnostic work-up as clinically indicated

Consider or re-evaluate antifungals and/or antivirals

Re-assess at Day 5

If febrile, consult Infectious Diseases if not already consulted for further work-up and disposition

Repeat cultures

CT chest, aspergillus antigen, and/or other diagnostic work-up as clinically indicated

Re-evaluate antibiotics

Consider antifungal and/or antivirals

Consult Infectious Diseases

● If afebrile, disposition per Primary Team and reassess as clinically indicated

1 Refer to institutional renal dosing guide (internal only) or tertiary dosing references (e.g., Lexicomp) for dosing recommendations

2 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)

3 In the absence of steroids or antipyretics

4 Consider transition to antimicrobial prophylaxis if otherwise indicated and no clear infectious source of fever is identified
APPENDIX A: Potential Indications for use of Therapeutic G-CSF

Consider therapeutic use if the following risk factor(s) are present:

- Sepsis
- Age > 65 years old
- Pneumonia or other documented infection
- Invasive fungal infection
- ANC < 100 K/microliter
- Expected neutropenia duration > 10 days
- Hospitalization at the time of fever or prior episode of neutropenic fever

Note: Continue G-CSF if patient was receiving as daily prophylaxis.
SUGGESTED READINGS


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

**Core Development Team Leads**
Antimicrobial Stewardship Team

**Workgroup Members**
Javier Adachi, MD (Infectious Diseases)
Wendy Garcia, BS*
Alison Gulbis, PharmD (Pharmacy Clinical Programs)
Alexandra Hacker, MSN, APRN, FNP-BC*
Ella Ariza Heredia, MD (Infectious Diseases)
Tami Johnson, PharmD (Pharmacy Clinical Programs)
Kayleigh Marx, PharmD (Pharmacy Clinical Programs)
Joseph Nates, MD (Critical Care & Respiratory Care)
Adrienne Sevin, PharmD (Pharmacy Clinical Programs)

* Clinical Effectiveness Development Team

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. Local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics. This algorithm should not be used to treat pregnant women.