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 can also be used for patients receiving stem cell transplantation or immune effector cell (IEC) therapy.

**PRESENTATION**

Patient with neutropenia and fever\(^1\)

**ASSESSMENT**

Does patient meet sepsis screening criteria?\(^2\)

- Physical exam
- IV hydration
- CBC with differential, basic metabolic panel, lactic acid
- Blood cultures (collected from each lumen simultaneously if CVAD present and 1 peripheral site)
- Other diagnostics (e.g., MRSA nasal swab, sputum culture, respiratory viral PCR, urinalysis with reflex culture) only if clinically indicated
- Imaging (chest x-ray, abdominal x-ray, etc.) or other tests as clinically indicated

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

**TREATMENT**

See Pages 2-3 for antibacterial recommendations

CVAD = central venous access device
PCR = polymerase chain reaction
MRSA = methicillin-resistant *Staphylococcus aureus*

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

\(^2\) See Inpatient Sepsis Management - Adult algorithm for sepsis screening criteria
**ASSESSMENT**

- For serious documented beta-lactam allergy, see Page 3
- For selecting antibacterial therapy consider the following:
  - Recent culture and sensitivity results
  - History of resistant gram negative organism infection or colonization
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Drug interactions
  - Local/institutional antibiogram
- 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

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**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.

Select one:
- Cefepime
  - If mucositis ≥ grade 2, suspected intra-abdominal or perirectal infection, or other indication for anaerobic coverage consider adding:
    - Metronidazole
    - Piperacillin-tazobactam
    - Meropenem

If septic shock on vaspressors, 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 and/or bacteremia add:**
- Vancomycin
  - **or**
  - Daptomycin (if no evidence of pneumonia)

If MRSA colonization or skin and soft tissue infection or pneumonia 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)

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For serious documented beta-lactam allergy, see Page 3

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- Source of infection, if identified
- Organ dysfunction
- Drug interactions
- Local/institutional antibiogram

Consider the use of therapeutic G-CSF if risk factors are present (see Appendix A)

G-CSF = granulocyte colony stimulating factor

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For gram positive coverage, select from the following findings:
- If suspected line infection and/or bacteremia add:
  - Vancomycin
  - Daptomycin (if no evidence of pneumonia)
- If MRSA colonization or skin and soft tissue infection or pneumonia or mucositis ≥ grade 2 add:
  - Vancomycin
  - Linezolid (not preferred for MRSA bloodstream infections) or
  - Daptomycin (if no evidence of pneumonia)
- If none of the above add:
  - Vancomycin
  - Linezolid

For gram negative coverage, select from the following:
- Aztreonam
- Consider adding:
  - Amikacin or
  - Ciprofloxacin (only if no fluoroquinolone prophylaxis or therapy in past 90 days)
- If mucositis ≥ grade 2, suspected intra-abdominal or perirectal infection, or other indication for anaerobic coverage consider adding:
  - Metronidazole

**ASSESSMENT**

- For selecting antibacterial therapy consider the following:
  - Recent culture and sensitivity results
  - History of resistant gram negative organism\(^1\) infection or colonization
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Drug interactions
  - Local/institutional antibiogram\(^4\)
  - Consider the use of therapeutic G-CSF if risk factors are present (see Appendix A)

- For gram negative coverage select:
  - Aztreonam
  - Consider adding:
    - Amikacin or
    - Ciprofloxacin (only if no fluoroquinolone prophylaxis or therapy in past 90 days)
  - If mucositis ≥ grade 2, suspected intra-abdominal or perirectal infection, or other indication for anaerobic coverage consider adding:
    - Metronidazole

- Add gram positive coverage

**ANTIBACTERIAL RECOMMENDATIONS**

- For gram positive coverage, select from the following findings:
  - If suspected line infection\(^6\) and/or bacteremia add:
    - Vancomycin or
    - Daptomycin (if no evidence of pneumonia)
  - If MRSA colonization or skin and soft tissue infection or pneumonia\(^7\) or mucositis ≥ grade 2 add:
    - Vancomycin or
    - Linezolid (not preferred for MRSA bloodstream infections) or
    - Daptomycin (if no evidence of pneumonia)
  - If none of the above add:
    - Vancomycin or
    - Linezolid

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\(^1\) 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 antimicrobial 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

\(^4\) Refer to gram negative and gram positive antibiograms (internal only)

\(^5\) Double gram negative coverage recommended due to reduced gram negative pathogen susceptibility to aztreonam according to local antibiograms

\(^6\) Chills, rigors with infusion through catheter, cellulitis or discharge around the catheter entry site

\(^7\) If patient was not previously on fluoroquinolone prophylaxis, consider adding a fluoroquinolone, azithromycin, or doxycycline for atypical pathogen coverage

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RE-ASSESSMENT

Has source of fever been identified?

Patient afebrile

Yes

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

No

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 in the absence of steroids or antipyretics

Has source of fever been identified?

Patient febrile

Yes

- 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

No

- Consult Infectious Diseases
- Repeat cultures
- CT sinuses, CT chest, aspergillus antigen, and/or other diagnostic work-up as clinically indicated
- Re-evaluate antibiotics for need to broaden coverage
- Consider adding or expanding antifungal and/or antivirals
- Evaluate thoroughly for non-infectious causes of fever (e.g., medications, thrombosis, underlying malignancy)

EVALUATION

Reassess at Day 5

- If afebrile, disposition per Primary Team and reassess as clinically indicated
- If febrile, consult Infectious Diseases if not already consulted for further work-up and disposition

TREATMENT

1 Refer to institutional antimicrobial 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, negative MRSA nares swab, and/or no active cellulitis)

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

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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


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DEVELOPMENT CREDITS

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:

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