Febrile Neutropenia INPATIENT Management Guidelines

1. Identify patients with neutropenic fever and consider their underlying risk level:

Neutropenic fever: a single temperature >101 or temp >100.4 on 2 consecutive measurements or signs of early sepsis/hemodynamic instability * and ANC <500 (or expected to be <500 in next 48hrs).

* Classical signs/symptoms may be absent, especially early in the clinical course- use clinical judgment at all times; maintain a low threshold for antibiotics in patients who do not fit the above criteria but are clinically concerning

A ‘High Risk’ patient is defined as someone with an anticipated neutropenia >7 days, clinical instability, or multiple medical comorbidities.

2. Begin diagnostic workup by obtaining the following:
   - Blood cultures (2 sets), urinalysis/urine culture, and 2-view chest X-ray.
   - If symptomatic and seasonally appropriate, consider Flu/RSV, RVP, and/or SARS-CoV-2 PCR.
   - If diarrhea present, send stool for C. difficile and GI pathogen panel if appropriate
   - If no prior h/o MRSA infection, send MRSA nasal swab

3. Treatment:

Begin cefepime 2g IV q8h (if CrCl>60) for empiric coverage

Renally adjust as below:
CrCl 30-60 → 2g IV q12h
CrCl 10-29 → 1g IV q12h or 2g IV q24h
CrCl <10 or HD → 1g IV q24h
CVVH → 2g IV q12h

*If patient is hemodynamically unstable, or concern for multidrug resistant infection, consider addition of gentamicin to cefepime. If plan to continue gentamicin, recommend ID consultation

Is the patient allergic to cefepime?

a. If mild or unclear allergy to penicillin, consider using cefepime and monitor closely. Cross reactivity of penicillin with cephalosporin is 2-3%

b. If concern for anaphylaxis / IgE mediated allergy (hives, bronchospasm, angioedema), treat with aztreonam 2g IV q8h +/- gentamicin 5-7mg/kg IV q24h (if c/f MDRO or severe sepsis) + vancomycin per nomogram
4. Determine need for vancomycin coverage (in addition to cefepime):

<table>
<thead>
<tr>
<th>Reasons to add IV vancomycin coverage empirically in neutropenic fever</th>
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<tbody>
<tr>
<td>Evidence of pneumonia on imaging</td>
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<tr>
<td>Skin or soft tissue infection (also consider adding clindamycin+ surgery consult if nec fasc concern)</td>
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<tr>
<td>Suspected central line infection</td>
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<tr>
<td>Known recent prior MRSA infection</td>
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<tr>
<td>Gram positive bacteremia</td>
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<tr>
<td>Septic shock</td>
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* Mucositis is NOT a reason to add vancomycin if using cefepime monotherapy

**If vancomycin is continued for >72 hours and renal function remains stable, AUC monitoring should be used to minimize toxicity and maximize efficacy. Please contact ID pharmacy or ID for further assistance with this**

5. Reevaluate at 48hr- need for escalation vs de-escalation of antibiotics:

a. Patient is still febrile:
   i. Have we found a source? Consider ID consult for further workup or possible antimicrobial adjustment
   ii. Consider stopping the vancomycin if MRSA nares negative or no findings to suggest gram positive infection

b. Patient is afebrile but still neutropenic:
   i. If source found, consider narrowing antibiotics to target cultured organism and set a recommended course of duration
   ii. If signs/symptoms of infection resolve, consider de-escalating cefepime back to levofloxacin prophylaxis until ANC >500 or stopping antibiotics altogether and monitoring off therapy

c. Patient is afebrile and no longer neutropenic:
   i. Stop antibiotics

Management of select clinical syndromes as a cause of neutropenic fever:

- Intra-abdominal infection suspected
  o Consider adding anaerobic coverage with metronidazole 500mg q8h or changing cefepime to piperacillin-tazobactam (adjusted for renal function)
  o Consider CT A/P

- *Clostridioides difficile* suspected
  o Send stool C diff test
  o Place patient in Contact (PLUS) isolation while test pending
  o Start patient on empiric PO vancomycin 125mg q6h or fidaxomicin 200mg q12h
    ▪ Fidaxomicin is preferred for recurrent C diff
    ▪ If concern for ileus / critically ill, choose PO vancomycin 500mg q6h + IV metronidazole and consult ID
- **Meningitis/encephalitis suspected**
  - Obtain imaging and LP – send CSF for cell count/diff, protein, glucose, bacterial culture, HSV PCR, VZV PCR, HHV6 PCR (and other tests if clinically indicated)
  - In addition to cefepime, add IV vancomycin (dosed per nomogram), ampicillin 2g IV q4h, +/- IV acyclovir 10mg/kg q8h IBW
  - Obtain ID consult

- **Respiratory viral illness suspected**
  - If concern for COVID-19 and last PCR >3 days prior, send one swab for repeat SARS-CoV2 PCR + FLU/RSV (FLUVID)
    - Place patient on special pathogen precautions while test pending
    - If positive, consult ID for treatment recommendations and move patient to single room with special pathogen precautions if not already on isolation
  - If above tests are negative, consider respiratory viral panel
    - Place patient in droplet/contact isolation while test pending
  - If influenza positive, start oseltamivir
  - If patient is in shared room with flu positive, start prophylactic oseltamivir for roommate (ID approval needed)

- **Pneumonia suspected**
  - Send sputum culture, urine legionella Ag, urine strep pneumo Ag

- **Severe soft/tissue infection with concern for necrotizing fasciitis**
  - Add clindamycin 900mg q8h
  - Consult surgery
1) Identify
- Single temp ≥ 101 or temp ≥ 100.4 on 2 consecutive measurements or evidence of hemodynamic instability or signs of early sepsis, and
- ANC < 500 or expected to be < 500 in next 48 hours

Classical signs/symptoms may be absent, especially early in the clinical course—use clinical judgment at all times; maintain a low threshold to start antibiotics in patients who do not fit the above criteria but are clinically concerning.

2) Obtain diagnostic workup
- 2 sets of blood cultures
- Urine (and urine culture)
- CXR (PA and lateral preferable, AP only if unable to leave the unit)
- Stool for C. diff, if diarrhea present
- MRSA nares

-SARS-CoV-2 PCR / Flu/RSV PCR, if negative, then respiratory viral panel (RVP), if seasonally appropriate

3) Begin cefepime (renally dosed as below)

<table>
<thead>
<tr>
<th>Ccr (ml/min)</th>
<th>Dose</th>
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<tbody>
<tr>
<td>&gt;60</td>
<td>2g q8hrs</td>
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<td>30-60</td>
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If hemodynamically unstable or concern for MDRO, consider addition of gentamicin to cefepime.

If suspected IgE mediated allergy to cefepime, begin:
- aztreonam + IV vancomycin
  +/- gentamicin (for critically ill and/or suspected gram negative infection)

4) Add IV vancomycin per nomogram if one or more of the following:
- Severe sepsis or hemodynamic instability
- Pneumonia documented on imaging
- Blood culture + for gram positive organism and identification/sensitivities pending
- Suspected serious catheter related infection (i.e., chills with infusion, cellulitis at insertion site)
- Skin or soft tissue infection
- Known colonization or previous MRSA infection or history of other multidrug resistant organisms (ID consultation recommended)

Note: severe mucositis while receiving fluoroquinolone prophylaxis is not an indication for Vancomycin if Cefepime is given as empiric therapy.

5) Re-evaluate for de-escalation or additional workup after 48-72 hours of empiric therapy (assuming negative workup above)

<table>
<thead>
<tr>
<th>Afebrile + ANC &lt; 500</th>
<th>Still febrile after 48-72hrs of empiric therapy</th>
<th>Afebrile + ANC &gt; 500</th>
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</thead>
<tbody>
<tr>
<td>Consider the following:</td>
<td>Consider ID consult for adjustment in antimicrobial regimen and further workup (see next page)</td>
<td>Discontinue antibiotics unless documented infection on workup</td>
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<tr>
<td>- Discontinue antibiotics after 3-5 days of apyrexia assuming negative work up</td>
<td>- Change to levofloxacin 500mg q24h prophylaxis until ANC &gt; 500</td>
<td>- Continue cefepime monotherapy until ANC &lt; 500</td>
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