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 (if symptomatic), and 2-view chest X-ray.
- If symptomatic and seasonally appropriate, obtain 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:

a. If initial episode of febrile neutropenia this admission, 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, begin meropenem and consult ID**

Is the patient allergic to cefepime?

i. If mild or unclear allergy to penicillin, consider using cefepime and monitor closely. Cross reactivity of penicillin with cephalosporin is 2-3%
ii. If concern for anaphylaxis / IgE mediated allergy (hives, bronchospasm, angioedema), treat with aztreonam 2g IV q8h +/- tobramycin 5-7mg/kg IV q24h (if c/f MDRO or severe sepsis) + vancomycin per nomogram

b. If previous episode of febrile neutropenia or patient has received >7 days of cefepime this admission, consider meropenem 500mg q6hrs (for CrCl>50)

Renally adjust as below:

CrCl 30-49 → 500mg IV q8h

CrCl 10-29→ 500mg IV q12h
CrCl <10 or HD → 500mg IV q24h
CVVH → 1g IV q12h

4. Determine need for vancomycin coverage (in addition to cefepime):

Reasons to add IV vancomycin coverage empirically in neutropenic fever
Evidence of pneumonia on imaging
Skin or soft tissue infection *(also consider adding clindamycin+ surgery consult if nec fasc concern)*
Suspected central line infection
Known recent prior MRSA infection
Gram positive bacteremia
Septic shock

* *Mucositis is NOT a reason to add vancomycin if using cefepime monotherapy*

If vancomycin is continued for >72hours 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

****If blood cultures are positive for Gram positive organisms, particularly in pairs and chains, strongly consider daptomycin for empiric coverage. Contact ID for approval****

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, narrow antibiotics to target the cultured organism and set a recommended course of duration
   ii. If no source found and signs/symptoms of infection resolve after 3days of therapy, de-escalate cefepime back to levofloxacin prophylaxis until ANC >500 or monitor off antibiotics
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
  - Consider adding anaerobic coverage with metronidazole 500mg q8h or changing cefepime to piperacillin-tazobactam (adjusted for renal function)
  - If septic shock and intraabdominal source suspected, start meropenem + tobramycin
  - Consider CT A/P
- *Clostridioides difficile* suspected
  - Send stool C diff test

    - Place patient in Contact (PLUS) isolation while test pending
    - 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, begin 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
    - Obtain SARS-CoV2 PCR + FLU/RSV
        - Place patient on special pathogen precautions while test pending
        - If positive for SARS-CoV2, consult ID for treatment recommendations and move patient to single room with special pathogen precautions if not already on isolation
        - If positive for influenza, start oseltamivir (renally dosed) and place patient in droplet isolation
            - If patient is in shared room, start prophylactic oseltamivir for roommate (ID approval needed)
    - If above tests are negative, consider respiratory viral panel
        - Place patient in droplet/contact isolation while test pending
- 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

References:

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1) Identify

-Single temp ≥101 or temp ≥ 100.4 on 2 consecutive measurements OR evidence of hemodynamic instability/ signs of early sepsis, 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 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
- Urinalysis and urine culture (if symptomatic)
- CXR (PA and lateral preferable, AP only if unable to leave the unit)
- Stool for C. diff, if diarrhea present
-MRSA nares
-SARS-CoV2 PCR / Flu/RSV PCR, if negative, then respiratory viral panel (RVP), if seasonally appropriate

3) Begin cefepime (renally dosed as below)

Crcl (ml/min)
>60→ 2g q8hrs
30-60→ 2g IV q12hrs
10-29→ 1g IV q12hrs or 2g IV q24hrs
<10 or HD→ 1g IV q24hrs
CVVH→ 2g IV q12hrs

If hemodynamically unstable, concern for MDRO, or extensive prior cefepime exposure this admission, begin meropenem

If suspected IgE mediated allergy to cefepime, begin:
aztreonam + IV vancomycin +/- tobramycin (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 48-72hours of empiric therapy (assuming negative work up above)

Afebrile + ANC <500

Consider the following:
- Discontinue antibiotics after 3 days of apyrexia assuming negative work up
OR
- Change to levofloxacin 500mg q24h prophylaxis until ANC >500

Still febrile after 48-72hrs of empiric therapy

Consider ID consult for adjustment in antimicrobial regimen and further work up (see next page)

Afebrile + ANC >500

Discontinue antibiotics unless documented infection on work up