**Neutropenic Fever (Uploaded on 9/24/2023)**

**Neutropenic Fever Inpatient Empiric Coverage**

**Guidelines approved by the divisions of Hematology/Oncology and Infectious Diseases**  
  
All patients, on admission for fever and neutropenia, should have the following sent:

* Basic labs as per usual clinical protocol and the powerplan
* Blood cultures from all central line lumens with ideally 2-5 mL per culture. Patients over 26kg should have adult blood culture bottles (aerobic and anaerobic 2-bottle sets) sent rather than pediatric.
  + Blood cultures should be sent daily x 3 days total, then no more sent unless one is positive or the patient has a clinical change in status, even if still febrile.
* Procalcitonin, CRP, lactate. This should be sent at the time of the initial blood culture and then Q24 hours x 3 days. Any patient who is not consented for the “Biomarkers of Sepsis in Febrile Neutropenia” study should be approached at this time or when patient is stable.

1. **Empiric Coverage**

1. **Cefepime monotherapy** EXCEPT in the following situations:
   1. the patient is clinically unstable (unstable vital signs, poor response to fluid resuscitation, need for pressor support)
   2. the patient has a documented culture history of resistant GNRs, MRSA, or VRE isolated from blood or another body location
   3. the patient has received high-dose ara-C (or another regimen with higher than average incidence of oral mucositis)
   4. Any obvious skin or oral source is apparent, suggesting gram-positive infection
2. *If* need to broaden GNR coverage for concern for gram-negative infection (sepsis, clinical worsening, intra-abdominal infection, etc.)
   1. Consider ID consult
   2. **Maintain cefepime and add tobramycin** (or **amikacin** if a history of MDR-GNRs/ESBLs)
      1. If there is a suspected need for atypical (mycoplasma) coverage, or if the patient is in renal failure with GFR < 30, would then add **levofloxacin** instead
      2. Dose aminoglycoside as once-daily dosing regimen
         1. for tobramycin: 7 mg/kg/dose once daily with trough level checked at 24 hours after 1st dose, levels should be <2 mcg/mL.
3. *If* broader Gram-positive coverage is desired for reasons outlined above (poor line appearance or concern for line sepsis, obvious gram-positive source such as skin or oral mucosa as above, receipt of high dose ara-C or equivalent as above, etc.)
   1. Consider ID consult
   2. **Maintain cefepime and add vancomycin** empirically, dosed at 15 mg/kg/dose IV q6h for patients under 50kg or tanner <4; for tanner 4 or >50 kg, use 1 gm q12h (adult dosing).
   3. Obtain trough 30 minutes prior to 4th dose with target troughs at 15-20 mcg/mL.
4. *If* concern for an intra-abdominal source (i.e. typhlitis) or anaerobic coverage is desired:
   1. use **piperacillin-tazobactam** **monotherapy** OR **cefepime + Flagyl**
5. *If* the patient is penicillin-allergic:
   1. Consider ID consult
   2. if rash alone, can use **cefepime monotherapy**
   3. if cephalosporin-allergic OR more severe penicillin-allergic (i.e. hives, anaphylaxis), use **levofloxacin** AND **vancomycin**

2. **When to Narrow or Discontinue Coverage**  
  
a. *If* NO organism found

1. *If* **no source** for fever is found, continue **cefepime monotherapy** until all below are satisfied:
   1. afebrile at least 48 hours
   2. clinically well (i.e. discharge-ready)
   3. with ANC ≥200 and actively rising
2. *If* a source for the fever is identified and the patient shows clinical improvement/resolution of symptoms, continue appropriate therapy for the identified source.
   1. This could continue as *oral antibiotics* after discharge, if needed, for a total course (including the inpatient therapy) of 14 days total at minimum, with total duration and antibiotic choice depending on the source.
   2. May call ID for guidance on oral transition
3. *If* **vancomycin** was added empirically
   1. *If* cultures are negative, and there is no clinical indication for continued use, would consider stopping vancomycin after 48 hours.
      1. Clinical indications for continued use would include improvement in clinical status with initiation of vancomycin, or indications for initial use as on page 1.
4. *If* double gram-negative coverage was added empirically
   1. It may be more difficult to narrow coverage given the patient’s prior instability.
   2. Narrowing should be considered on a case-by-case basis, depending on the reason for adding the drug.
   3. May call ID for guidance

b. *If* an organism is found

1. Gram-Negative Infections
   1. **stop vancomycin** if it was empirically added and patient is clinically stable
   2. narrow based on sensitivities but no narrower than **cefepime monotherapy**.
   3. can stop double coverage if patient afebrile and clinically stable for at least 48 hours
2. Gram-Positive Infections
   1. *If* required by sensitivities,**add Vancomycin**
   2. *If* there is good evidence for GPCs as the source of fever (see above and on page 1) and the patient is now clinically well and afebrile x 48 hours, could **consider discontinuing cefepime and continuing on vancomycin monotherapy** or narrower GPC coverage if appropriate.
   3. *If* the organism is sensitive to oxacillin or ampicillin or 1st-generation cephalosporins, can continue to use **cefepime monotherapy**.
3. *If* a more resistant GNR or GPC is grown
   1. strongly consider an ID consult
   2. treatment decision should still be guided by susceptibility panel and potential toxicity.

3. **When to Escalate to Antifungal Coverage**

1. *If* simply persistently febrile and not worsening/no clinical change, hold off on broadening coverage for 4-5 days.
   1. Initiate searches (if not already done) for a viral cause
   2. Repeat blood cultures daily (with fever spikes if possible / if still febrile. Consider sending fungal isolator blood cultures
   3. Perform repeat detailed physical exams for less easily observed sources—sites of skin breakdown, oral lesions, etc.
   4. Broaden antibacterial coverage if clinically worsens during this time period
2. *If* not defervescing and still neutropenic at 5 days
   1. consider starting antifungal workup including but not limited to:
      1. serum aspergillus galactomannan
      2. CT scan chest/abdomen/pelvis
      3. renal/liver/spleen ultrasound
      4. echocardiography
      5. blood culture sent in fungal isolator tubes
   2. Consider empiric antifungal coverage:
      1. start **liposomal amphotericin at 3 mg/kg/day**
      2. can escalate to 5-6 mg/kg if proven fungal infection
      3. *If* documented fungal infection known, should tailor antifungal coverage based on organism and sensitivities

4. O**ther non-bacterial cause for fever**

1. *If* a respiratory or enteric virus (i.e. RSV, influenza, etc.) is found as the presumptive source
   1. would continue to treat with **cefepime monotherapy** until afebrile and no longer neutropenic.

OVERALL:

1. Continuous reassessment based on repeat vital signs, repeat physical exam and assessment is essential to the proper care of this population.
   1. Sudden changes in clinical status could prompt equally sudden and urgent changes in antimicrobials or ongoing workup.
   2. Delay in instituting such care due to delays in accurate patient assessment could lead to increased morbidity or mortality.