**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:

1. Basic labs as per usual clinical protocol and the powerplan
2. 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.
   1. 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.
3. 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**

* **Cefepime monotherapy** EXCEPT in the following situations:
  + the patient is clinically unstable (unstable vital signs, poor response to fluid resuscitation, need for pressor support)
  + the patient has a documented culture history of resistant GNRs, MRSA, or VRE isolated from blood or another body location
  + the patient has received high-dose ara-C (or another regimen with higher than average incidence of oral mucositis)
  + Any obvious skin or oral source is apparent, suggesting gram-positive infection
* *If* need to broaden GNR coverage for concern for gram-negative infection (sepsis, clinical worsening, intra-abdominal infection, etc.)
  + Consider ID consult
  + **Maintain cefepime and add tobramycin** (or **amikacin** if a history of MDR-GNRs/ESBLs)
    - 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
    - Dose aminoglycoside as once-daily dosing regimen
      * for tobramycin: 7 mg/kg/dose once daily with trough level checked at 24 hours after 1st dose, levels should be <2 mcg/mL.
* *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.)
  + Consider ID consult
  + **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).
  + Obtain trough 30 minutes prior to 4th dose with target troughs at 15-20 mcg/mL.
* *If* concern for an intra-abdominal source (i.e. typhlitis) or anaerobic coverage is desired:
  + use **piperacillin-tazobactam** **monotherapy** OR **cefepime + Flagyl**
* *If* the patient is penicillin-allergic:
  + Consider ID consult
  + if rash alone, can use **cefepime monotherapy**
  + 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

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

b. *If* an organism is found

* Gram-Negative Infections
  + **stop vancomycin** if it was empirically added and patient is clinically stable
  + narrow based on sensitivities but no narrower than **cefepime monotherapy**.
  + can stop double coverage if patient afebrile and clinically stable for at least 48 hours
* Gram-Positive Infections
  + *If* required by sensitivities,**add Vancomycin**
  + *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.
  + *If* the organism is sensitive to oxacillin or ampicillin or 1st-generation cephalosporins, can continue to use **cefepime monotherapy**.
* *If* a more resistant GNR or GPC is grown
  + strongly consider an ID consult
  + treatment decision should still be guided by susceptibility panel and potential toxicity.

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

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

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

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

OVERALL:

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