GUIDELINES FOR THE TREATMENT OF NEUTROPENIC FEVER IN ADULT BONE MARROW TRANSPLANT PATIENTS

I. SCOPE: The algorithm covers the antibiotic management of the first neutropenic fever. Guidelines are also included for the management of persistent fever and sepsis.

II. GUIDELINE:

A. FIRST Neutropenic FEVER [ANC <1000, temperature ≥38°C oral or axillary [Empirical Therapy]

   If the patient is febrile but hemodynamically stable:
   1. Continue fluconazole 100 mg PO daily if Autologous or Allogeneic transplant. If MUD or on etanercept then change to voriconazole 200 mg PO BID. (If liver enzymes elevated or IV therapy required then change to micafungin 100 mg IV daily.)
   2. If no allergy to penicillin or cephalosporin, start cefepime 2 g IV q8h
   3. If there are no positive cultures, continue cefepime
   4. If cultures become positive for Gram positive organism add vancomycin 15 mg/kg IV q12h (dose to be adjusted if needed based on pharmacokinetic parameters). (Round dose to nearest 250 mg.) If cultures become positive for gram positive cocci in chains substitute daptomycin 6 mg/kg IV daily for the vancomycin until culture and sensitivity obtained.
   5. If cultures become positive for gram negative organism and the patient is hemodynamically unstable, add tobramycin 5 mg/kg IV q24h (based on adjusted weight) and then dose adjust (based on pharmacokinetic parameters). Check 18-hour level after dose.
   6. Adjust antibiotic coverage based on culture and sensitivity.

B. FIRST Neutropenic FEVER and Hemodynamically UNSTABLE

   1. Continue fluconazole 100 mg PO daily if Autologous or Allogeneic transplant. If MUD then change to voriconazole 200 mg PO BID. (If liver enzymes elevated or IV therapy required then change to micafungin 100 mg IV daily.)
   2. No allergy to penicillin or cephalosporin start cefepime 2 g IV q8h plus vancomycin 15 mg/kg IV q12h plus tobramycin 5 mg/kg IV q24h (adjusted weight). If cultures become positive for Gram positive cocci in chains substitute daptomycin 6 mg/kg IV daily for the vancomycin.
   3. Adjust antibiotic coverage based on culture and sensitivity.
   4. If suspect GI as source, add metronidazole 500 mg IV q8h or change to piperacillin-tazobactam 4.5 g q6h

C. FIRST Neutropenic FEVER, hemodynamically STABLE but suspect one of the following:

   - erythema at the catheter exit site
   - tenderness at the catheter exit site
   - exudate at the catheter exit site
   - tunnel infection
   - cellulites
   - folliculitis

   1. No allergy to penicillin or cephalosporin start cefepime 2 g IV q8h (if decreased creatinine clearance, dose adjust as in IV. A-3) plus vancomycin 15mg/kg IV q12h (dose adjust as per pharmacokinetic parameters).
   2. Continue as in III. A.

D. FIRST Neutropenic FEVER, hemodynamically STABLE but allergic to penicillin/cephalosporin

   1. Continue fluconazole 100 mg PO daily if Autologous or Allogeneic transplant. If MUD then change to voriconazole 200 mg PO BID. (If liver enzymes elevated or IV therapy required then change to micafungin 50 mg IV daily)
   2. Start aztreonam 2 g IV q8h plus vancomycin 15 mg/kg IV q12h
   3. If fever resolves and patient is hemodynamically stable and no cultures for gram positive infection are present after 3 days, then DC vancomycin
   4. Continue as in II. A.

E. FIRST Neutropenic FEVER, hemodynamically UNSTABLE plus allergic to penicillin / cephalosporin

   1. As in II. B.
   2. Substitute aztreonam for cefepime.
F. CONTINUED FEVER during the FIRST neutropenic fever period, hemodynamically STABLE
1. Remains febrile longer than 72 hours from start of antibiotics
2. Investigate for other suspected sites of infection and adjust antibiotic cover accordingly
   • If GI source suspected, add metronidazole 500 mg IV q8h or change to broader spectrum agent (piperacillin-tazobactam 4.5 g IV q6h)
   • If HSV/Ab+ with severe esophagitis, consider addition of treatment dose acyclovir (5-10 mg/kg/dose IV q8h based on lean body wt) – Please round the dose of acyclovir to the nearest 25 mg (150 mg, 175 mg, 200 mg, etc.)
   • If invasive mold infection suspected
     ▪ Perform thorough skin exam, obtain chest CT. Consider sinus evaluation if sinus symptoms.
     ▪ If no evidence of invasive mold infection, do not change antifungal prophylaxis. (continue fluconazole)
     ▪ If evidence of fungal pneumonia on CT, obtain bronchoscopy and consider transplant ID consult
     ▪ Discontinue fluconazole
       Start voriconazole 6 mg/kg/dose IV/PO BID x1 day then 4 mg/kg/dose IV/PO BID or mafungin 100 mg every 24 hours (if unable to use voriconazole due to hepatic dysfunction or drug interactions) or liposomal amphotericin B (Ambisome®) 3-5 mg/kg IV daily
     • If evidence of fungal disease on sinus CT, consult Otorhinolaryngology and Transplant ID

G. SECOND fever spike during antibiotic therapy
1. If patient is stable and on cefepime, consider change to piperacillin-tazobactam 4.5 g IV q6h.
2. If becomes hemodynamically unstable on cefepime, change to piperacillin-tazobactam 4.5 g IV q6h and add tobramycin 5 mg/kg IV q24h (adjusted body weight and dose per pharmacokinetic parameters).
   • If already on tobramycin, change to amikacin 15 mg/kg IV q24h (adjusted body weight and dose per pharmacokinetic parameters)
   • Add vancomycin if suspect line sepsis
3. If invasive mold infection suspected
   • See section II. F. 2. above

H. Use of Vancomycin following line manipulations
1. The use of this antibiotic may be considered following traumatic line placement, or line repair.

I. Blood cultures:
1. AEROBIC and ANAEROBIC blood cultures should be obtained at initial F&N from one lumen (TPN line should be drawn first) and one set of peripheral cultures.
2. AEROBIC and ANAEROBIC blood cultures should be obtained from one lumen 24 and 48 hours following initial fever spike. The lumens should be different each day (ex. red then blue)
3. If patient remains febrile beyond 72 hours, but remain s clinically stable, culture one lumen every 48 hours.
4. If patient is afebrile for >24 hours, then develops new fever, repeat blood cultures per #1 above (AEROBIC and ANAEROBIC)

III. DEFINITIONS:
Neutropenia = ANC <1000
Fever = temperature >38°C
Creatinine clearance = ideal(lean) wt kg x [140-age years]/72 xSCr (*0.85 if female)
Ideal (lean) wt = 50 kg + 2.3 (# ins >5 feet) MALE
Ideal (lean) wt = 45.5 kg + 2.3 (# ins >5 feet) FEMALE

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