Neutropenic Fever Clinical Practice Guidelines (Short)

I. DEFINITION AND SCOPE OF PROBLEM
Fever in the child with a low absolute neutrophil count (ANC) constitutes a potentially severe life-threatening clinical situation in which overwhelming infection may quickly follow. Signs and symptoms may be few due to lack of white blood cells (WBC) to constitute an immunologic and inflammatory response. Delay in treatment until cultures return positive results in an increase in significant morbidity and mortality in the neutropenic host.

A. Neutropenia - Patients with ANC of \( \leq 500/\mu l \) or < 1000 and falling. Absolute Neutrophil Count (ANC) = (WBC count) x (neutrophil % & band %)

B. Fever In A Neutropenic Patient – Any temp (any site) \( \geq 38.5^\circ C \) or \( \geq 101.5^\circ F \).
   1. For recent bone marrow transplant recipients, fever is defined as temperatures (any site) \( \geq 38^\circ C \) (100.4°F) twice in one hour
   2. For oncology patients or congenital neutropenia patients, temperatures (any site) \( \geq 38^\circ C \) (100.4°F) should have a repeated measurement hourly until the temperature falls below 38°C (100.4°F) or becomes \( \geq 38.5^\circ C \)

C. Common Pathogens to consider in a neutropenic patient - Between 48% and 60% (or more) of febrile neutropenic patients have an established or occult infection, and 16%–20% (or more) of patients with neutrophil counts of <100/mm3 have bacteremia. With the onset of fever, bacteremia is most frequently due to aerobic gram-positive cocci (in particular, coagulase-negative staphylococci, viridans streptococci, or S. aureus) or aerobic gram-negative bacilli (especially Escherichia coli, Klebsiella pneumoniae, or Pseudomonas aeruginosa). Also to consider, but less frequent – Pneumocystis (consider with respiratory symptoms), viral infections including herpes and CMV, and fungal organisms (latter most often presents where neutropenia is >14 days or fever is >4-7 days)

II. OUTPATIENT INITIAL MANAGEMENT
A. When the families call, a series of questions are asked to obtain an estimate of the clinical severity of the child's illness. Criteria for subsequent care is also determined by the distance from the family's home to Children's Mercy Hospital.
   1. For Patients residing within one hour of Children's Mercy Hospital
      a. Patients thought to be at risk for cardiopulmonary instability are instructed to either go to the local ER (may be CMH if close) or to contact 911 for assistance and transportation to the local ER. The local ER is contacted by the person on call and informed of the patient's situation and H/O recommendations.
      b. Patients thought to have both stable cardiovascular and pulmonary systems are instructed to be admitted directly to the Oncology unit if known to be neutropenic.
   2. For Patients who reside >1 hour from Children's Mercy Hospital
      a. Families should have a planned local ER where they intend to go.
      b. All patients are to go to this predetermined ER to undergo formal assessment and to begin empiric therapy, prior to coming to CMH.
i. All families are to take their "Antibiotic kits" to the ER. This contains:
   Cefepime with dosing instructions, labs to order, blood culture vials
   (2) with instructions, and supplies needed to access an indwelling
   catheter, if present.

ii. The local ER's are contacted & informed of the child's anticipated
    arrival and that the antibiotic kit will accompany the patient. They
    are instructed to send the cultures with the families which will then go to
    the CMH Bacteriology lab.
    a) The local ER assesses the child's cardiovascular and respiratory
       status to determine any immediate needs and to determine whether
       the patient should proceed to CMH via medical transport or private
       vehicle.

B. Use of antipyretics
   1. PRN use of acetaminophen is the only method approved and only after
      consulting with their nurse or physician. Regular scheduled use of
      acetaminophen is discouraged to avoid masking fevers.
   2. Acetaminophen is not given to any patient for the purpose of reducing fever
      (regardless whether low or high grade) in any patient who is or potentially is
      neutropenic. Patients may be given acetaminophen prior to arrival to
      Children's Mercy Hospital if it has been determined that they will definitely
      be admitted.

III. ASSESSMENT UPON ARRIVAL TO CMH
    A. Patients who are neutropenic and febrile should be considered unstable and seen
       promptly with simultaneous assessment and treatment.
    B. Using an estimated weight from prior visits, complete and follow the power
       plans.
    C. Antibiotics, immediately after blood cultures are obtained, should be administered
       immediately upon the patient's arrival if not recently given at an outside medical
       facility.

IV. DIAGNOSTIC EVALUATIONS
    A. Historical information to obtain upon arrival to the hospital must include:
       1. Chemotherapy and dates received (to estimate time to ANC recovery)
       2. Duration of and height fever, presence of preceding low grade fevers
       3. Localizing symptoms suggestive of infected site (often negative)
       4. Use of antipyretics
       5. Current prophylactic antimicrobials
       6. Prior history of neutropenic fevers, organisms cultured, and sites of infection
    B. Complete review of systems
       A COMPLETE PHYSICAL EXAM must be performed. Most patients admitted
       for neutropenic fever have no localizing symptoms and no identifiable site of
       infection.
    C. A LABORATORY EXAM should include:
       1. Complete blood count with differential and platelets
       2. Aerobic and anaerobic blood cultures from all lines of the indwelling catheter.
          Peripheral blood cultures are not necessary in patients with central lines. (no
          more than once in a 24-hour period needed)
3. Electrolytes, BUN, Cr, Ca, Phos, Mg
4. Liver function tests (AST, ALT, Bili)
5. Urinalysis with microscopic exam (if symptomatic)
6. Cultures of other sites if symptomatic

D. MANAGEMENT / INITIAL

1. Empirical systemic antibiotic, Cefepime, should be started immediately. These antibiotics listed should be administered through each lumen of the central line in an alternating fashion.

2. Supportive care measures as needed including
   a. IVF's, factor in hydration status and fever – typically 1.5x maintenance
   b. Antipyretics should be limited to acetaminophen 10-15 mg/kg/dose q 4 hours prn fever. Ibuprofen may be used or alternated with acetaminophen if the platelet count is >100,000. Choline Magnesium Trisalicylate (Trilisate®) does not interfere with platelet function and can be used in patients with refractory fevers.
   c. Continue colony stimulating factor (eg, GCSF, GMCSF) if receiving them
   d. Hold home chemotherapy meds until reviewed by the H/O attending

E. MANAGEMENT / SUBSEQUENT

1. Based upon the patient's response to initial therapy, further management is determined, if:
   a. Patient is afebrile for at least 24 hours,
   b. Blood cultures are negative 36-48 hours after being obtained,
   c. There is no identification of a localized infection, and
   d. The patient appears well

   If all of these conditions are met, antibiotics may be stopped and the patient discharged home. There is no need to keep the patient an additional 24 hours after stopping antibiotics in this situation

2. If any of the above 4 criteria are NOT present, the patient should remain hospitalized and on antibiotics. For these patients:
   a. Consider changing antibiotics if fever persists >3-4 days.
   b. Consider adding antifungal medications if fever persists >4-7 days.
   c. Computerized tomography (CT) and / or nuclear scans (eg, gallium) are used most often in a setting of prolonged neutropenic fever (>4-7 days) without localizing symptoms.
   d. The CT should include the head, sinuses, chest, abdomen, and pelvis.
   e. Localized symptoms or whose cultures become positive for an organism, therapy should be adjusted accordingly.
   f. For patients who have persistent fever despite improvement of their ANC to >500, consider deep seated infections (eg, abscesses or hepatosplenic candidiasis)
   g. Further or repeated radiological investigation of potential
   h. Consider discontinuing antibiotics to rule out "drug fever". Need to be under very close observation in the hospital.

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References:

