Neutropenic Fever Clinical Practice Guidelines-Long

I. DEFINITION AND SCOPE OF PROBLEM
Neutropenia after administration of chemotherapy is a common complication. Its high frequency of occurrence precludes keeping the patients in the hospital until count recovery, with some exceptions. Most patients do not develop fever and thus can avoid prolonged hospitalizations and exposure to nosocomial infections. Therefore, children are sent home after chemotherapy has been completed with the knowledge that they will become neutropenic and be at risk for sepsis or other infections.

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
1. Absolute Neutrophil Count (ANC) calculation:
   \[ \text{ANC} = (\text{WBC count}) \times (\text{neutrophil} \% + \text{band} \%) \]
2. Patients with severe neutropenia will either have an:
   a. ANC of < 500/µl or less, or
   b. ANC < 1000 and falling.

B. Fever In A Neutropenic Patient – Any temperature (any site) \( \geq \) to 38.5°C (or \( \geq \) to 101.5°F).
1. For recent bone marrow transplant recipients, fever is defined as temperatures (any site) \( \geq \) to 38°C (100.4°F) twice in one hour
2. For oncology patients or congenital neutropenia patients, temperatures (any site) \( \geq \) to 38°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°C
3. Rectal temps are contraindicated in neutropenic patients

C. Common pathogens to consider in a neutropenic patient—between 48% and 60% (or more) of neutropenic patients who become febrile 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).
1. Gram positive bacteria
   Non-coagulase positive staphylococci are common pathogens. These most often are associated with central line infections and do not typically result in fulminate infections.
   Coagulase positive S. aureus is an occasional cause of infection in neutropenic patients. These infections may be precipitous with ensuing cardiovascular collapse. Streptococcal infections are primarily due to alpha-hemolytic species (viridans strep). These infections are primarily bloodstream and may be precipitous with ensuing cardiovascular collapse. A syndrome of ARDS and mental status changes are occasionally seen in these patients.
2. **Gram negative bacteria**
   Virtually all of the gram negative organisms have been implicated in neutropenic infections. More commonly found organisms include these gram negative rods: E. Coli, Enterobacter, Klebsiella, Pseudomonas, Citrobacter, and Serratia. These infections may be precipitous with ensuing cardiovascular collapse and DIC.

3. **Fungal infections**
   These occasionally are found at initial presentation of a patient with neutropenic fever, but more commonly are found to be the cause of infection in patients with prolonged fevers (>4 days). These organisms are typically very rare, but several of the more common ones include: Candida, Torulopsis, Aspergillus, Fusarium, and mucor.

4. **Parasitic infections**
   These are uncommon with the exception of the organism, Pneumocystis. This cause of pneumonia must be considered in any patient with bilateral infiltrates and respiratory distress.

5. **Viral infections**
   These probably constitute the majority of causes of infection in the neutropenic patient as fully 50% of admissions for neutropenic fever fail to find a causative organism or site. Particular infections to consider in these patients include: herpes, varicella, CMV, and adenovirus. Skin rashes and oral lesions should be sought out when considering these diagnoses.
   Other organisms to consider (though rare) include: atypical mycobacteria, Mycoplasma, and the parasites Toxoplasma and amoeba.

D. **Sites of Infection**
   Relatively few anatomical sites are affected, and the cause of these infections is limited to relatively few types of organisms. The primary sites of infection often include the alimentary tract, where cancer chemotherapy–induced mucosal damage allows invasion of opportunistic organisms. However, patients with chronic hereditary neutropenia tend to have upper respiratory tract infections, periodontal infections, and skin infections in patterns different than those for patients with cytotoxic therapy–induced neutropenia. Similarly, damage to the integument by invasive procedures, such as placement of vascular access devices, may serve as a portal for infection.

II. **OUTPATIENT INITIAL MANAGEMENT**
   Several steps at Children's Mercy Hospital are taken to improve the safety for these patients:

   A. Families undergo **extensive education** regarding neutropenia and fever. All families have a *Parents Handbook* which contains written guidelines for fever management.

      1. **Use of antipyretics**
         a. They are advised to only use acetaminophen and to only use it after consulting with their advanced-practice nurse or physician. Regular scheduled use of acetaminophen is discouraged to avoid masking fevers.
         b. 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.
            i. Patients may be given acetaminophen prior to arrival to Children's Mercy Hospital if it has been determined that they will definitely be admitted.
2. **Open communications are maintained** with the patient's family. Phone numbers of the hospital operator are given to the families. They are instructed, if their child has a fever and are known or suspected to be neutropenic, to contact their primary advanced-practice nurse, or physician, during the day or if after hours (evening and weekends) the nurse- or physician-on-call.

3. For patients who live greater than one hour from Children's Mercy Hospital, they are discharged from the hospital with an "**Antibiotic Kit**". This kit contains the following items:
   a. Cefepime
   b. Aerobic and anaerobic blood culture vials (2) with instructions
   c. Instructions for obtaining the cultures and labs
   d. Instructions on mixing and administering the antibiotics
   e. Supplies needed to access their port-a-cath device, if present

4. **When the families call**, they are asked a series of questions depending upon the clinical setting. This is 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.**
   a. **For Patients residing within one hour of Children's Mercy Hospital**
      i. Patients thought to be at risk for cardiopulmonary instability are instructed to either go to the local ER or to contact 911 for assistance and transportation to the local ER.
         a) The local ER or physician is contacted by the person on call who informs these caregivers of the patient's situation and the H/O recommendations. This local ER may be Children's Mercy Hospital if it is determined that this is the closest ER and or it is felt to be safe to transport to CMH directly.
         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.
   b. **For Patients who reside >1 hour from Children's Mercy Hospital**
      i. Families are encouraged to have a planned local ER to which they will take their child for this or other serious situations.
      ii. All families are advised to go to this predetermined ER to undergo formal assessment and to begin empiric therapy, prior to coming to CMH.
         a) All families are to take their "Antibiotic kits" to the ER
         b) The local ER's are contacted & informed of the child's anticipated arrival. They are advised that an antibiotic kit will accompany the patient and to follow the instructions contained within. These include: cultures to obtain and antibiotics to administer. They are instructed to send the cultures with the families or the transport personnel who will give these to the CMH nursing staff. These will then be sent to the CMH Bacteriology lab.
            1) 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.

III. **ASSESSMENT UPON ARRIVAL TO CMH**
A. **Patients who are neutropenic and febrile should be considered unstable and seen promptly.** Destabilization may occur rapidly and without warning. Simultaneous assessment and treatment are recommended. Medical records should be obtained prior to the patient's arrival when possible. Based upon the last two visits, an estimated weight can be determined. Using this estimated weight, the neutropenic fever orders should be completed prior to the patient's arrival.

B. **Antibiotics should be administered immediately upon the patient's arrival** if not given at an outside medical facility. For patients in whom antibiotics were given, determination of when the next dose is due should be made in case there has been a significant interval between their administration and the patient's arrival.

C. **Prior to any antibiotic administration, cultures must be obtained.** For most oncology patients, an indwelling central catheter may be used for this. All lines of the indwelling catheter should be cultured for both bacterial organisms. In certain circumstances fungal blood cultures should also be obtained. The use of peripheral sticks for blood culture is only necessary in those patients without an indwelling catheter or in those patients in whom, due to occlusion, bloodwork is unable to be obtained from the catheter.

D. **DIAGNOSTIC EVALUATIONS**

**Historical information to obtain upon arrival to the hospital must include:**
1. Chemotherapy recently received and dates received (to estimate time to ANC recovery)
2. Duration of fever, presence of preceding low grade fevers, and height of fever
3. Symptoms suggestive of infected site (often negative) and their duration and evolution over time
4. Use of antipyretics
5. Current medications (most are on some type of prophylactic antimicrobial)
6. Prior history of neutropenic fevers, infections, organisms cultured, and sites of infection
7. Complete review of systems, and in particular ask for the presence of:
   a. Upper airway congestion
   b. Any respiratory symptoms including tachypnea, dyspnea, cough
   c. Oral lesions, pain, dysphagia, or dyspepsia
   d. Abdominal pain
   e. Perirectal pain or tingling, known fissures or ulcerations
   f. Skin lesions or recent trauma to integument (these may be subtle and are often overlooked in the history), methods of skin and nail care (occasionally a cause of new portals of entry)

E. **A COMPLETE PHYSICAL EXAM must be performed.**

1. **Vitals:** Assessment of temperature, pulse, respiration rate, and BP must be performed with particular attention to trends during the first few hours after arrival. Onset of septic shock may be identified early with close observation. Orthostatic pulses and blood pressure should be considered depending upon the clinical situation. Refractory hypotension is often a manifestation of septic shock.
2. During the physical exam, the examiner must be aware that the signs and symptoms of localized infections may be very subtle or absent in the neutropenic patient. These include:
a. Skin – septic emboli whose significance may be unrecognized to the family; infected abrasions or lacerations often have no erythema, induration, or warmth.
b. Perirectal infections may have no tenderness, erythema, induration, or warmth. Often only a vague tingling sensation is present. Only upon WBC recovery may symptoms occur.
c. ENT infections may be without symptoms, especially fungal infections. Look for black anesthetic eschars in the nares or palate indicative of invasive fungi. Hoarseness may indicate infection. Thrush should be sought for.
d. Pulmonary infections likely will have symptoms. Observe for tachypnea, retractions, and oxygen deficits by pulse oximetry. Chest xray exam is only necessary in patients with pulmonary symptoms (though these may be minimal).
e. The presence of murmurs should be determined as they may indicate the presence of intracardiac vegetations. This may or may not be related to their indwelling central catheter. Many patients may also have flow murmurs due to anemia.
f. Oral mucositis is a common portal of infection and its presence should be determined. Its presence also increases the likelihood of esophageal, gastric, and intestinal mucosal ulcerations. Its absence does not preclude unseen lesions elsewhere in the GI tract.
g. The presence of an indwelling central line (hickman, portacath, or PICC) or home peripheral IV should be determined. Its entry site should be assessed for infection. Cultures should be obtained from all indwelling lines. Examination should include both the entry site and the tunnel through which the line travels.
h. GI symptoms should be investigated. These may include nausea, vomiting, diarrhea, melena, hematochezia, or abdominal pain. These infections may be luminal (c diff) or within the bowel wall (typhilitis or neutropenic enterocolitis). Surgical consultation should be sought if there is any consideration of an infected bowel wall.
i. Urinary tract infections may occur in neutropenic patients. The presence of symptoms should be determined. A urinalysis with microscopic examination should be obtained in all patients regardless of symptoms.
j. Musculoskeletal and central nervous system infections are rare in neutropenic patients but should be investigated if symptoms are present.

**Most patients admitted for neutropenic fever have no localizing symptoms and no identifiable site of infection.**

F. **LABORATORY EXAM** should include:

1. Complete blood count with differential and platelets
2. Aerobic and anaerobic cultures
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

IV. **MANAGEMENT / INITIAL**

A. Empirical systemic antibiotics should be started immediately. Empirical administration of broad-spectrum antibiotics is necessary for febrile neutropenic patients because the currently available diagnostic tests are not sufficiently rapid, sensitive, or specific enough for identifying or excluding the microbial cause of a febrile episode.
1. At Children's Mercy Hospitals, due to both gram positive infections (primarily S. aureus and viridans strep) and gram negative infections causing rapid clinical deterioration, cefepime is used empirically. Susceptibilities of organisms cultured at this time show that the cefepime provides adequate coverage in the empiric setting. Cefepime should be administered through each lumen of the central line. This is typically done in an alternating fashion.

2. Supportive care measures as needed including
   a. IVFs (factor in hydration status and fever – typically 1.5x maintenance is a good starting point),
   b. Antipyretics should be limited to acetaminophen 10-15 mg/kg/dose q 3-4 hours prn fever. Only give as needed, do not prescribe this as a scheduled medication (to avoid masking low grade fevers). No ASA products. Ibuprofen may be used or alternated with acetaminophen if the platelet count is >100,000. Choline Magnesium Trisalicylate (Trilisate®) is a salicylate which does not interfere with platelet function and can thus be used in patients with refractory fevers. See micromedex for the most current dosages.
   c. Continue colony stimulating factor (eg, GCSF, GMCSF)
   d. Cultures of the blood (1-2 depending upon the number of lumen in the patient's central line) are typically not performed more often than once in a 24-hour period. Cultures of any suspicious site should be performed as needed. Chest X-ray is reserved for patients with respiratory symptoms (upper or lower).

V. MANAGEMENT / SUBSEQUENT
A. Based upon the patient's response to initial therapy, further management is determined:
   1. 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. If the patient is:
      a. Afebrile for at least 24 hours
      b. The blood cultures are negative 36-48 hours after being obtained
      c. There is no identification of a localized infection
      d. The patient appears well
   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.
         These patients should be reassessed with cultures and PE’s daily for localizing signs and symptoms.
      b. If the suspicion is a possible gram negative organism, substitute or add another antibiotic, eg. meropenem. Aminoglycosides are typically held until there is positive identification of a gram negative organism. It should be considered as a third empiric antibiotic in a patient with septic shock.
      c. If the suspicion is a possible coagulase negative gram positive organism such as S. epidermidis, add vancomycin as a second empiric antibiotic. As these organisms are typically indolent and not causes of septic shock, many will wait to make this change until cultures identify these organisms.
      d. If the suspicion is an anaerobic organism (presence of mucositis increases this possibility), consider adding metronidazole or clindamycin to the two drug
regimen, or substituting imipenem/cilastatin for the antibiotic used to cover gram negative organisms.

B. **Consider adding antifungal medications if fever persists >4-7 days.**
   1. There is an intended overlap of days for this indication and that of changing antibiotics. For patients at high risk of fungal infection, early initiation of antifungal therapy is advised. These include: AML patients, bone marrow transplant patients, and patients with prolonged neutropenia (>14 days). All patients should receive antifungals if the fever persists >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.** The CT should include the head, sinuses, chest, abdomen, and pelvis.
   1. For patients who develop **localized symptoms or whose cultures become positive for an organism,** **therapy should be adjusted accordingly.**
   2. For patients who have **persistent fever despite improvement of their ANC to >500,** consider deep seated infections (eg, abscesses or hepatosplenic candidiasis) Options are:
      a. Pursuit of further or repeated radiological investigation of potential sources should be considered. With the advent of an ANC >500, previously unrecognized infections often become apparent, either by PE or by radiological exam, and/or
      b. Discontinuation of empiric antibiotics and close observation. Occasionally, a "drug fever" is determined to be the etiology. This method should be reserved for patients with recovered ANC's or who will be under very close observation in the hospital.

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References: