KEY WORDS:

Neutropenia
Infections
Fever
Sepsis

SEE ALSO:

CEQI Sepsis Seminar
uphsxnet.uphs.upenn.edu/ceqi/sepsis_learningday.html

PURPOSE

It is common for neutropenic patients to become febrile. Because mortality rates associated with untreated bacterial infections in neutropenic patients are high, the rapid empiric treatment of these patients is critical. It is also important to stress that even a severely infected neutropenic patient may not manifest a fever. Under these circumstances, infection may manifest with an abnormality in vital signs and/or evidence of new organ dysfunction including lactic acidosis. The purpose of this Guideline is to provide a systematic approach to neutropenic patients with fever or other signs of infection. The importance of individualizing the approach to care cannot be overemphasized. The practitioner may deviate from this Guideline based on clinical indication, if appropriate and documented, or in emergency or unusual circumstances.

DEFINITIONS

Sepsis: When a patient with neutropenic fever also has abnormalities in vital signs, either heart rate>90 or respiratory rate>20, the patient meets criteria for sepsis.

Severe Sepsis: When a patient with sepsis develops the new onset of any organ dysfunction (unexplained by an alternative etiology) the patient has severe sepsis and is at higher risk of death. All neutropenic patients with fever or suspected sepsis should be screened for cardiovascular dysfunction by assessing blood pressure and sending a lactic acid level STAT. Those with an initial lactate ≥4 and/or persistent hypotension i.e. systolic blood pressure<90 (despite 1.5 liters of fluid) by definition have a severe form of cardiac dysfunction called septic shock and should have antibiotics broadened within 1 hour and treated with early goal directed therapy (EGDT) in the ICU. For further information on the diagnosis and management of sepsis please refer to the CEQI website: (http://uphsxnet.uphs.upenn.edu/ceqi/sepsis_learningday.html).

IMPLEMENTATION AND MONITORING

An email announcement to educate members of the healthcare team including nurses, nurse practitioners, physicians and pharmacy personnel will occur with oversight from the medical board. In addition to email; in service education sessions will occur for health care personnel predicted to be affected most by this clinical guidelines including 1) nursing staff on medical oncology and gynecologic oncology units; 2) inpatient Nurse Practitioners caring for patients on the leukemia and bone marrow transplant service 3) medicine housestaff 4) emergency room clinicians 5) ICU clinicians 6) infectious disease clinicians 7) medicine and gynecologic oncology clinicians and 8) pharmacists. Compliance with these guidelines will be monitored by qualitative chart reviews conducted by members of the Neutropenic Pathway and Infection Control committees; these committees will also perform periodic review of the appropriateness of these guidelines. These guidelines will be reviewed during housestaff and nursing orientation sessions on Rhoades 3, 6 and 7.

SCOPE

Eligibility Criteria: Patients with an absolute neutrophil count (ANC) ≤ 500 or <1000 with predicted decrease to <500 and temperature ≥ 100.4 ˚F. (In the absence of fever, consider patients with other signs or symptoms of infection including hypothermia, signs of sepsis or new unexplained organ dysfunction.)

PROCEDURE

Key Points:

- All neutropenic patients who meet eligibility criteria should be:
  - Immediately assessed for localizing signs or symptoms of infection
  - Immediately assessed for signs of sepsis and septic shock. The latter includes a serum lactate, even in patients who are normotensive.
  - Treated empirically with antibiotics ***within one hour*** of fever or other eligibility criteria
- Initial workup should include blood cultures (See Table 1), urine cultures, urinalysis and chest xray. Other individualized assessments may include stool cultures, evaluation for rectal abscess, CT imaging to evaluate for fungal infections and cerebral spinal fluid evaluation.
- Patients with lactate ≥4 or systolic blood pressure ≤ 90 despite 1.5 liters of fluid should have antibiotics broadened and transferred to the ICU for EGDT.
- Clinical judgment should remain paramount and used in conjunction with these guidelines

Table 1: Blood Culture Protocol

- Every effort should be made to draw cultures before administration of antibiotics.
- Antibiotics should not be delayed due to delay in blood cultures.
- Cultures from periphery are preferred and are less likely to be contaminated.

1) For first neutropenic fever (or other eligibility criteria as defined above): Draw one set of peripheral and one set of central line cultures.
2) For recurrent fever (T>101) 24 hours after initial defervescence: Draw 2 sets of cultures from the central line. For patients with persistent fever and stable clinical status, follow up cultures should be drawn every 24 hours.
3) If central line cultures are positive, peripheral cultures should be sent. Repeat blood cultures should be drawn every 24 hours until documentation that the infection has cleared.
4) Consider decreased frequency of cultures, i.e. every 72 hours, for patients who are stable with at least 3 sets of negative cultures and persistent fevers.

Recommendations of Empiric Antibiotics for Neutropenic Fever

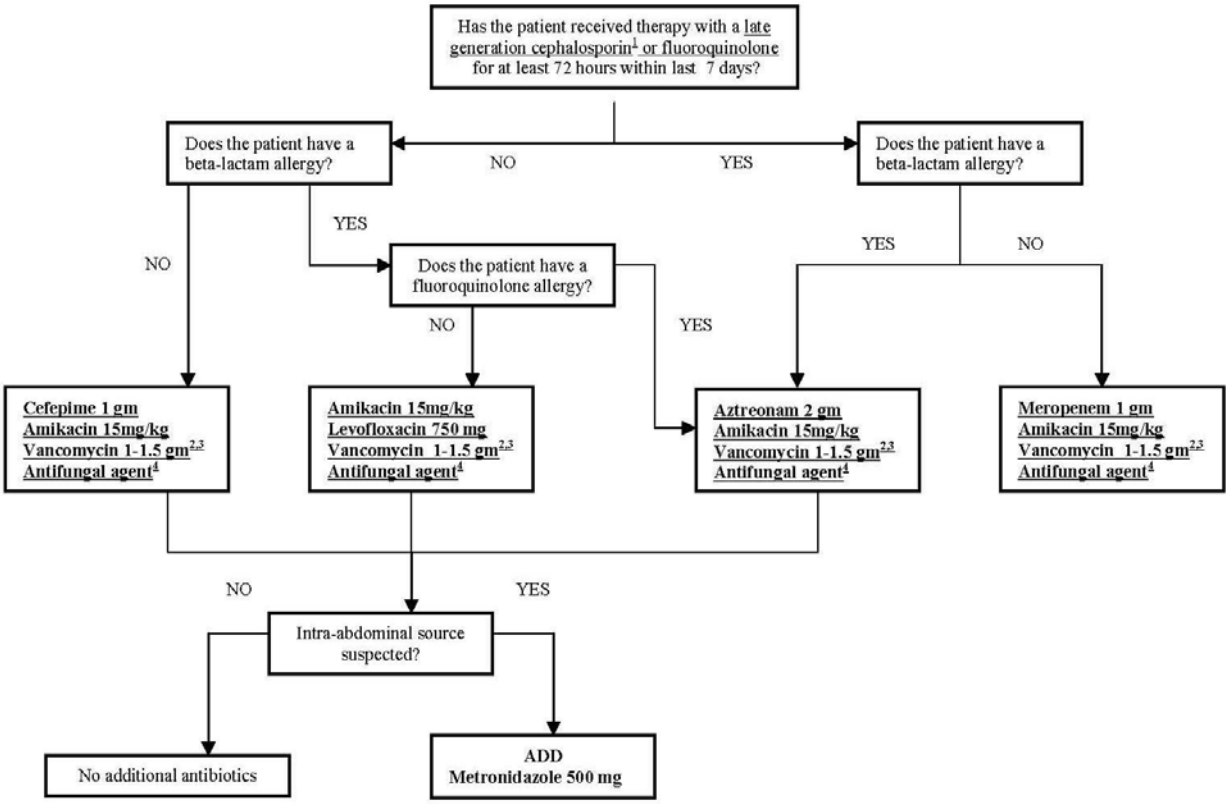
- These recommendations are for empiric coverage only. Antibiotics should be tailored based on cultures and radiographic findings. In the event a localized infection (such as fungal pneumonia) is found, broad spectrum gram negative antibiotics should be continued until neutropenia resolves. (See Chart Below)
- Empiric antibiotic recommendations may change based on evolving medical knowledge and HUP microbial sensitivity data. Please refer to the Bug Drug website (http://www.uphs.upenn.edu/bugdrug/) for most up to date recommendations.
- For cultures positive for gram positive cocci in pairs and chains treat with linezolid or daptomycin. Tailor antibiotics based on final speciation, antibiotic sensitivities and source of infection.
- Consider consultation with infectious diseases for persistent fevers or clinical deterioration.
- Continue empiric antibiotics until afebrile with ANC≥500. Monitor off antibiotics for 24 hours before discharge. Note: if a source of infection was identified, an appropriate course of antibiotics should be completed, even after ANC recovery.

Clinical Setting	Antibiotics	Dosing
Clinically stable	Cefepime (add vancomycin if evidence of line infection)	1 gm q 8 hrs
Clinically stable with beta-lactam allergy[1]	Levofloxacin +	750 mg q 24 hrs
	tobramycin	5 mg/kg q 24 hrs
Persistent fever for ≥ 4 days	Consider change in empiric antibiotics if indicated by change in clinical status. Consider ID consult.	
Persistent fever for ≥ 4 days or new fever with history of prolonged NP	Addition of one of the following antifungal agents:	
	voriconazole	400 mg PO q 12 hrs x 2 doses then 200 mg PO a 12 hrs
	liposomal amphotericin B	3 mg/kg q24 hrs
	caspofungin	70 mg x 1 then 50 mg q24 hrs
Signs of severe sepsis	Refer to Sepsis Protocol (See page 3)[2]	

[1]NOTE FOR PATIENTS WITH PENICILLIN ALLERGIES

- Optimal coverage is with a beta-lactam, or carbapenem (cefepime, piperacillin/tazobactam, or meropenem). For allergic patients, the use of fluoroquinolones and aminoglycosides may result in inferior outcomes. Every attempt should be made to clarify the patient's allergy. For patients with a history of maculopapular rash only to a penicillin, consideration should be given to using cefepime. The converse applies as well. For patients whose allergy history is worrisome for an immediate hypersensitivity reaction to beta-lactams, cephalosporins, penicillins and carbapenems should be avoided, unless the patient is desensitized.
- Consider desensitization. Consultation with Infectious Diseases and/or Allergy Immunology may be necessary.

[2]Antiobiotic Choices for the Neutropenic Patient with Severe Sepsis:



[1]3rd or 4th gen cephalosporins = cefepime, ceftazidime, ceftriaxone
[2]Vancomycin dose: weight ≤ 70kg = 1 gm x 1, weight > 70kg = 1.5gm x 1
[3]Infuse vancomycin before antifungal agent, but after other antibiotics have been given
[4]Either liposomal amphotericin B 5 mg/kg x1 or caspofungin 70mg x 1

SUPERSEDES: NEW	**ISSUED BY:** /s/ David McCarthy, MD