

## Management of Adult Febrile Neutropenia

Quick summary of the management of adult febrile neutropenia:

1. Fever  $>38.3 \times 1$  or  $>38$  for  $>1$  hr. in a patient who has received chemotherapy in last month.
2. Neutrophils  $<0.5$  or likely to fall to  $<0.5$ .
3. 1 + 2 = febrile neutropenia.
4. Assess for site of infection, culture blood and assess renal and liver function as well as for septic shock.
5. Treat with IV ceftazidime 2g q 8h plus IV fluids.
6. Admit the patient and telephone the Tom Baker Medical Oncologist on call (403) 944-1110 or the CCI Medical Oncologist on call (780 432-8771) for consultation. Call the Capital Health Authority's, Critical Care Line (780-413-4000) if septic shock is a concern or (403) 944-1110 in Calgary.

Background: Febrile neutropenia is considered a medical emergency. The use of empiric broad-spectrum antibiotics has significantly reduced the mortality and morbidity of this common chemotherapy complication. Rapid assessment and institution of the appropriate antibiotics are of paramount importance. A patient on chemotherapy should not wait in the ER for assessment for an extended period of time. Ideally a system would be in place for the rapid identification of a potential patient with febrile neutropenia who would then immediately have a CBC drawn and urgent assessment by a health care professional.

The following are guidelines on the management of a patient with febrile neutropenia. Every patient has a unique presentation and should be managed as such. Daily reassessments are required to ensure that the patient is recovering satisfactorily.

Assistance: Please notify the on call medical oncologist when any patient presents with febrile neutropenia. Please notify the responsible medical oncologist for any additional concerns relating to the care of a patient with febrile neutropenia. Another useful resource would be the on call infectious diseases specialist at the University of Alberta Hospital or Foothills Hospital.

Fever: Fever is usually defined by a single oral temperature of  $>38.3$  °C or a sustained oral temperature of  $>38.0$  °C for more than one hour. Patients are instructed to call telephone triage or go to the nearest ER with any oral temperature  $>38.0$  °C.

Neutropenia: Neutropenia is defined by an ANC  $<0.5 \times 10^9$  cells/L or an ANC  $<1.0$  with an expected fall to  $<0.5 \times 10^9$  cells/L.

Assessment: A careful history and detailed examination is required for all patients suspected of having febrile neutropenia. The assessment should include the following:

- Mental status
- Hydration status
- Oral and pharyngeal mucosa
- Skin including any indwelling IV sites
- Respiratory system
- Abdomen
- AVOID rectal exam but include perirectal inspection for abscess
- Cardiovascular system including signs of sepsis
- Special considerations: beware of the possibility of meningitis, sinusitis, herpes simplex, herpes zoster, thrush

Lab investigations: A complete hematological profile and chemistry profile should be done. The latter is done to assess comorbidities, any end-organ effects of sepsis and to determine if any antibiotic dose modifications or contraindications apply. These lab tests should include the following:

- CBC and differential
- Transaminases, bilirubin, alkaline phosphatase
- Electrolytes
- Creatinine and urea
- blood cultures
  - aerobic and anaerobic
  - peripheral and from any indwelling IV lines
- urinalysis and urine culture (absence of pus cells on urinalysis does not rule out UTI in the setting of neutropenia)
- sputum gram stain and culture if productive
- LP and CSF analysis should not be done routinely

Imaging investigations: Chest x-ray should be obtained even in the absence of pulmonary symptoms or signs. Pulmonary infiltrates may not develop until the neutropenia begins to recover. Thoracic CT has not been shown to improve outcomes in the absence of clinical pulmonary abnormalities but can be considered in the setting of clinical abnormalities and a normal chest x-ray. Other imaging tests should be guided by the clinical picture.

Empiric antibiotic therapy: Seeding of the bloodstream by endogenous bacteria from the GI tract is felt to be responsible for the majority of cases of febrile neutropenia. Many chemotherapy drugs can have adverse effects on the mucosal barrier (i.e. mucositis). Blood cultures are positive in about 30% of cases. Gram-positive organisms are isolated more commonly than gram-negative organisms but the latter are associated with more severe infections including sepsis. Since febrile neutropenia is considered a medical emergency with high mortality if untreated, empiric broad-spectrum antibiotics must be administered immediately. Patients transferred from the ER to a ward should already be receiving their antibiotics. Consider allergies, prior antibiotic history, clinical picture and local flora as guides but the initial antibiotic therapy should be one of the following broad spectrum regimens.

Broad spectrum antibiotics: The 2006 version of the CHA Bugs & Drugs provides an excellent reference for the management of febrile neutropenia. A version is also available for regions outside the Capital Health Authority (780-735-0007). Combination therapy is not clearly superior to monotherapy in most circumstances. Ensure that appropriate dosing guidelines are followed especially in the setting of renal dysfunction.

- Monotherapy:
  - Ceftazidime 2g IV q8h (standard regimen at ACB)
  - Cefipime 2g IV q8h
  - Imipenem 500mg IV q6h
  - Meropenem 500 mg IV q6h
- Combination therapy:
  - Piperacillin-tazobactam 4.5 g IV q8h ± gentamicin 7mg/kg IV q24h or tobramycin 7mg/kg IV q24h or
- Major  $\beta$ -lactam allergy:
  - Vancomycin 1g IV q12h and one of
    - Gentamicin 7mg/kg IV q24h
    - Tobramycin 7mg/kg IV q24h
    - Ciprofloxacin 400 mg IV q8-14 hours

- Empiric vancomycin should not be used routinely but should be considered in the following circumstances: obvious IV catheter/tunnel infection, positive gram-positive culture with organism not yet identified, known colonization with MRSA or penicillin-resistant *S. pneumoniae*, hypotension/shock, quinolone antibiotic prophylaxis. It should be stopped on day 3-5 if culture reveals pathogens that don't require vancomycin.

Duration of antibiotic therapy: The duration of antibiotic coverage depends on the early clinical course and the results of any cultures -especially blood cultures. If a definite source of infection is identified such as a UTI or pneumonia, the treatment duration should be appropriate for those infections. If a pathogen is identified in the blood cultures-especially gram negative bacilli-generally a 10-14 day course of antibiotics is recommended. If no source is identified either clinically or on blood cultures, antibiotics can be stopped if the patient is afebrile and the ANC has recovered to  $0.5 \times 10^9$  cells/L although some recommend a minimum of 7 days of therapy. If the fever resolves but the ANC is still low there is no consensus on duration of antibiotics but a reasonable strategy would be to continue the antibiotics for 5-10 days depending on the clinical picture. If the still neutropenic patient is unstable or has significant mucositis, antibiotics should be continued for at least 14 days even if afebrile.

Colony stimulating factors: Granulocyte colony stimulating factor (GCSF) can decrease the duration of neutropenia, fever and hospitalization but these benefits are modest and mortality is unaffected. They can be considered in the hospitalized patient with pneumonia, hypotension/sepsis, organ dysfunction or a patient on a regimen that is known to cause prolonged neutropenia. Prophylactic GCSF is outside of the scope of this document.

Step-down to oral antibiotics: Patients who have rapidly improved on IV antibiotics and who are afebrile, stable and no longer neutropenic can be switched to an appropriate oral regimen for the balance of the chosen antibiotic duration. If these patients are stable, have no unmanaged comorbidities and have a safe and reliable home environment they can also be discharged. If the patient has been on a prophylactic quinolone prior to the FN episode, these should be avoided on discharge. Ciprofloxacin (750mg BID) plus Clavulin (875mg BID) or Levofloxacin 500mg OD are reasonable step-down regimens. Culture and sensitivity results can also guide therapy. These results must be reviewed prior to discharge.

Persisting fever: Be aware that fever in the patient with cancer can be due to the disease itself but a persisting fever in the neutropenic patient usually suggests an ongoing infection not adequately treated by the current antibiotic regimen. The clinical picture must be thoroughly re-evaluated. Blood or other culture results should be verified and repeat cultures obtained if fever persists for more than 3 days. Empirically, vancomycin (1g IVq12h) is usually added at this point. Fungal cultures should be obtained and empiric antifungal therapy is recommended if fever persists beyond 5 days of appropriate antibacterial therapy. Please consult a medical oncologist or infectious disease specialist for advice regarding the most appropriate agent. Be aware that viral infections can also commonly occur in the patient with febrile neutropenia. Severe oral herpes can look like severe mucositis. Viral swabs and empiric antiviral therapy should be considered.

Special circumstances: Patients with febrile neutropenia can occasionally present in septic shock or have other critical care issues. These patients should be discussed with the medical oncologist as soon as possible to determine if critical care is appropriate. Patients on potentially curative or salvage regimens must be managed as aggressively as possible. It may be appropriate to contact the nearest critical care specialist. It may be challenging to determine the appropriate level of care for patients on palliative regimens and therefore advice should be sought in this regard from the attending or on call medical oncologist.

Central venous catheter and tunnel infections as well as septic thrombosis, endocarditis and osteomyelitis are special circumstances beyond the scope of this document and specific advice

from the appropriate specialist should be obtained. This also applies to any other situation not covered here. A medical oncologist can provide direction as well.

Low risk febrile neutropenia: Mortality and morbidity from the appropriately managed case of febrile neutropenia is very low. Inpatient management is considered the standard of care. There is, however, a subpopulation of FN patients felt to be a very low risk of complications who may benefit from outpatient management. Outpatient management should be reserved for centres with considerable experience in identifying and managing this low risk group. At the CCI, an outpatient program is currently being developed.