# Prophylaxis & Treatment of Febrile Neutropenia

**Updated May 2008 by Drs. Eugenia Piliotis & Anita Rachlis**

## Updates:
- Threshold neutropenia for chemotherapy approval is neutrophils 1.0
- Fungal prophylaxis for AML induction chemotherapy or Allo-BMT

## Introduction

Neutropenia is common during chemotherapy treatment for hematologic cancers [1]. The risk of developing infection associated with neutropenia is directly related to both the severity and duration of neutropenia. A number of published evidence-based guidelines are available to guide management including the Infectious Diseases Society of America guideline of the use of antimicrobial agents in neutropenic patients with unexplained fever [2], the American Society of Clinical Oncology [3] and Cancer Care Ontario [4].

## Risk of Neutropenic Complications

The risk of neutropenic complications can be predicted by:

- The intensity of the chemotherapy regimen
- Immunosuppression
- Bone marrow reserve
- Performance status
- Age
- Prior neutropenic complications
- Status of underlying cancer

Published incidence of febrile neutropenia for commonly used regimens are summarized below:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Febrile Neutropenia Rate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>2-10%</td>
<td>[5, 6]</td>
</tr>
<tr>
<td>CHOP</td>
<td>20-40%</td>
<td>[6-8]</td>
</tr>
<tr>
<td>Lymphoma salvage</td>
<td>30-60%</td>
<td>[6, 9, 10]</td>
</tr>
<tr>
<td>AML induction</td>
<td>100%</td>
<td>[11]</td>
</tr>
<tr>
<td>AML consolidation</td>
<td>&gt;85%</td>
<td>[11]</td>
</tr>
</tbody>
</table>

## Prophylaxis of Febrile Neutropenia

### Antibiotics:
Prophylaxis of febrile neutropenia with trimethoprim-sulfamethoxazole (Septra®) or fluoroquinolones, such as ciprofloxacin, have been shown to reduce the incidence of infection, compared to placebo, in a number of randomized controlled trials, and meta-analyses, but have not been shown to improve survival [6, 12-15].

Antifungal prophylaxis with fluconazole can reduce the incidence of fungal infections, but also does not affect mortality [2]. The use of both antibacterial and antifungal prophylaxis has been associated with the development of antibiotic resistance therefore the routine use of antibiotic prophylaxis is not recommended in the guidelines of the Infectious Diseases Society of America [2].

### G-CSF (Neupogen) Prophylaxis:
G-CSF prophylaxis has been shown to decrease the incidence of febrile episodes requiring hospitalization by 30-50%, but does not reduce treatment-related mortality for patients with hematologic malignancies [3, 4, 16]. In addition, G-CSF prophylaxis has been shown to reduce the need for dose reductions and delays, but has not been shown to decrease relapse rates.
Primary prophylaxis with G-CSF may be associated with economic benefit in patients expected to have $\geq 40\%$ incidence of febrile neutropenia either due to the myelosuppressive potential of their treatment regimen, disease status, or baseline medical factors such as age, co-morbidities or active infections [17-21].

Patients who have experienced a prior neutropenic complication (febrile neutropenia or dose delay/reduction) have a high risk of recurrence of neutropenia. The ASCO and CCO guidelines consider G-CSF use appropriate for this group of patients on curative therapy [3, 4].

A long acting formulation of filgrastim (peg-filgrastim or Neulasta) is now available. This agent can be administered as a single injection of 6 mg SC following each cycle of chemotherapy (typically given the day following chemotherapy) [22-27]. Randomized trials comparing this agent to short acting G-CSF (Neupogen) reveal it to be comparable and it may in fact be associated with a lower incidence of febrile neutropenia, although there is no evidence of lower hospitalization rates, improved quality of life or survival. This agent is currently not covered by ODB (Ontario Drug Benefit), but is covered by many third party insurers.

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**Odette Cancer Centre Policy**

**Primary Prophylaxis with Growth Factor Support**

Primary prophylaxis should be considered for all patients expected to have a $\geq 40\%$ chance of developing neutropenic complications. This includes:

- Patients treated with CHOP if IPI $> 2$ or LDH is increased
- Patients receiving salvage chemotherapy for lymphoma with DHAP, ESHAP, or mini-BEAM
- Patients receiving AML induction or consolidation if they will be outpatients during the neutropenic period
- Primary prophylaxis may also be considered for patients felt to be at high risk of complications from neutropenic fever (having co-morbidities, having bone marrow compromise from previous chemotherapy ± pelvic irradiation, receiving other immunosuppressive therapy, expected duration of neutropenia < 7 days, having cancer which is not controlled)

N.B. Primary prophylaxis is not currently approved for Section 16 coverage of ODB eligible patients.

**Secondary Prophylaxis with Growth Factor Support**

All patients on curative treatment who have experienced febrile neutropenia or a dose delay or reduction due to neutropenia should be considered for G-CSF prophylaxis starting with the following cycle.

**G-CSF Reimbursement:** The hospital or CCO does not directly reimburse G-CSF administered at home. The average cost per cycle is $1600 for CHOP and $2000 for ABVD (A + B parts). Most patients can receive reimbursement by third party insurance or through the Ontario Drug Benefit (ODB) Section 16 mechanism. An example of an ODB Section 16 letter is shown on page 7. Coverage should be requested for the following doses of G-CSF with each remaining cycle:

- CHOP: 300 µg x 8 days
- ABVD: 300 µg x 5 days for each of part A and B
- Lymphoma salvage & AML: 300 µg x 21 days

**Patients > 85 kg should be prescribed neupogen 480 mcg**

Neulasta (peg-filgastrim) is typically administered as a single 6 mg SC dose 1-2 days after chemotherapy. The cost is ~ $2500 per cycle.

In order for ODB to approve G-CSF, treatment must be curative and the patient must have a dose delay greater than a week or experience a febrile neutropenic episode.
**Figure 1** G-CSF DOSING ALGORITHM

Chemo given (day 1)

- Is ANC > 1.0?
  - NO
  - YES – Continue chemo as before
  - Is ANC < 0.8?
    - NO
    - YES – Delay chemo 1 week. Start G-CSF after next chemo
    - Do patient teaching (reason for use, mechanism of action, side effects, drug storage, self-injection, etc.)
    - Order G-CSF:
      - ABVD: 300 µg SC daily x 5d, start d4
      - CHOP: 300 µg SC daily x 8d, start d4
    - Order interim CBC’s twice weekly in first course and PRN in subsequent courses.
    - Provide patient with sufficient syringes, alcohol swabs, etc.

Did patient have F+N+ episode while on G-CSF?

- YES
  - Increase daily dose by 50% for remaining doses
    - Does patient have bone pain?
      - YES
      - Consider every 2nd day dosing (same total dose)
      - Patient comes in for next chemo.
        - Is ANC > 5.0?
          - YES
          - Decrease duration by 1 day
            - Is ANC < 1.5?
              - YES
              - Increase dose by 50% or increase duration by 1-2 days
            - NO
            - Continue as before
          - NO
        - NO
        - Continue as before
      - NO
    - NO
  - NO

Is ANC > 5.0?

Target ANC 10 x 10⁹/L or value that permits neutrophil count at least 2 on day of next chemotherapy.
Special Considerations

Fungal prophylaxis: Patients with prolonged severe neutropenia are at high risk for invasive fungal infections. Typical patients include those with acute myeloid leukemia undergoing aggressive induction chemotherapy, and patients undergoing allogeneic bone marrow transplantation. Prophylaxis with both fluconazole and itraconazole have been shown in randomized trials to decrease the rate of documented fungal infections as well as the need for empiric treatment of fungal infections during prolonged periods of febrile neutropenia. Fluconazole and itraconazole are likely equally effective in decreasing the incidence of fungal infections (despite superior coverage of aspergillus by itraconazole) and both appear to be more efficacious and less toxic than amphotericin B for prophylaxis, however there has been less convincing evidence that any of these agents improve survival in this patient population. More recently, however there is evidence in a randomized control trial of 600 patients with AML and MDS that posaconazole is more efficacious than either fluconazole or itraconazole in preventing fungal infections (8% vs 2%) with evidence of improved overall survival with a relative risk reduction in mortality of 33% at 100 days ($p = 0.04$). We recommend that all patients being treated with induction chemotherapy for AML or allogeneic bone marrow transplantation be provided with fungal prophylaxis with posaconazole 200 mg po tid. Voriconazole is a similar agent biochemically (second generation triazole) and with respect to antifungal spectrum therefore voriconazole 200 mg po bid would also be appropriate [28-37].

Intravenous Immunoglobulin (IVIG): Prophylaxis with intravenous immunoglobulin can decrease infection rates for patients with CLL or myeloma and hypogammaglobulinemia [38]. IVIG (0.4 g/kg every three weeks) should be considered for patients with CLL or myeloma and hypogammaglobulinemia who have experienced recurrent life-threatening infections.

Hematopoietic Stem Cell Transplants: There are no randomized controlled trials investigating infectious prophylaxis in stem cell transplant recipients. Most transplant centres develop individual prophylactic regimens based on the pathogen prevalence in each institution, however there are general guidelines for prophylaxis in allogeneic stem cell transplant recipients supported by the Infectious Diseases Society of America and the American Society of Blood and Transplantation. Allogeneic transplant recipients should be provided with fungal prophylaxis tailored to the pattern of their hospital's fungal pathogen prevalence. They should also be provided with PCP prophylaxis for the first 6 months post transplant as well as aggressive CMV surveillance and early treatment. Antibiotic prophylaxis is still controversial given the risk of developing resistant organisms and the lack of evidence showing survival benefits, however individual transplant centers may consider broad-spectrum fluoroquinolones or Septra based on individual infection rates. There is currently no consensus on the need for any prophylaxis for autologous transplant recipients [2, 39].

PCP: Prophylaxis with Septra® (1 double-strength tablet PO every Monday, Wednesday, and Friday) is recommended for patients at risk of Pneumocystis carinii pneumonia (PCP), including [2]:

- HIV positivity
- Purine analog use in past 24 months
- Prolonged high-dose steroid administration (ALL or Myeloma regimens)

Prophylaxis should also be considered for patients with CLL or myeloma with recurrent life-threatening infections.

Management of Febrile Neutropenia

Definition: Febrile neutropenia is defined as any fever of $\geq 38.3^\circ C$ ($101^\circ F$) or fever $\geq 38.0^\circ C$ lasting at least one hour and a neutrophil count of $< 0.5 \times 10^9/L$ or $< 1.0 \times 10^9/L$ if expected to fall to $< 0.5$.

Prognostic Factors: Many patients will have uneventful hospitalizations, however, serious medical complications, including hypotension, respiratory failure, ICU admission, or cardiac problems, can be expected in ~27% of patients and approximately 8% will die. Predictors of higher complication rates include:
- Being an inpatient at the time fever develops
- Having significant co-morbidities
- Having cancer which is not controlled
- Expected duration of neutropenia > 7 days
- Neutrophil count $\leq 0.1$
- Other immunosuppression
- Mucositis

A number of these factors have been included in a scoring system published by Talcott, et al [40].

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
<th>Complications</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Inpatient</td>
<td>35%</td>
<td>9%</td>
</tr>
<tr>
<td>II</td>
<td>Co-morbidities*</td>
<td>33%</td>
<td>12%</td>
</tr>
<tr>
<td>III</td>
<td>Uncontrolled cancer</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>IV</td>
<td>None of the above</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Co-morbidities:
- Hypotension
- Altered mental status
- Respiratory failure
- Uncontrolled bleeding
- Inadequate fluid intake

- Hypercalcemia
- Spinal cord compression
- AML induction
- Serious localized infections
- Acute abdomen

Initial Evaluation

The initial evaluation of patients with neutropenic fever should be prompt with the aim to initiate treatment within 1-2 hours of being recognized.

History (Key points)

- # days since last chemotherapy
- Antibiotic allergies
- Focal symptoms of infection
- Other reasons for immunosuppression

Physical Examination

- Hemodynamic stability
- Foci of infection (especially central venous catheters, oral cavity, perianal area – do not perform digital rectal examination)

Laboratory

- CBC, differential
- Electrolytes, liver function, creatinine
- Repeat blood work every third day
- Blood cultures from peripheral blood and CVC catheter
- Stool for C&S and *C. difficile* toxin (if diarrhea present)

Radiology

- Chest x-ray

Other investigations such as lumbar puncture, other cultures, abdominal ultrasound or CT scan may be warranted in individual patients.
Treatment (see algorithm on page 8)

Initial treatment in most patients with febrile neutropenia is with intravenous broad-spectrum antibiotics that has efficacy against pseudomonas sp. Our current hospital policy is to commence treatment with cefazolin 1 gm IV q 8h and tobramycin 6 mg/kg IV q 24 hrs. Tobramycin levels should be drawn immediately and 8 hours after first dose to ensure therapeutic levels. In patients who are penicillin allergic Clindamycin can be used instead of Cefazolin. If aminoglycosides are contraindicated, then single agent Ceftazidime is suggested, or ceftazidime and vancomycin in those patients in whom it is clinically indicated (see below).

Patients at low risk of complications who become afebrile within 48 hours and are culture negative should be converted to oral antibiotic therapy with ciprofloxacin (500 mg PO BID) and cephalexin (500 mg PO QID) and be considered for discharge home. Clindamycin can be substituted for cephalaxin in case of allergy. Initial oral therapy should be considered for patients at the lowest risk (Talcott group IV) groups who are 1) clinically stable 2) do not have medical comorbidities and 3) develop fevers as outpatients. Patients who remain febrile for more than 72 hours should have an infectious disease consult and should be started on piperacillin.

Vancomycin should generally be reserved for patients who remain febrile despite initial therapy, who are colonized with multiresistant gram-positive organisms such as MRSA, who have central venous catheter infection, or have severe mucositis. If vancomycin is used in combination with aminoglycosides, renal function must be monitored closely. Most patients should continue to receive oral antibiotics until afebrile for 5-7 days or until counts recover. Therapy should be tailored for patients who are culture positive or who have a recognized focus of infection.

Antifungal therapy should be considered in patients who remain febrile for more than 5-7 days with no pathogen found. Either voriconazole or caspofungin are appropriate agents based on individual patient characteristics. Baseline CT scans of chest and abdomen should be ordered prior to initiating antifungal therapy

G-CSF Therapy: G-CSF administration is not routinely used in the treatment of patients with febrile neutropenia [3, 4]. G-CSF should be considered only for patients who remain persistently febrile despite appropriate antibiotic therapy or for those requiring amphotericin.

Infectious Diseases Consultation

Patients with uncomplicated febrile neutropenia do not necessarily require ID consultation. Consultation should be requested for:

1. Any patient in whom standard first line therapy of cefazolin and tobramycin is contraindicated
2. All patients who are bacteremic or fungemic (except for 1 of 2 bottles for S. Epi)
3. All patients who are hemodynamically unstable
4. All patients who remain febrile beyond 72 hours
5. All stem cell transplant patients
6. All patients with acute leukemia

Central Venous Catheter Removal

In febrile neutropenic patients with clinical or microbiologic evidence of a central venous catheters infection careful consideration should be given to catheter removal. Exceptions to this include coagulase negative Staphylococcal infections, which often respond to intravenous antibiotics for 10 days. Staphylococcus aureus is a more virulent organism with a propensity to cause distant infections. Catheter removal is usually indicated. Treatment with intravenous antibiotics with cloxacillin or cefazolin if susceptible or with vancomycin if MRSA or in patients with serious penicillin allergies should be continued for a minimum of 2 weeks [41].
Absolute indications to remove the catheter include:

- Evidence of subcutaneous-tunnel infection
- Septic emboli
- Hypotension associated with catheter use
- Nonpatent catheter
- Bacteremia with Staphylococcus aureus, Pseudomonas spp, any gram negative bacillus, Candida species, *Corynebacterium jeikeium*
- Persistent bacteremia despite appropriate antibiotics

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**G-CSF in Lymphoma**

*(Sample ODB Section 16 Letter)*

Director Drug Programs Branch  
Ministry of Health and Long Term Care  
5700 Yonge Street, 3rd Floor  
Toronto, Ontario, M2M 4K5

Fax #: 416-327-7526

Dear Sir/Madam:

I am writing to request ODB section 16 approval for Neupogen (G-CSF) for my patient R.B. for secondary prophylaxis of febrile neutropenia.

Ms. B. was diagnosed with diffuse large B-cell lymphoma (aggressive histology) in October of 2001 and is currently on curative therapy with CHOP chemotherapy. Her second cycle of CHOP was associated with grade IV neutropenia (ANC 0.7) which resulted in a one-week delay in delivering her treatment. Continued chemotherapy administration without G-CSF support is likely to be associated with a significantly **increased risk of febrile neutropenia** and **further dose reductions or delays** which will compromise effective delivery of curative chemotherapy.

The use of Neupogen for secondary prophylaxis of febrile neutropenia is supported by the guidelines of the American Society of Clinical Oncology and the Cancer Care Ontario Program in Evidence-Based Care as indicated below:


I am requesting ODB Section 16 coverage for Neupogen 300 µg SC daily for 10 doses after each remaining chemotherapy cycle (5 cycles).

Thank you for your prompt attention to this request.

Yours sincerely,

Dr. John Smith
**Figure 2 (Treatment Algorithm)**

**No Etiology**
- **Low risk** (clinically well, no mucositis, ANC likely to recover within 1 week)
  - Convert to oral antibiotics (e.g., Ciprofloxacin + cephalaxin, or + clindamycin for patients with severe beta-lactam allergy) treat until afebrile for 5-7 days.
  - **Afebrile** (temp < 38.3°C)
  - **Etiology**
  - **High risk** (mucositis, leukemia, bone marrow transplant, severe neutropenia [ANC ≤ 0.1] and unlikely to recover within 1 week, or previous history of prolonged neutropenia)
  - Modify antibiotics if necessary to optimize treatment. Continue broad-spectrum coverage.
  - **Persistent Fever** (temp ≥ 38.3°C)
  - **See next chart**

**Low risk** (as defined above)
- Stop antibiotics when afebrile for 5-7 days.

**High risk** (as defined above)
- Continue Cefazolin + Tobramycin with consideration to convert to oral antibiotics if clinically well.
- Treat until afebrile for 5-7 days. Longer duration may be necessary depending upon the clinical status and the type/site of infection.
- Modify antibiotics if necessary to optimize treatment. Continue broad-spectrum coverage.
- **Persistent Fever** (temp ≥ 38.3°C)
- **See next chart**

**Etiology**
- **No Etiology**
  - **Low risk**
    - Convert to oral antibiotics (e.g., Ciprofloxacin + cephalaxin, or + clindamycin for patients with severe beta-lactam allergy) treat until afebrile for 5-7 days.
    - **Afebrile** (temp < 38.3°C)
    - **Etiology**
    - **High risk** (mucositis, leukemia, bone marrow transplant, severe neutropenia [ANC ≤ 0.1] and unlikely to recover within 1 week, or previous history of prolonged neutropenia)
    - Modify antibiotics if necessary to optimize treatment. Continue broad-spectrum coverage.
    - **Persistent Fever** (temp ≥ 38.3°C)
    - **See next chart**

**Afebrile** (temp < 38.3°C)
- **Persistent Fever** (temp ≥ 38.3°C)
- **See next chart**

**Continued from previous chart**
- **Persistent Fever 72 hrs** (temp ≥ 38.3°C)
  - No change in patient (clinically stable)
  - Continue Cefazolin, Piperacillin and Tobramycin.
  - Persistent fever (day 7-10) with un-resolving neutropenia (ANC < 0.5 x 10^9/L)
  - CT chest/abdo for screening fungal infections
  - **ANC > 0.5**
  - Stop anti-infectives 3-5 days after ANC > 0.5 (in the absence of documented infection
  - Reassess
  - **ANC < 0.5**
  - Continue anti-infectives x 2 weeks
  - Reassess

**Prophylaxis & Treatment of Febrile Neutropenia**

*Original treatment policy prepared by Drs. Kevin Imire, Anita Rachilis & Julia Elia-Pacitti BScPhm*
# DOCTOR'S ORDER SHEET

## PATIENT IDENTIFICATION

<table>
<thead>
<tr>
<th>Time &amp; Date</th>
<th>Sent to Pharmacy</th>
<th>□ NO KNOWN ALLERGIES</th>
<th>ALLERGIES</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

#### COMPLETE ABOVE ALLERGY BOX AT TIME OF INITIAL ORDERS

## FEBRILE NEUTROPENIA ADMISSION ORDERS

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor must check off Yes/No for all orders</td>
<td></td>
</tr>
</tbody>
</table>

### INVESTIGATIONS

- CBC, electrolytes, BUN, Creatinine
- Blood Cultures x _________________
- Urine – R&M, C&S
- Swab of central line
- Chest x-ray
- Tobramycin (7 mg/kg) wt = __________ Dose = ___________ IV q24h to administer over 30 minutes (round off to multiples of 50 mg)
- Cefazolin 1 g IV q8h
- Tobramycin levels 30 min and 8 hrs post Tobramycin administration (MD to reassess antibiotic if patient allergic to penicillins – see checklist)

### ELIGIBLE FOR HOME IV ANTIBIOTICS?

**PLEASE NOTIFY**

- Community Care Case Manager
- Pharmacy

### Planned Date of Discharge:

- **VENOUS ACCESS**

  - Peripheral __________________  Port __________________
  - Hickman __________________  PICC __________________

### DOCTOR'S SIGNATURE:  

**DATE:**
**References**