Febrile Neutropenia in Oncology Patients

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Medical Director – Regional Palliative Care Program – Southern Health-Santé Sud
Specific Learning Objectives

At the end of this session, participants will:

• Describe how to diagnose and treat febrile neutropenia
• Select which patients can be managed as outpatients
• Explain the role of growth factors in the prevention of febrile neutropenia in moderate and high risk systemic therapy regimens
Faculty/Presenter Disclosure

• **Faculty:** Cornelius Woelk MD

• **Relationships with financial sponsors:**
  – **Grants/Research Support:** none
  – **Speakers Bureau/Honoraria:** none
  – **Consulting Fees:**
    – *Canadian Virtual Hospice* – NO expected influence
  – **Patents:** none
  – **Other:** none
Case Study: Cynthia

- 38 yr old, being treated with 2 FEC-D for Stage 2A Breast Cancer
- Presents to Family Physician’s clinic Friday morning (Day 10)
- Complains of achiness, some rigors, runny nose, mild sore throat, temperature not measured
- Afebrile, looked “well”, throat normal, TM’s normal, few small nodes in neck
- Advised to follow up if develops fevers
Case Study: Cynthia

- 24 hours later she presents to the ER of local hospital
- She has had chills, more rigors, and had a fever of 39.1 degrees at home
- Slight sore throat, slight runny nose, no cough, hasn’t felt like eating or drinking for the past day
- R.O.S. otherwise negative
- Exam: flushed, temp 37.9, BP 104/64, PR 88, RR 12, exam otherwise unremarkable
- Bloodwork: WBC 1.1, ANC 0.19, Hgb 124, Plts 320
Case Study: Cynthia

• Does she require antibiotics?
  • Which one(s)?
• Does she require admission?
  • Should she receive G-CSF now?
• Should anything be changed with her next treatment – different doses, early antibiotics, G-CSF?
Febrile Neutropenia Facts

- 8/1000 patients receiving cancer chemotherapy
- 20-30% require hospitalization
- In-hospital mortality rate approaches 10%
  (~15% in patients with a documented infection)

Factors Responsible for Increasing Risk of FN

- Chemotherapy Regimen
  - High risk (>20%), moderate risk (10-20%), low risk (<10%)
- Patient age
- Advanced disease
- History of prior episode of febrile neutropenia
- No antibiotic prophylaxis or G-CSF use
- Mucositis
- Poor performance status
- Cardiovascular disease

Fever - definition

- Single oral Temp $\geq 38.3^\circ C (101^\circ F)$
- $> 38^\circ C (100.4^\circ F)$ lasting at least one hour
- $> 38^\circ C (100.4^\circ F)$ documented at least twice over a 12-hour period
Neutropenia - definition

- ANC < 0.5 x 10^9/L
- ANC < 1.0 x 10^9/L and a predicted decline of the ANC to < 0.5 x 10^9/L within the next 48 hours
Febrile Neutropenia - Pathophysiology

• Leukopenia induces cytokines including IL-6 and TNF, both of which can cause fever

• Duration and degree of neutropenia are directly related to risk of infection

• Other effects of chemotherapy disrupt normal barriers to bacteria (e.g. oral and gut mucosa)
Febrile Neutropenia - Evaluation

Thorough Clinical History including:

- When and what chemotherapy
- Previous infections
- Previous febrile episodes
- Previous herpetic disease
- Recent exposures, travel history
- Symptoms suggestive of an infection:
  - Respiratory, GI, Skin, Genitourinary, Oropharynx, CNS
Febrile Neutropenia - Evaluation

Thorough Physical Examination including:

• Alimentary Canal: mouth, pharynx, esophagus, bowel, perirectal tissues
• Skin and soft tissues: especially biopsy sites, genitourinary sites, and sites associated with indwelling catheters
• Upper and lower respiratory tracts
Febrile Neutropenia - Evaluation

Investigations, including:
- Bone marrow, renal and liver function tests
- Coagulation
- Chest X-ray
- Cultures if specific foci are suspected, including:
  - Urinalysis and culture
  - Sputum microscopy and culture
  - Stool microscopy and culture
  - Skin lesions (swabs or aspirates)
Febrile Neutropenia - Evaluation

**Blood cultures**

*LABEL SITES*

- In patients with central lines:
  - 10 mls from EACH lumen => aerobic culture
  - 20 mls peripherally => 10 mls each, aerobic + anaerobic

- When there is no central line:
  - 20 mls from at least two sites => 10 mls each, aerobic + anaerobic

Febrile Neutropenia - Evaluation

For consideration:

- Mark requisitions: Febrile Neutropenia
- CT chest if symptoms suggest chest infection, but CXR is non-diagnostic
- If diarrhea, think of *Clostridium difficile* culture/toxin, and enteric viruses
- Viral cultures:
  - mucosal or cutaneous vesicular/ulcerated lesions
  - Nasopharyngeal swabs may be appropriate in some seasons
SIRS
(Systemic Inflammatory Response Syndrome)

Two or more of the following criteria:
• body temperature >38°C or <36°C
• heart rate >90 beats/min
• respiratory rate >20/min
• Pa CO2 <32 mmHg
• alteration in the total leukocyte count to >12x10⁹/L
  or <4x10⁹/L  OR  presence of >10% band neutrophils in the leukocyte differential
Hypoperfusion

- Hypotension
  - Systolic BP <90 mmHg
  - Mean arterial pressure <70 mmHg
  - Systolic BP decrease of >40 mmHg
  - BP <2 standard deviations below mean for age
- Acute alteration in mental status
- Elevated serum lactate >4mmol/L
- Oliguria (urine output <0.5 ml/kg/hr)
SEPSIS = SIRS with Infection
SEVERE SEPSIS = SEPSIS with Hypoperfusion
SEPTIC SHOCK = SEVERE SEPSIS persistent despite fluid resuscitation

Get help!
## Febrile Neutropenia - Determining Treatment

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Outpatient</td>
<td>• Inpatient</td>
</tr>
<tr>
<td>• No associated acute co-morbidities requiring admission and/or close observation</td>
<td>• Significant medical co-morbidities or clinical instability</td>
</tr>
<tr>
<td>• Anticipated duration neutropenia of &lt;7 days</td>
<td>• Anticipated duration of neutropenia of &gt;7 days</td>
</tr>
<tr>
<td>• Good performance status (ECOG:0-1)</td>
<td>• Elevated serum Cr</td>
</tr>
<tr>
<td>• Normal serum Cr</td>
<td>• LFTs &gt; three times ULN</td>
</tr>
<tr>
<td>• LFTs &lt; three times ULN</td>
<td>• Uncontrolled or progressive underlying cancer</td>
</tr>
<tr>
<td></td>
<td>• Pneumonia or other complex infection at clinical presentation</td>
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</table>
ECOG Performance Status

0  Fully active, able to carry on all pre-disease performance without restriction

1  Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work

2  Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3  Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4  Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
# Febrile Neutropenia - Determining Treatment

## Low Risk
- Outpatient
- No associated acute co-morbidities requiring admission and/or close observation
- Anticipated duration neutropenia of <7 days
- Good performance status (ECOG:0-1)
- Normal serum Cr
- LFTs < three times ULN

- MASCRC Risk Index Score ≥21

## High Risk
- Inpatient
- Significant medical co-morbidities or clinical instability
- Anticipated duration of neutropenia of ≥7 days
- Elevated serum Cr
- LFTs > three times ULN
- Uncontrolled or progressive underlying cancer
- Pneumonia or other complex infection at clinical presentation

- MASCRC Risk Index Score ≥21
Multinational Association of Supportive Care of Cancer (MASCC) Risk Index Score (_/26)

- Burden of illness (*choose one*):
  - No or mild symptoms 5
  - Moderate symptoms 3
  - Severe symptoms 0
- No hypotension 5
- No C.O.P.D. 4
- Solid tumour or lymphoma diagnosis and no previous invasive fungal infection 4
- No dehydration 3
- Outpatient status at the time of febrile neutropenic episode 3
- Age less than 60 years 2
Febrile Neutropenia - Determining Treatment

**Low Risk**

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**High Risk**

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- Pneumonia or other complex infection at clinical presentation
- MASCC Risk Index Sore <21
Initial Empiric Antibiotics

- Lower Risk patients can usually be managed as outpatients
- High Risk patients require admission and intravenous antibiotics
- If multi-lumen lines present, antibiotics should be rotated sequentially through each lumen of the device
The total time from triage-to-initial empirical anti-bacterial therapy shall be less than one hour (60 minutes).
Guidelines for Initial Empiric Antibacterial Therapy

• “Low Risk” patients
  – Ciprofloxacin 750 mg q12h PO or
    Levofloxacin 750 mg daily PO
    + Amox/Clav 625 mg PO q8h
  – Ciprofloxacin 750 mg q12h PO or
    Levofloxacin 750 mg daily PO
    + Clinda 600 mg PO q8h
  – Others in certain circumstances
  – CLOSE CLINICAL FOLLOW UP
Guidelines for Initial Empiric Antibacterial Therapy

• “High Risk” patients
  – Piperacillin/Tazobactam 4.5 gm q8h IV
  – Meropenem 1 gm q8h IV
  – Consider Vancomycin 1 gm IV q12h IF evidence of a skin/soft tissue or bloodstream infection due to coag neg Staph, or if methicillin-resistant S. aureus is present

  ❖ Continue prior antibacterial prophylaxis
How Long to Treat?

• Average time to fever resolution:
  – 2-3 days for lower risk
  – 5 days for high risk

• Continue with initial antibiotics unless:
  – Clinical deterioration
  – Progression
  – Antibiotic susceptibilities suggest suboptimal coverage
How Long to Treat?

• Treatment should continue until the patient has been afebrile for 5 days

• If fever persists beyond five days, or if clinical deterioration occurs, re-evaluate and modify the antibiotics (see protocol)
Should we give filgrastim?
Myeloid CSFs are not recommended as adjuncts to antibiotics for treating established fever and neutropenia. Although days of neutropenia, duration of fever, and length of hospital stay have been minimally (but statistically significantly) decreased in some randomized studies, the actual clinical benefit of these reductions is not convincing. None of the studies have demonstrated a survival benefit associated with therapeutic CSFs. Given the cost of and adverse effects associated with the CSFs, as well as the lack of consistent clinical data, addition of G-CSF or GM-CSF at the onset of fever and neutropenia is generally not advocated by the Panel.
Preventing Complications of Febrile Neutropenia

- Patient and Caregiver Education
- Chemoprophylaxis (Antibiotics)
- Granulocyte Colony Stimulating Factor (G-CSF)
Febrile Neutropenia Card

Name: ____________________________

Allergies: ____________________________

Boundary Trails Cancer Care Physician: ____________________________

Oncologist: ____________________________

Diagnosis: ____________________________

Chemo Regime: ____________________________

I am a patient at the Boundary Trails Community Cancer Program.

I have been advised to seek immediate medical attention should I develop a fever.

<table>
<thead>
<tr>
<th>Health Care Team:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Please refer to the Central RHA Management of Febrile Neutropenic cancer patients protocol and perform stat tests as indicated.</td>
</tr>
<tr>
<td>• In diagnosis box on lab requisitions, please indicate fever? Neutropenia.</td>
</tr>
<tr>
<td>• Take baseline vital signs.</td>
</tr>
<tr>
<td>• Complete Assessment within 30 minutes of triage.</td>
</tr>
<tr>
<td>• Consult BTHC Cancer Care physician. If not available call CancerCare Manitoba oncologist on call.</td>
</tr>
<tr>
<td>• Notify Boundary Trails Cancer Care clinic of ER visit, if after hours please leave message.</td>
</tr>
</tbody>
</table>

* With low white blood counts, fever may be the only sign of infection, so please do not underestimate the importance of this clinical condition.
Should we give prophylactic antibiotics?

• Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC <100 cells/mm$^3$ for >7 days)

Should we give prophylactic filgrastim?
NEUTROPHILS
EOSINOPHILS
BASOPHILS
LINEAGE-COMMITTED CELLS
GRANULOCYTE - COLONY STIMULATING FACTOR
NEUTROPHILS
EOSINOPHILS
BASOPHILS
Maintaining Correct Numbers of Neutrophils

Cytokinesis
- Mobilization
- Demarginalization

Granulopoiesis
- Accelerated mitosis
- Decreased maturation time

G-CSF blood concentration

Circulating neutrophil pool

G-CSF – Adverse Effects

• Injection site discomfort

• Constitutional symptoms: fever, malaise, influenza-like symptoms

• Bone pain (10-30%) – may be severe

• Rarely associated with development of acute myeloid leukemia if given after chemotherapy (this has not been shown in over 43,000 European stem cell donors)
**G-CSF - Current Guidelines**

- Prophylactic use if risk of FN > 20% and if equally effective treatments not requiring its support are not available

- Avoid use for primary prophylaxis in patients undergoing cancer therapy if the risk of chemotherapy-induced FN is < 20 %

- Co-existing factors should play a role in deciding:
  - Intent of treatment
  - Comorbidities
Pegfilgrastim

Predominant eliminating pathway is Neutrophil-mediated clearance

Pegfilgrastim increases the production of neutrophils and neutrophil precursors, which in turn clear the drug from the circulation when the body no longer needs it.
Pegfilgrastim vs ANC

**G-CSF - $$**

**Filgrastim:**
- Neupogen 300 mcg subcut
- Neupogen 480 mcg subcut
- Grastofil 300 mcg subcut
- Grastofil 480 mcg subcut

**Pegfilgrastim:**
- Neulasta 6 mg subcut
Case Study: Cynthia

**MASCC Risk Score**

- Burden of illness (*choose one*):
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- No dehydration 3
- Outpatient status at the time of febrile neutropenic episode 3
- Age less than 60 years

**TOTAL:** 23
Case Study: Cynthia

• She is treated as an outpatient with oral antibiotics and does well.
• She returns for Cycle 3

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1 Day 1</th>
<th>Cycle 2 Day 1</th>
<th>Cycle 3 Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC:</td>
<td>8.4</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>ANC:</td>
<td>3.2</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>HGB:</td>
<td>128</td>
<td>121</td>
<td>120</td>
</tr>
<tr>
<td>Plts:</td>
<td>270</td>
<td>290</td>
<td>255</td>
</tr>
</tbody>
</table>

• Should she be treated with G-CSP with the next course of chemotherapy?
Should we give G-CSF with the next course of chemotherapy?

Options:
• Post-chemotherapy G-CSF
• Reduce doses of chemotherapy
• Stop chemotherapy

Consider:
• Co-morbidities
• Treatment intent
• Patient preference
Febrile Neutropenia - Take Home Messages

- FN is relatively common
- FN is a Medical Emergency
- Act Quickly
- Stratify risk and treat accordingly
- Consider Consultation with Oncology / Infectious Diseases
- Carefully consider prevention
Selected References