Symptom Management Guidelines: FEVER AND NEUTROPENIA

**Definition**
- **Fever**: A single oral temperature of ≥ 38.3°C (101°F) OR a temperature ≥ 38°C (100.4°F) which lasts more than 1h
- **Neutropenia**: An abnormally low number of neutrophils in the blood (ANC <1.0 X 10^9/L). The lower the neutrophil count, the greater the risk of infection
- **Febrile neutropenia**: Fever and Neutropenia

**Contributing Factors of Neutropenia**

<table>
<thead>
<tr>
<th>Cancer Related &amp; Cancer Treatment Related</th>
<th>Medicine that induce neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chemotherapy agents</td>
<td>- Antibiotics, antifungals, antimalarials</td>
</tr>
<tr>
<td>- Monoclonal antibodies (e.g. alemtuzumab)</td>
<td>- Anticonvulsants, anti-inflammatory, antithyroid</td>
</tr>
<tr>
<td>- Extensive radiation to bone marrow (e.g. pelvis, legs, and sternum)</td>
<td>- Cardiovascular agents, diuretics</td>
</tr>
<tr>
<td>- Stem cell transplants - at risk for severe, prolonged neutropenia</td>
<td>- Gastrointestinal agents, immunosuppressants</td>
</tr>
<tr>
<td>- Cancers that affect bone marrow (e.g. lymphoma, leukemia or myeloma)</td>
<td>- Phenothiazines, psychotropic drugs</td>
</tr>
<tr>
<td>- Solid tumors</td>
<td></td>
</tr>
<tr>
<td>- Febrile neutropenia in previous course of therapy</td>
<td></td>
</tr>
<tr>
<td>- Immunotherapy – Checkpoint inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

**Co-morbidities**
- Autoimmune diseases
- AIDS
- Hypersplenism
- Aplastic anemia
- Congestive heart failure
- Diabetes
- Cerebrovascular disease
- Tuberculosis

**Other**
- Age ≥ 65 years
- Ethnic groups known to have a slightly lower ANC (e.g. African Americans, Yemenite Jews, Ethiopians and certain Arabs)
- Pre-existing infections (e.g. bacterial, viral, fungal, rickettsial, protozoal)
- Vitamin deficiencies (e.g. vitamin B_{12}, folate, copper); albumin level < 35 g/L; dehydration
- Hemodialysis, hypotension
- Recent exposures: travel, blood product administration

**Causative Factors of Infection in Patients with Neutropenia**

<table>
<thead>
<tr>
<th>Factors Related to Infection</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Immunosuppression. Herpes Simplex Virus (HSV) reactivation in immunocompromised patients may be as high as 75%</td>
<td>- <strong>Febrile neutropenia</strong> is considered an <strong>ONCOLOGICAL EMERGENCY</strong> which if left untreated, can quickly lead to <strong>sepsis</strong>, acute respiratory distress syndrome and/or septic shock See Appendix A</td>
</tr>
<tr>
<td>- Prior infection and /or antibiotic use in last 90 days</td>
<td>- Severe or prolonged neutropenia increases patient risk of infection (moderate risk: 7-10 days; high risk: &gt;10 days)</td>
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<tr>
<td>- Chemotherapy- induced mucositis</td>
<td>- Chemotherapy dose delays, reductions, or discontinuation of treatment</td>
</tr>
<tr>
<td>- Presence of open wounds, catheters or drains</td>
<td></td>
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<tr>
<td>- Obstruction of the lymphatic system, biliary tract, bronchial, gastrointestinal or urinary systems by tumours or secondary to surgical procedures</td>
<td></td>
</tr>
<tr>
<td>- Graft versus host disease - may be at higher risk of developing fungal infections up to 6 months after transplant</td>
<td></td>
</tr>
<tr>
<td>- Potential exposure to pathogens during hospital stay</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Focused Health Assessment</th>
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<tbody>
<tr>
<td><strong>GENERAL ASSESSMENT</strong></td>
<td><strong>SYMPTOM ASSESSMENT</strong></td>
<td><strong>PHYSICAL ASSESSMENT</strong></td>
</tr>
<tr>
<td><strong>Contact &amp; General Information</strong></td>
<td>Normal</td>
<td>Vital Signs</td>
</tr>
<tr>
<td>● Physician name – oncologist, family physician</td>
<td>Refer to pretreatment nursing or oncology assessment</td>
<td>• Frequency – as clinically indicated. If severe neutropenia, presence of fever or infection then every 4 hours and prn</td>
</tr>
<tr>
<td>● Pharmacy</td>
<td>Onset</td>
<td><strong>Consider Causative Factors</strong></td>
</tr>
<tr>
<td>● Home health care</td>
<td>When did symptoms begin?</td>
<td>● Cancer diagnosis and treatment(s) – note type and date of last treatment</td>
</tr>
<tr>
<td>● Other health care providers</td>
<td>Provoking / Palliating</td>
<td>● Post BMT</td>
</tr>
<tr>
<td>● Allergies</td>
<td>● What makes it better? Worse?</td>
<td>● Medical history</td>
</tr>
<tr>
<td></td>
<td>Quality (in last 24 hours)</td>
<td>− Recent infections, antibiotic therapy</td>
</tr>
<tr>
<td></td>
<td>• Can you describe your symptoms?</td>
<td>− Recent reports of diarrhea, constipation, vomiting, dysphagia, urinary symptoms</td>
</tr>
<tr>
<td><strong>Consider Causative Factors</strong></td>
<td>• What is your temperature? For how long?</td>
<td></td>
</tr>
<tr>
<td>● Cancer diagnosis and treatment(s) – note type and date of last treatment</td>
<td><strong>Region / Radiation</strong></td>
<td></td>
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<tr>
<td>● Post BMT</td>
<td>● Where are your symptoms?</td>
<td></td>
</tr>
<tr>
<td>● Medical history</td>
<td></td>
<td></td>
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<tr>
<td>− Recent infections, antibiotic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>− Recent reports of diarrhea, constipation, vomiting, dysphagia, urinary symptoms</td>
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<td></td>
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<tr>
<td>● Medication profile</td>
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<td></td>
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<tr>
<td>Review recent lab, diagnostic reports</td>
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<tr>
<td><strong>Severity / Other Symptoms</strong></td>
<td><strong>Systems Assessment</strong></td>
<td></td>
</tr>
<tr>
<td>● Have you been experiencing any other symptoms such as:</td>
<td>● Presence of shaking (rigors), chills, diaphoresis</td>
<td></td>
</tr>
<tr>
<td>− Chills, sweating</td>
<td>● level of consciousness and orientation</td>
<td></td>
</tr>
<tr>
<td>− Shortness of breath</td>
<td>● skin and oral mucosa for signs of infection</td>
<td></td>
</tr>
<tr>
<td>− Cough, with sputum (colour?)</td>
<td>− Note any areas of redness, swelling, pain, warmth, impaired skin integrity, exudate</td>
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<tr>
<td>− Fatigue or feeling unwell</td>
<td>● Respiratory tract:</td>
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<tr>
<td>− Mouth sores or sore throat</td>
<td>− Respiration – note ease, presence of adventitious sounds</td>
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</tr>
<tr>
<td>− Urination (Burning, urgency, frequency)</td>
<td>− Cough – note quality of phlegm, duration of cough or phlegm</td>
<td></td>
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<tr>
<td>− Vaginal discharge, itching</td>
<td>− Sinuses –congestion, tenderness, unilateral eye tearing or facial swelling, bleeding, periorbital cellulitis</td>
<td></td>
</tr>
<tr>
<td>− Constipation/diarrhea?</td>
<td>− Nares –ulcerations, drainage</td>
<td></td>
</tr>
<tr>
<td>− Any areas of redness/ swelling/pain?</td>
<td>● Drains and catheters (e.g. central vascular device, bladder catheters) for function and signs of infection</td>
<td></td>
</tr>
<tr>
<td>− Recent blood transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>− Recent travel or exposure to sick individuals</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Using any antipyretics? If so, what type?</td>
<td></td>
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</tr>
<tr>
<td>● Any other medications or treatments? (e.g. anti-diarrheas, granulocyte colony-stimulating factors)</td>
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<tr>
<td><strong>Understanding / Impact on You</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● How much are you eating or drinking?</td>
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<td></td>
</tr>
<tr>
<td>● What do you believe is causing these symptoms?</td>
<td></td>
<td></td>
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<tr>
<td>● How is this affecting you?</td>
<td></td>
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</tbody>
</table>

* Special Consideration*

**High Risk Indicators Requiring Medical Attention such as:**

- Recent chemotherapy/radiation regimen of high risk for febrile neutropenia
- Prior febrile neutropenia
- Post BMT
- Fever, chills, rigors
- Recent or current infection
- Poor performance status
- Change in mental status
- Diarrhea, cough, dyspnea, chest or abdominal pain, headache, stiff neck, rash
- Age > 65
- Potential for infection (Central vascular devices, IV lines, drains and catheters, prosthetic devices (e.g. cardiac valves))

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# FEBRILE NEUTROPENIA GRADING SCALE (Adapted NCI CTCAE Version 4.03)

<table>
<thead>
<tr>
<th>Normal</th>
<th>GRADE 1 (Mild)</th>
<th>GRADE 2 (Moderate)</th>
<th>GRADE 3 (Severe)</th>
<th>GRADE 4 (Life threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>___</td>
<td>___</td>
<td>ANC &lt;1.0 X 10^9/L with a single temperature of &gt;38.3 °C (101°F) OR a sustained temperature of ≥ 38 °C (100.4 °F) for more than 1h</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

*Step-Up Approach to Symptom Management: Interventions Should Be Based On Current Grade Level and Include Lower Level Grade Interventions As Appropriate

## NORMAL

### NON – URGENT:
Prevention, Support, teaching & follow-up care as required

**Patient Care and Assessment**
- Review cancer treatment and potential for neutropenia
- Refer to specific chemotherapy protocol for direction: [http://www.bccancer.bc.ca/health-professionals-professional-resources/chemotherapy-protocols](http://www.bccancer.bc.ca/health-professionals-professional-resources/chemotherapy-protocols)
- Not all patients with neutropenia exhibit a fever in the presence of an infection (e.g. elderly, patients on corticosteroids)- assess for other signs of clinical deterioration (e.g. hypothermia, hypotension, confusion)

**Recommendations for Prevention of Infection**
- Maintaining adequate hydration and nutrition incorporating protein, vitamin B and C during treatment assists with maintaining skin integrity.
- Use an electric shaver rather than a razor for shaving.
- Have a flu shot and other immunizations as indicated
- Vaccination should be at least 2 weeks before receiving chemotherapy or immunosuppressive therapy. Patients having chemotherapy or radiation therapy should not receive live attenuated vaccines unless instructed by physician.
- Inform dentist of current treatment prior to dental treatment and to limit treatment, if possible, to periods when counts will be higher (within a couple of days of chemotherapy treatment).
- Use a water-soluble lubricant during intercourse. If unsure of partner disease status, use lubricated condoms to protect against sexually transmitted diseases. If severely neutropenic, check with health care team to determine if intercourse should be avoided during this time.
- Avoid handling pet feces, including fish tanks, bird cages and cat litter boxes
- Avoid large crowds or anyone with signs of infection (e.g. chicken pox, measles, cold, flu, and shingles) especially during nadir (typically 7 to 14 days).
- Avoid constipation and straining to prevent trauma to rectal tissue. Do not use suppositories and/or enemas when neutrophil count low unless advised by physician.

**Hygiene**
- Bathe daily using warm water, pat skin dry
- Hand hygiene: Soap and warm water or antiseptic hand sanitizer
- Wash hands: prior to handling foods, before and after eating, after using the washroom, coughing or sneezing in hands
- Avoid touching face and mucous membranes as much as possible
- Keep mouth clean by brushing with a soft toothbrush at least twice dailyIf there is an alteration in skin integrity, a dressing and/or topical agents may be indicated.

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Safe Food Handling
- Maintain appropriate temperatures for foods (cold and hot)
- Wash all fresh fruits and vegetables thoroughly
- During periods of severe neutropenia avoid: raw or rare cooked meats, seafood, eggs; unpasteurized juices or cheese.

Pharmacological Management
- Antibiotic prophylaxis may be considered in patients with expected duration of neutropenia (ANC <1.0 X 10^9/L) for > 7 days or for patients receiving immunosuppressive regimens (e.g. systemic corticosteroids).
- Antifungal prophylaxis may be recommended for high risk patients (e.g. those with acute leukemia and stem cell transplantation).
- Granulocyte colony stimulating factor (GCSF- e.g. filgrastim, pegfilgrastim) may be prescribed prophylactically following previous episodes of chemotherapy induced neutropenia.

Patient Education and Follow-Up
- Demonstrate how to perform regular temperature checks and advise patient to keep a record at home
- Provide contact information and access to resources.
- Teach patients signs and symptoms of infection and to notify doctor and/or nurse immediately if:
  - Oral temperature ≥ 38.0° C. (Do not take acetaminophen, ibuprofen, or acetylsalicylic acid for fever unless advised by physician).
  - Cough with or without sputum
  - Sore throat or sores in mouth
  - Any areas of redness or swelling
  - Headache, stiff neck, or rash
  - Loose or liquid stools or constipation
  - Increased frequency or burning with urination
  - Vaginal drainage or itching
  - Flu-like symptoms - body aches, general fatigue
  - Chills, sweating, shortness of breath, changes in mental status

GRADE 3- GRADE 4

EMERGENT: Requires IMMEDIATE medical attention

Patient Assessment and Care
- Have patient go to nearest emergency department or ambulatory setting immediately for further assessment. Low risk, reliable patients may be able to be treated as an outpatient with close follow-up. Notify oncologist of assessment and facilitate arrangements as necessary.
- If on active treatment, will require chemotherapy dosage reductions, delays or discontinuation of treatment. Refer to specific chemotherapy protocols for specific direction: [http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols](http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols)
- If patient on Immunotherapy, remind patient to present Immunotherapy alert card
- Lab and diagnostic testing:
  - Review most recent lab reports.
  - Lab or diagnostic tests that may be ordered: complete blood count, leukocyte differential, blood cultures (two sets), creatinine, C-reactive protein, electrolytes, BUN, blood glucose, serum lactate, and liver function tests, stool or urine cultures, throat or skin swabs, chest x-ray.
  - Assess for drug toxicities from support medications (e.g. antibiotics).
- Frequent nursing assessments including:
  - Vital signs (every four hours and as clinically indicated)
  - Assess for signs and symptoms of infection: culture any suspected areas, assess CVC and/or IV sites If there is an alteration in skin integrity, a dressing and/or topical agents may be indicated.
- High efficiency particulate air (HEPA) filtration is recommended for allogeneic stem cell transplant patients and patients with prolonged neutropenia (if available).

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Pharmacological Management

- Prompt initiation of antibacterial therapy impacts patient outcomes
- May require new or change in prescription for anti-infective agents (oral, IV), analgesics, granulocyte colony stimulating factor (GCSF- e.g. filgrastim, pegfilgrastim). Administer medications as prescribed.

Follow-up

- Follow-up is recommended for any positive cultures, persistent fever lasting 3 to 5 days, subsequent infection, adverse events, or if unable to continue prescribed antibiotic regimen

RESOURCES & REFERRALS

Referrals

- Patient Support Centre
- Telephone Care for follow – up
- Home Health Nursing
- Oncologist
- Infectious Disease Physician

Cancer Management Guidelines

Febrile Neutropenia – Solid Tumour/Lymphoma:

- Patient Assessment for Hospital Admission - http://www.bccancer.bc.ca/nursing-site/Documents/PatientAssessment2.pdf

Patient Education


Immunotherapy

- Immunotherapy Alert Card
- Please refer to protocol specific algorithms to guide management of immune mediated side effects.

Related Online Resources

- E.g. Fair Pharmacare; BC Palliative Benefits. Can be found in “Other Sources of Drug Funding Section” http://www.bccancer.bc.ca/health-professionals/professional-resources/pharmacy/drug-funding

Bibliography List

- http://www.bccancer.bc.ca/health-professionals/professional-resources/nursing/symptom-management

Appendix A: Septic Shock

SEPTIC SHOCK

EMERGENT: Requires IMMEDIATE medical attention

- Sepsis: a systemic inflammatory response to infection in the blood.
- Septic Shock: a condition caused by sepsis that leads to severe hypotension which results inadequate blood flow, impaired tissue perfusion and organ dysfunction. This is a MEDICAL EMERGENCY that can have a fatal outcome.

Early Signs of Septic Shock

- Dry, warm, flushed skin
- Fever, chills
- Hypotension
- Tachypnea, tachycardia, widening pulse pressure
- Anxiety, apprehension
- Restlessness, confusion, disorientation, reduced mental alertness
- Decreased urinary output
- Decreased breath sounds and crackles
- Hyperglycemia

Late Signs of Septic Shock

- Cold, pale, clammy skin
- Temperature > 38°C or <36°C
- Hypotension
- Tachycardia, narrowing pulse pressure
- Disorientation
- Dyspnea, shortness of breath, cyanosis
- Oliguria, anuria
- Lethargy, obtundation
- Decreased breath sounds, crackles, wheezes
- Hyperglycemia or hypoglycemia

Date of Print:
Revised: October, 2014
Created: January, 2010

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