

Definition

- **Fever:** A single oral temperature of $\geq 38.3^{\circ}\text{C}$ (101°F) **OR** a temperature $\geq 38^{\circ}\text{C}$ (100.4°F) which lasts more than 1h
- **Neutropenia:** Presence of absolute neutrophil count $<0.5 \times 10^9/\text{L}$, or $<1.0 \times 10^9/\text{L}$ predicted to fall below $0.5 \times 10^9/\text{L}$ within 48 h. The lower the neutrophil count, the greater the risk of infection
- **Febrile neutropenia:** Neutropenia with fever. A life-threatening oncology emergency requiring immediate attention and treatment.

Focused Health Assessment

PHYSICAL ASSESSMENT	SYMPTOM ASSESSMENT
<p>Vital Signs</p> <ul style="list-style-type: none"> • Frequency – as clinically indicated. If severe neutropenia, presence of fever or infection then every 4 hours and prn <p>Systems Assessment</p> <ul style="list-style-type: none"> • Presence of shaking (rigors), chills, diaphoresis • Neurological <ul style="list-style-type: none"> – Level of consciousness and orientation • Skin and oral mucosa for signs of infection <ul style="list-style-type: none"> – Note any areas of redness, swelling, pain, warmth, impaired skin integrity, exudate • Respiratory tract: <ul style="list-style-type: none"> – Respiration – note ease, presence of adventitious sounds – Cough – note quality of phlegm, duration of cough or phlegm – Ears and Sinuses –congestion, tenderness, unilateral eye tearing or facial swelling, bleeding, periorbital cellulitis – Nares –ulcerations, drainage • Drains and catheters (e.g. central vascular device, bladder catheters) for function and signs of infection <p>Diagnostics</p> <ul style="list-style-type: none"> • Consider all the following in the laboratory workup: complete blood count, hepatic transaminase, bilirubin levels, electrolytes, serum creatinine, and blood-urea-nitrogen levels. <p>Functional Status</p> <ul style="list-style-type: none"> • Activity level/ECOG or PPS 	<p>*Consider contributing factors</p> <p>Normal</p> <ul style="list-style-type: none"> • Refer to pre-treatment nursing or oncology assessment <p>Onset</p> <ul style="list-style-type: none"> • When did symptoms begin? <p>Provoking / Palliating</p> <ul style="list-style-type: none"> • What makes it better? Worse? <p>Quality (in last 24 hours)</p> <ul style="list-style-type: none"> • Can you describe your symptoms? • What is your temperature? For how long? <p>Region / Radiation</p> <ul style="list-style-type: none"> • Where are your symptoms? <p>Severity / Other Symptoms</p> <ul style="list-style-type: none"> • Have you been experiencing any other symptoms such as: <ul style="list-style-type: none"> - Chills, sweating - Shortness of breath - Cough, with sputum (colour?) - Fatigue or feeling unwell - Mouth sores or sore throat - Urination (Burning, urgency, frequency) - Vaginal discharge, itching - Constipation/diarrhea? - Any areas of redness/ swelling/pain? - Recent blood transfusion - Recent travel or exposure to sick individuals - Altered behaviour - faintness, shuffling gait, excessive sleepiness - dizziness or light-headedness with standing <p>Treatment</p> <ul style="list-style-type: none"> • Using any antipyretics? If so, what type? When was the last dose? • Any other medications or treatments? (e.g. anti-diarrheas, granulocyte colony-stimulating factors) <p>Understanding / Impact on You</p> <ul style="list-style-type: none"> • How much are you eating or drinking? • What do you believe is causing these symptoms? <p>How is this affecting you?</p>

FEBRILE NEUTROPENIA GRADING SCALE

NCI Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0)

GRADE 1 (Mild)	GRADE 2 (Moderate)	<u>GRADE 3</u> (Severe)	<u>GRADE 4</u> (Life - threatening)	Grade 5
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Special Considerations for Immunotherapy (Checkpoint Inhibitors)

Immune-Mediated Adverse Reactions

- Can cause **severe and fatal** immune-mediated adverse reactions including: enterocolitis, intestinal perforation, hepatitis, dermatitis, neuropathy, endocrinopathy, and toxicities in other organ systems
- Permanent discontinuation of treatment is recommended for severe immune-mediated reactions
- Onset usually occurs during the beginning of treatment, but may occur months after last dose
- All patients should be given an [immunotherapy alert card](#), [Immunotherapy Patient Letter](#), and [SCIMMUNE patient handout](#) when treatment is started

Special Considerations for Immunotherapy (Bispecific Antibodies)

Overactivation and dysregulation of immune system

- Fever and rigors are hallmark clinical symptom indicative of cytokine release syndrome
- Prompt recognition and intervention are critical to prevent progression of symptoms
- Refer to [SCCRS](#) protocol for directions on symptomatic treatment
- All patients should be given [bispecific antibodies alert card](#), [bispecific antibodies patient letter](#), and [SCCRS/SCICANS patient handout](#) when treatment is started

***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 systemic therapy protocol for direction: <http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols>
- If patients are on checkpoint inhibitors, fever may not be a direct side effect of the treatment, but rather a product of immune mediated side effects.
- If patients are on bispecific antibodies, fever may not be a direct side effect of the treatment, but rather a symptom related to CRS
- Assessment and management of contributing factors, if immunotherapy checkpoint inhibitor or bispecific antibody-related see [Special considerations for patients on Checkpoint Inhibitors or Bispecific Antibodies](#)

	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 systemic therapy 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). • Avoid constipation and straining to prevent trauma to rectal tissue. Avoid digital rectal examinations, rectal thermometers, tampons, enemas, and suppositories during periods of neutropenia. • Isolation procedures according to the specific condition and standard precautions should be carried out. Follow additional precautions outlined in IPAC Manual http://policyandorders.cw.bc.ca/ipac • All visitors should be instructed on basic infection prevention including hand hygiene techniques and isolation procedures. • All visitors with an upper respiratory tract infection, a flu-like illness, a herpes zoster rash or recent known exposure to any transmittable disease should be restricted. Advise visitors to reschedule their trips if they experience the following: a new rash, cough, fever or diarrhea. • Fresh or dried flowers and plants should be prohibited • All CVC's must be accessed using maximal sterile barrier precautions.
Hygiene	<ul style="list-style-type: none"> • Bathe daily using warm water, pat skin dry • Use soap and warm water or antiseptic hand sanitizer to wash hands prior to handling foods, before and after eating, after using the washroom, coughing or sneezing in hands • Healthcare providers follow 4 moments of hand hygiene: before initial patient/environment contact, before aseptic procedure, after body fluid exposure risk, and after patient/environment contact • Avoid touching face and mucous membranes as much as possible • Avoid petting zoos • Keep mouth clean by brushing with a soft toothbrush at least twice daily. Oral rinses with sterile water or normal saline are recommended 4-7 times per day. If there is an alteration in skin integrity, a dressing and/or topical agents may be indicated.
Safe Food Handling	<ul style="list-style-type: none"> • Maintain appropriate temperatures for foods (cold and hot) • Wash all fresh fruits and vegetables thoroughly • Prevent Cross-contamination of raw meats and produce. • Avoid food sources such as salad bars and street vendors due to high risk of exposure to bacteria that causes food borne illnesses. • During periods of severe neutropenia avoid: raw or rare cooked meats, seafood, eggs; unpasteurized juices or dairy products and spoiled or expired food.
Pharmacological Management	<ul style="list-style-type: none"> • Antibiotic prophylaxis may be considered in patients with expected duration of neutropenia (ANC <1.0 X 10⁹/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) and patients on bispecific antibody therapy • Antiviral prophylaxis may be recommended for patients with lymphoid, plasma cell, and myeloid malignancies. See SCHBV for guidance. • Granulocyte colony stimulating factor (G-CSF e.g. filgrastim, pegfilgrastim) may be

	prescribed throughout all cycles of chemotherapy for high-risk patients of developing febrile neutropenia (when the anticipated incidence is in the range of 20% or higher).
Patient Education and Follow-Up	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Oral temperature $\geq 38.0^{\circ}$ 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 • Please refer to Patient Information for Neutropenia for more information listed below

GRADE 3- GRADE 4



EMERGENCY: Requires IMMEDIATE medical attention	
Patient Assessment and Care	<ul style="list-style-type: none"> • Have patient go to nearest emergency department or ambulatory setting immediately for further assessment. • Notify oncologist of assessment and facilitate arrangements as necessary. • If on active treatment, will require dosage reductions, delays or discontinuation of treatment. Refer to specific protocols for direction: http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols • If patient is on checkpoint inhibitors remind patient to present Immunotherapy Alert Card and patient letter • If patient is on bispecific antibody treatment: <ul style="list-style-type: none"> – fever may be indicative of cytokine release syndrome, refer to SCCRS protocol for directions and symptom management. – remind patient to present Bispecific Antibodies Alert Card and patient letter – At initial presentation of fever, consider other differential diagnoses including infection/sepsis (blood and urine cultures, CXR, and/or other investigations directed at symptoms) and consider broad-spectrum antibiotics, particularly if neutropenic, concurrently while treating CRS. Do not wait for infectious work up before starting treatment for CRS • Lab and diagnostic testing: <ul style="list-style-type: none"> – 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; <ul style="list-style-type: none"> – Vital signs (every four hours and as clinically indicated) – Asses 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. • Hematopoietic stem cell transplant recipient rooms should have directed air flow and positive air pressure relative to the corridor, be properly ventilated and well-sealed, and be designed

	to minimize dust.
Pharmacological Management	<ul style="list-style-type: none"> • Prompt initiation of antibacterial therapy impacts patient outcomes. Follow B.C. Cancer Empiric Treatment of Febrile Neutropenia guidelines to determine appropriate antibiotic treatment: • If patient on bispecific antibody, prompt initiation of SCCRS protocol including administration of tocilizumab and/or steroids is critical. <p>*See special considerations for patients on Checkpoint Inhibitors or Bispecific antibodies</p> <ul style="list-style-type: none"> • http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-manual/supportive-care/febrile-neutropenia • Initial assessments and investigations should be performed before applying antimicrobial therapy. A comprehensive history should be taken, which includes information with the nature of administered systemic therapy, prior antimicrobial prophylaxis, concomitant steroid use, recent surgical procedures, presence of allergies, infection exposures, prior documented infection or pathogen colonization, coexistence of non-infectious causes of fever and underlying comorbidities. After that physical examination, blood tests, microbiologic cultures and radiographic tests should be further investigated. <ul style="list-style-type: none"> – Tests on complete blood cell counts, serum creatinine levels, and urea nitrogen levels are recommended to be performed at least every 3 days during the antibiotic therapy, in order to monitor and manage possible drug toxicity – The use of procalcitonin (PCT) as a biomarker can identify early infectious complications and guide the antibiotic usage • May require new or change in prescription for anti-infective agents (oral, IV), analgesics, granulocyte colony stimulating factor (G-CSF- e.g. filgrastim, pegfilgrastim). Administer medications as prescribed. • If patients experience persistent fever, antifungal therapy should be considered.
Follow-up	<ul style="list-style-type: none"> • 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 • Direct patient to patient handout for neutropenia and discuss signs and symptoms to report to the health care provider. http://www.bccancer.bc.ca/health-info/coping-with-cancer/managing-symptoms-side-effects/neutropenia-(low-white-blood-cells)

RESOURCES & REFERRALS	
Referrals	<ul style="list-style-type: none"> • Patient Support Centre • Telephone care for follow-up • Home Health Nursing • Oncologist • Infectious Disease Physician
Cancer Management Guidelines	<p>Febrile Neutropenia – Solid Tumour/Lymphoma:</p> <ul style="list-style-type: none"> • Patient Assessment and Treatment for Adults - https://shop.healthcarebc.ca/phsa/BCcancer/Provincial%20Pharmacy/70568.pdf
Patient Education	<ul style="list-style-type: none"> • Neutropenia – What is it? http://www.bccancer.bc.ca/health-info/coping-with-cancer/managing-symptoms-side-effects/neutropenia-(low-white-blood-cells) • Filgrastim fact sheet for patients http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Filgrastim_handout.pdf
Immunotherapy - Checkpoint Inhibitors	<ul style="list-style-type: none"> • Immunotherapy Nursing Process • Immunotherapy Patient Letter • Immunotherapy Alert Card • SCIMMUNE protocol • SCIMMUNE patient handout
Immunotherapy - Bispecific Antibodies	<ul style="list-style-type: none"> • Bispecific Antibodies Nursing Process • Bispecific Antibodies Patient letter • Bispecific Antibodies Alert Card • SCICANS protocol • SCCRS protocol

Bibliography List	http://www.bccancer.bc.ca/nursing-site/Documents/Bibliography%20-%20Master%20List.pdf
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Contributing Factors of Neutropenia

Cancer Related & Cancer Treatment Related	<ul style="list-style-type: none"> • Myelosuppressive therapy (e.g. chemotherapy and radiation therapy) • Monoclonal antibodies (e.g. alemtuzumab) • Stem cell transplants - at risk for severe, prolonged neutropenia • Hematological malignancies • Solid tumors • Febrile neutropenia in previous course of therapy • Immunotherapy – Checkpoint inhibitors • Immunotherapy - Bispecific Antibodies- fever is a hallmark symptom of cytokine release syndrome (CRS)
Medications that induce neutropenia	<ul style="list-style-type: none"> • Antibiotics, antifungals, antimalarials • Anticonvulsants, anti-inflammatories, antithyroid • Cardiovascular agents, diuretics • Gastrointestinal agents, immunosuppressants • Antipsychotic drugs
Co-morbidities	<ul style="list-style-type: none"> • Autoimmune diseases • AIDS • Hypersplenism • Aplastic anemia • Cardiovascular conditions • Diabetes • Cerebrovascular disease • Tuberculosis & chronic respiratory disease • Hepatic and renal dysfunction • Arthritis • Previous cancer • Thyroid disease
Other	<ul style="list-style-type: none"> • 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, rickettsia, protozoal) • Vitamin deficiencies (e.g. vitamin B₁₂, folate, copper); albumin level < 35 g/L; dehydration • Hemodialysis, hypotension • Recent exposures: travel, blood product administration

Causative Factors of Infection in Patients with Neutropenia

Factors Related to Infection	<ul style="list-style-type: none"> • Immunosuppression- Herpes Simplex Virus (HSV) and other viruses (VZV, CMV, EBV, and etc.) reactivation in immunocompromised patients may be as high as 75% • Prior infection and /or antibiotic use in last 90 days- risk of C. difficile infection due to use of antibiotics/chemotherapy • Chemotherapy- induced gastrointestinal mucositis • Bispecific antibodies can cause profound hypogammaglobulinemia, which increases risk of prolonged infections • Presence of open wounds, catheters or drains • Obstruction of the lymphatic system, biliary tract, bronchial, gastrointestinal or urinary systems by tumors or secondary to surgical procedures • Graft versus host disease - may be at higher risk of developing fungal infections up to 6 months after transplant • Potential exposure to pathogens during hospital stay
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Appendix A: Septic Shock

The information contained in these documents is a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use, available at www.bccancer.bc.ca/terms-of-use

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 (refractory to fluid resuscitation) OR hyperlactatemia which results in inadequate blood flow, impaired tissue perfusion and organ dysfunction. This is a **MEDICAL EMERGENCY** that can have a fatal outcome.

Signs of Septic Shock

- Hyperlactatemia OR Severe hypotension;
 - AND Sepsis (suspected infection plus one of more of the following):
- General variables**
- Fever (core temperature, > 38 °C)
 - Hypothermia (core temperature, < 36°C)
 - Elevated heart rate (> 90 beats per min or >2 SD above the upper limit of the normal range for age)
 - Tachypnea
 - Altered mental status
 - Substantial edema or positive fluid balance (> 20ml/kg of body weight over a 24-hr period)
 - Hyperglycemia (plasma glucose, > 6.7mmol/l) in the absence of diabetes
- Inflammatory variables**
- Leukocytosis (white-cell count, >12,000/mm³)
 - Leukopenia (white-cell count, <4000/mm³)
 - Normal white-cell count with >10% immature forms
 - Elevated plasma C-reactive protein (>2 SD above the upper limit of normal range)
 - Elevated plasma procalcitonin (>2 SD above the upper limit of normal range)
- Hemodynamic variables**
- Arterial hypotension (systolic pressure, <90 mmHg; mean arterial pressure, < 70 mmHg; or decrease in systolic pressure of >40 mmHg in adults or to > 2 SD below the lower limit of the normal range for age)
 - Elevated mixed venous oxygen saturation (> 70%)
 - Elevated cardiac index (>3.5 l/min/square meter of body-surface area)
- Organ-dysfunction variables**
- Arterial hypoxemia (ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, <300)
 - Acute oliguria (urine output, <0.5 ml/kg/hr or 45 ml/hr for at least 2 hr)
 - Increased creatinine level of >44 µmol/l
 - Coagulation abnormalities (international normalized ratio, >1.5; or activated partial-thromboplastin time, >60 sec)
 - Paralytic ileus (absence of bowel sounds)
 - Thrombocytopenia (platelet count, <100,000/mm³)
 - Hyperbilirubinemia (plasma total bilirubin, 68 µmol/l)
- Tissue-perfusion variables**
- Decreased capillary refill or mottling

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Contributing Authors:

Revised (2025) by: Jeevan Dosanjh, RN BScN, Michelle LaFreniere, RN; Brittany Freeman, RN CON(c); Megan Crosby, RN CON(c); Taslin Janmohamed-Velani, RN, MN; Anne Tremblay, RN

Revised by: Jeevan Dosanjh, RN, BScN; Bandanjit Sanghera, Langara SN; Jr-Luen (Vivian) Wang, Langara SN

Created by: Colleen Sherriff, RN; Vanessa Buduhan, RN MN; Rosemary Cashman, RN MSc(A), MA (ACNP);

Elizabeth Cooper, RN BScN, CON(c); Karen Levy, RN MSN; Ann Syme RN PhD(C)

Reviewed by: Shirin Abadi, BSc (Pharm), ACPR, Pharm D, DPLA, MBA, FCSHP, RPh; Kerstin Humbert-Droz, RN, BScN; Alison Chant, RN, BScN; Judy Tearoe, RN, BScN; Harjothe Kahlon, RN, BScN