Health PEI

ANTIMICROBIAL STEWARDSHIP SUBCOMMITTEE

Febrile Neutropenia in High-Risk Adults

Febrile Neutropenia is a Medical Emergency

- Patient is to be assessed and have antimicrobials administered **within 1 hour of presentation**
- Draw samples for culture before administering antibiotic therapy
- Do not wait for test results before initiating antibiotics

Background

This guideline applies to patients with febrile neutropenia who are at high risk of complications

Definitions

Febrile neutropenia:

1. **Fever:** single oral temperature of 38.3 °C or temperature of greater than or equal to 38 °C sustained over a one-hour period
   AND
2. **Neutropenia:** absolute neutrophil count (ANC) less than or equal to 0.5 x 10^9 cells/L or less than 1 x 10^9 cells/L and predicted to fall below 0.5 x 10^9 cells/L within 48 hours.

Neutropenic Fever Syndromes:

- **Microbiologically defined infection** – Neutropenic fever with an associated causative pathogen
- **Clinically documented infection** – Neutropenic fever with a focus of infection, such as cellulitis or pneumonia, but without the isolation of an associated pathogen
- **Unexplained fever** – Neutropenic fever without a clinical focus of infection or an identified pathogen

Most Common Organisms

- Methicillin Susceptible *Staphylococcus aureus* (MSSA), Methicillin Resistant *Staphylococcus aureus* (MRSA), Viridans group Streptococci, Coagulase Negative Staphylococci, *Escherichia coli*, Klebsiella spp, Other Enterobacteriaciae, *Pseudomonas aeruginosa*

Initial Laboratory and Diagnostic Considerations

- Vitals signs (temperature, respiratory rate, blood pressure, and pulse) and oxygen saturation via pulse oximetry at presentation and as needed based on patient's condition
- Intake and output if patient initiated on IV therapy
- Blood cultures
  - If venous access device present: One blood culture from each lumen and one from a peripheral site
  - If NO venous access device: Two blood cultures from different peripheral sites
- Microbiological testing from other sites of suspected infection should be obtained as clinically indicated, examples include:

  - Urine culture
  - If respiratory symptoms are present:
    - Sputum for culture if productive cough
    - NP swab for Influenza/COVID/RSV
    - Legionella urinary antigen
  - *C. difficile* stool sample if diarrhea present
  - If vesicular lesions: HSV PCR, VZV PCR
  - Note: many people have oropharyngeal colonization with *Candida*. Oropharyngeal candidiasis (thrush) is a clinical diagnosis. Swabs are rarely indicated but may be done if uncertainty of diagnosis or if refractory to nystatin or fluconazole.
- A chest radiograph
  - A chest CT should be done if persistent fever of unclear cause, unexplained respiratory symptoms, or abnormal CXR requiring diagnostic clarification
- CBC with differential, electrolytes, creatinine, ALT, ALK Phos, total and direct bilirubin, PT-INR, LDH, glucose, C-Reactive protein, VBG if indicated

Vanessa's Law

Febrile neutropenia requiring observation in emergency department or admission to hospital meets Health Canada's mandatory reporting criteria as a serious adverse drug reaction. To meet reporting requirements through Health Canada, a member of the health care team is asked to enter a medication event incident in the Provincial Safety Management System (PSMS) using **adverse drug reaction** as the specific event type. In the incident form, select "yes" for injury/damage occurred and complete the mandatory fields on the incident form.

High Risk = Multinational Association for Supportive Care in Cancer (MASCC) score less than 21 OR one or more high risk criteria present (see below)

MASCC Score	Potential Score	Patient Score
Burden of illness **(select one)** (i.e. how sick the patient appears at presentation)		
No symptoms or mild symptoms.....	5	
Moderate symptoms.....	3	
Severe Symptoms	0	
Systolic Blood Pressure greater than 90 mmHg	5	
No chronic obstructive pulmonary disease	4	
Solid tumor or no previous fungal infection in patient with hematological malignancy	4	
No dehydration requiring parenteral fluids	3	
Outpatient status at time of fever	3	
Age less than 60 years	2	
Total score	26	

High Risk = ONE or more high risk criteria present

	High Risk Criteria
	Prolonged severe neutropenia anticipated: ANC less than $0.1x10^9$cells/L AND/OR anticipated neutropenia greater than 7 days
	Acute leukemia
	Hemodynamic instability or evidence of severe sepsis (ex. hypotension, systolic blood pressure less than 90 mmHg)
	New pulmonary infiltrate or hypoxemia, pneumonia or underlying chronic lung disease
	New onset gastrointestinal symptoms, including abdominal pain, nausea, vomiting or diarrhea
	New onset neurologic or mental status changes
	Intravascular catheter infection
	Severe cellulitis
	Hepatic insufficiency defined as ALT OR AST greater than 5 times upper limit of normal
	Renal insufficiency defined as a creatinine clearance less than 30 mL/min
	Mucositis affecting oral intake (i.e. unable to eat/unable to swallow oral medication)
	Other serious medical comorbidities or clinically unstable
	Uncontrolled or progressive cancer (i.e. leukemia not in complete remission or patients without leukemia with evidence of disease progression after more than 2 courses of chemotherapy
	Patient receiving fluoroquinolone prophylaxis
	Patient receiving IV alemtuzumab
	Patient with risk factors for Methicillin-Resistant Staphylococcus Aureus (MRSA) ¥

¥ MRSA Risk Factors: History of MRSA infection or colonization; Household contact with a MRSA colonized individual; IV drug use; Homelessness; Incarcerated persons; Recent travel to or residing in an MRSA endemic region or community

This document is designed to aid Prince Edward Island practitioners in the appropriate use of antimicrobials. These guidelines provide general recommendations and are not a substitute for clinical judgement or consultation with Infectious Disease experts.

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Empiric Antibiotic Therapy for High Risk Adults with Febrile Neutropenia

Preferred Empiric Regimen	
No penicillin allergy	piperacillin-tazobactam 4.5 g IV every 6 hours*
Alternate Empiric Regimens	
Known/suspected infection with **multi-drug resistant gram-negative organism** (i.e. ESBL/AMP C producing)	meropenem 500 mg IV every 6 hours*
True immediate penicillin allergy▲ **OR** **Drug-drug interactions** (e.g. patient is receiving high-dose methotrexate)	cefepime 2 g IV every 8 hours* +/- metronidazole 500 mg PO/IV q12h$^{\mu}$ **OR** meropenem 500 mg IV every 6 hours*
Severe non-IgE mediated reaction to a β-lactam (i.e. Stevens Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, serum sicknesses). Avoid ALL Beta-Lactams	ciprofloxacin 400 mg IV every 8 hours* **AND** vancomycin IV§ **AND** metronidazole 500 mg IV every 12 hours
ADDITIONS to empiric therapy	
MRSA coverage: Consider for patients with • IV catheter-related infection OR • Skin and soft tissue infection at any site OR • Known colonization with Methicillin-resistant *Staphylococcus aureus* (MRSA) OR • Septic shock	vancomycin IV§
Atypical coverage for pneumonia	azithromycin 500 mg IV/PO every 24 hours
Additional gram-negative bacteria coverage: Consider for patients with signs of **septic shock** while awaiting culture results **AND** • Recent history (past 90 days) of receiving broad-spectrum antimicrobials (i.e. piperacillin-tazobactam or carbapenem) **OR** • Recent infection/history of colonization with multidrug resistant Gram-negative bacteria	tobramycin 7 mg/kg** IV every 24 hours*

▲ True, immediate IgE-mediated allergies include, but are not limited to: anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, and pruritis.

* dose adjustment required in renal impairment

** If obese (20% greater than IBW); dosing weight = IBW + 0.4 (ABW-IBW). See Health PEI IV manual or Firstline app for more information

§ See Health PEI IV manual or Firstline app for dosing

$^{\mu}$ If anaerobic coverage needed (i.e. GI source suspected)

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Re-evaluation and De-escalation

Infectious cause of fever is identified:

- **Microbiologically defined infection:**
  - After 72 hours of empiric therapy: treat according to the susceptibility results and clinical syndrome with a narrow spectrum antimicrobial targeting the identified pathogen(s) if the patient is stable and afebrile.
  - *S. aureus* and *Candida* bloodstream infections: 14 days minimum of therapy from negative blood cultures -consider ID consultation

- **Clinically documented infection:** If no pathogen is isolated but a focus of infection is identified, such as cellulitis or pneumonia, treat according to the syndrome.

  - Generally, antimicrobials are continued until the infection is microbiologically eradicated and all clinical signs of infection are resolved: 7 -14 for most syndromes

Unexplained fever (Infectious cause of fever is not identified):

- Microbiology results are often negative, and patients usually improve with empiric therapy. In such cases, antimicrobials can be narrowed or discontinued as outlined below:
  - If vancomycin was started, it should be stopped after 48 – 72 hours if there is no indication such as MRSA, *E. faecium*, or Coagulase-negative staphylococci (CoNS) infection
  - If tobramycin was started, it should be stopped after 48 – 72 hours if there is no indication such as a multidrug resistant gram-negative infection
- Stop **ALL** antibiotics **REGARDLESS of ANC recovery** after 3 - 5 days of antimicrobials if neutropenic fever without a clinical focus of infection or an identified pathogen and:
  - afebrile for at least 48hrs **AND**
  - negative blood cultures after 72h incubation **AND**
  - no severe mucositis **AND**
  - no localizing signs or symptoms of infection **AND**
  - No septic shock at onset

References

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