

PROTOCOL TITLE: **Neutropenia Protocol – Identification and Management of Neutropenic Fever Syndromes**

SECTION: Infection Control Services	PROTOCOL NO.: 12.500	APPROVED BY THE PRESIDENT AND CEO, CCMB <i>Original signed by Dr. S. Navaratnam</i>
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1.0 **BACKGROUND:**

- 1.1 Patients with cytotoxic therapy-induced severe neutropenia and mucositis are at risk for potentially life-threatening invasive bacterial infections.<sup>1,2</sup>
- 1.2 Risk factors for developing a neutropenic fever syndrome include older age, female sex, marrow invasion by cancer, reduced granulopoiesis, poor nutritional status, integumental damage, hematological malignancy, and active co-morbid conditions.<sup>3,4</sup>
- 1.3 Delayed and/or inappropriate treatment of neutropenic fever syndromes is associated with increased morbidity and mortality.<sup>5</sup>
- 1.4 Successful management of neutropenic fever syndromes in cancer patients is time-sensitive.<sup>6</sup> Timely intervention may be life-saving.<sup>7</sup>
- 1.5 Rapid triage to recognize and prioritize neutropenic sepsis syndromes for emergent initial empirical anti-bacterial therapy is critical to successful outcome of such events.<sup>8</sup>

2.0 **PURPOSE:**

- 2.1 To provide healthcare providers at CancerCare Manitoba (CCMB), the Winnipeg Regional Health Authority (WRHA), and the provincial regional health authorities with standardized guidelines for the rapid triage, assessment, and initial management of new onset of suspected sepsis syndromes in cancer patients with fever and neutropenia.
- 2.2 To provide nursing and medical staff with a **timeline of one hour** (60 minutes) for the provision of triage, “sepsis syndrome” assessment, and initial empirical anti-bacterial treatment services for suspected neutropenic sepsis syndromes in accordance with the time-dependent **CTAS Level II (Emergent)** standard. This framework should allow the clinician to make an initial clinical assessment and therapeutic plan based upon the patient history, vital signs, and clinical examination in the absence of laboratory test results or diagnostic imaging.
- 2.3 To provide healthcare providers with a guideline for the management of new onset neutropenic sepsis syndromes over the subsequent 72 to 120 hours from the administration of initial empirical anti-bacterial therapy.
- 2.4 To provide differential guidelines for the identification and initial management of

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febrile neutropenic patients who are at “low-risk” and “high-risk” for medical complications, respectively, to facilitate clinical decisions regarding the venue of initial management (in-patient or out-patient), and route of administration of initial empirical anti-bacterial therapy (intravenous or oral).<sup>8,9</sup>

### 3.0 **DEFINITIONS:**

#### 3.1 Fever

3.1.1 A fever is defined as a single oral temperature (T)  $\geq 38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ), or  $> 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) lasting at least one hour, or  $> 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) documented at least twice over a 12-hour period.<sup>8,9</sup>

3.1.2 An infection-related febrile episode is characterized by the exclusion of temporal associations with other potentially pyrogenic factors such as:

- i) PRBC transfusion
- ii) Platelet transfusion
- iii) Cytotoxic agents
- iv) Hematopoietic growth factors (e.g. G-CSF)
- v) Amphotericin B formulations
- vi) Inflammatory response to the underlying malignant disease.

3.1.3 Cancer patients with neutropenic sepsis syndromes may present for medical assistance with body temperature of less than  $38^{\circ}\text{C}$ . It is important to note the following:

- i) Patients may have infection without being febrile
- ii) Lack of fever may be a function of anti-pyretic therapy such as acetaminophen, salicylates, metamizole (dipyrone), or glucocorticoid therapy
- iii) Patients presenting with hypothermia (body temperature  $< 36^{\circ}\text{C}$ ) have a higher likelihood of bacteremic events.

#### 3.2 Neutropenia

3.2.1 “Severe” neutropenia is defined by an absolute neutrophil count (ANC)  $< 0.5 \times 10^9/\text{L}$ , or  $\text{ANC} < 1.0 \times 10^9/\text{L}$  and a predicted decline of the ANC to  $< 0.5 \times 10^9/\text{L}$  over the next 48 hours.<sup>10</sup>

3.2.2 “Profound” neutropenia is defined by an  $\text{ANC} < 0.1 \times 10^9/\text{L}$ .

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### 3.3 Risk

Risk, in the context of this protocol, refers to risk for developing medical complications that may require admission to hospital or prolong hospitalization.<sup>11-13</sup>

3.3.1 “Low-risk” (Such patients have most, if not all, of the following characteristics):

- i) Out-patient status at the time of development of fever
- ii) No associated acute active co-morbidities that would require admission and/or close observation
- iii) Anticipated duration of severe neutropenia of < 7 days
- iv) Good performance status (ECOG 0-1)
- v) Normal serum creatinine
- vi) Liver function tests less than 3x the upper limit of normal
- vii) A Multinational Association of Supportive Care in Cancer (MASCC) Risk Index score<sup>13</sup> of  $\geq 21$ .

Table. MASCC Scoring System (Maximum score = 26)

<b>Characteristic</b>	<b>Points</b>
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor diagnosis or no previous IFI	4
No dehydration	3
Burden of illness: moderate symptoms	3
Out-patient status at onset of FNE	3
Age < 60 years	2

A Risk Index score of  $\geq 21$  indicates that the patient is likely to be at low risk for complications and morbidity.

Abbreviations: IFI, Invasive fungal infection; FNE, Febrile neutropenic episode.

3.3.2 “High-risk” (Such patients are defined by presence of any factor listed below, and should be considered for hospital admission and parenteral antibacterial therapy):<sup>9</sup>

- i) Hemodynamic instability
- ii) Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea
- iii) New onset of neurological or mental status changes

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- iv) Profound neutropenia (ANC < 0.1 x 10<sup>9</sup>/L) expected to last ≥ 7 days
- v) Renal insufficiency: estimated creatinine clearance of < 30 mL/minute
- vi) Hepatic insufficiency: aminotransferases > 5x the upper limit of normal
- vii) Pneumonia or other complex infection at clinical presentation
- viii) MASCC Risk Index score < 21.

### 3.4 Systemic Inflammatory Response Syndrome (SIRS)

3.4.1 SIRS is a physiological systemic response to infection or non-infectious processes including pancreatitis, ischemia, multiple trauma and tissue injury, hemorrhagic shock, immune-mediated organ injury, and administration of exogenous mediators of inflammation such as tissue necrosis factor or other cytokines.

3.4.2 SIRS<sup>14</sup> may be defined by the presence of ≥ 2 of the following criteria:

- i) Body temperature of > 38°C or < 36°C
- ii) Tachycardia, defined by a heart rate > 90 beats per minute
- iii) Tachypnea, defined by a respiratory rate > 20 breaths per minute, or hyperventilation as defined by a PaCO<sub>2</sub> of < 32 mmHg
- iv) An alteration in peripheral leukocyte count characterized by leukocytosis (WBC > 12.0 x 10<sup>9</sup>/L) or leukopenia (WBC < 4.0 x 10<sup>9</sup>/L), or a left shift with > 10% band neutrophils in the leukocyte differential count.

3.5 Sepsis Syndrome - The term “sepsis” is defined as SIRS that is as a result of a confirmed infectious process.<sup>15-17</sup>

3.6 Severe Sepsis Syndrome - The term “severe sepsis” is defined as a sepsis syndrome associated with organ dysfunction, hypoperfusion, or hypotension.<sup>15-17</sup>

Hypoperfusion and abnormalities of tissue perfusion may include, but are not limited to, lactic acidosis, oliguria (urine output < 0.5 millilitres/kg/hour) or mental confusion.

3.7 Septic Shock - The term “septic shock” is defined sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. (Note: Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured).<sup>15-17</sup>

3.8 Penicillin Allergy<sup>18</sup>

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3.8.1 Immediate-type Hypersensitivity Reaction – This is defined by the onset of the reaction within one (1) hour of drug administration. This reaction is typically IgE-mediated and driven by the release of vasoactive histamine and cytokines from sensitized mast cells. Such reactions include facial and body subcutaneous angioedema, urticaria (hives), generalized erythroderma, generalized pruritus, tongue swelling, laryngeal and/or broncho-spasm (wheezing or stridor), lightheadedness, hypotension, and nausea. A diagnosis of “anaphylaxis” may be established by the onset of a skin manifestation plus either a cardiovascular component (systolic hypotension, altered state of consciousness, incontinence, or collapse) or a respiratory component (dyspnea, wheezing, stridor, hypoxia [SaO<sub>2</sub> < 92%]). The likelihood of such reactions to penicillin may be predicted by a positive skin test to detect IgE-mediated skin reaction to the major and minor determinants of the penicillin molecule.

3.8.2 Accelerated-type Hypersensitivity Reaction - This is defined by the onset of the reaction within 72 hours of drug administration, and is also IgE-mediated and histamine-driven. The clinical severity may be less than the immediate-type. This variant may be predicted by a positive skin test to the major and minor determinants of the penicillin molecule.

3.8.3 Delayed-type Hypersensitivity Reaction - This is defined by the onset of the reaction after 72 hours from drug administration. These reactions are not an IgE-mediated process, and are not predictable on the basis of skin testing. IgG, complement, and immune complexes may mediate these reactions. The clinical expression is most often one of a morbilliform skin rash; however, such reactions may also include serum sickness, urticaria (rarely late), Stevens-Johnson syndrome, interstitial nephritis, pulmonary infiltration, vasculitis, hemolytic anemia, neutropenia, or thrombocytopenia.

### 3.9 Central Venous Access Device (CVAD)

3.9.1 These are defined as medical devices that provide venous access to the central circulation for the purposes of blood sampling and for infusions. They may be externalized venous catheters (e.g. peripherally implanted central catheters [PICC], or tunneled or non-tunneled externalized central venous catheters) or surgically implanted subcutaneous port systems (e.g. totally implanted venous access port).

## 4.0 POLICY:

4.1 The likelihood that the patient has a neutropenic fever syndrome shall be determined by initial triage history.

4.2 A patient with a suspected neutropenic fever syndrome shall be Triage classification **CTAS Level II (Emergent: Physician assessment within 15 minutes)**.

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- 4.3 Acute sepsis assessment shall be based upon standardized **clinical** criteria for SIRS, Sepsis Syndrome, Severe Sepsis Syndrome, or Septic Shock as part of the initial triage assessment process.
- 4.4 **The total time from triage-to-initial empirical anti-bacterial therapy shall be less than one hour (60 minutes).**
- 4.5 The “risk” for the development of medical complications that require hospitalization or that prolong hospitalization shall be determined using a standardized assessment tool such as the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index Score. The risk (“high” or “low”) shall be used to judge the safety of out-patient administration of oral initial empirical anti-bacterial therapy.

5.0 **PROCEDURE: (see also Appendix 1: Neutropenic Fever Protocol Algorithm + Notes)**

5.1 **Triage**

5.1.1 All cancer patients presenting for emergency medical care and who have received systemic chemotherapy within the preceding six (6) weeks must be presumed to have a neutropenic fever or sepsis syndrome.

5.1.2 The initial triage history<sup>19,20</sup> should consume 2-5 minutes to establish the patient’s chief complaint, that the patient has cancer, and that he/she has received systemic therapy within the preceding 6 weeks. The chief complaint should be validated and characterized by the following:

- i) A description of the onset of symptoms
- ii) Duration of the symptoms
- iii) Anatomic location of the symptoms
- iv) Severity of the symptoms
- v) Alleviating and aggravating factors
- vi) Previous history of similar symptoms.

5.1.3 Additional information should be sought, including:

- i) Date of the last systemic chemotherapy (from which the time of nadir can be estimated, usually day +14 from the first day of the current chemotherapy cycle)
- ii) State of the underlying cancer, and the presence of an advance care plan (ACP)
- iii) Adverse drug reaction history
- iv) Current medications, including antimicrobial therapy.

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## 5.2 Assessment of Sepsis Syndrome

The presence of SIRS criteria and potential foci of infection are based upon clinical criteria; the former upon vital signs (blood pressure, heart rate, respiratory rate, and arterial O<sub>2</sub> saturation), and the latter by a thorough physical examination.

### 5.2.1 Initial Interventions<sup>9,15,16</sup>

- i) **Intravenous (IV) access.** The patient may have an existing central venous access device (CVAD) in situ available for use; otherwise peripheral venous access with a large bore needle (18 gauge) is recommended.
- ii) **IV fluids.** Normal (0.9%) saline is recommended, pending assessment of electrolytes. If the patient is hypotensive (systolic blood pressure < 90 mmHg or mean BP < 65 mmHg), an initial 500 millilitre “fluid challenge” with crystalloid (at rate consistent with the updated Surviving Sepsis Campaign guideline of 30 millilitres/kilogram/3 hours)<sup>21</sup> over 30 minutes is recommended, otherwise initial crystalloid IV infusion of 125-150 millilitres/ hour is recommended to maintain a urine output of > 0.5 millilitres/kilogram/hour.
- iii) **Blood cultures – before antibiotic administration.** At least 2 sets (1 set = 1 aerobic + 1 anaerobic bottle) of blood cultures should be obtained each from separate anatomic sites (10 millilitre aerobic blood sample from each lumen of an existing CVAD plus an aerobic and an anaerobic bottle from a peripheral site; or in the absence of a CVAD, one set each from at least two peripheral sites).
- iv) **Blood work.** This should include the following:
  - a. Complete blood count (CBC) with leukocyte differential count
  - b. Electrolytes (Na<sup>+</sup>, K<sup>+</sup>, CL<sup>-</sup>, total CO<sub>2</sub>)
  - c. Glucose
  - d. Urea and creatinine
  - e. Venous blood gases
  - f. Lactate
  - g. Coagulation studies: INR, prothrombin time
  - h. Transaminases (alanine transaminase and aspartate transaminase), lactate dehydrogenase, and cholestatic enzymes (gamma glutamyl transferase and alkaline phosphatase)
  - i. Total bilirubin.
- v) **Diagnostic imaging.** Where signs and symptoms suggest lower respiratory tract infection, a chest radiograph (posterior-anterior & lateral views) should be performed.

### 5.2.2 Medical Assessment

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Initial medical assessment should occur within 15 minutes of the patient's presentation for medical triage.<sup>19,20</sup> The objectives of the assessment are as follows:

- i) To distinguish SIRS, sepsis syndrome, severe sepsis syndrome, and septic shock, and to distinguish neutropenic fever syndromes as unexplained fevers (defined as a neutropenic fever syndrome characterized by neither a clinical focus or isolation of a pathogen) versus documented infections (defined as a neutropenic fever associated with a clinical focus but not an identified pathogen [a clinically documented infection] or a neutropenic fever syndrome associated with both a clinical focus and a pathogen [a microbiologically documented infection])
- ii) To assess "risk" for medical complications that either require hospitalization or prolong hospitalization
- iii) To initiate empirical anti-bacterial therapy
- iv) To begin an initial fixed volume fluid resuscitation (30 mL/kg/3 hours) for patients with severe sepsis/septic shock who are hypotensive (mean arterial pressure [MAP] defined as  $\{ \text{Diastolic BP} \times 2 \} + \text{Systolic BP} / 3$ ) with or without a lactic acidosis (serum lactate > 4 mmol/L) in order to maintain a MAP of > 65 mmHg, and urine output of > 0.5 mL/kg/hour.<sup>21</sup>

## 6.0 **Guidelines for Initial Empiric Antibacterial Therapy**

6.1 Oral (PO) regimens for "**low-risk**" (MASCC Risk Index score  $\geq 21$ , *vide supra* 3.3.1) patients with an unexplained neutropenic fever syndrome (SIRS or sepsis syndrome).<sup>8,9</sup>

6.1.1 ciprofloxacin 750 milligrams PO every 12 hours **or**  
levofloxacin 750 milligrams PO every 24 hours

**plus**

amoxicillin/clavulanate 500/125 milligrams PO every 8 hours, **or** 875/125 milligrams PO every 12 hours.

6.1.2 In the circumstances of penicillin-related immediate-type (onset with one hour of drug administration) or accelerated-type (onset within 72 hours of drug administration) hypersensitivity:

ciprofloxacin 750 milligrams PO every 12 hours **or**  
levofloxacin 750 milligrams PO every 24 hours

**plus**

clindamycin 600 milligrams PO every 8 hours.



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- 6.1.3 In the circumstances where the patient reports a delayed-type penicillin “allergy” (onset, usually a rash, after 72 hours following beginning the drug), a combination may be recommended:

ciprofloxacin 750 milligrams PO every 12 hours **or**  
levofloxacin 750 milligrams PO every 24 hours

**plus either**

clindamycin 600 milligrams PO every 8 hours **or**  
cefixime<sup>22,23</sup> 400 milligrams PO every 24 hours **or**  
cefuroxime 500 milligrams PO every 12 hours<sup>24</sup>

**Out-patient alternatives also include:**

monotherapy with moxifloxacin<sup>25</sup> 400 milligrams PO every 24 hours

**or**

ceftriaxone 2 grams IV every 24 hours **plus** amikacin 15-20 milligrams per kilogram IV every 24 hours.<sup>22</sup>

- 6.1.4 In the circumstances where initial oral out-patient management is being considered, the patient should be observed for at least 4 hours following the first dose for tolerance and for hemodynamic stability before discharge from the clinic or triage facility.

- 6.1.5 Out-patient follow-up recommendations:

- i) Contact by telephone within 24 hours; and
- ii) Clinic visit within 48-72 hours, and every 2<sup>nd</sup> day until defervescence and myeloid reconstitution
- iii) Patient’s residence ≤ 1 hour or ≤ 30 miles (48 km) from clinic or hospital
- iv) Agreement from the patient’s primary care physician and/or oncologist with out-patient management
- v) The patient must be able to comply with logistical requirements, including frequent clinic visits
- vi) A family member or care giver should be available at home 24 hours each day
- vii) The patient must have 24-hours-a-day access to a telephone and transportation; and
- viii) There must be no prior history of non-compliance with treatment protocols.

- 6.1.6 Treatment duration for documented infections is determined by the syndrome and site of infection (usually 7-14 days). Treatment duration for unexplained fevers is 2-3 days after defervescence (usually 5-7 days in

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total).

6.1.7 Hematopoietic growth factors (HGFs) such as filgrastim (G-CSF) are not recommended for routine use as adjuvant therapy in the treatment of neutropenic fever syndromes.<sup>26-28</sup> Under circumstances where HGFs are being used prophylactically in support of the chemotherapeutic anti-cancer regimen, they should be continued until myeloid reconstitution.

6.2 Initial empirical intravenous (IV) antibacterial therapy for febrile neutropenic patients at “**high-risk**” for medical complications (MASCC Risk Index score < 21):<sup>9</sup>

6.2.1 Piperacillin/tazobactam 4.5 grams IV every 8 hours is the preferred agent at CCMB and the WRHA Oncology Program. Meropenem 1 gram IV every 8 hours is a suitable alternative.

6.2.2 In the circumstances of penicillin-related immediate-type (onset within one hour of drug administration) or accelerated-type (onset within 72 hours of drug administration) hypersensitivity:

**either**

meropenem 1 gram IV every 8 hours

**or**

ciprofloxacin (only in the circumstances where the patient has not been receiving fluoroquinolone-based antibacterial prophylaxis) 400 milligrams IV every 12 hours **plus** vancomycin 15 milligrams per kilogram per dose IV every 12 hours.

6.2.3 In the circumstances of penicillin-related delayed-type (onset after 72 hours of drug administration) acceptable alternatives include:

meropenem 1 gram IV every 8 hours

**or**

ceftazidime 2 grams IV every 8 hours **plus** vancomycin 15 milligrams per kilogram per dose IV every 12 hours

**or**

ciprofloxacin (only in the circumstances where the patient has not been receiving fluoroquinolone-based antibacterial prophylaxis) 400 milligrams IV every 12 hours **plus** vancomycin 15 milligrams per kilogram per dose IV every 12 hours.

**(For 6.2.2 and 6.2.3, see also Appendix II: Approach to the Initial Empirical Anti-bacterial Therapy Choice for Febrile Neutropaenic Patients with a History of Penicillin Allergy)**

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- 6.2.4 In the circumstances of severe sepsis/septic shock, consider adding an aminoglycoside<sup>29</sup> such as:

gentamicin **or** tobramycin 7 milligrams per kilogram intravenously daily

**or**

amikacin 15-20 milligrams per kilogram intravenously daily in one or more divided doses.

Note: trough aminoglycoside levels are recommended to guide dosing.

- 6.2.5 In the circumstances of skin and soft tissue infection due to suspected methicillin-resistant *Staphylococcus aureus* (MRSA), or a CVAD-related infection due to MRSA or a coagulase-negative *Staphylococcus* spp., consider adding vancomycin 15 milligrams per kilogram per dose IV every 12 hours. Further, in the circumstances of a CVAD-related bloodstream infection due to *S. aureus* or a *Candida* spp., removal of the CVAD is recommended.
- 6.2.6 In the circumstances of colonization by MRSA, consider adding vancomycin 15 milligrams per kilogram per dose IV every 12 hours.
- 6.2.7 In the circumstances of vancomycin-resistant *Enterococcus* (VRE) colonization, consider adding linezolid 600 milligrams IV every 12 hours.
- 6.2.8 In the circumstance of suspected or documented infection due to *Pseudomonas aeruginosa* a higher total daily dose of piperacillin/tazobactam should be considered, 4.5 grams IV every 6 hours.
- 6.2.9 In the circumstances of colonization or infection by extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacillus, consider a carbapenem, meropenem, 1 gram IV every 8 hours.
- 6.2.10 In the circumstances of infection or colonization by a carbapenem-resistant Gram-negative bacillus, consider:

colistimethate sodium 2.5 - 5.0 milligrams per kilogram per day IV in 2-4 divided doses

**or**

tigecycline 100 milligrams IV loading dose, **then** 50 milligrams IV every 12 hours.

Patients with these infections and who require these anti-bacterial agents should be considered for management in tertiary care facilities with multi-agent regimens that may include an aminoglycoside, colistimethate, tigecycline, fosfomycin, rifampin, or even meropenem (where the MIC is  $\leq$  8 milligrams per litre).<sup>30,31</sup>

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- 6.2.11 The median time to defervescence for high-risk patients is 5 days. Total treatment duration for documented infections is determined by the syndrome and site of infection (usually 10-14 days). Treatment duration for unexplained fevers is 5 days after defervescence (usually 7-10 days in total).
- 6.2.12 Unless a specific protocol dictates otherwise, antibacterial prophylaxis may be continued or discontinued during initial empiric antibacterial therapy at the physician's discretion.
- 6.2.13 Antimicrobial infusions should be rotated sequentially through each lumen of the central venous access device with each dose.
- 6.2.14 Hematopoietic growth factors (HGFs) such as filgrastim (G-CSF) are not recommended for routine use as adjuvant therapy in the treatment of neutropenic fever syndromes.<sup>26-28</sup> There may be circumstances in individual cases (e.g. severe sepsis/septic shock<sup>27</sup> or high-risk circumstances such as prolonged [ $> 10$  days] profound [ $ANC < 0.1 \times 10^9/L$ ] neutropenia, invasive fungal infection, or older age [ $> 65$  years]) where adjuvant HGFs may be considered.<sup>26-28</sup>

### 6.3 Duration of Antibacterial Therapy and Empirical Anti-fungal Therapy

- 6.3.1 The average time to defervescence with initial therapy for low-risk and high-risk patients is 2-3 days<sup>32,33</sup> and 5 days<sup>34-36</sup> respectively. Regimen modification is not recommended before this time in the absence of clinical deterioration or progression or unless antibacterial susceptibility testing suggests that the spectrum of antibacterial activity is suboptimal.
- 6.3.2 Treatment with systemic therapy should continue until the patient has been afebrile for 5 days.
- 6.3.3 Failure to defervesce after 5 days of initial therapy or clinical deterioration occurring within the first 5 days of initial therapy should compel the physician to consider re-assessment and regimen modification in consultation with the regional Infectious Diseases Consultation Services. Suggested modifications include:
  - i) Vancomycin if a skin or soft tissue site of infection due to MRSA is suspected
  - ii) Metronidazole, 500 milligrams PO or IV every 8 hours if necrotizing gingivitis or an intra-abdominal focus is suspected
  - iii) Empirical anti-fungal therapy may be considered if the patient remains febrile despite 7 days of broad-spectrum antibacterial therapy while remaining severely neutropenic, and if colonized by fungi.<sup>37,38</sup>  
Acceptable regimens include:

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- liposomal amphotericin B, 3 milligrams per kilogram IV daily
  
- voriconazole 6 milligrams per kilogram IV every 12 hours x 2 doses load, **followed by** 4 milligrams per kilogram IV every 12 hours  
**or**  
voriconazole 400 milligrams PO every 12 hours x 2 doses load, **followed by** 200 milligrams PO every 12 hours
  
- itraconazole 200 milligrams every 12 hours IV  
**or**
- caspofungin 70 milligrams IV day 1, **then** 50 milligrams IV daily  
**or**
- micafungin 100 milligrams IV daily.

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**DOCUMENTATION**

**Policy Location:**

This policy is located (hard and e-copy formats):

- |    |  |
|----|--|
| 1. | The original signed and approved policy is on file in the Executive Office, CCMB |
| 2. | The e-copy is located in the CCMB Policy Library (Infection Control Services)    |
| 3. |  |

**Revision History:**

Date	Version	Status	Author	Summary of Changes
dd/mm/yyyy	#	Initial, Draft Final Minor/Major revision		
20/10/2010	1	Initial	EJ Bow, MD	Development of new protocol for CCMB
16/09/2011	2	Revision 1	EJ Bow, MD	Revisions
17/11/2011	3	Revision 3	EJ Bow, MD	Revisions
06/02/2012	4	Final	EJ Bow, MD	Final revisions
04/11/2016	5	Revision 4	EJ Bow, MD	Update of management for penicillin allergic patients, related definitions, and references.
26/02/2017	6	Revision 5	EJ Bow, MD	Update section 6 on severe sepsis/septic shock with addition of an AMB; clarification regarding CRE management.
06/04/2017	7	Revision 6	EJ Bow, MD	Update section 5, removal of “goal directed therapy”; addition of initial fixed volume fluid resuscitation. Addition Appendix 1,2. References updated. Hypothermia statement added
24/04/2017	8	Revision 7	EJ Bow, MD	Alignment with HSC ED Order Sheet
08/05/2017	9	Revision 8	EJ Bow, MD	References update

**Approvals Record:**

This Policy requires approval by:

Approval Date	Name / Title	Signature
11 May 2017	Dr. P. Czaykowski Chief Medical Officer, CCMB	<i>Original signed by Dr. P. Czaykowski</i>

**FINAL APPROVAL:**

Date	Name / Title	Signature
12 May 2017	Dr. S. Navaratnam President and CEO, CCMB	<i>Original signed by Dr. S. Navaratnam</i>

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**APPENDIX I**

## Neutropaenic Fever Protocol Algorithm

**Triage-to-Initial Empirical Anti-bacterial Therapy**  
(APPENDIX I, CCMB Neutropaenia Protocol, 12.500, May 8<sup>th</sup>, 2017)

**0 MINUTES**

**TRIAGE**

**Triage History:**

All “unwell” cancer patients (with or without fever) seeking emergency medical care and who have received systemic anticancer therapy within the previous 6 weeks<sup>1</sup>

**Working diagnosis: Possible Neutropaenic fever/sepsis syndrome**  
CTAS Level II (Emergent)<sup>2</sup>

**Initial objective assessment**

Temperature, pulse, respiratory rate, blood pressure, arterial O<sub>2</sub> saturation to document presence of SIRS criteria or a sepsis syndrome

**Initial interventions**

1. IV Access (CVAD, if in situ, or peripheral line, 18G) plus 0.9% saline
2. Blood work: CBC & leukocyte differential, electrolytes (Na, K, Cl, TCO<sub>2</sub>), glucose, urea, creatinine, venous blood gases, lactate, INR, prothrombin time, AST, ALT, LDH, GGT, ALP, total bilirubin, blood cultures (CVAD + peripheral site, or two separate peripheral sites)

**15 MINUTES**

**Medical Assessment**  
(within 15 minutes of triage)

**SEVERE SEPSIS SYNDROME**

(SIRS<sup>3</sup> + Infection + Organ dysfunction or Hypoperfusion<sup>4</sup>)

**YES**

**Haemodynamic/Perfusion Stabilization<sup>5</sup>**

- Resuscitation facilities
- Optimize haemodynamics & O<sub>2</sub> delivery
- Initiate combination IV empirical anti-bacterial therapy<sup>6</sup>
- Consider haematopoietic growth factors<sup>7</sup>
- Consider critical care services

**NO**

**Sepsis Syndrome or SIRS**

- Identification of anatomical sites of infection
- Unexplained fever vs documented infection

**30 MINUTES**

**Sepsis Syndrome**  
(SIRS + Documented Infection)

**YES**

- Supplemental O<sub>2</sub> as appropriate
- Empirical antibacterial therapy
- IV 0.9% saline 1L over 1-2 hours

**NO**

- SIRS with unexplained fever

**60 MINUTES**

**Treatment by Risk for Medical Complications**  
(MASCC Risk Index Score/IDSA Criteria)<sup>8</sup>

**High risk**

(Score < 21, ANC < 0.1 > 7 days, Co-morbidities, hepatic and/or renal dysfunction)

- Admission
- IV antibacterial therapy<sup>6</sup>
- Discharge: Clinical stability, controlled co-morbidities
- Duration: 4-5 afebrile days (Total 7-10 days)

**Low risk**

(Score ≥ 21, ANC < .5 < 7 days, no Co-morbidities)

- Consider IV → PO or PO therapy<sup>9,10</sup>
- Consider in-patient → out-patient
- Discharge: Clinical stability, controlled co-morbidities
- Duration: 3 afebrile days (total 5-7 days)

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Abbreviations: CTAS, Canadian Emergency Department Triage and Acuity Scale; CVAD, central venous access device; Na, sodium; K, potassium; Cl, chloride; TCO<sub>2</sub>, total carbon dioxide; SIRS, systemic inflammatory response syndrome; LRT, lower respiratory tract; URT, upper respiratory tract; GI, gastrointestinal tract; GU, genitourinary tract; O<sub>2</sub>, oxygen; IV, intravenous; MASCC, Multinational Association for Supportive Care in Cancer; PO, per os (by mouth); CBC, complete blood count; INR, international normalized ratio; ASP, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase.

### Footnotes:

1. Neutropaenic sepsis is a “time-dependent” condition, the successful management of which is dependent upon the early recognition of the likelihood that the cancer patient’s problem represents a neutropaenic fever/sepsis syndrome. Since more than 70% of cancer treatment-related syndromes including neutropaenic fever manifest within 4-6 weeks of systemic treatment, receipt of cytotoxic therapy within 6 weeks may be considered a sensitive (but not specific) discriminator for the detection of patients with neutropaenic fever/sepsis syndromes by triage services in healthcare facilities. The triage process should consume 2-5 minutes and should ascertain the following:
  - i) The chief complaint that has developed in a cancer patient who is receiving active chemotherapy;
  - ii) Validation and assessment of the patient’s chief complaint (onset of symptom(s), duration of symptom(s), anatomic location of the symptom(s), severity of the symptom(s), alleviating and aggravating factors, and previous history of similar symptoms);
  - iii) Additional information: date of first dose of the last chemotherapy cycle, state of the underlying cancer, allergies and adverse drug reactions, and current medications (including antimicrobial therapy).
2. CTAS<sup>19,20</sup> recommends that **level II (Emergent)** should be designated for febrile immunocompromised cancer patients who may be neutropaenic or suspected as being neutropaenic and “look septic” defined as patients who have evidence of infection, have 3 SIRS (Systemic Inflammatory Response Syndrome, *vide infra*) criteria positive, or show evidence of haemodynamic compromise, moderate respiratory distress or altered level of consciousness. It is recommended that such patients be seen by a physician within **15 minutes** of arrival in the triage facility.
3. SIRS (Systemic Inflammatory Response Syndrome)<sup>14</sup> may be defined by 2 or more of the following criteria: body temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20/min; Pa CO<sub>2</sub> <32 mmHg; or an alteration in the total leukocyte count to >12x10<sup>9</sup>/L or <4x10<sup>9</sup>/L; or the presence of >10% band neutrophils in the leukocyte differential. Note that patients with neutropaenic sepsis syndromes may present without fever (oral temperature < 38°C).
4. Haemodynamic/perfusion stabilization refers to reversal of hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, systolic blood pressure decrease of >40 mmHg, or <2 standard deviations below the mean for age), by an acute alteration in mental status, by an elevated serum lactate >4 mmol/L, or by oliguria (urine output <0.5 ml/kg/hr)<sup>15</sup>.
5. Initial fixed volume fluid resuscitation (30 mL/kg/3 hours) is recommended for patients with severe sepsis/septic shock who are hypotensive (mean arterial pressure [MAP] defined as [(Diastolic BP x 2) + Systolic BP] / 3) with or without a lactic acidosis (serum lactate > 4 mmol/L) in order to maintain a MAP of > 65 mmHg, and urine output of > 0.5 mL/kg/hour<sup>21</sup>.
6. Initial empirical intravenous (IV) antibacterial therapy for febrile neutropaenic patients at **high-risk** for medical complications<sup>9</sup>:

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- a. Piperacillin/tazobactam 4.5 grams IV every 8 hours. In the circumstance of suspected or documented infection due to *Pseudomonas aeruginosa* a higher total daily dose of piperacillin/tazobactam should be considered, 4.5 grams IV every 6 hours.
  - b. In the circumstances of penicillin-related immediate-type hypersensitivity, meropenem 1 gram IV every 8 hours, or ciprofloxacin (if the patient has not been receiving fluoroquinolone anti-bacterial prophylaxis) 400 milligrams IV every 12 hours plus vancomycin 15 milligrams per kilogram per dose IV every 12 hours.
  - c. In the circumstances of skin and soft tissue infection due to methicillin-resistant *Staphylococcus aureus* (MRSA), or a CVAD-related infection due to MRSA or coagulase-negative *Staphylococcus* spp., consider adding vancomycin 15 milligrams per kilogram per dose IV every 12 hours.
  - d. In the circumstances of colonization by MRSA, consider adding vancomycin 15 milligrams per kilogram per dose IV every 12 hours.
  - e. In the circumstances of vancomycin-resistant *Enterococcus* (VRE) colonization, consider adding linezolid 600 milligrams IV every 12 hours.
  - f. In the circumstances of colonization or infection by extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacillus, consider a carbapenem, meropenem, 1 gram IV every 8 hours.
  - g. In the circumstances of infection or colonization by a carbapenem-resistant Gram-negative bacillus, consider colistimethate sodium 2.5-5.0 milligrams per kilogram per day IV in 2-4 divided doses, or tigecycline 100 milligrams IV loading dose, then 50 milligrams IV every 12 hours.
  - h. In the circumstances of severe sepsis/septic shock, consider adding an aminoglycoside<sup>29</sup> such as gentamicin or tobramycin 7 milligrams per kilogram intravenously daily or amikacin 15-20 milligrams per kilogram intravenously daily in one or more divided doses. Note that trough aminoglycoside levels are recommended to guide dosing.
7. The American Society of Clinical Oncology (ASCO)<sup>28</sup> and the European Society of Medical Oncology(ESMO)<sup>26</sup> do **not** recommend routine adjuvant haematopoietic growth factor (HGF) therapy in patients with neutropaenic fevers. These organizations do suggest that HGF may be considered for febrile neutropaenic patients with “high-risk” characteristics for infection-related complications or poor clinical outcomes. Such high-risk characteristics include prolonged (>7-10 days) profound neutropaenia (ANC <0.1 x 10<sup>9</sup>/L), age greater than 65 years, uncontrolled primary malignancy, pneumonia, hypotension and multi-organ dysfunction (severe sepsis/septic shock syndrome), invasive fungal infection, or in-patient status at the time of the neutropaenic fever syndrome.
8. Multinational Association for Supportive Care in Cancer (MASCC) Risk Index Score. A score of ≥21 predicts a low risk for medical complications of neutropaenic fever syndromes that would require hospitalization or prolonged length of hospitalization. A score of <21 predicts patients at high risk for such complications<sup>13</sup>. The presence of “complex” infection at the baseline evaluation regardless of MASCC score has been used to classify the neutropaenic fever syndrome as “high-risk”<sup>39</sup> and improve the predictive value of the MASCC Risk Index Score. “Complex” is defined by infection of major organs (lungs, liver, kidneys, colon, bones, joints, veins, heart, meninges), sepsis syndromes, skin and soft tissue infection (>5 centimetres in size without necrosis, but any size with necrosis), and oral mucositis (>grade 2).

The IDSA defines patients at “**high-risk**” for serious neutropaenic fever-related complications according to the following criteria: profound neutropaenia (ANC ≤0.1 x 10<sup>9</sup>/L) with an expected duration of >7 days; and the presence of any co-morbidity including (but not limited to) haemodynamic instability, oral or gastrointestinal mucositis that impairs oral intake or causes severe diarrhoea, new onset of neurological or mental status changes, indwelling central venous access device infection (especially a tunnel site infection), new pulmonary infiltrates, hypoxaemia, or underlying chronic lung disease; evidence of hepatic (transaminases >5 times the upper limit of normal) or renal (creatinine clearance <30 millilitres per minute) insufficiency.<sup>9</sup> Febrile neutropaenic patients at “**low-risk**” for medical complications are those for whom the neutropaenia is

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expected to resolve within 7 days, and who have no active medical co-morbidity, and stable and adequate hepatic and renal function.<sup>9</sup>

9. Initial outpatient empirical intravenous (IV) antibacterial therapy for febrile neutropaenic patients at **low-risk** for medical complications and who may not be able to tolerate oral agents<sup>9</sup>:

- a. Ceftriaxone 2 grams IV every 24 hours plus amikacin 15-20 milligrams per kilogram IV every 24 hours, with subsequent amikacin dosing governed by therapeutic drug monitoring<sup>22</sup>. Note that inability to tolerate oral intake may be considered a high-risk factor that may warrant inpatient management.

10. Initial empirical orally administered (PO) antibacterial therapy for febrile neutropaenic patients at **low-risk** for medical complications and who are not receiving fluoroquinolone-based anti-bacterial prophylaxis<sup>9</sup>:

- a. Ciprofloxacin 750 milligrams PO every 8-12 hours or levofloxacin 750 milligrams PO every 24 hours, plus amoxicillin/clavulanate 500/125 milligrams PO every 8 hours, or amoxicillin/clavulanate 875/125 milligrams PO every 12 hours.
- b. In the circumstances of penicillin-related immediate-type hypersensitivity, ciprofloxacin 750 milligrams PO every 12 hours or levofloxacin 750 milligrams PO every 24 hours, plus clindamycin 600 milligrams PO every 8 hours.
- c. The patient should be observed for at least 4 hours following the first dose for tolerance and for haemodynamic stability before discharge from the clinic or triage facility.
- d. Patient follow-up by telephone within 24 hours and by clinic visit within 48-72 hours is recommended.
- e. Treatment duration for documented infections is determined by the syndrome and site of infection (usually 7-14 days). Treatment duration for unexplained fevers is 2-3 days after defervescence (usually 5-7 days).

**Contact Resource:**

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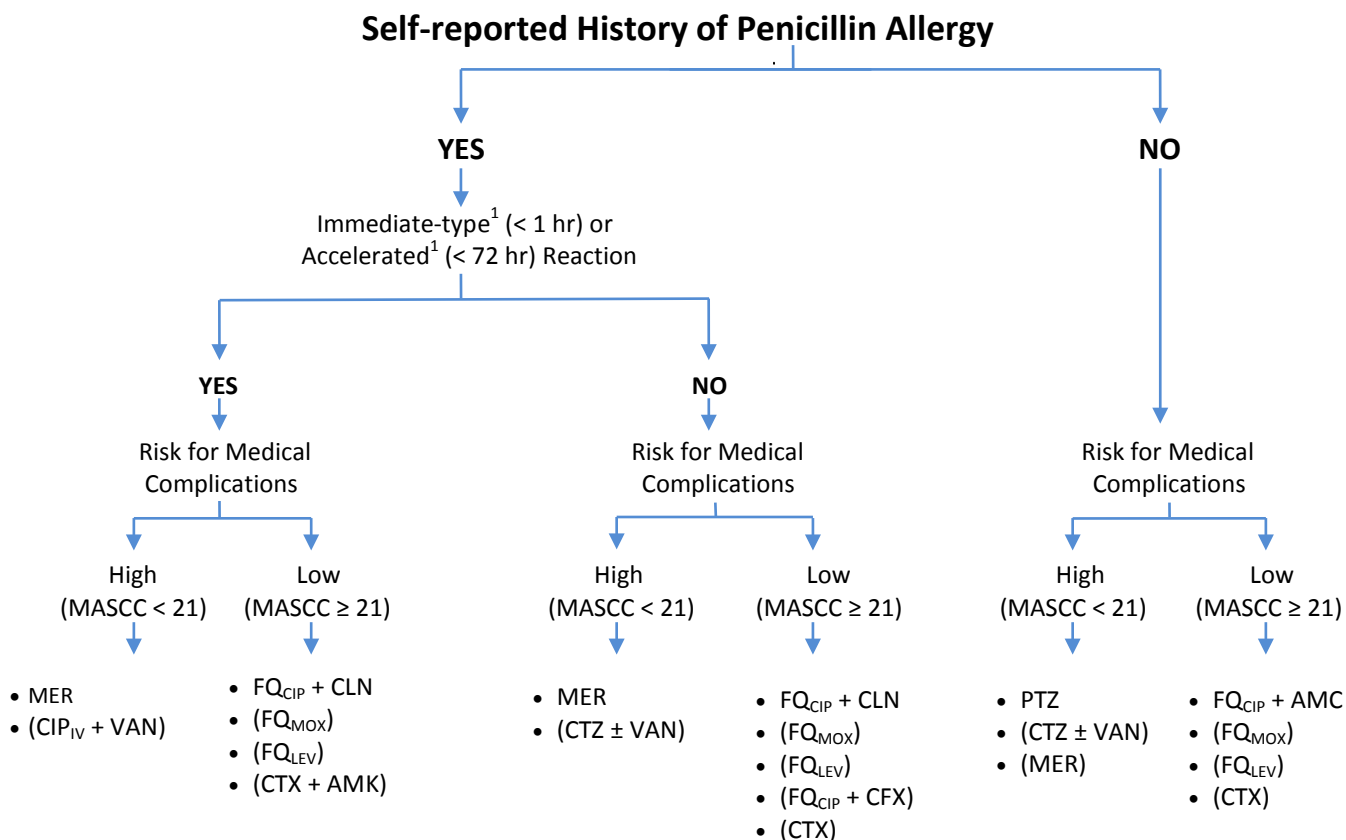
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**APPENDIX II**

**Approach to the Initial Empirical Anti-bacterial Therapy Choice for  
Febrile Neutropaenic Patients with a History of Penicillin Allergy**

APPENDIX II, CCMB Neutropaenia Protocol, 12.500, May 8<sup>th</sup>, 2017



<sup>1</sup> **Immediate-type IgE Reactions less than 1 hour (or Accelerated-type within 72 hours)**

- Angioedema
- Laryngeal spasm
- Tongue edema
- Bronchospasm
- Hypotension
- Urticaria

**Abbreviations:** MASSC, Multinational Association for Supportive Care in Cancer; CIP<sub>IV</sub>, Ciprofloxacin 400 mg IV Q12H; VAN, Vancomycin 1 gm IV Q12H; MER, Meropenem 1 gm IV Q8H; CTX, Ceftriaxone 2 gm IV OD; CTZ, Cefazidime 2 gm IV Q8H; PTZ, Piperacillin/tazobactam 4.5 gm IV Q8H; FQ, Fluoroquinolone; MOX, Moxifloxacin 400 mg PO OD; CIP, Ciprofloxacin 750 mg PO Q12H; LEV, Levofloxacin 750 mg PO OD; CFX, Cefuroxime axetil 500 mg PO Q12H; AMC, Amoxicillin/Clavulanate 875/125 mg PO Q12H; AMK, amikacin 15-20 mg/kg/d IV; ( ), second choice

**Reference**

1. Lagace-Wiens P.; Rubinstein E. Adverse reactions to beta-lactam antimicrobials. Expert Opin Drug Saf, 2012. 11(3): 381-99