

MANAGEMENT OF FEBRILE NEUTROPENIA IN ADULT CANCER PATIENTS

Effective Date: January, 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

SUMMARY OF KEY POINTS

1. Febrile neutropenia is defined as:
 - Fever higher than 38.3°C OR higher than 38.0°C for more than 1 hour, in a patient who has received chemotherapy in the past month, AND
 - Neutrophils less than 0.5×10^9 cells/L
2. Patients suspected of having febrile neutropenia should undergo:
 - History and physical exam to determine the site of infection
 - Complete hematological profile and chemistry profile, including blood cultures, urine cultures, and nasopharyngeal swab if respiratory symptoms are present
 - Chest-x-ray
3. The preferred initial antibiotic therapy is intravenous piperacillin-tazobactam 4.5 grams IV every 8 hours, plus intravenous fluids. Cefepime monotherapy is an alternative to piperacillin-tazobactam for penicillin-allergic and anaphylactic patients.
4. Patients with febrile neutropenia who are felt to be at low risk of complications may be managed as outpatients.
5. Neutropenia alone is expected for patients receiving chemotherapy; therefore *asymptomatic* neutropenia without fever is not an oncologic emergency.

Important Contact Information

After assessing the patient, call the responsible medical oncologist or the after-hours medical oncologist on-call for a consultation:

- **Calgary (Tom Baker Cancer Centre):** (403) 944-1110
- **Edmonton (Cross Cancer Institute):** (780) 432-8771
- **Medicine Hat (Margery E. Yuill Cancer Centre):** (403) 529-8817
- **Red Deer (Central Alberta Cancer Centre):** (403) 343-4526
- **Lethbridge (Jack Ady Cancer Centre):** (403) 329-0633
- **Grande Prairie Cancer Centre:** (780) 538-7588

If septic shock is a concern, physicians and health-care providers can call the RAAPID line once the patient has been stabilized:

- **Northern Alberta:** 1-800-282-9911
- **Southern Alberta:** 1-800-661-1700

BACKGROUND

Febrile neutropenia is considered an oncologic and medical emergency. Mortality rates of 5 to 20% have been reported.^{1,2} More than 70% of patients presenting with febrile neutropenia have an underlying hematological disease (e.g., leukemia, lymphoma, other), while the majority of remaining cases often present with underlying neoplasms (i.e., solid tumours) or multiple myeloma.³ Chemotherapy has been reported as the cause of neutropenia in nearly 90% of cases.³ Solid tumours requiring chemotherapy that

may put patients at an increased risk of febrile neutropenia include breast cancer, colorectal cancer, lung cancer (small cell and non-small cell), and ovarian cancer.⁴⁻⁶

The use of empiric broad-spectrum antibiotics has significantly reduced the mortality and morbidity of this common chemotherapy complication. However, rapid assessment and institution of the appropriate antibiotics are of paramount importance. A patient on chemotherapy should not wait in the emergency department for assessment for an extended period of time; ideally a system would be in place for the rapid identification of a potential patient with febrile neutropenia who would then immediately have a complete blood count (CBC) drawn and urgent assessment by a health care professional.

The objective of this guideline is to provide clinicians (i.e., emergency room physicians and nurses) and family physicians with strategies for the management of adult patients with solid tumours or hematologic malignancies who present with febrile neutropenia.

GUIDELINE QUESTIONS

1. What is the definition of febrile neutropenia for adult patients with solid tumours or hematologic malignancies?
2. What are the risk factors for febrile neutropenia?
3. What pre-treatment investigations should be conducted for adult outpatients suspected of having febrile neutropenia?
4. What antibiotic therapy regimens are recommended for the treatment of febrile neutropenia in adult patients with solid tumours or hematologic malignancies?
5. What are the recommended management strategies for adult patients with low-risk febrile neutropenia?

DEVELOPMENT AND REVISION HISTORY

The original version of this guideline was created and reviewed by the Alberta Medical Affairs and Community Oncology (MACO) Medical Liaison Team in November 2008; the guideline was updated and approved by the MACO team in January 2012 and was reviewed and approved by members of the CancerControl Alberta Medical Liaison Committee in January 2014. For the development of the original guideline, evidence was selected, reviewed, and endorsed by a working group comprised of oncologists specializing in breast, ovarian, colorectal, and lung cancers, hematologists, and family physicians, as well as two Knowledge Management Specialists from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

In order to achieve consensus on the key points in the original guideline, a survey based on the AGREE II instrument was sent to oncologists, hematologists, infectious diseases specialists, and family physicians.^{7,8} The survey contained items that asked reviewers to rate their level agreement with each of the key points, as well as their level of agreement that the key points were evidence-based. Other survey items included level of agreement that the guideline questions, search strategy, and target audience were each clearly described, overall agreement with the guideline, and willingness to recommend use of the guideline. For all items, a 7-point scale, ranging from strongly agree (7) to strongly disagree (1), was

used. Respondents were also permitted to provide open-ended comments on each item. A total of eight reviewers responded with feedback. There were five medical oncologists, one family physician, one infectious diseases specialist, and one general internist working mainly in oncology, representing Calgary, Edmonton, Red Deer, Grande Prairie, and Medicine Hat. Survey items that achieved a score of 6 to 7 from at least 80% of the reviewers were deemed acceptable without further edits; all other survey items were deemed important areas for consideration and/or revision. Overall, revisions were considered for the following eight items: target population, key points #2, #3, and #4, contact information, balance of benefits and risks, linkage of the recommendations to the evidence base, and appearance of the key recommendations. The guideline was then edited to better reflect the majority opinion.

SEARCH STRATEGY

For the January 2014 guideline update, medical journal articles were searched using Medline (1985 to September Week 1, 2013), EMBASE (1985 to November Week 1, 2013), Cochrane Database of Systematic Reviews (1985 to 3rd Quarter, 2013), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources.

The search terms included: Neutropenia [MeSH term] AND Fever [MeSH term], AND Neoplasms [MeSH term] OR Lymphoma [MeSH term], AND Drug Therapy [MeSH term] OR Drug Therapy Combination [MeSH term], AND clinical trial OR controlled clinical trial OR meta-analysis OR multicenter study OR practice guideline OR randomized controlled trial.

Articles were excluded from the final review if they: had a non-English abstract, involved only pediatric patients, or were published prior to January 1985. A systematic search for new or updated practice guidelines published since January 2010 was also conducted. Guidelines from the National Comprehensive Cancer Network (NCCN), British Columbia Cancer Agency (BCCA), and Infectious Diseases Society of America (IDSA) were deemed to be most relevant and corresponded best with local context and practice.

TARGET POPULATION

The following recommendations apply to adult outpatients who have been treated with chemotherapy for solid tumours or hematologic malignancies within the past month and who present with febrile neutropenia. Different principles may apply to inpatients and to pediatric patients.

RECOMMENDATIONS AND DISCUSSION

The following are *guidelines* for the management of adult cancer patients with febrile neutropenia. Every patient has a unique presentation and should be managed as such. Daily reassessments are required to ensure that the patient is recovering satisfactorily.

Who to Contact

The on-call medical oncologist or responsible medical oncologist (if available) should be contacted when any patient with cancer presents with febrile neutropenia. The responsible medical oncologist should be contacted for any additional or ongoing concerns relating to the care of a cancer patient with febrile

neutropenia. Another useful resource is the on-call infectious diseases specialist at the University of Alberta Hospital (Edmonton) or at the Foothills Hospital (Calgary).

Guideline Question 1. How is febrile neutropenia defined?

The working group reviewed several descriptions of febrile neutropenia from published studies;⁹⁻²⁰ in addition, definitions included in published clinical practice guidelines were reviewed and are summarized below in Table 1.²¹⁻²⁷

Table 1. Published definitions of febrile neutropenia.

Source	Fever (°C)	Neutropenia (x 10 ⁹ cells/L)
<i>Bugs & Drugs, 2012</i> ²¹	≥38.3 oral temp. or ≥38.0 over 1 hour	ANC < 0.5 x 10 ⁹ /L
<i>Infectious Diseases Society of America, 2011</i> ²²	≥38.3 oral temp. or ≥38.0 over 1 hour	ANC <0.5 or predicted decline to <0.5 over next 48 hours
<i>National Comprehensive Cancer Network, 2011</i> ²³	≥38.3 oral temp. or ≥38.0 over 1 hour	ANC <0.5 or <1.0 with predicted decline to ≤0.5 over next 48 hours
<i>European Society of Medical Oncology, 2010</i> ²⁴	>38.5 oral temp. or 2 consecutive readings of >38.0 for 2 hours	ANC <0.5 or predicted decline to <0.5
<i>British Columbia Cancer Agency, 2008</i> ²⁵	≥38.3	ANC <0.5
<i>Japan Febrile Neutropenia Study Group, 2005</i> ^{26,27}	≥38.0 single oral or ear probe temp. or ≥37.5 single axillary temp.	ANC <0.5 or <1.0 in subjects with predictably deteriorating clinical condition

Abbreviations: ANC, absolute neutrophil count

Based on a review of the descriptions in Table 1, the working group agreed on the following consensus definitions:

- **Fever:** Fever is usually defined by a single oral temperature higher than 38.3°C or a sustained oral temperature higher than 38.0°C for more than one hour.
- **Neutropenia:** Neutropenia is defined by an absolute neutrophil count (ANC) less than 0.5x10⁹ cells/L or an ANC less than 1.0x10⁹ cells/L with an expected fall to less than 0.5x10⁹ cells/L within the next 48 hours.

Guideline Question 2. What are the risk factors for febrile neutropenia?

Advanced age is one of the most common risk factors for developing febrile neutropenia;²⁸ other common risk factors include:²⁹

- Female sex
- Low performance status
- Low albumin level
- Low body surface area
- Low baseline counts
- Low lymphocyte counts
- Low hemoglobin level
- High lactate dehydrogenase level
- Bone marrow involvement

Guideline Question 3. What pre-treatment assessments and investigations should be performed?

A careful history and detailed examination is required for all cancer patients suspected of having febrile neutropenia. The examination should include assessments of:^{21,22}

- Mental status
- Hydration status
- Oral and pharyngeal mucosa
- Skin, including any indwelling IV sites
- Respiratory system
- Abdomen
- Perianal area
- AVOID rectal exam but include peri-rectal inspection for abscess
- Cardiovascular system including signs of sepsis
- Special considerations: beware of the possibility of meningitis, sinusitis, herpes simplex, herpes zoster, thrush (including the possibility of thrush under dentures).

A complete hematological profile and chemistry profile should be completed. The latter is done to assess for co-morbidities or any end-organ effects of sepsis, and to determine if any antibiotic dose modifications or contraindications may apply. Laboratory tests should include:^{21,22}

- CBC and differential
- Transaminases (AST or ALT), bilirubin, alkaline phosphatase
- Electrolytes
- Creatinine and urea
- Blood cultures
 - aerobic and anaerobic
 - peripheral and from any indwelling IV lines
 - note: RSV is usually detected by PCR
- Urinalysis and urine culture (absence of pus cells on urinalysis does not rule out UTI in the setting of neutropenia)
- Sputum gram stain and culture if productive
- LP and CSF analysis **should not** be done routinely
- Nasopharyngeal swab for viral respiratory panel PCR, if respiratory symptoms are present

A chest x-ray should be obtained even in the absence of pulmonary symptoms or signs. Pulmonary infiltrates may not develop until the neutropenia begins to recover. Thoracic CT has not been shown to improve outcomes in the absence of clinical pulmonary abnormalities but can be considered in the setting of clinical abnormalities and a normal chest x-ray. Other imaging tests should be guided by the clinical picture.

Supplementary historical information (e.g., major comorbid illness, time since last chemotherapy administration, history of prior documented infections, recent antibiotic therapy/prophylaxis, medications, HIV status, and recent exposures) as well as site-specific cultures (e.g., diarrhea, skin lesions) and viral cultures (e.g., vesicular/ulcerated skin lesions, respiratory virus symptoms) should also be obtained, as necessary.²¹⁻³⁴

Guideline Question 4. What empiric antibiotic therapy should be given?

Seeding of the bloodstream by endogenous bacteria from the gastrointestinal tract is felt to be responsible for the majority of cases of febrile neutropenia. Many chemotherapy drugs can have adverse effects on the mucosal barrier (i.e. mucositis). Blood cultures are positive in about 30 percent of cases, and gram-positive organisms are isolated more commonly than gram-negative organisms; the latter, however, are associated with more severe infections, including sepsis.^{22,30}

Febrile neutropenia is considered an oncologic and medical emergency with high mortality if untreated, and empiric broad-spectrum antibiotics must be administered immediately.^{22,23,30,32} **Patients transferred from the emergency department to a ward should already be receiving their antibiotics.** Allergies, prior antibiotic history, clinical picture and local flora should be considered as guides.^{22,23,32}

The initial antibiotic therapy should be one of the following broad spectrum regimens:²¹⁻³⁴

1. Combination therapy:
 - Piperacillin-tazobactam 4.5 grams IV every 8 hours is the treatment of choice.
 - β -Lactam plus an aminoglycoside plus vancomycin is recommended until C&S results are available in patients who are hemodynamically unstable or have septic shock
 - In such circumstances, vancomycin 15 mg per kg IV every 12 hours should be administered, in combination with either gentamicin 5-7 mg/kg IV every 24 hours or tobramycin 7 mg/kg IV every 24 hours.
 - Combination therapy is not clearly superior to monotherapy in most circumstances. Ensure that appropriate dosing guidelines are followed, especially in the setting of renal dysfunction.
2. Monotherapy:
 - Cefepime 2 grams IV every 8 hours for penicillin-allergic or anaphylactic patients.
 - Carbapenem monotherapy is an alternative to piperacillin-tazobactam. In order to prevent the selection of carbapenem resistance, carbapenems should not be used in first line unless there is a known or suspected infection with ESBL/Amp C cephalosporinase-producing organisms or a penicillin allergy.
3. Empiric vancomycin:
 - Empiric vancomycin should not be used routinely, but should be considered in the following circumstances:
 - Concern of a major β -lactam allergy
 - Obvious IV catheter/tunnel infection
 - Gram stain of culture reveals gram-positive organism, with organism not yet identified
 - Known colonization with MRSA or penicillin-resistant *S. pneumoniae*
 - Hypotension/shock
 - Quinolone antibiotic prophylaxis
 - Skin or soft tissue infection
 - Pneumonia
 - Hemodynamic instability

- Vancomycin therapy should be stopped on day 2 or 3 if cultures are negative for β -lactam resistant Gram positive organisms.

Antibiotic therapy may require modification, according to clinical and microbiological indicators. Reasons for modifications may include: the source/organism of the infection is identified, the infection is found not to be caused by a gram-positive organism, the patient continues to be unstable after initial therapy, or the patient becomes stable.

For a more complete summary of the studies investigating these antibiotic regimens, please refer to Appendix B.

How long should antibiotic therapy be given?

The duration of antibiotic coverage depends on the early clinical course and the results of any cultures - especially blood cultures. If a definite source of infection is identified, such as a UTI or pneumonia, the treatment duration should be appropriate for those infections. If a pathogen is identified in the blood cultures, especially gram negative bacilli, generally a 10 to 14 day course of antibiotics is recommended. If no source is identified either clinically or on blood cultures, antibiotics can be stopped if the patient is afebrile and the ANC has recovered to 0.5×10^9 cells/L, although some recommend a minimum of seven days of therapy. If the fever resolves but the ANC is still low, there is no consensus on duration of antibiotics but a reasonable strategy would be to continue the antibiotics for five to ten days, depending on the clinical picture. If the still neutropenic patient is unstable or has significant mucositis, antibiotics should be continued for at least 14 days even if the patient is afebrile.

The 2012 version of the Alberta Health Bugs & Drugs manual provides an excellent reference for the management of febrile neutropenia.²¹ Ordering information is available online at www.bugsanddrugs.ca.

When can oral antibiotics be given?

A recent systematic review of 22 trials concluded that patients who have improved on IV antibiotics and who are hemodynamically stable have no organ failure, pneumonia, infection of a central line or severe soft-tissue infection, and do not have acute leukemia, can be switched to an appropriate oral regimen for the balance of the chosen antibiotic duration.³⁴ If these patients are stable (non-septic presentation, mucositis resolving, neutrophils $>0.1 \times 10^9$ /L, adequate GI absorption), have no unmanaged comorbidities and have a safe and reliable home environment, they can also be discharged. If the patient has been on a prophylactic quinolone prior to the episode of febrile neutropenia, these should be avoided on discharge. Ciprofloxacin (750mg twice daily) plus amoxicillin – clavulanate (875mg twice daily) or levofloxacin (500mg once daily) are reasonable step-down regimens.²² Culture and sensitivity results can also guide therapy. These results must be reviewed prior to discharge.

What should be done in the case of persisting fever?

Fever in the patient with cancer can be due to the disease itself but a persisting fever in the neutropenic patient usually suggests an ongoing infection not adequately treated by the current antibiotic regimen. The clinical picture must be thoroughly re-evaluated. Blood or other culture results should be verified and repeat cultures obtained if fever persists for more than three days. Empirically, vancomycin (1 gram IV every 12 hours) is usually added at this point. Fungal cultures should be obtained and empiric antifungal therapy is recommended if fever persists beyond five days of appropriate antibacterial therapy. A medical

oncologist or infectious disease specialist should be consulted for advice regarding the most appropriate agent.

Be aware that viral infections can also commonly occur in the patient with febrile neutropenia. Severe oral herpes can look like severe mucositis. Viral swabs and empiric antiviral therapy should be considered.

Is there a role for colony stimulating factors?

Granulocyte colony stimulating factor (G-CSF) can decrease the duration of neutropenia, fever and hospitalization but these benefits are modest and mortality is unaffected.²⁹ G-CSF can be considered in hospitalized patients with pneumonia, hypotension/sepsis, organ dysfunction or a patient on a regimen that is known to cause prolonged neutropenia.^{35,36} Guidelines for the use of prophylactic G-CSF are outside of the scope of this document.

Are there special circumstances that require more urgent attention?

Patients with febrile neutropenia can occasionally present in septic shock or have other critical care issues. These patients should be discussed with the medical oncologist as soon as possible to determine if critical care is appropriate. Patients on potentially curative or salvage regimens must be managed as aggressively as possible. It may be appropriate to contact the nearest critical care specialist. It may be challenging to determine the appropriate level of care for patients on palliative regimens and therefore advice should be sought in this regard from the attending or on call medical oncologist.

Central venous catheter and tunnel infections as well as septic thrombosis, endocarditis and osteomyelitis are special circumstances beyond the scope of this document and specific advice from the appropriate specialist should be obtained. This also applies to any other situation not covered here. A medical oncologist can provide direction as well.

Guideline Question 5. How should low risk febrile neutropenia be managed?

Table 2 describes the characteristics of patients at low risk for complications and high risk for complications from febrile neutropenia.

Inpatient management is considered the standard of care.

A subpopulation of patients with febrile neutropenia who are felt to be at low risk of complications may benefit from outpatient management.^{22,37-39} A 2004 study by Escalante and colleagues demonstrated a response rate of 80 percent among low-risk febrile neutropenic patients with cancer (n=191) treated in an outpatient setting with oral ampicillin/clavulanate (500 mg) and ciprofloxacin (500 mg); the remaining 20 percent of patients were treated subsequently as inpatients.¹¹ Similar results have been reported elsewhere.^{14,40} **Outpatient management should be reserved for tertiary centres with considerable experience in identifying and managing this low risk group.** Mortality and morbidity from the appropriately managed case of febrile neutropenia is very low.

Table 2. Characteristics of patients at risk for complications from febrile neutropenia.^{21-23,28}

Low risk (most of the factors listed below)	High risk (any of the factors listed below)
no high risk factors	
outpatient status at time of development of fever	inpatient status at time of development of fever
no associated acute comorbid illness independently indicating inpatient treatment or close observation	significant clinical comorbidity or medically unstable, including: <ul style="list-style-type: none"> • Hemodynamic instability • Oral/GI mucositis impairs swallowing, causes severe diarrhea • New onset abdominal pain , nausea, vomiting or diarrhea • Neurologic changes/confusion • Intravascular catheter infection
anticipated short duration of severe neutropenia (≤ 100 cells/mcL for <7 days)	anticipated prolonged severe neutropenia (≤ 100 cells/mcL and ≥ 7 days)
good performance status (ECOG 0-1)	uncontrolled/ progressive cancer; pneumonia or other complex infections at clinical presentation; alemtuzumab therapy; mucositis grade 3-4
no hepatic insufficiency	hepatic insufficiency (five times ULN for aminotransferases)
no renal insufficiency	renal insufficiency (creatinine clearance <30 mL/minute)
MASCC risk index score ≥ 21 (see Appendix A) ^{41,42}	MASCC risk index score less than 21 (see Appendix A) ^{41,42}
<60 years	
Cancer partial or complete remission	
No focal findings of infection	
Temp <39 °C	
Normal chest x ray	
Absence hypotension	
Respiratory rate ≤ 24	
No chronic lung disease or diabetes	
No dehydration/ confusion	
No history of fungal infection or antifungal therapy in past six months	

Table 3 is adapted from the Bugs & Drugs manual, and summarizes the definitions, recommended investigations, and therapy for the treatment of febrile neutropenia.^{21,22}

Table 3. Summary of recommendations from Bugs & Drugs manual.^{21,22}

Definition	<p>Febrile = oral temperature ≥ 38.3 °C once or ≥ 38 °C for ≥ 1 hour</p> <p>Neutropenia = ANC $< 0.5 \times 10^9$ /L or predicted to decline to $< 0.5 \times 10^9$ /L over next 48 hours</p>
Investigations	<ul style="list-style-type: none"> • CBC and differential • Transaminases, bilirubin, alkaline phosphatase • Electrolytes • Creatinine and urea • Blood and urine cultures • Sputum gram stain and culture if productive • AST • Nasopharyngeal swab for viral respiratory panel PCR, if respiratory symptoms are present • Chest x-ray (should be obtained even in the absence of pulmonary symptoms or signs)
Monotherapy	<ul style="list-style-type: none"> • Cefipime 2 grams IV every 8 hours. • Carbapenem monotherapy is an alternative to piperacillin-tazobactam. In order to prevent the selection of carbapenem resistance, carbapenems should not be used in first line unless there is a known or suspected infection with ESBL/AmpC cephalosporinase-producing organisms or a penicillin allergy. • Ceftazidime monotherapy is not recommended, as it: <ul style="list-style-type: none"> ○ has no reliable Gram positive (Enterococci, Streptococci, Staphylococci) activity compared to piperacillin-tazobactam ○ may promote antimicrobial resistance (ESBL and AmpC cephalosporinases) ○ is not optimal in patients with profound ($< 0.1 \times 10^9$/L)/prolonged neutropenia
Combination Therapy	<ul style="list-style-type: none"> • Piperacillin-tazobactam 4.5 grams IV every 8 hours is the treatment of choice. • β-Lactam plus an aminoglycoside plus vancomycin is recommended until C&S results are available in patients who are hemodynamically unstable or have septic shock <ul style="list-style-type: none"> ○ In such circumstances, vancomycin 15 mg per kg IV every 12 hours should be administered, in combination with either gentamicin 5-7 mg/kg IV every 24 hours or tobramycin 7 mg/kg IV every 24 hours.
Recommendations for the Use of Vancomycin	<ul style="list-style-type: none"> • Empiric vancomycin should not be used routinely, but should be considered in the following circumstances: <ul style="list-style-type: none"> ○ Concern of a major β-lactam allergy ○ Obvious IV catheter/tunnel infection ○ Gram stain of culture reveals gram-positive organism, with organism not yet identified ○ Known colonization with MRSA or penicillin-resistant <i>S. pneumonia</i> ○ Hypotension/shock ○ Quinolone antibiotic prophylaxis ○ Skin or soft tissue infection ○ Pneumonia ○ Hemodynamic instability • Vancomycin therapy should be stopped on day 2 or 3 if cultures are negative for β-lactam resistant Gram positive organisms.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
AHS	Alberta Health Services
ALT	alanine aminotransferase test
ANC	absolute neutrophil count
AST	aspartate aminotransferase test
BCCA	British Columbia Cancer Agency
C & S	culture & sensitivity
CBC	complete blood count
CSF	cerebrospinal fluid
CT	computed tomography scan
ESBL	extended-spectrum β -lactamases
GCSF	granulocyte colony stimulating factor
IDSA	Infectious Diseases Society of America
IV	intravenous
LP	lumbar puncture
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NCCN	National Comprehensive Cancer Network
PCR	polymerase chain reaction
RAAPID	Referral, Access, Advice, Placement, Information, and Destination
RSV	respiratory syncytial virus
UTI	urinary tract infection

DISSEMINATION

- Post the guideline on the Alberta Health Services website.
- Circulate an electronic version of the guideline to members of the Alberta Provincial Tumour Teams.
- Include a link to document in other relevant clinical practice guidelines on the Alberta Health Services website.

MAINTENANCE

A formal review will be conducted annually. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of the working group members in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. While some members of the working group are involved in research funded by industry or have other such potential conflicts of interest, the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX A: Multinational Association for Supportive Care in Cancer (MASCC) Risk Index ^{41,42}

Characteristic	Point Score
Burden of illness – no or mild symptoms	5
Burden of illness – moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or no previous fungal infection in hematologic tumour	4
Outpatient status	3
No dehydration	3
Age less than 60 years	2

Maximum score: 26

Score ≥ 21 predicts <5% risk of severe complications and very low mortality (<1%)

APPENDIX B: Summary of Studies Assessing Antibiotic Therapy for Febrile Neutropenia

Author, Year	Patient Population	Treatments	Outcomes
Randomized controlled trials			
<i>Naseem A, et al. 2011</i> ⁴³	Pts w/ febrile neutropenia in lymphoma (n=117)	Randomization: 1. Cefepime (n=55) 2. Ticarcillin/clavulanate(TC) (n=52)	<ul style="list-style-type: none"> Significant difference, with success rates of 51% for cefepime and 42% for ticarcillin/clavulanate. Fewer pts. Required modification of antibiotic regimen in cefepime group (35% vs 52% respectively). Successful eradication rate of microbiologically infections were higher in cefepime group (10 of 12 pts.) vs ticarcillin/clavulanate group (6 of 14 pts).
<i>Sebban, et al. 2008</i> ⁴⁴	Pts w/ low-risk neutropenic fever, received chemotherapy for solid tumour, lymphoma or myeloma, >18 yrs	Randomization: 1. Oral moxifloxacin (n=49) 2. Intravenous ceftriaxone (n=47)	<ul style="list-style-type: none"> Trial was closed prematurely due to low accrual. Success rate 73.9% and 79.2% for ceftriaxone and moxifloxacin respectively. Calculated risk difference between monifloxacin arm and ceftriaxone arm 5.3%. No toxic death was observed in the study along with no severe complications or significant morbidity.
<i>Jimeno, et al. 2006</i> ⁴⁵	Pts w/ solid tumors treated with high dose chemo (HDC) and peripheral blood stem cell support (PBSCS) with febrile neutropenia	Randomization: 1. Ceftazidime plus amikacin (n=27) 2. Cefepime (n=24)	<ul style="list-style-type: none"> This trial was closed prematurely. Major efficacy endpoints did not show sig differences, with success rates of 44.4% and 54.2% (p = 0.481) for the combination and monotherapy arms, respectively. The proportion of patients that became afebrile in the first 24 hours was significantly higher in the cefepime group (41.7% vs 11.1%, respectively; p = 0.012).
<i>Chamorey, et al. 2004</i> ¹⁰	Patients with cancer in whom febrile neutropenia had developed (n=94)	Treatment: Once-daily ceftriaxone (CFX) alone (2 g daily intravenous CFX alone until NC>500)	<ul style="list-style-type: none"> The median duration of neutropenia was 3.5 days (range 1-22). Median CFX treat duration was 5 days. Successful response was obtained in 87% of cases; no deaths occurred. Treatment failure was mostly observed in patients with PS > or = 2 (p=0.0001). Among the 13 failures, 4 resolved in less than 4 days with CFX alone and 9 required additional or modified antimicrobial treatment.
<i>Peacock, et al. 2002</i> ¹²	Febrile neutropenic patients (n=471)	Randomization: 1. Piperacillin (50 mg/kg IV every 4 hours) and cipro-floxacin (400 mg IV every 8 hours) (n=234) 2. Piperacillin-tobramycin (2 mg/kg intravenously every 8 hours) (n=237)	<ul style="list-style-type: none"> Success rates in the ciprofloxacin-piperacillin group (63 of 234 febrile episodes) and tobramycin-piperacillin group (52 of 237 episodes) were similar (27% vs. 22%, respectively; diff 5% [95% CI, -2.3-12.8%]) Survival also similar (96.2% of pts receiving cipro-floxacin-piperacillin vs. 94.1% of pts receiving tobramycin-piperacillin; diff 2.1% [CI, -2.2-6.4%]) Fevers resolved faster in pts receiving ciprofloxacin-piperacillin than in pts receiving tobramycin-piperacillin (mean 5 vs. 6 days; P=0.005)
<i>Bauduer, et al. 2001</i> ¹³	Patients with chemo- or stem cell transplantation-induced neutropenia (n=208)	Randomization: 1. Cefpirome (CPO; 2 g x 2/day; n=105) 2. Piperacillin-tazobactam (PT; 4 g	<ul style="list-style-type: none"> Two days after antibiotics initiation, clinical (fever disappearance) and microbiological (culture negatvation) success rates (SR) were 62% for CPO versus 61% for PT and 50% vs. 55% respectively in case of MDI (p = 0.89).

Author, Year	Patient Population	Treatments	Outcomes
		x 3/day; n=103) alone (CPO: 15/PT: 15) 3. Plus aminoglycoside (n=165)	<ul style="list-style-type: none"> Two deaths and 77 failures; SR (no antibiotic change/absence of superinfection) was 59% with CPO versus 50% with PT ($p = 0.27$) and 53% versus 40% respectively ($p = 0.17$).
<i>Antabli, et al. 1999</i> ⁴⁶	Neutropenic febrile pts undergoing high dose myeloablative therapy and HSCT for solid tumours, leukemia, lymphoma, or multiple myeloma (n=106)	Treatment: Ceftazidime (2 g IV every 8 h) and ciprofloxacin (400 mg IV every 12 h) if they developed fever while they were neutropenic.	<ul style="list-style-type: none"> The success rate was 99%. Sixty-one of the patients (57.5%) defervesced within 48-72 h and remained afebrile without regimen modification. In 41.5% of the cases (44/106), the regimen was modified due to persistent fever.
<i>Ozyilkkan, et al. 1999</i> ⁴⁷	Febrile neutropenic patients with liquids and solid tumours (n=30)	Randomization: 1. Imipenem-cilastatin (n=15) 2. Sulbactam-cefoperazone and amikacin (n=15)	<ul style="list-style-type: none"> 73% of episodes were culture-positive. The initial clinical response rate for both regimens was 60% ($p > 0.05$).
<i>Behre, et al. 1998</i> ¹⁶	Neutropenic cancer pts (n=71; 55% hematological and 45% solid)	Randomization: 1. Monotherapy: carbapenem meropenem (1g q 8h; n=34) 2. Standard combination therapy with ceftazidime (2 g q 8 h) and amikacin (15 mg/kg/d; n=37) IV	<ul style="list-style-type: none"> Meropenem and ceftazidime/amikacin were equivalent with respect to the clinical response at 72 h (62% versus 68%) ($p > 0.05$) and at the end of unmodified therapy (59% versus 62%). Gram-positive bacteremia responded poorly in the meropenem and ceftazidime/amikacin group (29% versus 25%). All gram-negative bacteremias responded except for one in the meropenem group (<i>Pseudomonas aeruginosa</i>).
<i>Ghazal, et al. 1997</i> ⁴⁸	Pts developing FN during high-dose myeloablation and HSCT for solid tumors, leukemias, lymphomas, multiple myeloma (n=45)	Treatment: Open-label ceftazidime 2 g IV q 8 hrs and ciprofloxacin 400 mg IV q 12 hrs if fever during neutropenia	<ul style="list-style-type: none"> The success rate was 98% (survival through neutropenic period). Sixty-two percent (28 of 45) of the patients achieved defervescence within 48 to 72 hours and remained afebrile without regimen modification.
<i>Laszlo, et al. 1997</i> ¹⁸	Bone marrow transplant (BMT) febrile neutropenic patients (pts; n=66)	Randomization: 1. Netilmicin plus imipenem-cilastatin (Net + Imi) 2. Netilmicin plus ceftazidime (Net + Cef) as empiric therapy	<ul style="list-style-type: none"> Overall outcome based on clinical responses was as follows: 80% of pts on Net + Imi responded (lasting return of temperature to normal and complete disappearance of either clinical or cultural signs of infection without any modification of therapy) compared to 73% of those on Net + Cef. For microbiologically documented infections response rates were 70% in Net + Imi group and 43% in the Net + Cef group ($p = ns$).
<i>Aparicio, et al. 1996</i> ⁴⁹	Neutropenic patients with solid tumours or lymphoma (n=111)	Randomization: 1. Monotherapy with ceftazidime 2. Monotherapy with imipenem If no response, amikacin and/or vancomycin added	<ul style="list-style-type: none"> Febrile episodes were classified as microbiologically (34%) or clinically documented (42%), and fever of unknown origin (24%). Gram-negative infections (57%) predominated over gram-positive isolates (30%). Overall success rate with monotherapy (69% versus 70%), or with modification (20% versus 23%) were equivalent for ceftazidime and imipenem ($P = 0.75$).
<i>Velasco, et al. 1995</i> ⁵⁰	Febrile neutropenic cancer patients with solid tumor or nonlymphoblastic lymphoma (n=108)	Randomization: 1. Oral ciprofloxacin + penicillin V (n=55) 2. Amikacin +carbenicillin or ceftazidime (n=48)	<ul style="list-style-type: none"> Both regimens were well tolerated. Oral regimen was substantially cheaper than parenteral regimen. Treatment success without regimen modification was 94.5% for C + P group and 93.8% for A + C group ($p = .86$; CI -0.08-0.10).

Author, Year	Patient Population	Treatments	Outcomes
<i>Freifeld, et al.</i> 1995 ⁵¹	Adult and pediatric patients undergoing chemotherapy for solid tumors, leukemias, or lymphomas	Randomization: 1. Open-label ceftazidime (n=204) 2. Imipenem (n=195) on presentation with fever and neutropenia	<ul style="list-style-type: none"> Overall success (survival through neutropenia) was >98% with or without modification, regardless of initial antibiotic regimen. Antianaerobic agents more often added to ceftazidime (P<.001), but addition of other antibiotics was similar between two groups. Imipenem therapy associated with significantly greater toxicity, requiring discontinuation in 10% of recipients.
<i>Pico, et al.</i> 1993 ²⁰	Pts with therapy-induced neutropenia and fever for at least three hours (n=102; 89 hematological and 13 solid tumours)	Randomization: 1. Ceftazidime (3 g/d) (C) 2. C + amikacin (15 mg/kg/d) (CA) 3. C + vancomycin (1.5 g/d) (CV)	<ul style="list-style-type: none"> Eight (22%) patients in group C developed major infectious events compared with four (13%) in group CA and none in group CV (p < 0.01). Major infectious events were mainly due to Gram-positive, particularly Streptococcus.
<i>Oturai, et al.</i> 1993 ⁵²	Neutropenic patients treated with cytotoxic chemotherapy for solid tumours (n=121)	Randomization: 1. Ceftriaxone monotherapy 2. Latamoxef monotherapy	<ul style="list-style-type: none"> No significant differences were observed between the two groups with respect to efficacy and fatal failure rates. Of episodes treated with ceftriaxone, 67% showed a favourable clinical response vs. 61% in the latamoxef group. The clinical response rates in episodes with documented bacterial infections were 67 and 56% in the two groups.
<i>Kattan, et al.</i> 1992 ⁵³	Febrile neutropenic cancer patients treated with nephrotoxic chemotherapy (n=40; 34 solid tumour patients & 6 non-Hodgkin lymphoma patients)	Treatment: Piperacillin (4 g IV q 8 h) and pefloxacin (400 mg IV q 12 h). If patient remained febrile after 72 h, 1 g/h IV vancomycin IV was added	Temperature became normal in 38 patients with piperacillin-pefloxacin and 12 further episodes were resolved by the addition of vancomycin.
Meta-Analyses			
<i>Jørgensen, et al.</i> 2014 ⁵⁴	Cancer patients with neutropenia 1,840 pts (3 trials)	Cochrane Central Register of Controlled Trials (2014, issue 1), MEDLINE (to Jan 2014), were searched for RCTs. Letters, abstracts and unpublished trials were accepted. Contact was made with trial authors and industry.	<ul style="list-style-type: none"> Liposomal amphotericin B is significantly more effective than voriconazole for empirical therapy of fungal infections in neutropenic cancer patients. For treatment of aspergillosis, there are no trials that have compared voriconazole with amphotericin B given under optimal conditions. For prophylactic fungal treatment in patients receiving allogeneic stem cell transplantation, there was no difference between voriconazole and fluconazole regarding fungal free survival or invasive fungal infections.
<i>Vidal, et al.</i> 2013 ³⁴	Febrile neutropenic cancer patients 2,372 pts (22 trials)	Cochrane Central Register of Controlled Trials (2013, issue 1), MEDLINE (1966 to Jan week 4, 2013), EMBASE (1980- week 4, 2013), LILACS (1982-2007) were searched for RCTs	Mortality rate similar between oral vs. IV antibiotic treatment (RR 0.95, 95% CI 0.54-1.68). Treatment failure rates were also similar (RR 0.96, 95% CI 0.86-1.06).

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