Atlantic Provinces Pediatric Hematology Oncology Network
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Reviewed and approved by specialists at the IWK Health Centre, Halifax, NS

Guidelines for the Management of Febrile Neutropenia in Children

APPHON/ROHPPA supportive care guidelines have been developed by appropriate Atlantic Provinces health professional specialists (physicians, pharmacists, nurses and other health professionals) using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

Unofficial document if printed. To ensure that this printed is the latest version, please check website http://www.apphon-rohppa.com.

Update - October 16, 2023

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1. INTRODUCTION

The explanation for the supporting evidence for this guideline is in the reference section. This guideline was originally based on the C17 endorsed guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation 2012 and the 2017 update and more recent evidence based upon guidance from **the recent publication Lehrnbecher T, Robinson PD, Amman RA, et al. Guideline for the Management of Fever and Neutropenia in Pediatric Patients with Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update. *JCO* 2023;41((0:1774-1785. *and has been revised for use in the Maritime Provinces.***

These guidelines apply to the management of patients:

1. With fever and neutropenia as the result of a known or suspected malignancy or the use of antineoplastic agents.
2. Hematopoietic stem cell transplant (HSCT) patients who present with fever or evidence of infection within 6 months of their transplant, regardless of their absolute neutrophil count (ANC), or…
3. Patients who continue to receive immunosuppressant agents after transplant, regardless of their ANC or the length of time post-HSCT.
4. Children with fever or evidence of infection who are receiving antineoplastics or who have completed cancer therapy within 3 months **even if they are NOT neutropenic**.
5. Children with neutropenia from causes other than cancer who present with fever.

In addition, all hematology/oncology patients who are febrile should go to the closest emergency for a minimum of 3 months after completion of chemotherapy/ immunotherapy or immunosuppressant agents for CBC, physical exam, and decision about antibiotics. The decision to treat with antibiotics is determined by the clinical assessment and status of the patient, the results of initial investigations and the presence/absence of a central venous access device (CVAD). Please discuss care of those who have undergone a bone marrow transplant or have an underlying immunodeficiency with the oncologist on call. These patients may require prolonged and specific interventions.

Beyond 3 months after the end of treatment with chemotherapy/immunotherapy, the decision on how to manage a fever would be similar to management of any other child unless the child is known to have prolonged recovery of counts, is post-rituximab with hypogammaglobulinemia, or if their central line is still in place.

2. DEFINITIONS

Fever is defined as a single oral or tympanic temperature greater than or equal to 38.3°C or oral or tympanic temperature greater than or equal to 38°C for 1 hour or more. Oral temperatures (and/or thermometers that read core body temperature, e.g., tympanic thermometers) are more reliable and are thus preferred. However, when axillary temperatures are the only option (e.g., very young children or when a tympanic thermometer does not yield an accurate temperature), fever is defined as a single axillary temperature of greater than or equal to 37.8°C or axillary temperature greater than or equal to 37.5°C for 1 hour or more. NOTE: A non-contact infrared thermometer or fever strips are not recommended.

Do NOT take rectal temperatures.

Neutropenia is defined as an absolute neutrophil count (ANC) less than 0.5×10^9/L or expected to fall below 0.5×10^9/L within the next 48 hours.

ANC (absolute neutrophil count) is defined as the sum of the counts of mature neutrophils and band forms. The use of automated differentials is preferred over manual differentials.

3. CLINICAL PATHWAY FOR PATIENTS WHO MEET THE CRITERIA FOR TREATMENT OF FEBRILE NEUTROPENIA:

- Basic centers must call the pediatric hematologist/oncologist immediately to discuss transfer of the patient.
- Intermediate centers must call the pediatric hematologist/oncologist immediately to discuss the appropriate center to admit the patient.
- Advanced centers must call the pediatric hematologist/oncologist within 24 hours of assessment of the patient.

4. CLINICAL PRACTICE RECOMMENDATIONS

SIGNS AND SYMPTOMS

Signs and symptoms which may be present in a child presenting with febrile neutropenia:

- fever (may be masked by steroids, especially dexamethasone)
- irritability
- hot or cold shivers (rigors), sweating
- warm forehead with flushed or pale face
- rapid heart rate
- new rash (note erythema due to infection may be absent in profound neutropenia)
- vomiting
- a sore which does not heal
- sores in the mouth or throat and/or drooling
- pain on swallowing [food/saliva]
- coughing
- pain with a bowel movement
- diarrhea
- change in level of consciousness
- meningism
- painful or frequent urination
- abdominal pain
- perianal pain or ulcers
- rarely, fever may not be present despite a significant infection; unwell children should always be managed with infection in mind even in the absence of fever.

SECTION I. INITIAL MANAGEMENT

Complete history, including past exposure and history of infection, expected period of neutropenia and drug allergies. **Ask parents for child's "Treat Promptly" card.**

Investigations:

1. Complete physical examination by a physician or a nurse practitioner - including skin, mouth, respiratory tract, genitalia, perianal region and fundi (if indicated). Rectal examination should only be done if absolutely necessary for the (surgical) assessment of the patient and should be performed after antibiotics have been given. Examine for signs and symptoms of meningitis [may be very subtle].

2. Immediately access the CVAD **regardless of whether anesthetic cream has been applied to the port site**. If patient does not have a CVAD or unable to access CVAD within 30 minutes, establish a peripheral intravenous line.

3. Obtain CBC and differential, lactate and **aerobic and anaerobic** blood **c**ultures from all lumens of CVAD **within 30 minutes** of arrival. If patient does not have a CVAD draw a peripheral culture. (NOTE: Pediatric culture bottles automatically include testing for both aerobic and anaerobic. Also aerobic blood cultures automatically include fungal cultures as all fungi are aerobic.)

   NOTE: Repeat lactate levels should be considered in patients who have high levels on presentation and/or those that are unwell. Routine repeat measurement of lactate levels outside a clinical concern for sepsis is not required.

4. If **anaerobic infection** is suspected (e.g., intra-abdominal, intra-pelvic, peri-rectal or peri-anal processes, including typhlitis, or abscess of the head, neck or mediastinum), or empyema present obtain an **anaerobic blood culture** as well, if a pediatric culture bottle was not already utilized.

5. Viral swabs, or cultures are only required for patients with signs or symptoms suggestive of viral illness (e.g., vesicular rash, upper respiratory tract infection, cough, diarrhea, mucositis etc.).

6. Current recommendations regarding screening and swabbing for COVID-19 should be followed as appropriate.

7. Chest x-ray (if clinically warranted – note the yield is low in the absence of signs and symptoms), additional laboratory tests (plasma urea, creatinine, sodium, potassium, and chloride), and the following cultures (in addition to CVAD and peripheral cultures as noted above):
   a) Urinalysis and culture (if clinically warranted)
   b) swab any apparent site of infection
   c) other investigations (e.g., mycoplasma throat swab) judged to be warranted by the evaluating healthcare professional

Monitoring:

Vital signs q1h until stable and then at least q4h or as needed. Note that patients may initially deteriorate when starting antibiotics because of bacterial cell lysis.

Treatment:

1. Administer ANTIBIOTICS STAT as below. Antibiotics should be given **within 1 hour** of arrival at the hospital. Record which lumen has been used for the initial doses of antibiotics if a patient has a device with more than one lumen. The antibiotics should be given prior to patient transfer to any other area and prior to administration of blood products.

   Note: Serious infection may be present in children without fever ever being documented. Antibiotic therapy should be considered in the sick, neutropenic child irrespective of fever.

2. Start IV and give fluids at about 1.5 x maintenance rate with reassessment in 12-24 hours.

3. Stop all antineoplastic/chemotherapy agents until discussed with the staff oncologist. If platelets are low consider holding prophylactic cotrimoxazole (Septra®).

4. Always consider the patient's past history regarding resistance patterns of **previously cultured organisms, VRE history, MRSA colonization,** and clinical status (e.g., septic shock) when selecting antibiotics. Standard initial antibiotics for the stable patient as recommended in Tables 1 and 2 may not be appropriate in a patient who has a history of serious infection due to an antibiotic-resistant organism.

5. Central line associated bloodstream infection (CLABSI) is a primary bloodstream infection (that is, there is no apparent infection at another site) that develops in a patient with a central line. CLABSI may present as fever +/- rigors related to recent access to the CVAD, infection at the catheter exit site or as infection along the subcutaneous course of the catheter. If this is the case, antibiotics directed at this site of infection (e.g., vancomycin) should be initiated **IN ADDITION** to the broad-spectrum empiric antibiotic regimen below. The antibiotics should be alternated through all lumens. If CVAD cultures confirm infection, a full course of antibiotics is indicated. Removal of the catheter may be required. Consultation with Infectious Diseases is recommended to facilitate this decision.

6. Acetaminophen is the preferred antipyretic agent. Ibuprofen and other non-steroidal anti-inflammatory agents are not generally recommended for neutropenic patients because of frequent associated thrombocytopenia.

7. Daily physical examination, CBCD, creatinine and serum chemistries as indicated. Monitor closely for evolving infection requiring addition or modification of antimicrobial therapy.

Figure 1: Initial management of children with fever and neutropenia

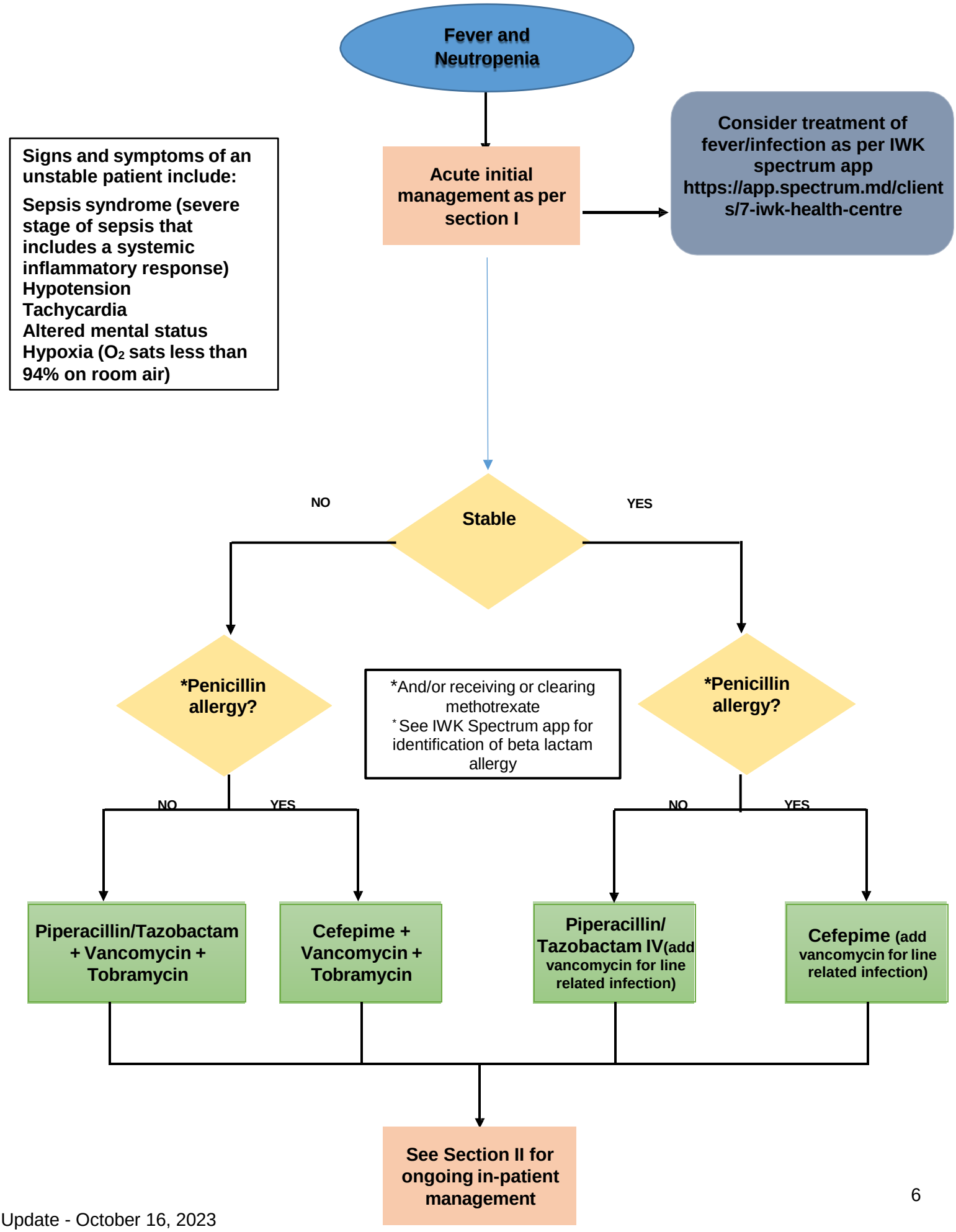

Table 1: Antibiotic management of patients who present with fever and neutropenia and are STABLE:

<table>
<tr><td colspan="2">Patients younger than 2 months: If the patient is a neonate, please consult Spectrum app/ e-formulary for specific dosing of antibiotics</td></tr>
<tr><td>Ampicillin
50-100 mg/kg/dose IV q6h AND (max single dose:2 g)
Ceftazidime
50 mg/kg/dose IV q8h (max single dose:2 g)

<u>If patient is suspected to have a central line associated infection* add</u>:
Vancomycin
15 mg/kg/dose IV q6h (max single dose: 1 g)

For full coverage of coagulase negative staphylococcus.
Central line associated bloodstream infection (CLABSI) may present as fever and/or rigors related to recent access to the CVAD, infection at the catheter exit site or as infection along the subcutaneous course of the catheter.</td><td>Immediately discuss the care of all infants with febrile neutropenia with the pediatric oncologist.
In addition, regardless of where the infant presents discuss the care of all infants with febrile neutropenia with Infectious Disease soon after presentation.

Additional empiric antimicrobial agents (including coverage for herpes simplex virus) will be considered on a case-by-case basis.

Cerebrospinal Fluid (CSF) should be obtained for culture as long as it does not significantly delay the initiation of antibiotics.</td></tr>
<tr><td colspan="2">Patients older than 2 months with NO significant beta-lactam allergy</td></tr>
<tr><td>Piperacillin-Tazobactam
80 mg piperacillin/kg/dose IV q6h (2-6 months) and
100mg/kg/dose IV q6h > 6 months
(max single dose: 4 g)

<u>If patient is suspected to have a central line associated infection* add</u>:
Vancomycin
12 years and older: 15mg/kg/dose IV q8h (max single dose: 1 g)
less than 12 years:15 mg/kg/dose IV q6h (max single dose: 1 g)
For full coverage of coagulase negative staphylococcus.
Central line associated bloodstream infection (CLABSI) may present as fever and/or rigors related to recent access to the CVAD, infection at the catheter exit site or as infection along the subcutaneous course of the catheter.</td><td>Piperacillin-tazobactam provides empiric coverage against Gram positive organisms including Streptococcus viridians and MSSA.</td></tr>
<tr><td colspan="2">Patients older than 2 months with significant beta-lactam allergy (i.e., anaphylaxis)</td></tr>
<tr><td>Cefepime
50 mg/kg/dose IV q 8h (max single dose: 2000 mg)

<u>If patient has central line associated infection* add:</u>
Vancomycin
12 years and older: 15mg/kg/dose IV q8h (max single dose: 1 g)
less than 12 years: 15 mg/kg/dose IV q6h (max single dose: 1 g)
For full coverage of coagulase negative staphylococcus.
Central line associated bloodstream infection (CLABSI) may present as fever and/or rigors related to recent access to the CVAD, infection at the catheter exit site or as infection along the subcutaneous course of the catheter.</td><td></td></tr>
</table>

Table 2: Antibiotic management of patients who present with fever and neutropenia and are UNSTABLE:

Patients younger than 2 months. If the patient is a neonate, please consult Spectrum app/e-formulary for specific dosing of antibiotics	
With suspicion of meningitis: **Meropenem** 40 mg/kg/dose IV q8h (max single dose: 2 g) AND **Tobramycin**[*] 10.5 mg/kg/dose IV q24h (maximum initial dose 800 mg prior to TDM[*]) AND **Vancomycin** 15 mg/kg/dose IV q6h (max single dose: 1 g) Without suspicion of meningitis: **Piperacillin-Tazobactam** 80 mg/kg/dose IV q6h (max single dose: 4 g) AND **Tobramycin** 10.5 mg/kg/dose IV q24h (maximum initial dose 800 mg prior to TDM[*]) AND **Vancomycin** 15 mg/kg/dose IV q6h (max single dose: 1 g)	Immediately discuss the care of all infants with febrile neutropenia with the pediatric oncologist. In addition, regardless of where the infant presents discuss the care of all infants with febrile neutropenia with Infectious Disease soon after presentation. Additional empiric antimicrobial agents (including coverage for herpes simplex virus) will be considered on a case-by-case basis. Cerebrospinal fluid (CSF) should be obtained for culture as long as it does not significantly delay the initiation of antibiotics.
Patients who are older than 2 months with NO significant beta- lactam allergy	
Piperacillin-Tazobactam 80 mg piperacillin/kg/dose IV q6h (2-6 months) and 100mg/kg/dose IV q6h > 6 months (max single dose: 4 g) **AND Tobramycin**[*] 2 m to < 6 yrs**:**10.5 mg/kg/dose IV q24h; ≥ 6 yrs:8 mg/kg/dose IV q24h Maximum initial dose of 400 mg prior to TDM[*] **AND Vancomycin** 12 years and older: Vancomycin 15mg/kg/dose IV q8h (max single dose: 1 g) less than 12 years: Vancomycin 15 mg/kg/dose IV q6h (max single dose: 1 g)	
Patients who are older than 2 months with significant beta-lactam allergy (i.e., anaphylaxis)	
Cefepime 50 mg/kg/dose IV q 8h (max single dose: 2 g) **AND Tobramycin**[*] 2 m to < 6 yrs**:** 10.5 mg/kg/dose IV q24h; ≥ 6 yrs: 8 mg/kg/dose IV q24h Maximum initial dose of 400 mg prior to TDM[*] **AND Vancomycin** 12 years and older: Vancomycin 15mg/kg/dose IV q8h (max single dose: 1 g) less than 12 years: Vancomycin 15 mg/kg/dose IV q6h (max single dose: 1 g)	

[*] **TDM – therapeutic drug monitoring.**

Any patient with hearing loss (sensorineural hearing loss 30 dB HL or greater at one or more frequencies between 250 Hz to 4000 Hz) OR renal impairment (i.e., GFR 60 mL/min/1.73 m or less, serum creatinine 1.5 times upper limit of normal for age) or patients receiving cisplatin or cranial radiation AVOID aminoglycoside and contact pediatric hematologist/oncologist or infectious disease specialist. In these cases, antibiotics of choice are meropenem (20 to 40 mg/kg/dose IV q8h maximum 6 g/day) AND vancomycin

NOTE: Monitor vancomycin and tobramycin levels as per IWK spectrum app and ensure adequate hydration. When administering IV tobramycin monitor urine output and serum creatinine daily.

SECTION II. CONTINUED MANAGEMENT OF INPATIENTS

Patients who remain febrile after initiation of appropriate antibiotic therapy ordinarily should have aerobic CVAD cultures drawn no more than once daily, and if feasible, timed with fever spikes. Anaerobic cultures are not routinely obtained in this circumstance and should be ordered only when clinically appropriate.

If patient is receiving IV antibiotics, alternate antibiotic therapy among all lumens once daily for the duration of antibiotic therapy in patients with **multi-lumen CVADs**.

If the patient's clinical status is **stable or improving**:

- Continue empiric antibiotic regimen.

- "Step-down" to the empiric IV antibiotic regimen recommended for patients who were stable at presentation (see Table 1) may be considered in patients who experienced a period of instability but become stable and continue to require broad spectrum antibiotics (see section IV) i.e., discontinue tobramycin and vancomycin

If the patient's **clinical status deteriorates or fever persists** despite empiric antibiotic administration:

- PATIENTS WHO ARE PERSISTENTLY FEBRILE but STABLE should continue to receive the initial empiric antibiotic regimen. If the patient's clinical condition indicates evolving infection at a particular site (e.g., abdominal pain, severe mucositis, pneumonia), antibiotics directed toward possible causative organisms should be added to **empiric** broad spectrum therapy if the initial antibiotics do not provide adequate coverage. Discuss with Haematology/Oncology fellow or Staff on-call.

- PATIENTS WHO DETERIORATE (becoming hemodynamically unstable) or appear to be progressively deteriorating should be brought to the immediate attention of the Haematology/Oncology Fellow or Staff on-call. The caller should request an Infectious Disease consult.

- After 5-days of persistent fever or if a new fever develops after 5-days of empiric antibiotic therapy, consider the addition of empiric antifungal coverage in consultation with Infectious Disease. The time and initiation of antifungal therapy is highly dependent **on the patient's inherent risk of invasive fungal infection.**

SECTION III. PATIENTS WITH POSITIVE BLOOD CULTURE(S)

Each patient with a positive blood culture should be managed in consultation with Infectious Diseases on a case-by-case basis. The following recommendations are provided for general guidance:

- If initial blood cultures (peripheral or central) are positive, repeat cultures should be drawn when this result becomes known. Antibiotics specifically directed toward the identified organism should ordinarily be **added to** empiric broad spectrum therapy if the initial antibiotics do not provide adequate coverage.

- **Broad spectrum coverage must not be replaced by organism- specific antibiotic(s) alone in the neutropenic patient.**

- The addition of tobramycin to the regimen of a patient with a gram-negative culture receiving monotherapy with piperacillin-tazobactam should be based on clinical judgement. If the patient is hemodynamically stable, even in the presence of fever, continuation of monotherapy is advised. If tobramycin is initiated, this must be reevaluated when the organism is identified, and sensitivities are available. In patients who were stable on presentation, monotherapy with an antibiotic to which the organism is known to be sensitive is encouraged for other organisms.

- CVAD removal: This is strongly recommended in patients with fungemia, non-tuberculous mycobacterial infection and Staphylococcus aureus infection. This should also be strongly considered in patients with persistently positive blood cultures despite appropriate antibiotics, and in cases of infection due to Bacillus spp., Clostridium spp., Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Enterobacter spp., or multiply resistant organisms. This should also be considered for patients with infective endocarditis or relapse of infection with the same pathogen after completion of an appropriate course of antibiotics.

- If the symptoms include perianal tenderness, abdominal tenderness, or possible typhilitis, call the pediatric hematologist/oncologist to potentially initiate metronidazole 10mg/kg/dose PO q8h (maximum 500mg/dose) if patient is currently receiving cefepime or ceftazidime or another cephalosporin.

SECTION IV. TREATMENT OF VIRAL AND FUNGAL INFECTIONS

- Consult with pediatric hematologist/oncologist. Patients with suspected invasive fungal, PJP and viral infections (CMV, VZV, disseminated HSV) usually require transfer to the subspecialty center.

Viral

Herpes Simplex and Varicella Zoster Infections

- Oral acyclovir should not be used to initiate antiviral treatment. Absorption of oral acyclovir is only 15-30%. Occasionally, oral acyclovir is given to patients with mild or recovering infection to facilitate early discharge.
- Ensure adequate hydration when administering IV acyclovir monitor urine output and serum creatinine daily.
- For treatment of cutaneous/mucosal **herpes simplex** infection, **acyclovir*** **5-10mg/kg/dose IV q8h** for 7-14 days.
- For treatment of **varicella zoster**, **acyclovir 10-15 mg/kg/dose IV q8h** for 7-10 days. After response to initial IV therapy, may switch to **acyclovir 20 mg/kg/dose PO QID** [maximum 800 mg/dose] **OR** For children greater than 2 years of age; valacyclovir 20 mg/kg/dose 3 times per day (maximum 3000 mg/ day). Continue until no new lesions for 48 hours and no or moderate immune suppression.
- *Ideal body weight (IBW) should be used for obese patients requiring intravenous therapy. Go to IWK Drug Dosing Guidelines for IBW calculator https://www.dir.iwk.nshealth.ca

Cytomegalovirus

- For treatment of **cytomegalovirus**, **ganciclovir 5 mg/kg/dose IV q12h** for 14-21 days then 5 mg/kg/day IV once daily. Then maintenance dosing initiated and **CMV immune globulin 400 mg/kg/day IV** for 3 days/week given as per infectious diseases specialist.

Fungal

- If patient is persistently febrile for 5-days while receiving empiric antibiotics and/or clinically unwell consider fungal workup.
- Consult with pediatric hematologist/oncologist. Patients with suspected invasive fungal infection usually require transfer to the subspecialty center.

Recommendations on when to consider starting empiric antifungal therapy on patients with neutropenia and persistent fever (5-days or longer) and/or who are clinically deteriorating.

Patient parameters	Plan for pediatric hematologist/oncologist

High risk patients for IFD:
• **AML**
• **Prolonged neutropenia and:**
  • **HR/VHR ALL (includes T-cell and infant ALL)**
  • **Relapsed ALL**
• **High dose steroids**
• **HSCT (1st year post without evidence of T-cell reconstitution, or receiving steroids or multiple immune suppressive agents for GVHD)**
	Start caspofungin pre-emptively in post HSCT patients.
	Consider deferring empiric antifungal therapy and consulting ID and conducting full fungal workup with CT chest and abdomen +/- CNS) AND initiating caspofungin only if evaluation suggests or indicates IFD.
	IF patient is already on caspofungin for fungal prevention consult ID.

Low risk patients for IFD (All patients who are not high risk) with fever greater than or equal to 38.3 ◦ C for 96 hours.	**Consider withholding empiric antifungal therapy and consult ID + a full fungal workup (CT chest +/- abdomen +/- CNS)**

Pneumocystis jirovecii

- If documented or suspected PJP pneumonia (Pneumocystis jirovecii [formally known as carinii]), use **cotrimoxazole 5 mg//kg/dose of trimethoprim component IV q6h** for 21 days.

SECTION V. DURATION OF ANTIBIOTIC THERAPY

Patient Parameters	Plan
• newly diagnosed with cancer. • antibiotics initiated in response to fever at presentation. • had not yet received antineoplastic therapy at time of first fever. • not neutropenic at time of first fever. • cultures negative at 48 hrs.; • ANC ≥ 0.2 x 10^9/L and rising AND • clinically well +/- fever	CONSIDER discontinuing antibiotics.
• afebrile for a minimum of 24 hours • cultures negative at 48 hrs • antibiotic duration ≥ 48 hours • clinically well AND • evidence of hematological recovery*	DISCONTINUE antibiotics. (see criteria in Management on Discharge section)
• afebrile for a minimum of 24 hours • cultures negative at 48 hrs • antibiotic duration ≥ 7 -14 days • clinically well AND • no evidence of hematological recovery*	CONSIDER discontinuing antibiotics after 7 to 14 days in patients with persistent neutropenia who are clinically well with no focus of infection. Administration of empiric antibiotics for longer than 14 days may entail a risk of drug toxicity and super-infection with fungi or drug-resistant bacteria.
• afebrile for a minimum of 24 hours • cultures **positive** • IV antibiotic directed to organism cultured duration at least 10 days after first negative culture • clinically well AND • evidence of hematological recovery*	CONSIDER discontinuing specific therapy. CONSIDER discontinuing broad spectrum therapy after at least 10 days in patients with persistent neutropenia who have negative **repeat cultures**, are clinically well with no further evidence of infection.

*** Hematological recovery is defined as: minimum ANC of 0.2 x 10^9/L and rising**

NOTE: <u>Indicators of marrow recovery include:</u>

- increase in circulating monocytes [often precedes neutrophil recovery]
- increase in platelet count
- presence of young myeloid precursors [e.g., myelocytes, metamyelocytes]

SECTION VI. CONSIDERATIONS FOR DISCHARGE OF PATIENTS WHO WERE ADMITTED FOR MANAGEMENT

Discharge of patients with **localized sites of infection** who meet the criteria in Section V should be considered on a case-by-case basis.

Discharged families must be advised to continue close follow-up with their treatment team. Any recurrence of fever should be approached as a *de novo* fever in an immunocompromised host and requires immediate evaluation.

Afebrile for a minimum of 24 hours • Cultures negative at 48 hours • Antibiotic duration greater than or equal to 48 hours • Clinically well **AND** • Evidence of hematological recovery**	DISCONTINUE antibiotics. If patient is early on in therapy and/or antibiotics were started due to fever and instability at presentation, discuss possible discontinuation of antibiotics with tertiary centre.
Afebrile for a minimum of 24 hours • Cultures positive • Clinically well **AND** • Evidence of hematological recovery**	CONSIDER discontinuing broad spectrum coverage. CONTINUE specific therapy to complete necessary treatment period.
**** Hematological recovery is defined as: Minimum ANC of 0.2 x 10^9 /L and rising**	

NOTE: Discharged families must have access to a phone, rapid vehicle transport and adequate adult supervision of the patient.

SECTION VII: MANAGEMENT OF FEVER IN HEMATOLOGY/ONCOLOGY PATIENTS WHO HAVE COMPLETED THERAPY WITHIN THE LAST 3 MONTHS AND/OR ARE ON THERAPY BUT ARE NOT NEUTROPENIC

a) If the child is not neutropenic but is unwell: Obtain a blood culture from all lumens of the CVAD and start appropriate antibiotics for clinical illness (e.g., pneumonia).

b) If the child is not neutropenic and not unwell but has a central line: Obtain a blood culture from all lumens of the CVAD. Physician should assess the need to initiate antibiotic treatment based on clinical judgment. If an antibiotic is required, start Ceftriaxone until cultures available unless specific focus of infection is present. This treatment can be outpatient.

c) If the child is not neutropenic, and not unwell, does not have a central line, and has not received rituximab, the child should be treated like any other child with a fever.

AUDIT AND GUIDELINE UPDATE

APPHON will prospectively audit the change in practice based on this guideline to monitor for appropriateness of monotherapy in the Maritimes.
The guideline will be reviewed and updated within 3 years unless information becomes available that suggests best practice has changed.

REFERENCES

The evidence for this guideline was obtained from the C17 endorsed guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation 2023 update.

Lehrnbecher T, Robinson PD, Amman RA, et al. Guideline for the Management of Fever and Neutropenia in Pediatric Patients With Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update. *JCO* 2023;41((0:1774-1785.

Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the Management of Fever and Neutropenia in Children with Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. *Journal of Clinical Oncology*. 2017;35(18):2082-2094.

Lehrnbecher T, Phillip R, Alexander S, et al. Guideline for the Management of Fever and Neutropenia in Children with Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2012. *Journal of Clinical Oncology*. 2012;30(35):4427-4438.

Reference for dosing for once daily aminoglycoside in oncology children:
Dupuis L, Sung L, Taylor T, et al. Tobramycin pharmacokinetics in children with febrile neutropenia undergoing stem cell transplantation: once-daily versus thrice-daily administration. *Pharmacotherapy*. 2004; 24(5):564-73.