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.

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INTRODUCTION

The explanation for the supporting evidence for this guideline is on page 18 under references. This guideline was 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 adapted for use in the Maritime Provinces.

These guidelines apply to the management of patients:

1. With fever and neutropenia as a 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 actual neutrophil count, and

3. HSCT patients who continue to receive immunosuppressant agents after transplant, regardless of their actual neutrophil count 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 who do not have a cancer diagnosis but present with fever.

All hematology/oncology patients who are febrile should go to the closest emergency for a minimum of 3 months after completion of chemotherapy/ immunotherapy for CBC, physical exam and decision about antibiotics. Please discuss care of those who have undergone a bone marrow transplant or have an underlying immunodeficiency with the oncologist on call. These patients 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 rituxumab and has hypogammaglobulinemia, or if their central line is still in place.

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. 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 72 hours.

ANC (absolute neutrophil count) is defined as the sum of the counts of mature neutrophils and band forms.

1. **<u>Patients who meet the criteria for Monotherapy (pipercillin-tazobactam):</u>**

   - Include patients who are stable with no other underlying serious signs (shaking, chills, or hypotension).
   - Includes patients who are NOT at increased risk of resistant gram positive infections.
   - All **centres should assess and treat a febrile neutropenia patient within 1 hour of arrival** at the emergency department.
   - In general, these patients **may be treated in intermediate and advanced complexity care centres**.
   - Basic centres must call the pediatric hematologist/oncologist immediately to discuss transfer of the patient
   - Intermediate centres must call the pediatric hematologist/oncologist immediately to discuss the appropriate centre to admit the patient
   - Advanced centres must call the pediatric hematologist/oncologist within 24 hours of assessment of the patient.

2. **<u>Patients who meet the criteria for Dual therapy (pipercillin-tazobactam AND vancomycin):</u>**

   - Includes:
     - Hematopoietic stem cell transplant less than 100 days post-transplant and or with graft versus host disease.
     - Acute myeloid leukemia (AML)
     - Infant less than 12 months with acute lymphoblastic leukemia (ALL)
     - Downs Syndrome
     - Burkitt's Lymphoma Group C Induction
     - Mucositis

   - Basic and Intermediate centres should call the pediatric hematologist/oncologist and arrange transfer of patients to the appropriate centre after obtaining blood cultures and initiating antibiotic therapy within one hour of the patients arrival in the emergency department.
   - Advanced centres should notify the pediatric hematologist/oncologist immediately upon assessment of patient to discuss the appropriate centre for treatment.

3. **<u>Patients who meet the criteria for triple therapy (pipercillin-tazobactam AND tobramycin AND vancomycin):</u>**

   - Includes:
     - Sepsis Syndrome
     - Hypotension
     - Tachypnea
     - Hypoxia (O_2 sats<94% on room air)
     - New infiltrates on Chest x-ray
     - Altered mental status
     - Vomiting
     - Abdominal pain
     - Evidence of local infection

- Basic and Intermediate centres should call the pediatric hematologist/oncologist and arrange transfer of patients to the appropriate centre after obtaining blood cultures and initiating antibiotic therapy within one hour of the patients arrival in the emergency department.
- Advanced centres should notify the pediatric hematologist/oncologist immediately upon assessment of patient to discuss the appropriate centre for treatment.

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
- 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
- painful or frequent urination
- abdominal pain
- 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.

EVALUATION

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

2. Complete physical examination - including skin, mouth, respiratory tract, genitalia, perianal region and fundi. Do NOT take the temperature rectally, or perform a rectal examination beyond inspection of the perianal region. Examine for signs and symptoms of meningitis [may be very subtle].

INITIAL MANAGEMENT

1. Immediately access the central venous catheter **regardless of whether anesthetic cream has been applied to the port site**. If patient does not have a central venous catheter, establish a peripheral intravenous line.

2. Obtain CBC and differential. Obtain **aerobic** blood **c**ultures from all lumens of indwelling venous lines. If patient does not have a central venous catheter draw a peripheral culture. Obtain lactate level, CBC and blood cultures **within 30 minutes** of arrival.
   NOTE: aerobic blood cultures automatically include fungal cultures as all fungi are aerobic.

3. 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.

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

5. Administer ANTIBIOTICS STAT as below. Antibiotics should be given **within 1 hour** of arrival at the hospital. 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.

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

7. Vital signs q1h until stable and then q4h and more often as needed. Note that patients may deteriorate with antibiotics because of bacterial cell lysis.

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

9. Order a chest x-ray (if clinically warranted), laboratory tests (plasma urea, creatinine, sodium, potassium, and chloride), and the following cultures (in addition to CVAD and peripheral cultures as noted above):
   a) urine (if clinically warranted)
   b) any apparent site of infection
   c) other investigations (e.g. urinalysis, NP swab) judged to be warranted by the evaluating healthcare professional

10. If the child remains febrile, culture every 24 hours for three days then reassess. If the child becomes and remains afebrile, no further cultures are required if the initial cultures are negative.

11. 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.

12. Catheter-associated infection may present as fever 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 (usually vancomycin) should be initiated **IN ADDITION** to the broad spectrum empiric antibiotic regimen below. If CVAD cultures confirm infection, a full course of antibiotics, alternated through all lumens, is indicated. Removal of the catheter may be required. Consultation with Infectious Diseases is recommended to facilitate this decision.

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

14. Daily physical examination, CBC, creatinine and serum chemistries as indicated. Monitor closely for secondary infections requiring addition or modification of antimicrobial therapy.

15. Please contact the pediatric oncologist within 1 HOUR of presentation to discuss the management.

Table 1: Guidelines for initial empiric antibiotic selection in patients who present as <u>stable</u> and who are not already receiving empiric antibiotics. (see Appendix A for preprinted orders and management algorithm).

Patient Condition	Antibiotic & Doses	Comments
Patients who are stable on presentation with no significant penicillin allergy	**piperacillin-tazobactam** 240 mg piperacillin/kg/day IV divided q8h (max single dose: 4g)	• Adjust antibiotic doses for renal impairment. • If patient is clinically well and has been afebrile for 48 hours with negative cultures, clinically well and a rising ANC and has not had a recent episode of sepsis STOP all antibiotics. **AND** Discharge immediately
Patients who are stable on presentation with significant penicillin allergy OR receiving and clearing high dose methotrexate	**Ceftazidime** 150 mg/kg/day IV divided q8h (maximum 6 g/day)	• Adjust antibiotic doses for renal impairment. • If patient is clinically well and has been afebrile for 48 hours with negative cultures, clinically well and a rising ANC and has not had a recent episode of sepsis STOP all antibiotics **AND** Discharge immediately
For all of the above categories if culture is positive treat for at least 10 days with broad spectrum antibiotic		

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 [myelocytes, meta-myelocytes]

Table 2: Guidelines for initial empiric antibiotic selection in patients who present as <u>stable</u> but require DUAL antibiotic therapy and who are not already receiving empiric antibiotics. (see Appendix A for preprinted orders and management algorithm).

<u>List of patients who require DUAL antibiotic therapy:</u>

- **Hematopoietic stem cell transplant less than 100 days post-transplant and or with graft versus host disease.**
- **Acute myeloid leukemia (AML)**
- **Infant less than 12 months with acute lymphoblastic leukemia (ALL)**
- **Downs Syndrome**
- **Burkitt's Lymphoma Group C Induction**
- **Mucositis**

Patient Condition	Antibiotic & Doses	Comments
Patients who are stable on presentation with no significant penicillin allergy	**piperacillin-tazobactam** 240 mg piperacillin/kg/day IV divided q8h (max single dose: 4g) **AND** **Vancomycin:** Less than 12 years: 50 mg/kg/day IV divided q6h (maximum single dose 1 g). Children 12 years and older: 1 g IV q12 hours For vancomycin to convert from micrograms/mL to micromole multiply by 0.67.	• Adjust antibiotic doses for renal impairment. • If patient is clinically well and has been afebrile for 48 hours with negative cultures, clinically well and a rising ANC and has not had a recent episode of sepsis STOP all antibiotics. **AND** Discharge immediately
Patients who are stable on presentation with significant penicillin allergy OR receiving and clearing high dose methotrexate	**Ceftazidime** 150 mg/kg/day IV divided q8h (maximum 6 g/day) **AND** **Vancomycin:** Less than 12 years: 50 mg/kg/day IV divided q6h (maximum single dose 1 g). Children 12 years and older: 1 g IV q12 hours For vancomycin to convert from micrograms/mL to micromole multiply by 0.67.	• Adjust antibiotic doses for renal impairment. • If patient is clinically well and has been afebrile for 48 hours with negative cultures, clinically well and a rising ANC and has not had a recent episode of sepsis STOP all antibiotics **AND** Discharge immediately
For all of the above categories if culture is positive treat for at least 10 days with broad spectrum antibiotic		

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 [myelocytes, meta-myelocytes]

Table 3: Guidelines for initial empiric antibiotic selection in patients who present as <u>unstable</u> and who are not already receiving empiric antibiotics. (see Appendix A for preprinted orders and management algorithm).

Patient Condition	Antibiotic & Doses	Comments
Patients who are unstable on presentation with no significant penicillin allergy	**piperacillin-tazobactam** 240 mg piperacillin/kg/day IV divided q8h (max single dose: 4g) **AND** **tobramycin:*** 1 month to less than 6 yrs**:** 10 mg/kg/day IV q24h; 6 yrs and older: 8 mg/kg/day IV q24h **AND** **Vancomycin:** Less than 12 years: 50 mg/kg/day IV divided q6h (maximum single dose 1 g). Children 12 years and older: 1 g IV q12 hours *See dosing for aminoglycoside in Appendix A See below for unit conversion for levels for tobramycin and vancomycin.	• Adjust antibiotic doses for renal impairment. • If patient is clinically well and has been afebrile for 48 hours with negative cultures and has not had a recent episode of sepsis STOP the aminoglycoside. • Reassess at 72 hours from admission and if patient is clinically well, still afebrile, with negative cultures , and an ANC of 0.5 x 10^9/L and rising consider stopping all antibiotics in consultation with the pediatric oncologist.
Patients who are unstable on presentation with significant penicillin allergy OR receiving and clearing high dose methotrexate	**Ceftazidime** 150 mg/kg/day IV divided q8h (maximum 6 g/day) **AND** **tobramycin:*** 1 month to less than 6 yrs**:** 10 mg/kg/day IV q24h; 6 yrs and older: 8 mg/kg/day IV q24h **AND** **Vancomycin:** Less than 12 years: 50 mg/kg/day IV divided q6h (maximum single dose 1 g) Children 12 years and older: 1 g IV q12 hours *See dosing for aminoglycoside in Appendix A See below for unit conversion for levels for tobramycin and vancomycin	• Adjust antibiotic doses for renal impairment. • If patient is clinically well and has been afebrile for 48 hours with negative cultures and has not had a recent episode of sepsis STOP the aminoglycoside. • Reassess at 72 hours from admission and if patient is clinically well, still afebrile, with negative cultures, and an ANC of 0.5 x 10^9/L and consider stopping all antibiotics in consultation with the pediatric oncologist.
For all of the above categories if culture is positive treat for at least 10 days with broad spectrum antibiotic		

*In an effort to avoid or minimize aminoglycoside-induced hearing loss, patients with known, significant, pre-existing **hearing loss** (sensorineural hearing loss greater than or equal to 30dBHL at one or more frequencies between 250Hz-4000Hz) or **renal impairment** (i.e. GFR less than or equal to 60mL/min/1.73m^2, serum creatinine 1.5 times upper limit of normal for age, or tobramycin/gentamicin/amikacin elimination half-life greater than or equal to 4 hr) should receive meropenem 60-120 mg/kg/day IV q8h (maximum 6 g/day). Infectious Disease and Allergy Services should be consulted.

Note:
Calculate tobramycin dose based on actual body weight unless patient weighs greater than and equal to125% of ideal body weight in which case dose is based on effective body weight (see APPENDIX A for ideal and effective body weight formulas).

Note:
For vancomycin to convert from micrograms/mL to micromole multiply by 0.67.
For tobramycin to convert from micrograms/mL to micromole/L multiply by 2.1

Note:
Indicators of marrow recovery include:

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

CONTINUED MANAGEMENT OF INPATIENTS

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

1. Continue antibiotic regimen initiated as per previous section.

2. If the child is still febrile after 48 hours of empiric broad spectrum antibiotic therapy, call the pediatric hematologist/oncologist to determine next steps.

3. If patient is receiving IV antibiotics, alternate antibiotic therapy among all lumens either daily or with every dose of antibiotic in patients with **multi-lumen CVAD's** until antibiotics are discontinued.

4. If **initial blood cultures (peripheral or central) are positive**, then repeat cultures should be drawn when this result becomes known. Antibiotics specifically directed toward the identified organism should be **added to** the broad spectrum therapy if the initial antibiotics do not provide adequate coverage. Alternatively, the antibiotic regimen may be adjusted to provide BOTH broad spectrum AND organism-specific coverage. **Broad spectrum coverage must not be replaced by organism-specific antibiotic(s) alone in the neutropenic patient.**

5. "Step-down" to the empiric IV antibiotic regimen recommended for patients who were stable at presentation (see Tables 1 and 2) may be considered in patients who experienced a period of instability but become stable and continue to require broad spectrum antibiotics.

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

7. Peripheral cultures are of limited value at this point in therapy and should not be routinely drawn under most circumstances.

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

1. PATIENTS WHO ARE PERSISTENTLY FEBRILE but STABLE should continue to receive the initial empiric antibiotic regimen described above. If the patient's 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 the broad spectrum coverage. After 3 to 5 days of persistent fever or if a new fever develops after 3 to 5 days of empiric antibiotic therapy, consider the addition of vancomycin. If at day 5-7 the fever is still persistent despite the addition of vancomycin consider adding an antifungal agent. The patient should be discussed with a pediatric hematologist/oncologist.
2. PATIENTS WHO DETERIORATE (become hemodynamically unstable) or appear to be progressively deteriorating should be brought to the immediate attention of the pediatric hematologist/oncologist. Please also request an Infectious Disease consult. If the patient has received 3 to 5 days of empiric antibiotic therapy, also consider the addition of empiric antifungal coverage.

3. Patients with persistent fever and/or clinical deterioration should be transferred to the sub-specialty center.

MANAGEMENT BASED ON CULTURE RESULTS

1. Negative cultures and no clinical focus of infection:

- Maintain broad spectrum antibiotic coverage until afebrile for 24 hours, clinically well and ANC rising [recovering marrow].
- If fever recurs in patient with ANC less than 0.5 x 10^9/L, call pediatric hematologist/oncologist to consider changing antibiotic coverage and/or adding antifungal therapy.
- If child deteriorates at any time OR fever and neutropenia persists after 3-4 days of broad spectrum antibiotic therapy, call pediatric hematologist/oncologist.

2. Positive cultures: Following consultation with a pediatric hematologist/oncologist

Bacterial

- Continue broad spectrum antibiotic coverage and ensure specific pathogen coverage. Tailor antibiotic therapy to specific pathogen once afebrile for 24 hours and ANC greater than 0.5 x 10^9/L and rising.
- After consultation with pediatric hematologist/oncologist, treatment duration: uncomplicated infection 10 days; CVAD x 14 days; and osteomyelitis or perianal cellulitis for as long as 6 weeks.
- In some cases a step down to oral and/or a shorter OR longer course of antibiotics may be appropriate, discuss with Hematology/Oncology and Infectious Disease.
- If CVAD infection is suspected, then treat empirically with vancomycin and tailor treatment when microbial sensitivities known. (If blood cultures remain positive and/or no clinical improvement occurs in 3 days, or if patient deteriorates at any time, then call pediatric hematologist/oncologist for potential removal of the CVAD.)
- After consultation with pediatric hematologist/oncologist, for breakthrough gram-positive bacteremia, add vancomycin; for breakthrough gram-negative bacteremia add an aminoglycoside.
- If the symptoms include perianal tenderness, abdominal tenderness, possible typhilitis or severe mucositis, call the pediatric hematologist/oncologist to potentially initiate metronidazole
  30 mg/kg/day IV divided q8h (maximum 1 gm/dose) and or consideration of amphotericin B.

Fungal

- The routine use of fluconazole or other antifungal drugs for prophylaxis against fungal infections is recommended in some Children's Oncology Group (COG) protocols and include AML and infant ALL patients and patients with GVHD (this will be determined by Pediatric Hematology/Oncology).
- Amphotericin B liposome (Ambisome®) 3 mg/kg/dose IV once daily is the drug of choice for empiric antifungal treatment. An alternative would be amphotericin B lipid complex (Abelcet®).
- If amphotericin B is started empirically, it is continued for a minimum of 7 days and until the ANC is greater than 0.5×10^9/L.
- Consult with pediatric hematologist/oncologist. Patients with suspected fungal infection likely require transfer to the subspecialty center.

Viral

- 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.
- Hydration must be greater than1500 mL/m^2/day, monitor urine output and serum creatinine daily.
- For treatment of cutaneous/mucosal **herpes simplex** infection, **acyclovir* 15-30 mg/kg/day IV divided q8h** for 7-14 days.
- For prophylaxis for herpes simplex infection, **acyclovir 50 mg/kg/day PO divided BID-QID** [maximum 800 mg/day] or for frequent recurrences 80 mg/kg/day divided three times a day [maximum 800 mg/day]
- For long term maintenance of viral suppression, **acyclovir 20 mg/kg/day PO divided BID** [maximum 800 mg/day].
- For treatment of **varicella zoster**, **acyclovir 30-45 mg/kg/day IV divided q8h** for 7-10 days. After response to initial IV therapy, may switch to **acyclovir 80 mg/kg/day PO divided QID** until no new lesions for 48 hours and no or moderate immune suppression [maximum 800 mg/dose].
- For treatment of **cytomegalovirus**, **ganciclovir 10 mg/kg/day IV divided 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.

*For obese patients use IBW to calculate dosing for intravenous acyclovir.

Pneumocystis

- If documented or suspected PCP pneumonia (Pneumocystis jiroveci [formally known as carinii]), use **cotrimoxazole 15-20 mg/kg/day of trimethoprim component IV divided q6-8h** for 14 days.

MANAGEMENT OF FEVER IN HEMATOLOGY/ONCOLOGY PATIENTS WHO HAVE COMPLETED THERAPY AND/OR ARE ON THERAPY BUT ARE NOT NEUTROPENIC

a) If the child is neutropenic or is known to be hypogammaglobulinemic secondary to rituximab: Obtain a culture and use febrile neutropenia protocol and treat with pipercillin-tazobactam.
b) If the child is not neutropenic but is unwell: Obtain a culture and start Pipercillin-tazobactam OR appropriate antibiotics for clinical illness (e.g. pneumonia).
c) If the child is not neutropenic and not unwell but has a central line: Obtain culture. Physician should assess the need to initiate antibiotic treatment based on clinical judgment. If an antibiotic is required, start Ceftriaxone until cultures available unless very specific focus of infection is present. This treatment can be outpatient.
d) If the child is not neutropenic, and not unwell, does not have a central line, and has not received rituxumab: the child should be treated like any other child with a fever.

EXTERNAL REVIEW

An external review of this adapted guideline was conducted throughout Atlantic Canada by APPHON/ROHPPA. Fifty-six health care professionals responded to the external review, including 4 hematologists/oncologists, 20 registered nurses, 10 pediatricians, 2 child life specialists, 1 emergency room physician, 3 pharmacists and 16 unknown health care professionals. The guidelines were adapted by Tamara MacDonald, PharmD, in collaboration with hematologists/oncologists, pediatric infectious diseases and pediatricians. Below are the reviewers' comments as well as the response by the development team.

Comment	Response
The linkage between the empirical data and current best practice is not clear until almost the end of the document.	The statement that this guideline utilizes the systematic review completed by the C17 endorsed guideline for the "management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation 2012" has been moved to the introduction section.
Why is the maintenance fluid in the protocol D5W+0.45%NaCL rather than D5W+0.9%NaCl as recent literature suggests that avoidance of hypotonic solutions is very important in out hospitalized patients, especially the sickest who could be at risk for SIADH from illness, meds, etc.	Agree have updated the maintenance fluid on the preprinted orders to D5W+0.9%NaCl.
Under Low Risk patients, I would change the word "co-morbitities" to "serious signs"	Done
The guideline focuses on managing FN, there is nothing described about how to prevent FN or recognize it early. Yet the title of the guideline is "Guidelines for Febrile Neutropenia".	Have revised the title to "Guidelines for the management of Febrile Neutropenia".

Risk stratification only speaks to admission of a low risk patient. Could these patients not be managed in the community as per C17 endorsed guidelines? If not, it may be useful to identify why in the guideline.	This guideline does support children with low risk febrile neutropenia being admitted and treated at an intermediate centre with intravenous antibiotics in consultation with the pediatric oncologist. At the present time it is felt that the evidence is not robust for the management of low risk febrile neutropenia patients in the outpatient setting. The evidence is limited for the use of oral antibiotics to treat low risk febrile neutropenia but APPHON/ROHPPA may look at the supports needed to treat with intravenous antibiotics in the outpatient setting once more evidence for this practice becomes available.
Where did you get the definition of febrile neutropenia	There is more than one definition. However, we used a standard although not universally accepted definition of fever that errs on the side of caution. Similarly, the absolute neutrophil count used reflects a generally accepted value. It is clear that the risk of serious infection rises as the ANC decreases and the duration of neutropenia increases. The exact cut-off is somewhat arbitrary, but, as noted, this (0.5×10^9/L) is a generally accepted value.
Are the definitions for high risk and low risk from the guideline endorsed by C17?	The C17 document does not recommend one risk stratification and none of the risk stratifications are comprehensive so the developers of the guideline produced a list based on anecdotal information and evidence in the literature.
Are the list of signs and symptoms of febrile neutropenia in the guideline endorsed by the C17 guideline?	The C17 guideline does not address signs and symptoms.

It might be clearer to say establish IV access. If the child has a CVC access it first.	Most children being treated for cancer have a CVC and best practice suggest accessing the port if present even if antibiotics are not necessary. Historically delays have occurred in accessing ports so it was felt that the statement to access the port should be first.
Is there a reference for the new dosing of the aminoglycoside for children less than 6 years.	Added in the reference section.
Should there be a calculation for GFR included?	GFR is a diagnostic test report. If not available, 1.5 X upper limit of normal for creatinine is a reasonable surrogate.
We use the IBW weight formula that Sickkids uses. Is there a reason why you use the two IBW calculations in the current guideline?	The IBW calculation are the ones the IWK currently uses and was felt best to be consistent. This is a guidance document so if you want to use a different accepted IBW calculation for children that would be acceptable.
Levels for aminoglycosides and vancomycin are not done at our site so delays in reporting occur often by days.	It is important that the tobramycin/gentamicin peak level be determined with the first dose and reported in less than 24 hours before the next dose is due, since under-treating can lead to poor outcomes. Would advocate for sampling to be conducted on site. Same argument for vancomycin.
Some labs report aminoglycoside levels in micromoles/L and not micrograms/mL.	Target ranges for both units are now in the guideline.
Can maintenance fluid be orderedper kg as do not always know the height of the child.	Fluid orders per kg vary for different weights so for simplicity per m^2 rates have been recommended. The preprinted orders have been changed to 1.5 x maintenance.
For patients with significant penicillin allergy, I would suggest using ceftazidime (also a Beta-Lactam) with some caution.	The guideline does recommend ceftazidime for penicillin allergic children. Meropenem would be used in patients who are not able to receive an aminoglycoside due to significant renal and/or ototoxicity.
Can you put a bolus hydration order on the preprinted orders	It is felt that a fluid bolus should be a clinical decision and the risk of a bolus being given unnecessarily more likely to occur if an option on the order set.
How do we manage children who have a fever but are not neutropenic on therapy?	The management is addressed in section VIII of the guideline.

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 2012 and adapted for use in the Maritime Provinces. The complete guideline, a short version (published in the *Journal of Clinical Oncology)* and associated supporting materials are available at:
http://www.sickkids.ca/HaematologyOncology/IPFNG/index.html

The rationale for not adopting the use of monotherapy for all patients as recommended by the above C17 guideline in the current APPHON/ROHPPA guideline is that it is felt the risk of resistant gram positive infections in a small subset of patients is high enough to warrant the upfront addition of vancomycin in those patients.

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.

Appendix A

Ideal and Effective Body Weight Formulas for Dosing Aminoglycosides

Ideal body weight (IBW): (children 1-18 years)

Less than 5 feet:
IBW = [(height cm)^2 X 1.65]/1000

5 feet and taller:
Males: IBW = 39 + (2.27 X height in inches over 5 feet)
Females: IBW = 42.2 + (2.27 X height in inches over 5 feet)

Effective body weight = IBW + 0.4 (actual body weight – IBW)