Provincial Clinical Knowledge Topic
Fever and Neutropenia, Pediatric – Acute Care
V 1.0

Document History

Version No.	Date	Description of Revision	Completed By / Revised By
1.0	March 16, 2017	Document completed	Lucie Lafay-Cousin
1.1	September 6, 2017	Addition of vancomycin in option 1 for patients Unwell/Hemodynamically Unstable on Arrival	Tony Truong/ Sunil Desai

Important Information Before You Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign, etc.

Introduction

Fever and neutropenia are common complications in children who receive chemotherapy for cancer or other conditions. This knowledge topic focuses on children and adolescents with cancer undergoing chemotherapy treatments who develop fever and neutropenia**.**

Definitions

Definition of Fever for this population: Single temperature greater than or equal to 38.3^{o}C OR temperature of greater than or equal to 38^{o}C lasting one hour or longer.

Definition of Neutropenia for this population: Absolute neutrophil count (ANC) less than 0.5 x 10^{9}/L.

Clinical Documentation

Initial Assessment

1. History of Present Illness
    - Temperature
    - Symptoms
2. Past History
    - Underlying diagnosis
    - Date of last chemotherapy
    - Most recent ANC count
3. Medications & Allergies
    - Time of last acetaminophen or any other medication that might alter temperature
4. Physical Examination
    - Careful physical examination to determine site of infection required including skin, oral mucosa, Central Venous Catheter (CVC) site, perianal area, respiratory system and abdomen

Decision Making

Initial Care

1. Fever and neutropenia is a medical emergency.
2. Patients presenting with a possible episode of fever and neutropenia must be triaged appropriately, placed in a separate waiting room/area where possible to minimize the risk of infection, and be assessed urgently.
3. Blood must be drawn for a CBC with differential, blood cultures and other septic work-up.
4. Antibiotics are recommended to be initiated within 1 hour of presentation
   See Fever and Neutropenia Admission Order Set

**For recommended management of Pediatric Oncology Patient Febrile but Non-Neutropenic see Appendix A.

Ongoing Care

Duration of admission, condition of discharge and monitoring varies depending on risk group.

A. Low Risk Fever and Neutropenia

Following a short admission of 12 to 24 hours on intravenous antibiotics, eligible patients in **tertiary centers** may be discharged on oral antibiotic.

1. Once admitted to a **tertiary center** (as appropriate follow-up in rural sites may not be available), patient to be assessed by a pediatric oncologist. Patient must meet **both** clinical (Table 1) and social low risk criteria (Table 2).

Table 1. Low Risk Clinical Criteria

Outpatient at presentation and **EXCLUDING** all of the following criteria:

- History of sepsis within the previous 6 months
- Age less than 12 months
- Down Syndrome
- HSCT (hematopoietic stem cell transplantation) patient within 6 months of transplant and/or receiving immunosuppressant's
- Relapsed leukemia or progressive/relapsed malignancy with suspected or proven bone marrow involvement
- Stage 4 neuroblastoma
- Diagnosis of:
  - AML (acute myeloid leukemia)
  - BURKITT lymphoma/leukemia or Intensive B lymphoma protocol (except in maintenance)
  - T-cell lymphoma
  - ALL (acute lymphoblastic leukemia) not in maintenance or IM (interim-maintenance)
- Presence of any one or more of the following:
  - Sepsis syndrome
  - Hypotension

- Tachypnea
- Hypoxia (O2 saturation [IF checked] less than 94% on room air)
- New infiltrates on chest X-ray (IF X-ray is done)
- Altered mental status
- Mucositis greater than equal to grade 3
- Vomiting greater than equal to grade 3
- Abdominal pain greater than or equal to grade 3
- Clinical typhilitis
- Evidence of significant local infection (e.g. tunnel infection, peri-rectal abcess, cellulitis)

Table 2. Low Risk Social Criteria

Issue	Requirements (must meet all)
Access to hospital	1. Live within 30 to 60 minutes reliable travel time of Alberta Children's Hospital or the Stollery Children's Hospital 2. Have access to a car 24 hours a day in the event of change in clinical condition of child
Communication	1. Family has a working telephone in the home
Thermometer	1. Family has a working thermometer in the home
Caregiver	1. Available at home 24 hours a day 2. English-speaking /able to communicate with treating team 3. Available for daily contact (will phone hospital or receive daily phone calls) 4. Able to take temperatures as needed and document readings on log 5. Able to administer oral medications as scheduled 6. Agrees to follow-up clinic visit
Child	1. Able to tolerate oral medications 2. Remains home from school/daycare
Adherence	1. History of compliance with/adherence to other outpatient treatment

See Disposition Planning for Low Risk Fever and Neutropenia

B. Non-Low Risk Fever and Neutropenia

1. On admission continue initial intravenous antibiotic(s)
    - If an aminoglycoside is ordered reassess prior to second dose and consider therapeutic drug monitoring if continuing.

2. Ongoing Management
    a. Absence of documented infection:
        - Continue broad spectrum antibiotics
        - Continue blood culture daily as long as febrile and neutropenic
        - See Section 3 below for duration of antibiotic(s)

    b. Identified source of infection (positive blood culture, urine culture, ect):
        - Continue with broad spectrum antibiotic and add on antibiotic according to sensitivity of microorganism
        - Do not narrow down broad spectrum antibiotic
        - In case of positive blood culture perform daily blood culture until 2 consecutive negative blood culture even if afebrile and consider removing central line if persistent positive blood culture despite appropriate antibiotic coverage
        - Broaden antibiotics according to site of infection:
            i. vancomycin for skin site (tunnel central venous catheter [CVC] site infection)
            ii. Macrolide or Fluoroquinolone for suspected atypical pneumonia on imaging
        - Consider echocardiogram in consultation with infectious disease

    c. Patient becoming unstable:
        - Switch antibiotics to meropenem +/- Aminoglycoside(AG)/ Fluoroquinolone (FQ) +/- vancomycin

    d. Persistent fever after 4 to 7 days on broad spectrum antibiotic(s):
        - Consider work up to rule out fungal infection:
            i. First consider chest x-ray and abdominal ultrasound
            ii. Next consider (CT sinus, chest, abdomen, pelvis) +/- head if clinically indicated (MRI or CT)
        - If evidence of fungal infection, initiate treatment. Antifungal therapy is based on the clinical site of infection. Initiation of empirical antifungal should be discussed with the Infectious Disease team if no clinical site is apparent. If a clinical site is apparent attempt should be made to obtain samples (BAL [bronchoalveolar lavage] with Galactomannan, lesion biopsy etc.) for microbiology and pathology prior to or close after initiation of antifungal therapy.

3. Duration of antibiotic(s)
    a. If documented infection, continue antibiotics as per Infectious Disease recommendation according to microorganism, severity of infection and/or site of infection.

    b. If initial fever of uncertain origin, based on the expected duration of neutropenia:
        - If prolonged neutropenia is expected, complete a 10 to 14 day course of antibiotic therapy
        - If short duration of neutropenia expected, discontinue antibiotics when **all** criteria below are met:
            1. Negative blood and other cultures
            2. Afebrile for 24 hours or greater
            3. Recovering or rising ANC

    c. If antifungal therapy initiated empirically, continue both antibiotic and antifungal until count recovery

    See Disposition Planning for Non-Low Risk Fever and Neutropenia

Order Set - Fever and Neutropenia Admission Orders

Order Set Restrictions: For use in pediatric and infant patients greater than 1 month of age. For patients under 1 month of age, please consult pharmacy for dosing considerations.
Order Set Keywords: Fever, Febrile, Neutropenic, Neutropenia
Order Set Requirements: Weight

Required Orders for Care of Patient with Fever and Neutropenia

Laboratory Investigations

☑ Complete Blood Count with differential STAT
☐ Complete Blood Count with differential daily
☑ Blood Culture from central line all lumens (follow local institutional guidelines for collection in pediatric patients) STAT
☐ Blood Culture from peripheral (follow local institutional guidelines for collection in pediatric patients)

Conditional blood cultures:

☑ Blood culture from central line all lumens (follow local institutional guidelines for collection in pediatric patients). Collect daily if persistent fever for greater than 24 hours from the last blood culture.
☑ Blood culture from central line all lumens (follow local institutional guidelines for collection in pediatric patients). If a previous blood culture from central is positive repeat daily until negative.

Medications

☑ Hold chemotherapy pending physician review.

Antibiotics
****Goal first dose(s) within 60 minutes of arrival****

Stable on Arrival:

☐ piperacillin-tazobactam (240 to 300 mg/kg/day divided every 6 to 8 hours) _____ mg IV every _____ hours STAT(*maximum 4 grams piperacillin component/dose)*

+/- aminoglycoside *(Consider adding if locally indicated. Choose one.)*

☐ tobramycin (7 mg/kg) _____ mg IV x 1 dose STAT, reassess every 24 hours
OR
☐ gentamicin (7 mg/kg) _____ mg IV x 1 dose STAT, reassess every 24 hours

Unwell/Hemodynamically Unstable on Arrival *(choose one option):*

Option 1:

☐ piperacillin-tazobactam (240 to 300 mg/kg/day divided every 6 to 8 hours) _____mg IV every_____ hours STAT (*maximum 4 grams piperacillin component/dose)*
AND aminoglycoside *(Choose one)*
☐ tobramycin (7 mg/kg) _____mg IV x 1 dose STAT, reassess every 24 hours
OR
☐ gentamicin (7 mg/kg) _____mg IV x 1 dose STAT, reassess every 24 hours

AND vancomycin

☐ vancomycin (15 mg/kg/dose) _____ mg IV every 6 hours STAT (*maximum 1 gram/dose)*

Option 2:

☐ meropenem (60 mg/kg/day divided every 6 to 8 hours) _____ mg IV every _____ hours STAT (*maximum 2 grams/dose*)

AND

☐ vancomycin (15 mg/kg/dose) _____ mg IV every 6 hours STAT (*maximum 1 gram/dose)*

Allergy to penicillin *(choose one option):*

Option 1: *(not recommended if suspected gut pathology)*

☐ cefTAZidime (50 mg/kg/dose) _____ mg IV every 8 hours STAT (*maximum 2 grams/dose)*

AND

☐ vancomycin (15 mg/kg/dose) _____ mg IV every 6 hours STAT (*maximum 1 gram/dose)*

Option 2:

☐ meropenem (60 mg/kg/day divided every 6 to 8 hours) _____ mg IV every _____hours STAT (*maximum 2 grams/dose*)

Option 3:

☐ cefePIME (50 mg/kg/dose) _____ mg IV every 8 hours STAT (*maximum 2 grams/dose*)

Upfront empiric addition of vancomycin (if not ordered above) should be considered in:

- *clinically obvious central venous catheter-related infections (tunnel infection)*
- *skin or soft tissue infections*
- *known colonization with MRSA*
- *previous history of penicillin resistant pneumococcus*
- *patients with Acute Myleloid Leukemia*

☐ vancomycin (15 mg/kg/dose) _____ mg every 6 hours STAT *(maximum 1 gram/dose)*

Please check additional orders below as appropriate:

General Care

Goals of Care Designation

☐ Utilize appropriate Goal of Care

Precautions and Safety

☐ Isolation, if possible

Patient Care Orders

☐ Vital Signs: to include respiratory rate, pulse or heart rate, blood pressure, temperature (** no rectal temperatures) and oxygen saturation
- ☐ As per local standards
- ☐ every __ hour(s)
- ☐ every __ minutes
- ☑ Notify physician of abnormal vital signs or oxygen saturation

Ins and Outs

☐ Accurate intake/output every _____ hour(s). Call Physician if urine output less than 1 mL/kg/hr.

Other

☐ Neurological vital signs every_____hour(s).

Respiratory Care

☐ O_2 Therapy – Titrate to saturation greater than or equal to 92%

Intravenous Orders

IV maintenance

☐ potassium chloride 20 mmol/L in dextrose 5% - sodium chloride 0.9% at _____mL/hour (1.5 x maintenance)

IV bolus or rapid infusion including the following (*consider based on clinical stability*):

☐ sodium chloride 0.9% infusion _____ mL (10 to 20 mL/Kg) as fast as possible

☐ dextrose 5% - sodium chloride 0.9% infusion _____ mL (10 to 20 mL/Kg) as fast as possible

Referral

☐ Refer to Infectious Diseases

Additional Laboratory Investigations (based on presentation of patient)

Hematology

☐ PT INR

☐ PTT

☐ D-Dimer

☐ Fibrinogen

Chemistry

☐ Electrolytes (Na, K, Cl, CO2)

☐ Urea

☐ Creatinine

☐ Calcium

☐ Lactate

☐ Phosphate

☐ Glucose Random

☐ Magnesium

☐ Albumin

☐ Alkaline Phosphatase (ALP)
☐ ALT
☐ Bilirubin Direct
☐ Bilirubin Total
☐ GGT
☐ LD
☐ Protein Total

Microbiology
Where possible, microbiology tests should be obtained prior to commencing antibiotics but should not delay treatment. Send specimen from any sites of possible infection (stool, throat, respiratory, soft tissue, blood, CNS)
☐ Urine Bacterial Culture
☐ Urinalysis Random
☐ HSV and VZV Nucleic Testing (NAT) (*send if vesicles present by unroofing the vesicles and using a viral swab at the base. Send in universal transport media*)
☐ C. Difficile Test
☐ Stool Bacterial Culture
☐ Stool Viral Panel
☐ Ova and Parasite Examination
☐ Throat swab culture (Group A Beta Strep)
☐ Respiratory Infection Panel (Viral) (*send by NP swab or BAL in universal transport media)*
☐ Cerebrospinal Fluid Culture and Gram Stain *(CSF examination is not done unless there is clinical indication [meningitis is not common in these patients despite low neutrophil counts]. If CSF examination is required, platelet count should be greater than 20 x 10^9/L.)*

Transfusion Medicine
☐ Type and Screen

Blood Gases
☐ Blood Gas Capillary Request – test on current therapy

Blood Culture conditional:
☐ Blood culture from peripheral (*follow local institutional guidelines for collection in pediatric patients)*; if a previous blood culture from central is positive repeat daily until negative.

Diagnostic Imaging
Imaging is not always necessary on admission in patients with febrile neutropenia.
Consider chest x-ray and abdominal ultrasound prior to ordering a CT.
☐ Chest X-ray- 2 or more projections
☐ US Abdomen
☐ CT Chest
☐ CT Abdomen

Disposition Planning

Low Risk Fever and Neutropenia Patients

1. Following a short admission of 12 to 24 hours on intravenous antibiotics, eligible patients on low risk protocol can be discharged on oral antibiotics as follows:
   Option 1:
   For children less than 5 years of age:
   - levofloxacin (10 mg/kg/dose) _____ mg PO twice a day

   For children greater than or equal to 5 years of age:
   - levofloxacin (10 mg/kg/dose) _____ mg PO once a day (max 750 mg/day)

   Option 2:
   - ciprofloxacin (15 mg/kg/dose) _____mg PO BID (max 500mg/kg/dose)

   AND
   - amoxicillin-clavulanate (4:1) (40 mg amoxicillin/kg/DAY) _____ mg PO TID (max 500 mg/dose)

2. Low Risk Outpatient Follow-Up
   - Primary nurse to set up patient appointments and prepare the follow up chart for patient on low risk fever/neutropenia management.
   - Oncology clinic visit: 3 times/week.
   - One oncology clinic visit may be substituted by:
     - Hospital @Home (Calgary only)
     - Home care (Edmonton only)
   - Phone call by Primary RN on the rest of days – 2 times/week
   - CBC: 3 times/week – in clinic, Hospital@Home visit (Calgary only) or home care days (Edmonton only). Also add blood culture if patient febrile in previous 24 hours.

3. Reassessment and Readmission Criteria
   - Intolerance of oral antibiotic
   - Non-adherence to antibiotic administration schedule or monitoring requirements
   - Positive blood culture
   - Clinical deterioration
   - Remain febrile after more than 5 days of oral antibiotic administration, regardless of clinical status.

4. Antibiotic Duration
   - Stop antibiotic(s) if **all** of the following criteria met:
     - Afebrile for 24 hours
     - Clinically well
     - Culture negative at 48 hours
     - Hematological recovery (at least ANC greater than or equal to 0.1×10^9)

- Stop antibiotic after 7 days if all of the following criteria are met:
    - Afebrile for 24 hours
    - Clinically well
    - Culture negative at 48 hours
    - No hematological recovery

Non Low-Risk Fever and Neutropenia Patient Discharge Criteria

1. If documented infection, discharge after completing recommended course of antibiotics as per Infectious Disease recommendation according to microorganism, severity of infection and/or site of infection.

2. If initial fever of uncertain origin, duration of admission dependent on the expected duration of neutropenia:
    a. For expected shorter duration of neutropenia, discontinue antibiotics and discharge when all criteria below are met:
        - Negative blood and other cultures
        - Afebrile for 24 hours or greater
        - Recovering or rising ANC

    b. For expected prolonged duration of neutropenia (e.g. Bone marrow transplant patients and patients with acute myeloid leukemia), discharge once 10-14 day course of antibiotics complete and the following criteria met:
        - Count recovery
        - Afebrile
        - Negative blood culture
        - Clinically well

Rural Considerations

Rural sites should consult with the pediatric oncologist on call at either the Stollery Children's Hospital or the Alberta Children's Hospital. In discussion with the pediatric oncologist a decision will be made to either:

1. Admit and treat patient at rural site
    a. Rural site to contact pediatric oncologist if patient remains persistently febrile after 24 hours.
    b. Patient should be transferred to tertiary centre if remains febrile after 48 hours.
2. Discharge with appropriate follow-up instructions
3. Transfer to tertiary centre

Analytics

Baseline Analytic – Outcome Measure

Name of Measure	Order set Usage for topic: Fever and Neutropenia, Pediatrics – Acute Care
Definition	For all patients admitted with Fever and Neutropenia, number of times orderset is being used. Overall, by region, by sites, and by units
Rationale	Intended to measure if the order set cited in the knowledge topic is being used and what % of time. May indicate areas with adoption issues or gaps in topic
Notes for Interpretation	Site capacity, rural considerations, roll out of provincial CIS

Clinical Analytic – Outcome Measure

Name of Measure	Distribution of patients treated with Low Risk Fever and Neutropenia strategy
Definition	This measure is intended to show the distribution of low risk vs non-low risk fever and neutropenia.
Notes for Interpretation	To be eligible to meet the low risk criteria patients must be cared for in a tertiary centre therefore rural sites will show a higher percentage of non-low risk patients.

References

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

2. Robinson, P, Lehrnbecher, T, Phillips, R et al. Strategies for Empiric Management of Pediatric Fever and Neutropenia in Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: A Systematic Review of Randomized Trials. *Journal of Clinical Oncology.* 2016; 34(17): 2054-2060.

3. Rogers, A., Eisenman, K., Dolan, S. et al. Risk factors for bacteremia and central line–associated blood stream infections in children with acutemyelogenous leukemia: A single-institution report. *Pediatric Blood Cancer.* 2016; 00: 1-7.

Appendix A

Management of Non-Neutropenic Fever

Management of these patients is dependent on a number of factors and should be decided on an individual basis.

Options to consider:

1. Discharge home when no focus of infection and patient appears well. Suggest to repeat counts and reassess every 24 hours, especially in patients who have recently received chemotherapy and counts are expected to fall.
2. Treat focus of infection in home or hospital as appropriate in patients that appear well. Consider administration of cefTRIAXone 50 to 75 mg/kg (max 2 grams) every 24 hours until 48 hour blood culture reported negative if no focus apparent.
3. Admit unwell patients with no obvious source of infection and treat with cefTRIAXone 50 to 75 mg/kg every 24 hours.

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