4.1 Management of Fever and Neutropenia

This guidance document is adapted from the Guideline for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation[1] and developed through consensus of the POGO Fever and Neutropenia (F&N) Working Group. It applies to the management of patients greater than 60 days of age seen in the setting of POGO Satellite Clinic oncology care and with:

- Fever and neutropenia as a result of a known or suspected malignancy or the use of antineoplastic agents.
- Allogeneic haematopoietic progenitor cell transplant (HPCT) patients who present with fever or evidence of infection within 6 months of their transplant, regardless of their absolute neutrophil count (ANC), OR patients who continue to receive immunosuppressant agents after HPCT, regardless of their ANC or the length of time post-HPCT.

This guidance document may also apply to patients who are receiving antineoplastics or who have completed cancer therapy within the last 6 months **even if they are not neutropenic** and depending on the severity of the presenting signs and symptoms, the results of initial investigations and the presence/absence of a central venous catheter (CVC).

Definitions

Fever is defined as a single oral temperature ≥ 38.3°C or oral temperature ≥ 38°C for 1 hour or more. Oral temperatures are preferred. However, when axillary temperatures are the only option, fever is defined as a single axillary temperature of ≥ 37.8°C or axillary temperature ≥ 37.5°C for 1 hour or more.[2]

ANC is defined as the sum of the counts of mature neutrophils and band forms.

Neutropenia is defined as an ANC < 0.5 x 10^9/L or expected to fall below 0.5 x 10^9/L within the next 48 hours.

Initial Management

Investigations

1. Physical examination of the patient by a physician or nurse practitioner is required.
2. Obtain CBC and differential, blood cultures from all lumens of indwelling venous lines **AND** a peripheral site. In the event of difficulty obtaining cultures, proceed with antibiotic administration. Hospitals use different blood culture collection systems. Programs are encouraged to discuss with their microbiology labs the optimal volumes of blood for highest yield. Wherever possible, the maximum volume of blood should be used.
3. Order laboratory tests as clinically indicated. Electrolytes and renal function should be ordered at presentation if admission with IV fluid treatment is likely. Urine culture/urinalysis should be done where a clean catch, midstream specimen is readily available. Other studies including CXR, NP swab and other cultures should be sent **if clinically warranted**.

Monitoring

1. Vital signs q1h until stable and then q4h and/or as indicated.

Treatment

1. Stop all antineoplastic agents until discussed with the staff oncologist.
2. Cotrimoxazole prophylaxis should be continued unless advised otherwise by the specialized childhood cancer program.
3. Give IV fluids at about 1.5 times the maintenance rate. Electrolytes and renal function should be drawn at presentation and monitored daily for children receiving IV fluids. Consider monitoring extended electrolytes (Ca, Mg, Phos, albumin) for patients who have received cisplatin or high-dose ifosfamide.
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 or known to be colonized with a resistant organism. When available, POGO Satellite Clinics should refer to "Fever Cards" provided by specialized childhood cancer programs to patients with personalized recommended management in the event of fever (see sub-section 4.1.2 Sample Fever Cards).
5. Catheter-associated infection may present as fever related to recent access to the CVC, 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 recommended in Table 1 below. Tunnel infections are surgical emergencies and removal of the catheter is required. Consultation with the specialized childhood cancer program and early transfer is required in this instance.
6. Administer ANTIBIOTICS STAT as per Table 1 for stable patients and as per Table 2 for unstable patients. Ideally, the time between patient presentation and antibiotic administration should be less than 1 hour.[3] Antibiotics should be given prior to patient transfer to any other area and prior to administration of blood products.
7. Acetaminophen is the preferred antipyretic agent. Ibuprofen and other non-steroidal anti-inflammatory agents are not recommended for oncology patients.
8. Please contact the specialized childhood cancer program to discuss the patient immediately if unwell or within 24 hours of presentation if clinically stable.
9. Antibiograms will be requested from all provincial sites to be reviewed biannually. Data on positive cultures and resistance patterns will be collected prospectively for pediatric oncology patients specifically.

Table 1: Recommendations for initial empiric antibiotic selection in patients older than 60 days who are stable at presentation

Current recommendations differ from the 2005 POGO Blueprint and are based on most recent evidence. The most significant change is the move to monotherapy for the majority of stable patients with F/N and no beta-lactam allergy. There are two exceptions to this practice:

1. Patients from Children's Hospital, London Health Sciences Centre will receive an aminoglycoside in addition to piperacillin-tazobactam due to local resistance patterns.
2. Some patients have significant prior bacterial infections requiring additional consideration. Clinicians are referred to patient Fever Cards provided by the specialized childhood cancer program.

	Antibiotics and Doses	Comments
Stable, NO beta-lactam allergy	For age 2–<6 months: **piperacillin-tazobactam**** 80 mg piperacillin/kg/dose IV q6h For age ≥6 months: **piperacillin-tazobactam**** 100 mg piperacillin/kg/dose IV q6h (maximum single dose: 4 g)	Patients from Children's Hospital, London Health Sciences Centre also receive tobramycin. Tobramycin may be discontinued after 48h if cultures are negative. Adjust doses of piperacillin-tazobactam for renal impairment.
Stable, WITH beta-lactam allergy	**Ciprofloxacin** 10 mg/kg/dose IV q12h (maximum single dose: 400 mg) AND **tobramycin***** 2.5 mg/kg IV q8h OR **gentamicin** 2.5 mg/kg IV q8h AND **clindamycin** 10 mg/kg/dose IV q8h (maximum 600 mg/dose)	Consider discontinuation of clindamycin once culture and sensitivity results are available. Adjust doses of ciprofloxacin for renal impairment.

** Piperacillin-tazobactam usually provides adequate empiric coverage against Gram positive organisms including viridans streptococci. However, if additional coverage against Gram positive organisms is desired, the addition of **vancomycin** is recommended. Clindamycin is recommended with ciprofloxacin and an aminoglycoside for stable patients with F/N and a beta-lactam allergy to cover for streptococci.

*** **See Considerations Regarding the Use of Aminoglycosides below**. Institutions may use q24h dosing options for aminoglycosides if the therapeutic drug monitoring to ensure appropriate alteration to second dose and beyond is in place. Relevant aminoglycoside dosing for q24h administration is available on Lexicomp or local hospital formulary.

Table 2: Recommendation for initial empiric antibiotic selection in patients older than 60 days who are unstable at presentation or who deteriorate while receiving empiric antibiotics

An unstable patient is defined as one who appears septic or toxic or has significant tachycardia, hypotension, tachypnea, hypoxia, decreased level of consciousness and/or evolving evidence of significant local infection. Prompt transfer to the specialized childhood cancer program is recommended when it is safe to do so.

Penicillin Allergy Status	Antibiotics and Doses	Comments
No significant beta-lactam allergy	**Meropenem** 20 mg/kg/dose IV q8h (maximum single dose: 1 g) AND **Tobramycin***** 2.5 mg/kg IV q8h OR **Gentamicin** 2.5 mg/kg IV q8h AND **Vancomycin*** 15 mg/kg/dose IV q6h (maximum initial dose 1000 mg)	**Amikacin** is recommended in place of tobramycin or gentamicin for patients from The Hospital for Sick Children owing to local resistance patterns. **Dosing:** **Amikacin** 2 months to <11 years: 35 mg/kg/dose IV q24h 11 to <16 years: 25 mg/kg/dose IV q24h ≥16 years: 20 mg/kg/dose IV q24h Adjust meropenem and vancomycin doses for renal impairment. Adjust vancomycin dose to maintain trough level 10–15 mg/L.
Significant beta-lactam allergy (i.e., anaphylaxis)**	**Ciprofloxacin** 10 mg/kg/dose IV q12h (maximum single dose: 400 mg) AND **Tobramycin or Gentamicin** (dose as above) AND **Vancomycin*** (dose as above)	**Amikacin** is recommended in place of tobramycin or gentamicin for patients from The Hospital for Sick Children owing to local resistance patterns. Dosing as above. Adjust ciprofloxacin and vancomycin doses for renal impairment. Adjust vancomycin dose to maintain a trough level between 10–15 mg/L. This regimen does not include empiric coverage of usual intestinal anaerobic pathogens.

		Consider anaerobic coverage with signs of intra-abdominal or peri-rectal infection.

* Consider discontinuation of vancomycin once culture and susceptibility results are available.

** Note that this regimen does not include empiric coverage of usual intestinal anaerobic pathogens. Consider anaerobic coverage in patients who have signs of intra-abdominal or peri-rectal infection.

*** **See Considerations Regarding the Use of Aminoglycosides below**. Institutions may use q24h dosing options for aminoglycosides if the appropriate therapeutic drug monitoring program is in place. Relevant aminoglycoside dosing for q24h administration is available on Lexicomp or local hospital formulary.

Continued Management

Patients who remain febrile after initiation of appropriate antibiotic therapy ordinarily should have cultures drawn no more than once daily and ideally at the time of fever. Repeat peripheral cultures are not routinely required after initial presentation. IV antibiotics should be alternated among all lumens for the duration of antibiotic therapy in patients with **multi-lumen CVCs**.

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

1. Continue empiric antibiotic regimen.
2. "Step-down" to the empiric IV antibiotic regimen recommended for patients who were stable at presentation may be considered in patients who experienced a period of instability but become stable and continue to require broad-spectrum antibiotics.
3. Outpatient management may be considered in select patients who are considered low risk (see sub-section 4.1.3 Criteria for Low-Risk Designation). Significant resources are required to maintain an outpatient program and it is neither expected nor encouraged in the POGO Satellite Clinic care setting. However, if there is particular interest in developing such an outpatient program in the POGO Satellite Clinic program, the plan by which it will be set up must be developed in consultation with collaborating specialized childhood cancer programs and reviewed with the POGO Medical Director.

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. 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 the broad-spectrum coverage. The specialized childhood cancer program should be contacted about transfer for ongoing management. After 5 days of persistent fever or if a new fever develops after 5 days of empiric antibiotic therapy, the specialized childhood cancer program should be contacted about the possible addition of empiric antifungal coverage and transfer for ongoing management.
2. PATIENTS who present, or become, HEMODYNAMICALLY UNSTABLE OR APPEAR TO BE PROGRESSIVELY DETERIORATING should be brought to the immediate attention of the

specialized childhood cancer program for transfer. The empiric antibiotic regimen of these patients should be changed as per Table 2.

Considerations Regarding the Use of Aminoglycosides

Patients with NO SIGNIFICANT BETA-LACTAM ALLERGY and with pre-existing nephrotoxicity or developing nephrotoxicity while receiving gentamicin/tobramycin, and patients with sensorineural hearing loss, may receive ciprofloxacin in place of gentamicin/tobramycin (renal dosing if appropriate).

Antibiotic coverage for similar patients WITH SIGNIFICANT BETA-LACTAM ALLERGY should be discussed with the specialized childhood cancer program.

Ideally patients with pre-existing nephrotoxicity or ototoxicity will have been provided with a Fever Card to guide initial antibiotic therapy and/or there will have been explicit discussion with the POGO Satellite Clinic team by the specialized childhood cancer program around antibiotic choice.

Therapeutic Drug Monitoring

Therapeutic drug monitoring should be performed according to institutional norms to maintain antibiotic levels within the therapeutic range (vancomycin, aminoglycosides).

Patients with Positive Blood Culture

Each patient with a positive blood culture should be managed in consultation with the specialized childhood cancer program on a case-by-case basis. Where such a consult service exists, the local ID team should be consulted. 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 febrile neutropenic patient.[5,6]
- Vancomycin should be added to empiric antibiotic therapy of patients with a gram positive culture. When organism sensitivity results are available, vancomycin should be reevaluated.
- Gentamicin or tobramycin (or ciprofloxacin) should be added empirically to the regimen of patients with a gram negative culture and who are receiving monotherapy with piperacillin-tazobactam. The continued use of gentamicin or tobramycin must be reevaluated when the organism is identified and sensitivities are available. Patients in whom *P. aeruginosa* is cultured should continue to receive dual therapy with antibiotics to which the organism is known to be sensitive. 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.[7]
- All patients with a positive blood culture must be discussed with the specialized childhood cancer program team as CVC removal is indicated or should be strongly considered for specific infections and early transfer is required. CVC removal must be considered for patients with an apparent tunnel or port-site infection, persistent bacteremia after 48 to 72 hours of appropriate antimicrobial treatment in the absence of other obvious sites or sources of infection, infective

endocarditis or relapse of infection with the same pathogen after completion of an appropriate course of antibiotics.[8]

Duration of Antibiotic Therapy

Patient Parameters	Plan
Afebrile for a minimum of 24 hours Cultures negative at 48 hours Antibiotic duration ≥48 hours Clinically well Evidence of hematological recovery* 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 specialized childhood cancer program.	DISCONTINUE antibiotics.
Afebrile for a minimum of 24 hours Cultures **positive** Evidence of hematological recovery*	CONSIDER discontinuing broad-spectrum coverage. CONTINUE specific therapy to complete necessary treatment period.
Low-risk febrile neutropenia ONLY Afebrile for minimum of 24 hours Cultures **negative** Antibiotic duration of 72 hours **Irrespective of haematological recovery**	There remains considerable practice variation in this scenario and patient care must be determined in consultation with the specialized childhood cancer program. CONSIDER discontinuing antibiotic therapy if: Specialized childhood cancer program is in agreement. If discharged, careful follow-up is ensured, either by phone or patient visit 24–48 hours post-discharge. If discharged, the patient and their family can and will return in a timely fashion should fever recur. If discharged and the patient's fever returns, they are readmitted and started on empiric antibiotic coverage until evidence of count recovery.

* Hematological recovery is defined as: minimum ANC of 0.2 x 10^9/L or minimum monocyte count of 0.1 x 10^9/L.

Considerations for Discharge of Patients

- Patient parameters for discontinuation of antibiotic therapy are met as per section above (Duration of Antibiotic Therapy).
- Any localized sites of infection are resolved or significantly improved.

- Continued and close follow-up with the treatment team is ensured. Any recurrence of fever should be approached as a *de novo* fever in an immunocompromised host and requires immediate evaluation.

References

1. Lehrnbecher, Thomas 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 : official journal of the American Society of Clinical Oncology* vol. 35,18 (2017): 2082-2094. doi:10.1200/JCO.2016.71.7017.
2. Freifeld, Alison G et al. "Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* vol. 52,4 (2011): e56-93. doi:10.1093/cid/cir073.
3. Fletcher, Matthew et al. "Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer." *Pediatric blood & cancer* vol. 60,8 (2013): 1299-306. doi:10.1002/pbc.24485
4. Aquino, V M et al. "Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer." *Cancer* vol. 88,7 (2000): 1710-4. https://doi.org/10.1002/(SICI)1097-0142(20000401)88:7%3C1710::AID-CNCR27%3E3.0.CO;2-1
5. Carney, D N et al. "Bacteremia due to Staphylococcus aureus in patients with cancer: report on 45 cases in adults and review of the literature." *Reviews of infectious diseases* vol. 4,1 (1982): 1-12. doi:10.1093/clinids/4.1.1
6. Pizzo, P A et al. "Treatment of gram-positive septicemia in cancer patients." *Cancer* vol. 45,1 (1980): 206-7. doi:10.1002/1097-0142(19800101)45:1<206::aid-cncr2820450133>3.0.co;2-p
7. Safdar, Nasia et al. "Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis." *The Lancet. Infectious diseases* vol. 4,8 (2004): 519-27. doi:10.1016/S1473-3099(04)01108-9
8. Schiffer, Charles A et al. "Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* vol. 31,10 (2013): 1357-70. doi:10.1200/JCO.2012.45.5733

Primary author Dr. Angela Punnett, The Hospital for Sick Children, Toronto with input from Dr. Marina Salvadori, Children's Hospital, London Health Sciences Centre, London, Dr. Lee Dupuis, The Hospital for Sick Children, Toronto and Dr. Nicole Le Saux, Children's Hospital of Eastern Ontario, Ottawa. Reviewed by the POGO Satellite Manual Review Management of Fever and Neutropenia Working Group, 2016.

Disclaimer: Source Accuracy

Record of Updates

Version Number	Date of Effect	Summary of Revisions
1	1/10/2023	• Original version posted.