CLINICAL GUIDELINE

Initial Management of Fever in Oncology Patients with Risk for Neutropenia

Patients age >28 days

Children's MINNESOTA

Aim: To guide care for patients at risk for fever and neutropenia (absolute neutrophil count < 500) secondary to chemotherapy or bone marrow failure.

Fever Definition

≥ 38.3° C (101° F) once
or
≥ 38° C (100.4° F)
sustained for 1 hour

Oncology patient with fever

Evaluate with exam, vitals and obtain a CBC with differential, cultures from all central line lumens(Note 1) **and additional diagnostic testing as needed**(Note 2)

Is the patient ill appearing or high-risk patient (Note 3)**?**

Yes → **Cefepime IV**(Note 6 & 7, page 2) ± Vancomycin IV(Note 4)
If applicable, refer to Sepsis Guideline.

No

ANC < 500 anticipated or prior bacteremia?

Yes → **Cefepime IV** (Note 6 & 7, page 2)

No

Wait for CBC results before giving antibiotics.
Monitor for change in status.

ANC ≥ 500 confirmed?

No → **ANC ≥ 200 with viral source/ symptoms?**

Yes → **ED and Oncology providers to discuss outpatient management ± oral antibiotics if meet all outpatient criteria** (see Table 2, page 4).

If does not meet all criteria, consider admission for observation.

Yes

ANC < 200 or ≥ 200 to < 500 without viral source/ symptoms?

Yes → **Inpatient management recommended if any of the following:**

- ANC < 200 or ≥ 200 to < 500 without viral source/symptoms
- **High-risk patients**(Note 3)
- **High-risk clinical concerns**(Note 5)
- ANC < 500 and does not meet criteria for outpatient management (Table 2, page 4)

If at an outside facility transfer to Children's Minneapolis when stable.

See page 2 and 3 for inpatient management

No

Note 1. No peripheral culture unless unable to access central line

Note 2. Additional diagnostic testing based on clinical concerns (e.g. electrolytes, CRP, CXR, respiratory viral testing, MRSA, stool PCR testing, UA if able to void - call oncology provider prior to catheterization)

Note 3. High-Risk *Patients*:

- Hemodynamically unstable
- Neutropenic and anticipated to last ≥ 7 days
- AML diagnosis
- ALL diagnosis in induction
- Relapsed leukemia not in remission
- High-dose Cytarabine in most recent cycle
- High-dose steroids (see Table 1)
- Transplant in past 100 days
- On immunosuppression post-HSCT
- Concern for pneumonia (hypoxia, CXR changes) or skin/soft tissue infection
- History of MRSA in past 12 months
- Trisomy 21
- Infants

Note 4. Vancomycin Criteria:

- Hemodynamically unstable
- AML diagnosis
- HD Cytarabine during most recent cycle
- Post-transplant in first 100 days
- Concern for pneumonia (do not wait for imaging results)
- History of MRSA in past 12 months
- Concern for skin/soft tissue infection.

Note 5. High-Risk *Clinical Concerns*: hemodynamic instability, Grade ≥ 3 mucositis, respiratory distress, dehydration, moderate to severe abdominal pain, altered mental status, recent surgery, pneumonia or complex infection, concurrent medical complication (e.g. AKI, hepatic insufficiency).

Reviewer(s): Chihak, Hess, Maxa, Miller, Pomputius, Sicoli, Ullman | Rev 2/26 | Exp 12/27 |

INPATIENT GUIDELINE

Management of Febrile Neutropenia in First 96 Hours

Patients age >28 days

Children's MINNESOTA

Aim: To optimize antimicrobial use and facilitate safe discharge for inpatient oncology patients

Note 6: Antibiotic alternatives to Cefepime for pseudomonas & gram-positive coverage:

1. Piperacillin / Tazobactam
2. Meropenem
3. Ceftazidime + Vancomycin
4. Ciprofloxacin + Vancomycin
5. Levofloxacin - if not taking outpatient for prophylaxis

See Table 3 on page 5 for dosing.

Note 7. Recommend Cefepime monotherapy (or alternative) unless:

- Meets criteria for addition of Vancomycin (see page 1, including gram-positive culture), reassess need after 48 hours
- Meets criteria for addition of Metronidazole (moderate/severe abdominal pain or grade ≥3 mucositis)
- Meets criteria for addition of enteral Vancomycin for a Clostridium difficile infection
- Meets criteria for transition to Meropenem (documented history of colonization/infection with ESBL or resistant organism)
- Meets criteria for addition of Tobramycin (double coverage for history of or new *Pseudomonas spp* infection)

Also consider early fungal cultures and fungal coverage in AML or severely ill patients. See Table 3 on page 5 for dosing.

Management Between 24 - 96 Hours

Reassess daily and with clinical change

Perform daily blood cultures with ongoing fevers x 3 days or if clinical change

Low-Risk Inpatients
(if meets ALL criteria)

- No high-risk patient (Note 3) or disease related factors
- No high-risk clinical concerns (Note 5)
- Negative blood culture(s) > 24 hours
- Afebrile > 24 hours OR identified source of fever with improvement in fever curve (e.g. rhinovirus, strep pharyngitis)

High-Risk Inpatients
(if meets ANY criteria)

- Any high-risk patient (Note 3) or disease related factors
- Any high-risk clinical concerns (Note 5) or new clinical concerns
  - Refer to sepsis guidelines and consider PICU and Infectious Disease consult
- Positive blood culture(s)
- Ongoing fevers after 24 hours and does not meet low-risk inpatient criteria

Absolute Phagocyte Count (APC)
= WBC x (% neutrophils + % bands + % monocytes)

Low-Risk Inpatient Discharge Criteria

- If APC ≥ 200 post-nadir AND meets outpatient criteria (Table 2), discontinue IV antibiotics (+/- transition to appropriate oral therapy to complete course) and discharge
- If APC ≥ 100 post-nadir AND meets outpatient criteria (Table 2), consider transition to oral levofloxacin prophylaxis (or appropriate oral therapy to complete treatment course) with discharge home immediately OR after a period of further inpatient observation

Febrile with Documented Infection

- If gram negative or *Staphylococcus aureus* bacteremia, complex infection or not responding to initial antimicrobials, consult Infectious Disease. If febrile >96 hours refer to page 3
- Modify antimicrobials according to culture results and/or infection site. Once afebrile refer to the Afebrile with Documented Infection Pathway. If remains febrile >96 hours refer to page 3
- If responding, continue antimicrobials to complete a course as appropriate for diagnosis. Once afebrile refer to the Afebrile with Documented Infection Pathway.

Febrile without Documented Infection

Continue empiric antibiotics and assess daily for new sites of infection. After 96 hours refer to page 3

Afebrile with Documented Infection:

Modify antimicrobials according to results and/or infection site. If remains afebrile >24 hours and APC ≥ 100 post-nadir AND meets outpatient criteria (Table 2), discharge on appropriate therapy to complete course. If complex infection, recommend involving Infectious Disease.

Afebrile ≥ 24 Hours without Documented Infection + No Clinical Concerns

- If APC ≥ 200 post-nadir AND meets outpatient criteria (Table 2), discontinue antibiotics and discharge
- If APC ≥ 100 post-nadir AND meets outpatient criteria (Table 2), consider transition to oral levofloxacin prophylaxis with discharge home immediately OR after a period of further inpatient observation

INPATIENT GUIDELINE

Management of Prolonged (>96 hours) Febrile Neutropenia

Patients age >28 days

Children's MINNESOTA

Aim: To optimize antimicrobial use and facilitate complete evaluation inpatient oncology patients not responding to first line fever management.

Patient Criteria:

- ANC <200
- Unexplained, persistent fevers (occurring intermittently 0-48 hours apart)
- Continues on empiric antimicrobials

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Consult Infectious Disease

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Additional Diagnostic Work Up:

- Chest CT with contrast and abdomen ultrasound
- Consider CT sinus with contrast if localizing signs/symptoms
- Consider abdomen/pelvis CT with contrast if localizing signs/symptoms
- Consider additional infectious disease testing (e.g. fungal biomarkers, viral PCRs, Karius)

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Review Empiric Antimicrobial Coverage

- Check dosing and spectrum as directed by ID
- Add or expand antifungal/mold coverage
- Consider if need to:
  - Expand gram-positive coverage
  - Expand anaerobic coverage
  - Expand atypical bacterial coverage

↓

Continue empiric antimicrobials until ANC >200 post-nadir, unless evidence of documented infection and as directed by Infectious Disease

Febrile Neutropenia Reference Tables

Patients age >28 days

Table 1. High-Dose Steroid Definition

14 days or more of **prednisone/prednisolone**			14 days or more of **dexamethasone**		
≥ 2 mg/kg/day	OR	≥ 20 mg/day	≥ 0.3 mg/kg/day	OR	≥ 3 mg/day

Table 2. Outpatient Management Criteria

- ANC meets requirements on page 1-3
- Not a high-risk patient being evaluated for initial fever assessment (see Note 3, Page 1)
- No high-risk clinical concerns that require inpatient management (see Note 5, Page 1)
- Staying within 1 hour travel time of a hospital/ER able to reasonably care for the patient
  - Should be a hospital system familiar with the patient and has established care/coordination with the patient's clinical care team at Children's
- Have access to reliable transportation
- Has a working telephone and thermometer
- Caregiver available at home 24 hours a day
- Caregiver agrees to follow-up clinic visit and daily phone contact with the team until afebrile
- Demonstrates history of compliance and adherence, including medication adherence
- Patient able to tolerate medications by mouth or enteral tube
- Patient will remain home from school or daycare until afebrile

Aim: To optimize antimicrobial use in pediatric, adolescent and young adult oncology patients

Table 3. Initial Medication Dosing Recommendations

Dosing below may require adjustments for renal or hepatic impairment; consult drug information resource for additional guidance.

Anti-Infective	Recommended INITIAL Dosing for Fever and Neutropenia	Maximum Dose
Amoxicillin-clavulanate	PO: 45 mg/kg/dose BID (Amoxicillin component); "High dose" Use amoxicillin 600 mg/clavulanate 42.9 mg formulation	1000 mg
Cefepime	IV: 50 mg/kg/dose Q8H	2000 mg
Ceftazidime	IV: 50 mg/kg/dose Q8H	2000 mg
Ciprofloxacin	IV: 10 mg/kg/dose Q8H	400 mg
Clindamycin	IV: 10 mg/kg/dose Q8H	600 mg
Levofloxacin	IV/PO: If patient 6 months to <5 years use 10 mg/kg/dose Q12H If patient ≥5 years use 10 mg/kg/dose Q24H	750 mg
Meropenem	IV: 20 mg/kg/dose Q8H	1000 mg
Metronidazole	IV/PO: 10 mg/kg/dose Q8H	500 mg
Micafungin	IV: 3 mg/kg/dose Q24H	150 mg
Piperacillin-tazobactam	IV: 80 mg/kg/dose Q6H (Piperacillin component)	4000 mg
Posaconazole	Variable dosing based on formulation, route and age of patient. Contact clinical pharmacist for assistance. *Management of Posaconazole troughs is highly recommended with a goal trough for prophylaxis 700 – 3000 ng/mL and for treatment 1000 – 3000 ng/mL*	N/A
Vancomycin	IV: 20 mg/kg/dose Q8H, refer to Children's Vancomycin Guideline. PO: refer to Children's C.Difficile Infection Guideline	IV: N/A
Voriconazole	Consider pharmacogenomic information (CYP2C19 genotyping) if available. If patient < 12 years: IV/PO: 10 mg/kg/dose Q12H If patient ≥ 12 years: IV: 6 mg/kg/dose Q12H PO: 300 mg Q12H *Management of voriconazole troughs is highly recommended with a goal trough for prophylaxis 1 – 5.5 mcg/mL; treatment 2 – 5.5 mcg/mL*	N/A

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