CLINICAL GUIDELINE

# Initial Management of Fever in Oncology Patients with Risk for Neutropenia

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

**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.

**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 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).



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INPATIENT GUIDELINE

# Management of Febrile Neutropenia in First 96 Hours

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

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

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

# Febrile Neutropenia Reference Tables



## 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"<br>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<br>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.<br>*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 Clinical Guideline<br>PO: refer to Children's C.Difficile Infection Guideline | IV: N/A |
| **Voriconazole** | Consider pharmacogenomic information (CYP2C19 genotyping) if available.<br>If patient < 12 years: IV/PO: 10 mg/kg/dose Q12H<br>If patient ≥ 12 years: IV: 6 mg/kg/dose Q12H<br>PO: 300 mg Q12H<br>*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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