INPATIENT GUIDELINE

FEVER AND NEUTROPENIA

Children's MINNESOTA

Aim: To optimize anti-infective use in pediatric, adolescent and young adult oncology patients with fever and neutropenia (F&N).

FEVER AND NEUTROPENIA INITIAL MANAGEMENT

ANC < 200 & Temp ≥ 38.5°C

Initiate Cefepime + Probiotics* + See Note 1

LOW RISK

- Absence of any high risk factors
- Low risk of serious medical complication

*If patient develops **any** high risk episodic factors follow high risk pathway*

If patient remains clinically stable, continue with cefepime monotherapy

Reassess antibiotic regimen after 48 hours

HIGH RISK

- **Patient/disease-related factors**
  Age < 12 months, AML, ALL induction, ALL delayed intensification, infant ALL, Burkitt's or Burkitt's-like lymphoma, Down's Syndrome, high dose steroids*, HLH induction, progressive or relapsed disease with marrow involvement, Transplant/Cellular Therapy
- **Episode-specific factors**
  Hypotension, tachypnea, hypoxia with O2 requirement, new CXR changes, altered mental status, severe mucositis, moderate/severe vomiting or abdominal pain, focal infection, other clinical reason for inpatient treatment

If moderate/severe abdominal symptoms or mucositis present:

- Use cefepime + metronidazole **OR** switch to piperacillin-tazobactam
- For documented C. diff infection: Add enteral vancomycin

If below factor(s) present, add VANCOMYCIN:

- AML
- Clinically unstable (See Note 1)
- Moderate/severe cellulitis
- Severe mucositis
- History of alpha-hemolytic strep within the past 12 months
- Coagulase-negative staph x2 positive cultures
- Empiric coverage for a gram-positive culture with final speciation pending
- Concern for CNS infection

If below factor(s) present, add TOBRAMYCIN:

- Clinically unstable (See Note 1)
- Gram-negative rod bacteremia

If documented history of colonization or infection with ESBL organism or organism resistant to cefepime and piperacillin-tazobactam, switch cefepime to MEROPENEM (See Note 2)

Adjust antimicrobials based on specific clinical, radiographic and/or culture data

If patient responds to initial empiric antibiotic therapy, discontinue double coverage after 48 hours if no specific clinical, microbiologic or radiographic indication to continue combination therapy

NOTE 1

In children with fever who become clinically unstable, escalate empiric antibacterial regimen to include coverage for resistant gram negative, gram positive and anaerobic bacteria.

Clinically unstable may include hemodynamic instability and/or mental status changes.

See sepsis guidelines as applicable.

NOTE 2

Meropenem is a protected agent, ID consult required after 48 hours.

* See page 5 for definitions, dosing recommendations and alternatives for allergies

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FEVER & NEUTROPENIA MANAGEMENT

48 Hours After Empiric Therapy Initiation

LOW RISK See Note 3

- Persistent fever **AND** cultures negative **AND** clinically stable
  - Change cefepime to amoxicillin-clavulanate
  - Continue probiotics
- Afebrile for at least 24 hours **AND** cultures negative
  - ANC ≥ 200
    - Discontinue antibiotics and probiotics
  - ANC < 200
    - Change cefepime to amoxicillin-clavulanate
    - Continue probiotics for a minimum of 24 hours
    - Consider outpatient management if criteria listed on page 5 are met
      - Afebrile for at least 24 hours
      - Cultures negative
        - Discontinue antibiotics and probiotics

HIGH RISK

- with **documented infection**
  - Modify antimicrobials according to culture results and/or infection site
    - Responding?
      - Yes
        - Continue antimicrobials for 7–14 day course, as appropriate for documented infection or until ANC ≥ 200 (whichever is longer)
      - No
        - See sepsis guidelines as applicable
        - Examine and re-image (CT, MRI) for new or worsening sites of infection
        - Culture, biopsy and/or drain sites of worsening infection: assess bacterial, viral and fungal pathogens
        - Review antibiotic coverage for adequacy of dosing and spectrum
        - Consider adding empiric antifungal coverage
        - Broaden antimicrobial coverage for hemodynamic instability
        - Consider Karius testing
        - Consider ID consult
- Persistent fever **AND** cultures negative **AND** clinically stable
  - No change in empiric antibiotics
  - Assess for infection sites
- Clinically unstable and/or worsening signs and symptoms
  - See sepsis guidelines as applicable
  - Examine and re-image (CT, MRI) for new or worsening sites of infection
  - Culture, biopsy and/or drain sites of worsening infection: assess bacterial, viral and fungal pathogens
  - Review antibiotic coverage for adequacy of dosing and spectrum
  - Consider adding empiric antifungal coverage
  - Broaden antimicrobial coverage for hemodynamic instability
  - Consider Karius testing
  - Consider ID consult
- Afebrile for at least 24 hours **AND** cultures negative
  - ANC ≥ 200
    - Discontinue antibiotics
  - ANC < 200
    - No change in empiric antibiotics
    - Assess for infection sites

NOTE 3
Follow High Risk pathway if patient has persistent fevers and is clinically unstable.

FEVER AND NEUTROPENIA

Children's MINNESOTA

Aim: To optimize anti-infective use in pediatric, adolescent and young adult oncology patients with fever and neutropenia (F&N).

HIGH RISK
with > 96 hours of fever

- **Patient/Disease-related factors**
  Age < 12 months, AML, ALL induction, ALL delayed intensification, infant ALL, Burkitt's or Burkitt's-like lymphoma, Down's Syndrome, High dose steroids*, HLH induction, progressive or relapsed disease with marrow involvement, Transplant/Cellular Therapy
  OR
- Persistent fever despite prolonged (> 96 hours) broad spectrum antibiotic therapy **AND** expected neutropenia > 10 days

Unexplained Fever
- ANC ≥ 200
- Clinically stable

Observe
- No antimicrobial changes unless clinical, microbiologic or radiographic data suggest new infection
- Consider Karius testing
- Consider ID consult

Unexplained Fever
- ANC < 200
- Clinically stable

- Daily exam & history
- Blood cultures daily
- Consider fungal and viral cultures
- Cultures for any suspected sites of infection
- Consider imaging of lungs and abdomen, if appropriate
- Consider ENT evaluation for nasal fungal involvement
- Consider Karius testing
- Consider ID consult

Add empiric antifungal therapy
- Should include mold coverage
- Consider patient's previous antifungal exposure
- Possible initial agents: micafungin and/or voriconazole

Continue antifungal mold therapy until ANC ≥ 200 in the absence of documented or suspected invasive fungal disease

Clinically unstable and/or worsening signs and symptoms

- Examine and re-image (CT, MRI) for new or worsening sites of infection
- Culture, biopsy and/or drain sites of worsening infection: assess bacterial, viral and fungal pathogens
- Review antibiotic coverage for adequacy of dosing and spectrum
- Consider adding empiric antifungal coverage
- Broaden antimicrobial coverage for hemodynamic instability
- Consider Karius testing
- Consider ID consult

* See page 5 for definitions, dosing recommendations and alternatives for allergies

FEVER AND NEUTROPENIA

Aim: To optimize anti-infective use in pediatric, adolescent and young adult oncology patients with fever and neutropenia (F&N).

LOW RISK
with > 96 hours of fever

Absence of any patient/disease-related high risk factors

Unexplained Fever
- ANC ≥ 200
- Clinically stable

Observe
- No antimicrobial changes unless clinical, microbiologic or radiographic data suggest new infection
- Consider ID consult

Unexplained Fever
- ANC < 200
- Clinically stable

- Daily exam & history
- Blood cultures daily
- Consider fungal and viral cultures
- Cultures for any suspected sites of infection
- Consider imaging of lungs and abdomen, if appropriate
- Consider ENT evaluation for nasal fungal involvement
- Consider Karius testing
- Consider ID consult

Consider continuing current plan of care without adding additional anti-infective agents

Clinically unstable and/or worsening signs and symptoms

See High Risk pathway (page 3)

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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

Antibiotic selection*	
Preferred agent	Cefepime PO step-down therapy for **low risk** patients: → Amoxicillin/Clavulanate
Alternative agents	→ Vancomycin + Ciprofloxacin → Meropenem (obtain ID consult if meropenem is desired beyond 48 hours) PO step-down therapy for **low risk** patients: → Levofloxacin (if not used for prophylaxis

** See page 6 for dosing recommendations*

CRITERIA FOR OUTPATIENT MANAGEMENT OF LOW RISK PATIENTS

Hospital access

- Live within 1 hour reliable travel time of Children's Minnesota Minneapolis campus
- Have access to a car

Home environment

- Has a working telephone
- Has a working thermometer

Caregiver

- Available at home 24 hours a day
- Agrees to follow-up clinic visit and phone contact daily until afebrile **AND** ANC > 200
- Able and willing to communicate with Hematology/Oncology clinic
- Demonstrates history of compliance and adherence, including medication adherence

Child

- Able to tolerate medications by mouth or enteral tube (oral liquids, capsules or tablets)
- Remains home from school/daycare

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Anti-Infective	Recommended INITIAL dosing for F&N	Maximum per dose
Amoxicillin-clavulanate	PO: 20 mg/kg/dose BID (Amoxicillin component)	875 mg
Cefepime	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
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 **Goal troughs:** Prophy 700 to 3000 ng/ml Treatment 1000 to 3000 ng/ml	Variable dosing based on formulation, route, and age of patient. Contact pharmacist for assistance.	N/A
Tobramycin	IV: 2.5 mg/kg/dose Q8H	N/A
Vancomycin	IV: 15 mg/kg/dose Q6H PO (C.Diff only): Refer to C.diff Treatment Algorithm	IV: N/A
Voriconazole **Goal troughs:** Prophy 1 to 5.5 mcg/ml Treatment 2 to 5.5 mcg/ml	Consider pharmacogenomic information if available If < 12 years: • IV/PO: 10 mg/kg/dose Q12H If ≥ 12 years: • IV: 6 mg/kg/dose Q12H • PO: 300 mg PO Q12H	N/A

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REFERENCES

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