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 patient remains clinically stable, continue with cefepime monotherapy

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
  - Afebrile for at least 24 hours AND cultures negative
    - ANC ≥ 200
      - Change cefepime to amoxicillin-clavulanate
      - Continue 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

- Persistent fever AND cultures negative AND clinically stable
  - 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)
      - Discontinue antibiotics
    - 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

- Clinically unstable and/or worsening signs and symptoms
  - Afebrile for at least 24 hours AND cultures negative
    - Discontinue antibiotics
  - ANC ≥ 200
  - ANC < 200

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

**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
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

- Clinically unstable and/or worsening signs and symptoms

See High Risk pathway (page 3)

Consider continuing current plan of care without adding additional anti-infective agents
Aim: To optimize anti-infective use in pediatric, adolescent and young adult oncology patients with fever and neutropenia (F&N).

### High-dose steroid definition

<table>
<thead>
<tr>
<th>14 days or more of prednisone/prednisolone</th>
<th>14 days or more of dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 mg/kg/day OR ≥ 20 mg/day</td>
<td>≥ 0.3 mg/kg/day OR ≥ 3 mg/day</td>
</tr>
</tbody>
</table>

### 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

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

### Anti-Infectives and Recommended Dosing

<table>
<thead>
<tr>
<th>Anti-Infective</th>
<th>Recommended INITIAL dosing for F&amp;N</th>
<th>Maximum per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>PO: 20 mg/kg/dose BID</td>
<td>875 mg</td>
</tr>
<tr>
<td></td>
<td>(Amoxicillin component)</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>IV: 50 mg/kg/dose Q8H</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>IV: 10 mg/kg/dose Q8H</td>
<td>400 mg</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>IV: 10 mg/kg/dose Q8H</td>
<td>600 mg</td>
</tr>
<tr>
<td>Meropenem</td>
<td>IV: 20 mg/kg/dose Q8H</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>IV/PO: 10 mg/kg/dose Q8H</td>
<td>500 mg</td>
</tr>
<tr>
<td>Micafungin</td>
<td>IV: 3 mg/kg/dose Q24H</td>
<td>150 mg</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>IV: 80 mg/kg/dose Q6H</td>
<td>4000 mg</td>
</tr>
<tr>
<td></td>
<td>(Piperacillin component)</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Variable dosing based on formulation, route, and age of patient. Contact pharmacist for assistance.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Goal troughs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td>IV: 15 mg/kg/dose Q6H</td>
<td>IV: N/A</td>
</tr>
<tr>
<td></td>
<td>PO (C.Diff only): Refer to C.diff Treatment Algorithm</td>
<td></td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td>Consider pharmacogenomic information if available</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Goal troughs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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REFERENCES
5. National Comprehensive Cancer Network - Prevention and Treatment of Cancer-Related Infections; Version date 1 Jan 2021

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