**Guideline/Protocol Title:** Guidelines for Management of Fever in Pediatric Oncology and BMT Patients (UCSF Benioff Children’s Hospital San Francisco)

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**Approving committee(s):** P&T, Antimicrobial Subcommittee

**P&T Approval Date:** Adapted from prior service-specific guidelines 01/2016 (ED); 03/2016 (inpatient)

**Last revision Date:** 07/24/2019

**PURPOSE/SCOPE:** To provide standardized guidelines for management of fever in patients on the Pediatric Hematology/Oncology (Oncology) and Pediatric Blood and Marrow Transplant (BMT) services. For these guidelines, “BMT patient” refers to any patient on the BMT service who is undergoing or has undergone any form of hematopoietic stem cell transplantation (e.g. peripheral blood stem cell transplant, umbilical cord blood transplant, bone marrow transplant). These guidelines do not address all aspects of infection management in Oncology and BMT patients. Refer to Oncology and BMT Standards of Practice for supportive care practices not addressed in these guidelines.

**EXECUTIVE SUMMARY**

Patients who develop fever while undergoing cancer therapy or hematopoietic stem cell transplantation on the Pediatric Oncology or BMT services will be treated according to the best available clinical evidence and guidelines. Clinical algorithms for management of fever were developed based on national and international evidence-based guidelines, other published evidence, and local antimicrobial susceptibility data.

**BACKGROUND / INTRODUCTION**

Pediatric oncology and BMT patients are at high risk for infection and related complications. Management goals include:

1. Prompt initiation of broad-spectrum antibiotics (within 1 hour) for neutropenic patients and clinically unstable non-neutropenic patients.

2. Identification and appropriate treatment of serious infections.

3. Avoidance of antimicrobial resistance, superinfection, and other adverse effects of antimicrobial therapy.
SUPPORTING EVIDENCE

Sources considered in development of the guidelines include references below and bloodstream infection antibiogram data from 2016-2018 evaluated for the Pediatric Oncology and BMT services. Proposed changes and supporting evidence were presented to the Pediatric Oncology, BMT and ID services. Presentation materials are available upon request from the Pediatric ASP. The updated guideline has been reviewed by all key collaborators and their additional recommendations incorporated.

APPENDIX

1. Pediatric Oncology and BMT Patients with Fever: Emergency Department Management (page 4)
2. Pediatric Oncology and BMT Patients with Fever: Initial Inpatient Management (page 5)
3. Pediatric Oncology and BMT Patients with Fever: Inpatient Re-assessment (Initially Neutropenic and/or Clinically Unstable) (page 6)
4. Inpatient Management of Clinically Stable Patients with Non-Neutropenic Fever (page 7)
5. Antimicrobial Dosing Table and Alternatives for Patients with Beta-Lactam Allergy (page 8-9)

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Citation</th>
</tr>
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<tbody>
<tr>
<td>Revision Date</td>
<td>Update(s)</td>
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<tr>
<td>----------------</td>
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</tr>
<tr>
<td>July 24, 2019</td>
<td>• Format change to incorporate ED and inpatient algorithms together  &lt;br&gt;• Antimicrobial dosing removed from all but ED algorithm, to separate table  &lt;br&gt;• Adding inpatient re-assessment algorithm (Appendix 3) with guidelines for de-escalation of therapy  &lt;br&gt;• Referencing Oncology Standards of Practice for low-risk stepdown management and new diagnosis ALL antibiotic de-escalation  &lt;br&gt;• Changes incorporated due to levofloxacin prophylaxis adoption:  &lt;br&gt;  o Escalation with vancomycin + carbapenem rather than with second Gram-negative agent  &lt;br&gt;  o Guidance to discontinue levofloxacin at start of empiric therapy  &lt;br&gt;• Non-neutropenic fever  &lt;br&gt;  o Algorithm differentiates patients with intestinal GvHD at higher risk for bloodstream infection with antibiotic-resistant organisms  &lt;br&gt;  o Guidance not to routinely treat clinically stable, well-appearing patients with serotherapy-related fever on BMT service  &lt;br&gt;• Allergy alternatives modified to be concordant with Inpatient Beta-Lactam Allergy Guideline and add reference to Beta-Lactam Allergy Guideline  &lt;br&gt;• Therapeutic drug monitoring guidance added to antimicrobial dosing table</td>
</tr>
</tbody>
</table>
Goal: Administer First Antibiotic Dose < 60 minutes from Triage

Patient Arrives Without Oncology/BMT Referral
- Treat as if ANC < 500
- Contact Oncology/BMT

Patient Referred by Oncology/BMT with Neutropenic Status
- Patient Arrives to ED Bedside Triage Level I
- MD & RN Rapid Assessment (within 5 minutes)
  - Is the patient unstable?
    - Yes: Antibiotic Selection based on Neutropenic Status communicated by Oncology/BMT
    - No: Avoid rectal temperatures

Provider Assessment:
1. Assess for clinical instability
2. Evaluate for focal infectious source
3. Order labs and antibiotic(s) STAT using ED Fever & Neutropenia Order Set

Unstable = ANY sign:
- Shaking chills or rigors
- Hypotension
- Hypothermia
- Abnormal pulses or capillary refill
- Respiratory distress or hypoxia
- Altered mental status
- Tachycardia out of proportion to fever

Consider sepsis huddle & initial resuscitation
- Give antibiotics in this order:
  1. Cefepime 50mg/kg IV x 1 (max 2g)
  2. Vancomycin:
     - Age 3mo–<12yo: 17.5mg/kg IV x 1 (max 1g)
     - Age ≥12yo: 15mg/kg IV x 1 (max 1g)
  
- Consider adding:
  - Metronidazole 10mg/kg IV x 1 (max 500mg) for abdominal infection or perirectal abscess
  - Caspofungin 70mg/m2 IV x 1 (max 70mg) for patient with severe sepsis + recent steroids or TPN

Review patient's prior Microbiology history, ensure antibiotic spectrum covers prior drug-resistant organisms.
If patient worsens with infusions through central line, establish PIV access and discontinue use of central line.

Admit
- If patient received ceftriaxone, discuss inpatient antibiotic choice with Oncology/BMT
- Refer to Inpatient Oncology/BMT Fever Guidelines for further escalation of treatment if patient is persistently unstable.

ANTC Known < 500 or Unknown & Likely < 500
- Cefepime 50mg/kg IV x 1 (max 2g)

ANTC Unknown & Likely ≥500
- Ceftriaxone 50mg/kg IV x 1 (max 1g)

ANTC Known ≥500
- Ceftriaxone 50mg/kg IV x 1 (max 1g)
- No antibiotic unless focal source identified

Central Line Present?
- Yes: Can discharge if meets criteria. Stable, ANC ≥500, no serious infection identified, reliable follow-up, discussed with Oncology/BMT
- No: If patient initially received cefepime, give ceftriaxone before discharge

Primary Content Owner: Rachel Wattier (ASP), UCSF Pharmacy & Therapeutics Committee Approved 01/2016; Updates: 03/2016, 07/24/2019
Pediatric Oncology and BMT Patients with Fever: Initial Inpatient Management

Goal: Administer First Antibiotic Dose Within 60 Minutes for Neutropenic and/or Clinically Unstable Patients

Discuss with on-service fellow or attending any patient who is clinically unstable or has new onset fever and neutropenia.

**Inpatient on Oncology or BMT Service with Fever T≥ 38.3°C x 1 or T 38.0-38.2 x 1 hour**
*Except recipient of CAR-T cell therapy, for whom T≥38.0 x 1 defines fever

Immunocompromised patients may have serious infections without manifesting fever. If a patient is afebrile but demonstrates signs/symptoms of serious infection, follow this management pathway.

**Assess Patient Immediately**

**Is the patient unstable?**

- Shaking chills or rigors
- Hypotension
- Hypothermia
- Abnormal pulses or capillary refill
- Respiratory distress or hypoxia
- Altered mental status
- Tachycardia out of proportion to fever

Implement resuscitation measures concurrently with antibiotics, as clinically indicated. Alert PICU.

**Severe sepsis or septic shock?**

Yes

Give antibiotics in this order:
1. Meropenem
2. Vancomycin
Discontinue Levofoxacin if patient has been receiving prophyaxis

ADD Caspofungin if patient has received recent broad spectrum antibiotics, high dose steroids or TPN (and not already receiving Caspofungin)

ADD Tobramycin if patient is persistently unstable after initial antibiotics and resuscitation

Review patient’s prior Microbiology history, ensure antibiotic spectrum covers prior drug-resistant organisms.

If patient worsens with infusions through central line, establish PIV access and discontinue use of central line.

No

**Clinical Assessment:**
Carefully examine patient with particular attention to oral mucosa, sinuses, respiratory and abdominal exams, perianal area and central line exit site. Avoid urinary catheterization, rectal temperature and/or digital rectal examination.

Additional diagnostic evaluation (e.g. UA, UC, viral studies, CRX, abdominal imaging) should be performed as clinically indicated.

**Is the patient neutropenic? ANC < 500 or expected to decline to < 500 within 24h**

No

Follow Inpatient Non-Neutropenic Fever Algorithm

Yes

**Focal Infection:** If focal infection is identified, broaden the antibiotic regimen as needed to treat the infection, regardless of clinical stability or risk status - e.g. addition of vancomycin for cellulitis, abscess, or central line site infection, anaerobic therapy for intra-abdominal infection.

**Fever & Neutropenia Risk Stratification**

**High Risk = ANY of the following:**
- Clinically unstable (follow unstable pathway to left for these patients)
- Hematologic malignancy in induction, consolidation or delayed intensification
- Hematologic malignancy with relapsed or persistent disease
- Neutropenia anticipated to last > 7 days
- Significant mucositis
- BMT patient before engraftment
- Serious focal infection

**Low Risk = NO High Risk criteria AND ALL of the following:**
- Neutropenia anticipated to last <= 7 days
- Appears clinically well
- No focus of serious infection

If patient remains clinically unstable or develops severe sepsis/septic shock, CHANGE Cefepime to Meropenem

Follow additional guidelines for severe sepsis/septic shock

**Start Cefepime**

Discontinue Levofoxacin if patient has been receiving prophyaxis

Follow Inpatient Fever Re-assessment Algorithm

Patients may receive acetaminophen at age-appropriate dose for fever reduction after evaluation is initiated for fever. Do not give NSAIDs or aspirin due to platelet inactivation effects.

Refer to Antibiotic Dosing Table and Alternatives for Patients with Beta-Lactam Allergy (pg. 8-9)

Primary Content Owner: Rachel Wattier (ASP); Pharmacy & Therapeutics Approved 03/2016, Updated: 07/24/2019
Pediatric Oncology and BMT Patients with Fever: Inpatient Re-assessment (Initially Neutropenic and/or Clinically Unstable)

- Inpatient on Oncology or BMT Service with Fever and Neutropenia OR Without Neutropenia but Clinically Unstable on Initial Evaluation
  - Clinically or microbiologically documented infection identified?
    - Yes
      - Optimize antimicrobial therapy to treat identified infection. Consider ID consult.
      - If initial ANC < 500, continue antibiotic with broad spectrum Gram-negative activity until count recovery.
    - No
      - Re-assess for de-escalation of therapy at 48 hours, earlier for escalation of therapy if patient clinically unstable.

Patient with Initial Severe Sepsis/Sepic Shock
- Started Vancomycin +/- Tobramycin +/- Caspofungin
  - unstable = ANY sign:
    - Shaking chills or rigos
    - Hypotension
    - Hypothermia
    - Abnormal pulses or capillary refill
    - Respiratory distress or hypoxia
    - Altered mental status
    - Tachycardia out of proportion to fever

- ID consult recommended
  - Continue diagnostic evaluation to identify source
  - Further escalate therapy per Initial Management algorithm
  - If fever persists for greater than 96 hours in a High-Risk patient:
    1) Continue to re-assess for focal infection. Avoid modifying empiric antibacterial therapy based on fever alone if patient clinically stable.
    2) Add empiric antifungal therapy with one of the following, chosen based on consideration of patient’s fungal infection risk factors, clinical presentation, and toxicity risk:
       - Caspofungin
       - Voriconazole
       - Liposomal Amphotericin (AmBisome)
    3) Consider evaluation for invasive fungal infection (chest CT, abdominal US, targeted imaging of other clinically suspected areas of infection, serum galactomannan)
    4) Consider evaluation for reactivated viral infection (e.g. CMV)
    5) Consider ID consult

- Discontinue Vancomycin
- Discontinue Tobramycin if started
- Discontinue Caspofungin if started and no evidence of invasive candidiasis (and not needed for prophylaxis)
- Continue Meropenem for at least 7 days or until count recovery
- Consider de-escalating to Ceftazidime if patient clinically stable with ongoing neutropenia after 7d

Patient with High-Risk FN
- Initially Clinically Stable OR Unstable but Without Severe Sepsis/Sepic Shock
  - Started Ceftazidime
  - Patient has become or remains unstable?
    - Yes
      - Patient remains clinically stable?
        - Yes
          - Once patient has been afebrile x 24 hours, assess eligibility for early discharge per “Low-Risk FN Early Discharge” SOP
        - No
          - Continue antibiotic until count recovery
          - Ceftazidime if remaining inpatient
          - Levofloxacin if early discharge
    - No
      - Continue diagnostic evaluation to identify source
      - Escalate therapy per Initial Management algorithm (treating as High-Risk)

Criteria for discontinuing therapy (for patients without documented infection):
- Negative blood cultures x 48 hours, afebrile x 24 hours, and evidence of count recovery:
  --For Oncology patients, ANC > 200 and rising consistently and AMC > 100
  --For BMT patients, ANC > 500 x 1 day and rising consistently

If patient has newly diagnosed ALL and fever occurred prior to receiving chemotherapy, refer to Oncology SOP for “De-escalation of Antibiotics in Patients with Fever at Diagnosis of ALL”

Frequency of repeat blood cultures if patient continues to have fever:
- Repeat blood cultures q24h for the first 72h after onset of a new fever episode, then space to q48h cultures if patient remains febrile (new episode is defined by patient being afebrile for >4 preceding days)
- Obtain cultures more frequently than q48h for:
  --Clinical decompensation

These are guidelines only and are not intended to replace clinical judgment. Modification of therapy may be indicated based on patient comorbidities, previous antibiotic therapy or infection history. For additional guidance on antibiotic selection, contact the Pediatric Antimicrobial Stewardship Program or Pediatric ID.
Primary Content Owner: Rachel Watter (ASP); Pharmacy & Therapeutics Approved 03/2016, Updated: 07/24/2019
Inpatient Management of Clinically Stable Patients with Non-Neutropenic Fever

Unstable = ANY sign:
- Shaking chills or rigors
- Hypotension
- Hypothermia
- Abnormal pulses or capillary refill
- Respiratory distress or hypoxia
- Altered mental status
- Tachycardia out of proportion to fever

Clinically stable patients do not have any above criteria.

Non-neutropenic = ANC >=500 and not expected to decline to < 500 within 24 hours

If the patient does not meet these criteria, refer back to the Inpatient Initial Management Algorithm.

Start Ceftepime
Review patient’s prior Microbiology history, modify treatment as indicated to ensure antibiotic spectrum covers prior drug-resistant organisms, especially Gram-negative bacteria.
Broaden therapy per FN initial management algorithm if patient becomes clinically unstable.

Non-Neutropenic Fever in Clinically Stable Patient

Identified or suspected focal infectious source?

Yes  Evaluate and treat as clinically indicated based on focal source

No

Patient s/p BMT with gastrointestinal GvHD?

Yes

No

Central line present?

Yes

Assess risk for bacteremia

Higher risk for bacteremia:
- Age < 6 months
- s/p BMT within past 6 months
- Down syndrome
- Comorbid immunocompromising condition (e.g. asplenia, primary immunodeficiency)
- Patient not well-appearing (per provider’s assessment)

Lower risk for bacteremia:
- BMT patients with fever occurring within 24 hours of serotherapy (ATG, alemtuzumab [Campath]) who are clinically stable, well-appearing, and not neutropenic
- Oncology inpatients who are well-appearing, clinically stable, not neutropenic, and do not have any “Higher risk” criteria

Ceftriaxone x 1 dose
Avoid ordering q24h ceftriaxone

Fever resolves within 24h?

Yes

No further antibiotic therapy or cultures

No

Repeat BCx and Ceftriaxone dose x 1
Avoid continuing > 48h

For any patient with persistent, unexplained fever, pursue clinically directed evaluation. Repeat blood cultures per unit protocol.

No antibiotic therapy indicated, monitor for clinical instability or signs of focal infection

This guidance is meant for inpatients who can be monitored closely. For outpatients, refer to ED Management Algorithm.

Ensure that blood culture(s) sent regardless of whether patient receives antibiotic

Refer to Antibiotic Dosing Table and Alternatives for Patients with Beta-Lactam Allergy (pg. 8-9)

These are guidelines only and are not intended to replace clinical judgment. Modification of therapy may be indicated based on patient comorbidities, previous antibiotic therapy or infection history. For additional guidance on antibiotic selection, contact the Pediatric Antimicrobial Stewardship Program or Pediatric ID.

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# Antimicrobial Dosing Table and Alternatives for Patients with Beta-Lactam Allergy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Dose Adjustment</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B Liposomal (AmBisome*) IV</td>
<td>5mg/kg/dose q24h</td>
<td>No recommended dose adjustment for renal dysfunction, but drug should be used with caution due to nephrotoxicity risk</td>
<td>None</td>
</tr>
<tr>
<td>Aztreonam IV</td>
<td>30mg/kg/dose q8h</td>
<td>Adjust for CrCl &lt; 30 ml/min/1.73m²</td>
<td>2g q8h</td>
</tr>
<tr>
<td>Caspofungin IV</td>
<td>Age ≥3mo: 70mg/m²/dose x1 then 50mg/m²/dose q24h</td>
<td>Adjust maintenance dose for severe hepatic dysfunction 70mg/m²/dose x 1, then 35mg/m²/dose q24h</td>
<td>Loading Dose: 70mg  Maintenance Dose: 50mg q24h</td>
</tr>
<tr>
<td>Cefepime IV</td>
<td>50mg/kg/dose q8h</td>
<td>Adjust for CrCl &lt; 50 ml/min/1.73m²</td>
<td>2g q8h</td>
</tr>
<tr>
<td>Ceftazidime IV</td>
<td>50mg/kg/dose q8h</td>
<td>Adjust for CrCl &lt; 50 ml/min/1.73m²</td>
<td>2g q8h</td>
</tr>
<tr>
<td>Ceftriaxone IV</td>
<td>50mg/kg/dose q24h</td>
<td>No adjustment</td>
<td>1g q24h</td>
</tr>
<tr>
<td>Levofloxacin IV/PO</td>
<td>6 mo–&lt;5 yo: 10mg/kg/dose q12h  ≥5 yo: 10mg/kg/dose q24h</td>
<td>Adjust for CrCl &lt; 50 ml/min/1.73m²</td>
<td>750mg q24h</td>
</tr>
<tr>
<td>Meropenem IV</td>
<td>20 mg/kg/dose q8h</td>
<td>Adjust for CrCl &lt; 50 ml/min/1.73m²</td>
<td>1g q8h</td>
</tr>
<tr>
<td>Piperacillin-tazobactam (Zosyn®) IV</td>
<td>100mg piperacillin/kg/dose q6h</td>
<td>Adjust for CrCl &lt; 50 ml/min/1.73m²</td>
<td>4g piperacillin q6h</td>
</tr>
<tr>
<td>Tobramycin IV</td>
<td>2.5 mg/kg/dose q8h</td>
<td>Adjust for CrCl &lt; 50 ml/min/1.73m²</td>
<td>None</td>
</tr>
<tr>
<td>Vancomycin IV</td>
<td>Age 3mo–&lt;12yo: 17.5mg/kg/dose q6h*  Age ≥12 yo: 15mg/kg/dose q6h*</td>
<td>Consult pharmacy for renal dose adjustment</td>
<td>Initial max: 4g/day</td>
</tr>
</tbody>
</table>

*Consult pharmacy for patient-specific dosing

For renal dose adjustment, consult pharmacist or kdpnet.kdp.louisville.edu/drugbook/pediatric

Peak and trough levels around 4th dose, consult pharmacy for dose adjustment and level assessment
<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Dose Adjustment</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole IV</td>
<td><strong>Age 2-&lt;12 yo</strong>&lt;br&gt;OR 12-14 yo and &lt;50kg:&lt;br&gt;Loading Dose: 9mg/kg/dose q12h x 2, then&lt;br&gt;Maintenance Dose: 8mg/kg/dose q12h</td>
<td>No adjustment for renal dysfunction but avoid IV formulation if CrCl &lt; 50 ml/min/1.73m²</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>**&gt;14 yo OR 12-14 yo and ≥ 50kg:&lt;br&gt;Loading Dose: 6mg/kg/dose q12h x 2, then&lt;br&gt;Maintenance Dose: 4mg/kg/dose q12h</td>
<td>Avoid if severe hepatic dysfunction, decrease maintenance dose by 50% for mild-moderate hepatic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Voriconazole PO</td>
<td><strong>2-&lt;12 yo OR 12-14 yo and &lt; 50kg:&lt;br&gt;9mg/kg/dose BID</strong></td>
<td></td>
<td>Initial Max Maintenance Dose 2-&lt;12 yo OR 12-14 yo and &lt; 50kg: 350mg/dose</td>
</tr>
<tr>
<td></td>
<td><strong>&gt;14 yo OR 12-14 yo and ≥ 50kg:&lt;br&gt;Loading Dose: 400mg/dose BID x 2, then Maintenance Dose 200mg/dose BID</strong></td>
<td>Trough level after 5 days on stable maintenance dosing. Consult ID/ASP pharmacist for dose adjustment and level assessment</td>
<td></td>
</tr>
</tbody>
</table>

For patients with documented beta-lactam allergy:
- Assessment via the Inpatient Beta-Lactam Allergy Guideline is strongly encouraged early in the course of treatment:
  - Refer to [idmp.ucsf.edu/sites/idmp.ucsf.edu/files/beta-lactam_pathway.pdf](http://idmp.ucsf.edu/sites/idmp.ucsf.edu/files/beta-lactam_pathway.pdf)
- The guideline provides recommendations to assess prior reaction history, determine what antibiotic(s) can be given at full dose and/or test dose, and pathways for penicillin skin testing and beta-lactam test dose procedure.
- A beta-lactam based regimen is considered optimal if it can be given. Alternatives that can be given at full dose are provided below, but are not preferred therapy based on spectrum of activity and/or toxicity profile.

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>First Choice Therapy</th>
<th>May Give at Full Dose to Patient with Beta-Lactam Allergy</th>
<th>May Give if Previously Tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Risk FN</td>
<td>Cefepime</td>
<td>Aztreonam* + Vancomycin&lt;br&gt;ADD Tobramycin if clinically unstable</td>
<td>Piperacillin-tazobactam (Zosyn®)</td>
</tr>
<tr>
<td>Low-Risk FN</td>
<td>Ceftazidime</td>
<td>Aztreonam</td>
<td>Piperacillin-tazobactam (Zosyn®)</td>
</tr>
<tr>
<td>Non-Neutropenic Fever</td>
<td>Ceftriaxone</td>
<td>Levofloxacin</td>
<td></td>
</tr>
</tbody>
</table>

*Aztreonam does not have any Gram-positive activity, so concurrent Vancomycin is recommended for patients with High-Risk FN even if the patient is clinically stable.*