

<b>Guideline/Protocol Title:</b>	UCSF Benioff Children’s Hospitals Guidelines for Fever in Patients Receiving Cancer Therapy and/or Hematopoietic Transplantation
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<b>Approving committee(s):</b>	Cross-Bay Update 2024: Pediatric Medication Review Committee (3/5/2024), BCH Oakland P&T (3/12/2024), UCSF P&T (4/10/2024)
<b>P&amp;T Approval Date:</b>	SF: 01/2016 (ED); 03/2016 (inpatient); OAK: 04/2016
<b>Last revision Date:</b>	02/20/2024

<b>PURPOSE/SCOPE:</b>	To provide standardized guidelines for management of fever in patients who have received chemotherapy or hematopoietic transplantation, including all hospital units and emergency departments at Benioff Children’s Hospitals. These guidelines do not address all aspects of infection prevention, supportive care and management in patients who are receiving cancer therapy or transplantation. Refer to Oncology and BMT Standards of Practice for other topics not addressed in these guidelines.
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<b>EXECUTIVE SUMMARY</b>
Patients who develop fever while undergoing cancer therapy or hematopoietic stem cell transplantation 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, local antimicrobial susceptibility data, and consensus review with clinical services.

<b>BACKGROUND / INTRODUCTION</b>
Patients undergoing cancer therapy and/or receiving hematopoietic cell transplantation are at high risk for infection and related complications. Management goals include: <ol style="list-style-type: none"> <li>1. Prompt initiation of appropriate broad-spectrum antibiotics for patients with fever and neutropenia and for patients with fever without neutropenia who are clinically unstable.</li> <li>2. Identification and appropriate treatment of serious infections.</li> <li>3. Avoidance of antimicrobial resistance, superinfections, and other adverse effects of antimicrobial therapy.</li> </ol>

## SUPPORTING EVIDENCE

Sources considered in development of the guidelines include references below, and bloodstream infection antibiogram data for each BCH hospital Pediatric Oncology and BMT services. See Appendix 6 Summary and Rationale for Changes for description of changes in this version, rationale and supporting literature.

## APPENDIX

1. Emergency Department Algorithm (page 4)
2. Initial Inpatient Management Algorithm (page 5)
3. Inpatient Non-Neutropenic Fever Algorithm (page 6)
4. Inpatient Re-assessment Algorithm (page 7)
5. Prolonged Fever with Ongoing Neutropenia Algorithm (page 8)
5. Alternative Antibiotics for Patients with Beta-Lactam Allergy (page 9)
6. Summary and Rationale for Changes (page 10-14, online version see web link to Box folder)
7. Content Reviewers (page 15)

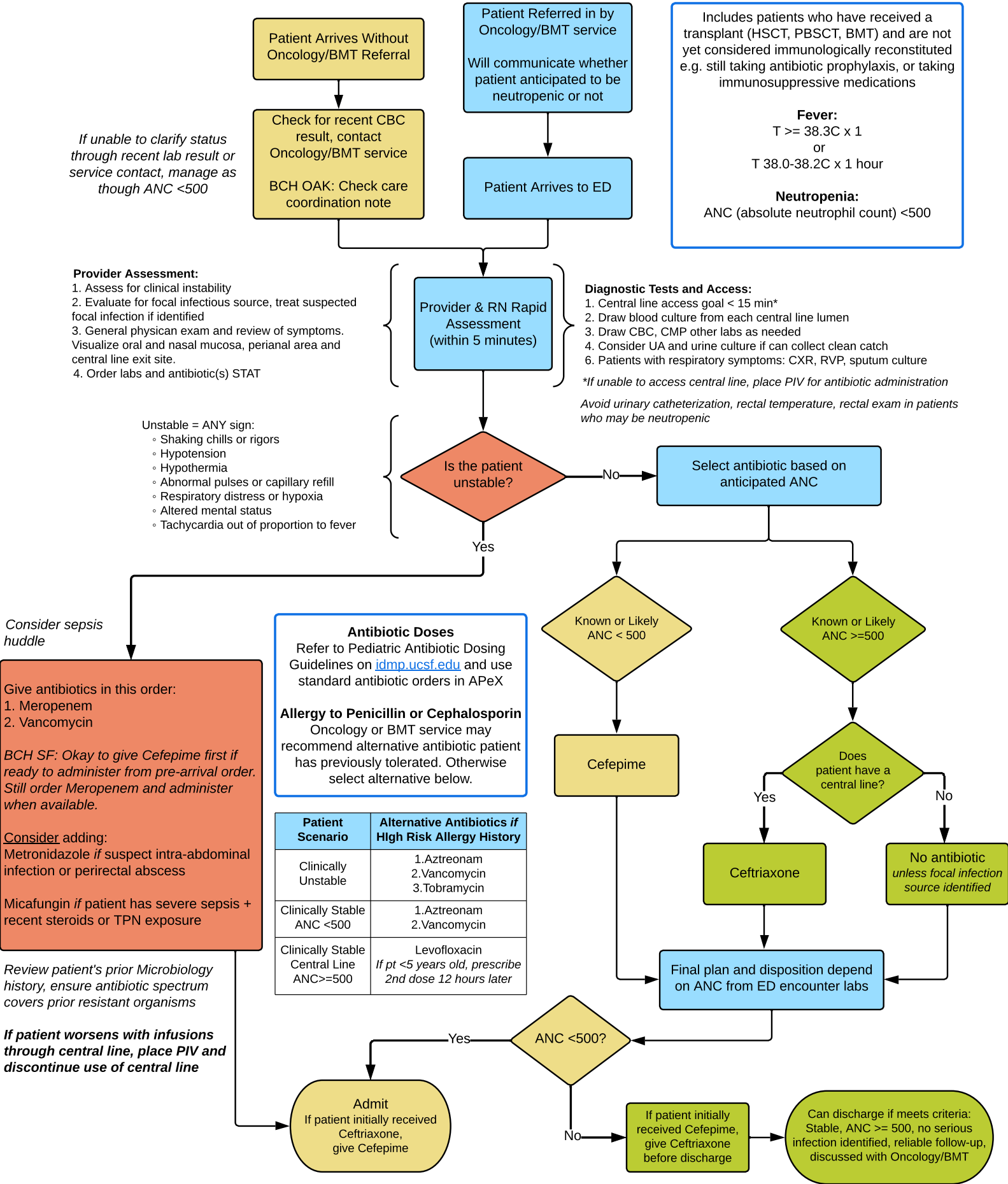
Reference #	Citation
1	Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2023 update. J Clin Oncol 2023;41:1774-1785.
2	Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013; 98:1826–1835.

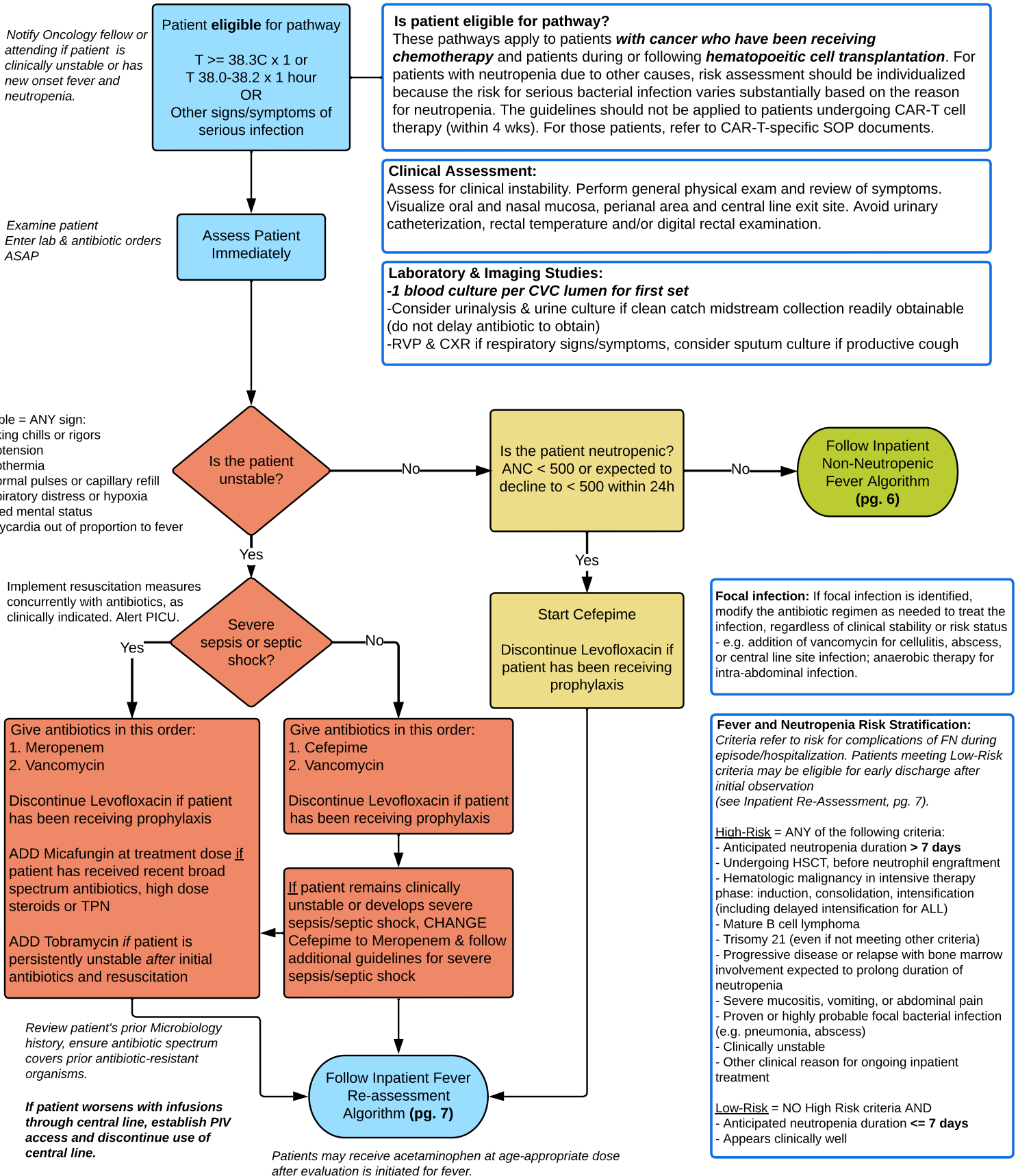
## Revision History

Revision Date	Update(s)
July 24, 2019	<ul style="list-style-type: none"><li>• Format change to incorporate ED and inpatient algorithms together</li><li>• Antimicrobial dosing removed from all but ED algorithm, to separate table</li><li>• Adding inpatient re-assessment algorithm (Appendix 3) with guidelines for de-escalation of therapy</li><li>• Referencing Oncology Standards of Practice for low-risk stepdown management and new diagnosis ALL antibiotic de-escalation</li><li>• Changes incorporated due to levofloxacin prophylaxis adoption:<ul style="list-style-type: none"><li>○ Escalation with vancomycin + carbapenem rather than with second Gram-negative agent</li></ul></li></ul>

	<ul style="list-style-type: none"> <li>○ Guidance to discontinue levofloxacin at start of empiric therapy</li> <li>● Non-neutropenic fever <ul style="list-style-type: none"> <li>○ Algorithm differentiates patients with intestinal GvHD at higher risk for bloodstream infection with antibiotic-resistant organisms</li> <li>○ Guidance not to routinely treat clinically stable, well-appearing patients with serotherapy-related fever on BMT service</li> </ul> </li> <li>● Allergy alternatives modified to be concordant with Inpatient Beta-Lactam Allergy Guideline and add reference to Beta-Lactam Allergy Guideline</li> <li>● Therapeutic drug monitoring guidance added to antimicrobial dosing table</li> </ul>
February 20, 2024	<ul style="list-style-type: none"> <li>● Cross-Bay Update combining BCH OAK and BCH SF guidelines</li> <li>● Added prolonged fever/invasive fungal disease evaluation pathway</li> <li>● Removed dosing from pathways and tables, referring to standard Pediatric Antimicrobial Dosing Guidelines as primary resource.</li> <li>● Added Appendix 6 Summary and Rationale for Changes, refer for more detail regarding changes from prior versions.</li> </ul>

# Fever in Patients Receiving Cancer Therapy and/or Hematopoietic Transplant Emergency Department Algorithm





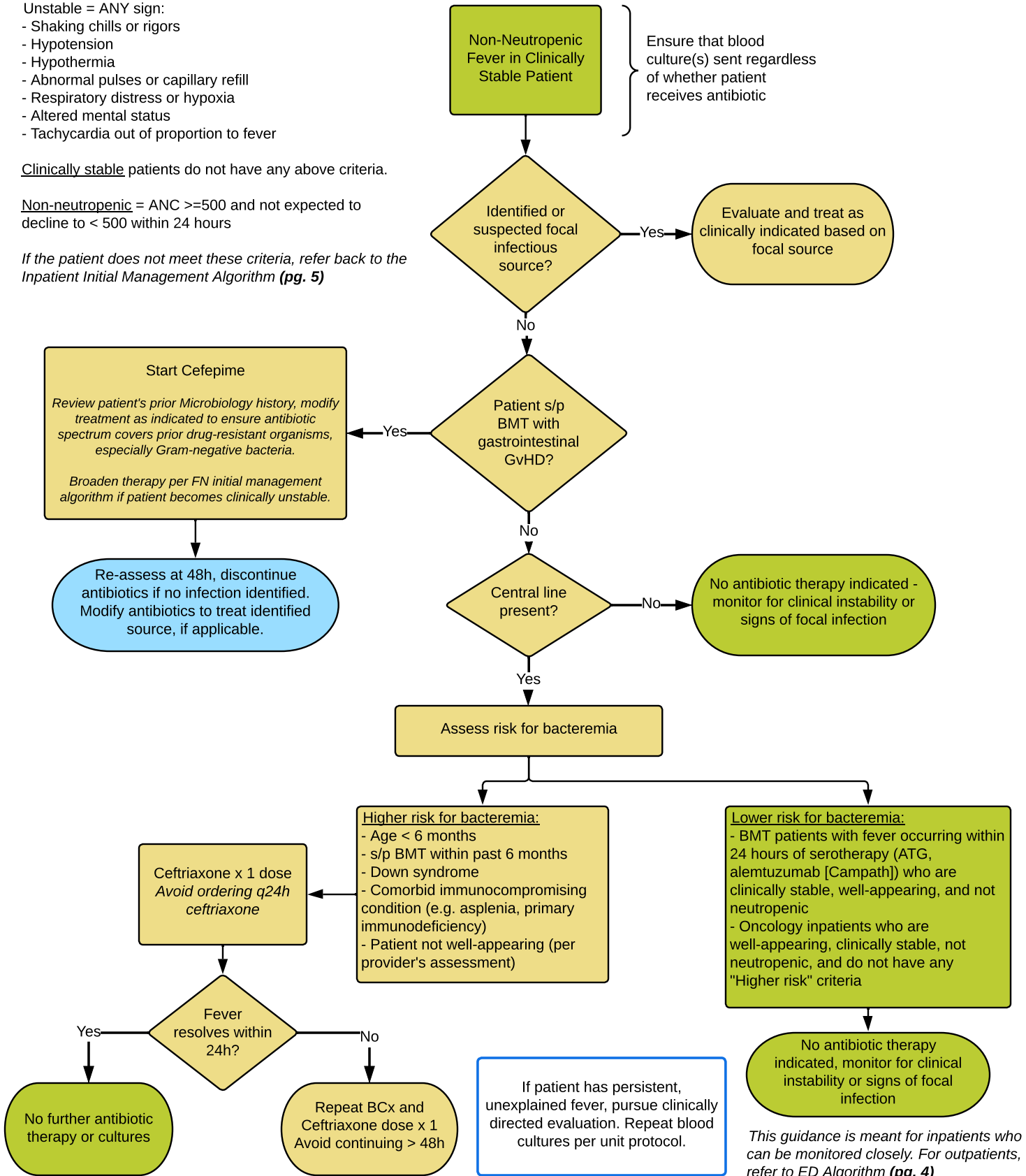
Refer to Table for Alternative Antibiotics in Patients with Penicillin or Cephalosporin Allergy (pg. 9)

- 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.

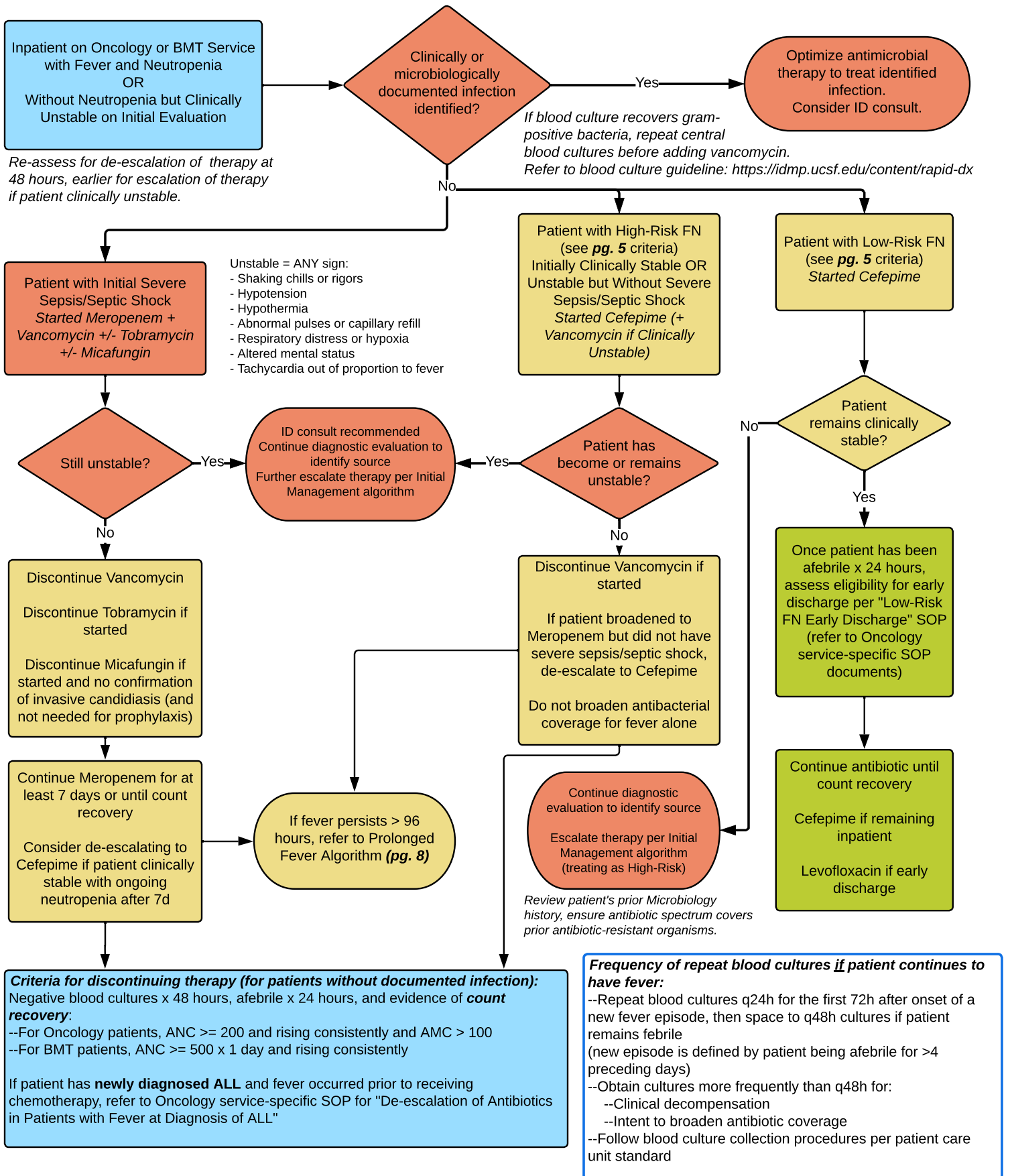
Non-neutropenic = ANC  $\geq$  500 and not expected to decline to  $<$  500 within 24 hours

If the patient does not meet these criteria, refer back to the Inpatient Initial Management Algorithm (pg. 5)



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.

**Refer to Table for Alternative Antibiotics  
in Patients with Penicillin or  
Cephalosporin Allergy (pg. 9)**



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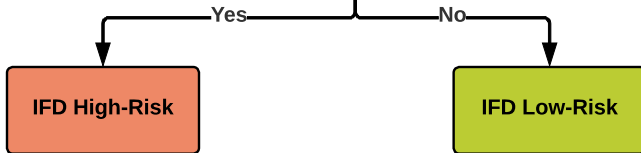
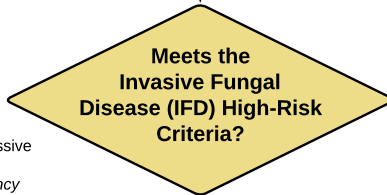
These criteria refer to risk for invasive fungal disease specifically and differ from the general FN High-Risk/ Low-Risk criteria (pg. 5)

**IFD High-Risk = ANY of the following criteria:**

- AML
  - High-risk or relapsed ALL
  - Prolonged neutropenia (>7 days)\*
  - High-dose corticosteroids\*
  - Allogeneic HSCT recipient prior to T-cell immune reconstitution
  - Receipt of corticosteroids or multiple immunosuppressive therapies to prevent or treat GvHD
- \*may apply to some patients with solid tumor malignancy

Resolution of fever is defined as being consistently afebrile for 96 hours.

**Prolonged Fever (≥96 hours) and Neutropenia**



**Diagnostic Evaluation:**

1. **CT chest (usually non-contrast) should be done** regardless of other signs/symptoms or lack of respiratory symptoms.
2. Perform review of symptoms, physical exam, and assess for patient risk factors and targeted diagnostic evaluation based on focal signs/symptoms (described in the blue border boxes).
3. Consider abdominal imaging (e.g. ultrasound or CT).
4. Consider sinus imaging (MRI preferred if high suspicion)
5. Consider testing for reactivated viral infection (e.g. CMV, adenovirus) based on patient risk factors.
6. Consider ID consultation.

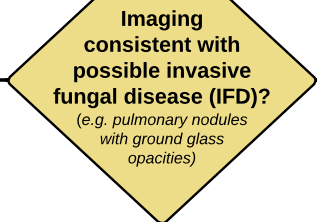
*Not recommended with prolonged fever alone: Fungal blood biomarker tests (e.g. galactomannan, beta-D-glucan), or fungal nucleic acid detection*

**Diagnostic Evaluation:**

1. Perform review of symptoms, physical exam, and assess for patient risk factors and targeted diagnostic evaluation based on focal signs/symptoms (described in the blue border boxes).
2. Consider ID consultation.

*Routine imaging is not recommended for prolonged fever alone*

**Antifungal Therapy:**  
Suggest not routinely starting empiric antifungal if patient has prolonged fever without other clinical evidence of IFD.



**Antifungal Therapy:**  
Start micafungin treatment dose or increase dose to treatment dose if patient has been receiving prophylaxis.

Continue until count recovery.

**Recommend ID consultation.**

**Diagnostic Evaluation:**

1. Plasma metagenomic NGS (BCH SF order titled "pathogen detection, mNGS", BCH OAK order titled "Karius Digital Culture Test")
2. Serum galactomannan
3. Diagnostic evaluation appropriate to involved site (e.g. BAL, biopsy, IR)

**Antifungal Therapy:**  
Recommend ID and pharmacy specialist consultation.

Start empiric antifungal therapy selected in consultation with ID based on patient's prior antifungal treatment/prophylaxis history, clinical presentation, and radiographic findings.

For an isolated finding of new pulmonary nodules, general parameters for antifungal selection:

- If patient has not received prior voriconazole, posaconazole, or isavuconazole, invasive aspergillosis is much more likely than other types of IFD such as mucormycosis. Voriconazole is considered first line. Posaconazole or isavuconazole are alternatives.
- If patient has received voriconazole, posaconazole, or isavuconazole, they are at higher risk for less common IFD such as mucormycosis but could still have invasive aspergillosis. Ambisome (liposomal amphotericin B) is recommended as empiric therapy.

**Provider Assessment and Directed Diagnostics for All Patients (Regardless of IFD Risk)**

**Provider Assessment:**

Assess patient at least daily by review of symptoms and physical exam to identify possible focal infections. IFD presentations include, but are not isolated to, pulmonary, sino-orbital, cutaneous, GI, CNS, and disseminated.

**Patient-specific risk factors to assess for:**

- Central lines: assess CVC function history with caregivers & RN (e.g. frequent clotting, difficulty drawing/flushing, requiring tPA)
- Community exposures and community-acquired infections (e.g. otitis media, respiratory viral infection)
- Risk for aspiration, impaired airway clearance
- Recent antibiotic use and C. difficile risk
- Surgery, surgical sites
- Devices (e.g. urinary catheter, VP shunt, orthopedic implant)
- Pressure ulcers in patients with neurologic impairment or other risk factors for pressure injury due to positioning or devices
- Immune-mediated or medication-related causes of fever

**Full physical exam should be performed, including:**

- **Sinofacial exam:** visualize palate, nasal septum, and mouth for abnormal lesions. Check ocular movement, and for signs of orbital edema, sinus or orbital tenderness, pressure, facial edema.
- **Skin and mucosal exam,** including areas covered by tape, pressure sites, and the peri-rectal area. Cutaneous IFD is associated with surgery, catheters, and adhesive tape. Minor-appearing skin & mucosal lesions may be clinically important. Evolving lesions could signify cutaneous or disseminated IFD, and increasing lesions in number or size should warrant immediate workup.
- **CVC exam:** visualize dressing and site for erythema, fluctuance, tenderness, or drainage around the exit site of the catheter.

**Directed Diagnostics Based on Focal Symptoms/Signs:**

If focal symptoms/signs present, especially if new during the febrile episode, strongly consider the following:

- **Respiratory signs/symptoms:**
  - Upper respiratory symptoms only: RVP
  - Lower respiratory signs/symptoms: RVP, non-contrast chest CT. A negative CXR does not rule out pulmonary disease.
- **Sinus or orbital symptoms/signs:**
  - MRI with contrast of sinus & orbit preferred over CT
  - Urgent OHNS +/- Ophthalmology consult depending on localization if an abnormal lesion is visualized directly or found on imaging
- **New or evolving skin lesions:** Dermatology consult, possible skin biopsy
- **Abdominal pain:** abdominal imaging (US or CT)
- **New or worsening diarrhea:**
  - Stop laxatives if applicable
  - If ≥3 loose stools in 24h: send stool C. difficile testing, viral GI panel (bacterial and parasitic panel not indicated if patient has been hospitalized >72 hours)
- **Peri- or intra-oral vesicles:** swab a freshly unroofed lesion for HSV PCR (preferred over blood/plasma PCR)

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.

Refer to [Pediatric Antimicrobial Dosing Guidelines](#) and Epic order panels for antimicrobial doses.

For patients with documented beta-lactam (penicillin or cephalosporin) allergy:

- Assessment via the [Inpatient Beta-Lactam Allergy Guideline](#) is strongly encouraged early during treatment or before antibiotic therapy is needed. Most (>90%) patients with history of allergy do not have true allergy and can safely tolerate beta-lactam antibiotic therapy. Having an allergy label and receiving non-first line antibiotics increases risk for adverse events, *Clostridioides difficile* infection and longer hospitalization.
- The beta-lactam allergy 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 test dose procedure.
- A beta-lactam based regimen is considered optimal if it can be given. Alternative regimens are provided below based on allergy risk assessment. An aztreonam-based regimen can be given at full dose but is not preferred therapy based on spectrum of activity and/or toxicity profile.

Indication for Antibiotic	First Choice Therapy	Penicillin allergy with lower risk for allergic reaction	Penicillin allergy with higher risk for allergic reaction	Cephalosporin allergy
Febrile Neutropenia	Cefepime	Cefepime	Aztreonam* + Vancomycin  ADD Tobramycin if clinically unstable  Test dose Cefepime per Beta Lactam Allergy guideline recommended after initiation of antibiotics	Aztreonam* + Vancomycin  ADD Tobramycin if clinically unstable  Refer to Beta Lactam Allergy guideline for options to give with/without test dose based on specific prior reaction
Non-Neutropenic Fever	Ceftriaxone	Ceftriaxone	Levofloxacin <i>For patient age &lt;5 years, prescribe second dose to give 12 hours later</i>  OR  Ceftriaxone by test dose procedure	Levofloxacin <i>For patient age &lt;5 years, prescribe second dose to give 12 hours later</i>

\*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. For Low-Risk FN may consider aztreonam alone.

## Content Reviewers

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