Guideline/Protocol Title:	UCSF Benioff Children's Hospitals Guidelines for Fever in Patients Receiving Cancer Therapy and/or Hematopoietic Transplantation
Original Author(s):	SF version: Rachel Wattier (Antibiotic Stewardship Program, ASP, primary content owner), Amit Sabnis (Oncology), Justin Wahlstrom (BMT), Christopher Dvorak (BMT) OAK version: Nahal Lalefar (Oncology/BMT), Anurag Agrawal (Oncology/BMT), Brian Lee (ASP)
Collaborator(s):	Cross-Bay Update 2024: Prachi Singh (ASP, BCH OAK content owner), Cynthia Huwe (ASP), Steve Grapentine (ASP) See Appendix 7 Content Reviewers
Approving committee(s):	Cross-Bay Update 2024: Pediatric Medication Review Committee (3/5/2024), BCH Oakland P&T (3/12/2024), UCSF P&T (4/10/2024)
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PURPOSE/SCOPE:	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.

EXECUTIVE SUMMARY

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.

BACKGROUND / INTRODUCTION

Patients undergoing cancer therapy and/or receiving hematopoietic cell transplantation are at high risk for infection and related complications. Management goals include:

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.
2. Identification and appropriate treatment of serious infections.
3. Avoidance of antimicrobial resistance, superinfections, and other adverse effects of antimicrobial therapy.

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	• Format change to incorporate ED and inpatient algorithms together • Antimicrobial dosing removed from all but ED algorithm, to separate table • Adding inpatient re-assessment algorithm (Appendix 3) with guidelines for de-escalation of therapy • Referencing Oncology Standards of Practice for low-risk stepdown management and new diagnosis ALL antibiotic de-escalation • Changes incorporated due to levofloxacin prophylaxis adoption: ○ Escalation with vancomycin + carbapenem rather than with second Gram-negative agent

	○ Guidance to discontinue levofloxacin at start of empiric therapy • Non-neutropenic fever ○ Algorithm differentiates patients with intestinal GvHD at higher risk for bloodstream infection with antibiotic-resistant organisms ○ Guidance not to routinely treat clinically stable, well-appearing patients with serotherapy-related fever on BMT service • Allergy alternatives modified to be concordant with Inpatient Beta-Lactam Allergy Guideline and add reference to Beta-Lactam Allergy Guideline • Therapeutic drug monitoring guidance added to antimicrobial dosing table
February 20, 2024	• Cross-Bay Update combining BCH OAK and BCH SF guidelines • Added prolonged fever/invasive fungal disease evaluation pathway • Removed dosing from pathways and tables, referring to standard Pediatric Antimicrobial Dosing Guidelines as primary resource. • Added Appendix 6 Summary and Rationale for Changes, refer for more detail regarding changes from prior versions.

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

Patient Arrives Without Oncology/BMT Referral

Check for recent CBC result, contact Oncology/BMT service

BCH OAK: Check care coordination note

If unable to clarify status through recent lab result or service contact, manage as though ANC <500

Patient Referred in by Oncology/BMT service

Will communicate whether patient anticipated to be neutropenic or not

Patient Arrives to ED

Includes patients who have received a transplant (HSCT, PBSCT, BMT) and are not yet considered immunologically reconstituted e.g. still taking antibiotic prophylaxis, or taking immunosuppressive medications

Fever:
T >= 38.3C x 1
or
T 38.0-38.2C x 1 hour

Neutropenia:
ANC (absolute neutrophil count) <500

Provider Assessment:
1. Assess for clinical instability
2. Evaluate for focal infectious source, treat suspected focal infection if identified
3. General physican exam and review of symptoms. Visualize oral and nasal mucosa, perianal area and central line exit site.
4. Order labs and antibiotic(s) STAT

Provider & RN Rapid Assessment (within 5 minutes)

Diagnostic Tests and Access:
1. Central line access goal < 15 min*
2. Draw blood culture from each central line lumen
3. Draw CBC, CMP other labs as needed
4. Consider UA and urine culture if can collect clean catch
6. Patients with respiratory symptoms: CXR, RVP, sputum culture

**If unable to access central line, place PIV for antibiotic administration*

Avoid urinary catheterization, rectal temperature, rectal exam in patients who may be neutropenic

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

Is the patient unstable?

No → Select antibiotic based on anticipated ANC

Yes

Consider sepsis huddle

Give antibiotics in this order:
1. Meropenem
2. Vancomycin

BCH SF: Okay to give Cefepime first if ready to administer from pre-arrival order. Still order Meropenem and administer when available.

Consider adding:
Metronidazole *if* suspect intra-abdominal infection or perirectal abscess

Micafungin *if* patient has severe sepsis + recent steroids or TPN exposure

Review patient's prior Microbiology history, ensure antibiotic spectrum covers prior resistant organisms

If patient worsens with infusions through central line, place PIV and discontinue use of central line

Antibiotic Doses
Refer to Pediatric Antibiotic Dosing Guidelines on idmp.ucsf.edu and use standard antibiotic orders in APeX

Allergy to Penicillin or Cephalosporin
Oncology or BMT service may recommend alternative antibiotic patient has previously tolerated. Otherwise select alternative below.

Patient Scenario	Alternative Antibiotics *if* HIgh Risk Allergy History
Clinically Unstable	1.Aztreonam 2.Vancomycin 3.Tobramycin
Clinically Stable ANC <500	1.Aztreonam 2.Vancomycin
Clinically Stable Central Line ANC>=500	Levofloxacin *If pt <5 years old, prescribe 2nd dose 12 hours later*

Known or Likely ANC < 500 → Cefepime

Known or Likely ANC >=500 → Does patient have a central line?

Yes → Ceftriaxone

No → No antibiotic *unless focal infection source identified*

Final plan and disposition depend on ANC from ED encounter labs

ANC <500?

Yes → Admit
If patient initially received Ceftriaxone, give Cefepime

No → If patient initially received Cefepime, give Ceftriaxone before discharge → Can discharge if meets criteria: Stable, ANC >= 500, no serious infection identified, reliable follow-up, discussed with Oncology/BMT

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 Owners: Prachi Singh (ASP) & Rachel Wattier (ASP); SF Pharmacy & Therapeutics Approved 01/2016, Updated Cross-Bay: 02/2024

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Fever in Patients Receiving Cancer Therapy and/or Hematopoeitic Transplant
Initial Inpatient Management Algorithm

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

Notify Oncology fellow or attending if patient is clinically unstable or has new onset fever and neutropenia.

Patient **eligible** for pathway

T >= 38.3C x 1 or
T 38.0-38.2 x 1 hour
OR
Other signs/symptoms of serious infection

Is patient eligible for pathway?
These pathways apply to patients ***with cancer who have been receiving chemotherapy*** and patients during or following ***hematopoeitic cell transplantation***. For patients with neutropenia due to other causes, risk assessment should be individualized because the risk for serious bacterial infection varies substantially based on the reason for neutropenia. The guidelines should not be applied to patients undergoing CAR-T cell therapy (within 4 wks). For those patients, refer to CAR-T-specific SOP documents.

Examine patient
Enter lab & antibiotic orders ASAP

Assess Patient Immediately

Clinical Assessment:
Assess for clinical instability. Perform general physical exam and review of symptoms. Visualize oral and nasal mucosa, perianal area and central line exit site. Avoid urinary catheterization, rectal temperature and/or digital rectal examination.

Laboratory & Imaging Studies:
-1 blood culture per CVC lumen for first set
-Consider urinalysis & urine culture if clean catch midstream collection readily obtainable (do not delay antibiotic to obtain)
-RVP & CXR if respiratory signs/symptoms, consider sputum culture if productive cough

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

Is the patient unstable?

No → Is the patient neutropenic? ANC < 500 or expected to decline to < 500 within 24h

No → Follow Inpatient Non-Neutropenic Fever Algorithm **(pg. 6)**

Yes

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 Levofloxacin if patient has been receiving prophylaxis

ADD Micafungin at treatment dose <u>if</u> patient has received recent broad spectrum antibiotics, high dose steroids or TPN

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

No

Give antibiotics in this order:
1. Cefepime
2. Vancomycin

Discontinue Levofloxacin if patient has been receiving prophylaxis

<u>If</u> patient remains clinically unstable or develops severe sepsis/septic shock, CHANGE Cefepime to Meropenem & follow additional guidelines for severe sepsis/septic shock

Yes

Start Cefepime

Discontinue Levofloxacin if patient has been receiving prophylaxis

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

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

Follow Inpatient Fever Re-assessment Algorithm **(pg. 7)**

Patients may receive acetaminophen at age-appropriate dose after evaluation is initiated for fever.

Focal infection: If focal infection is identified, modify 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 and Neutropenia Risk Stratification:
Criteria refer to risk for complications of FN during episode/hospitalization. Patients meeting Low-Risk criteria may be eligible for early discharge after initial observation
(see Inpatient Re-Assessment, pg. 7).

<u>High-Risk</u> = ANY of the following criteria:
- Anticipated neutropenia duration **> 7 days**
- Undergoing HSCT, before neutrophil engraftment
- Hematologic malignancy in intensive therapy phase: induction, consolidation, intensification (including delayed intensification for ALL)
- Mature B cell lymphoma
- Trisomy 21 (even if not meeting other criteria)
- Progressive disease or relapse with bone marrow involvement expected to prolong duration of neutropenia
- Severe mucositis, vomiting, or abdominal pain
- Proven or highly probable focal bacterial infection (e.g. pneumonia, abscess)
- Clinically unstable
- Other clinical reason for ongoing inpatient treatment

<u>Low-Risk</u> = NO High Risk criteria AND
- Anticipated neutropenia duration **<= 7 days**
- Appears clinically well

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 Owners: Prachi Singh (ASP) & Rachel Wattier (ASP); SF Pharmacy & Therapeutics Approved 03/2016, Updated Cross-Bay: 02/2024

Fever in Patients Receiving Cancer Therapy and/or Hematopoeitic Transplant
Inpatient Non-Neutropenic Fever Algorithm

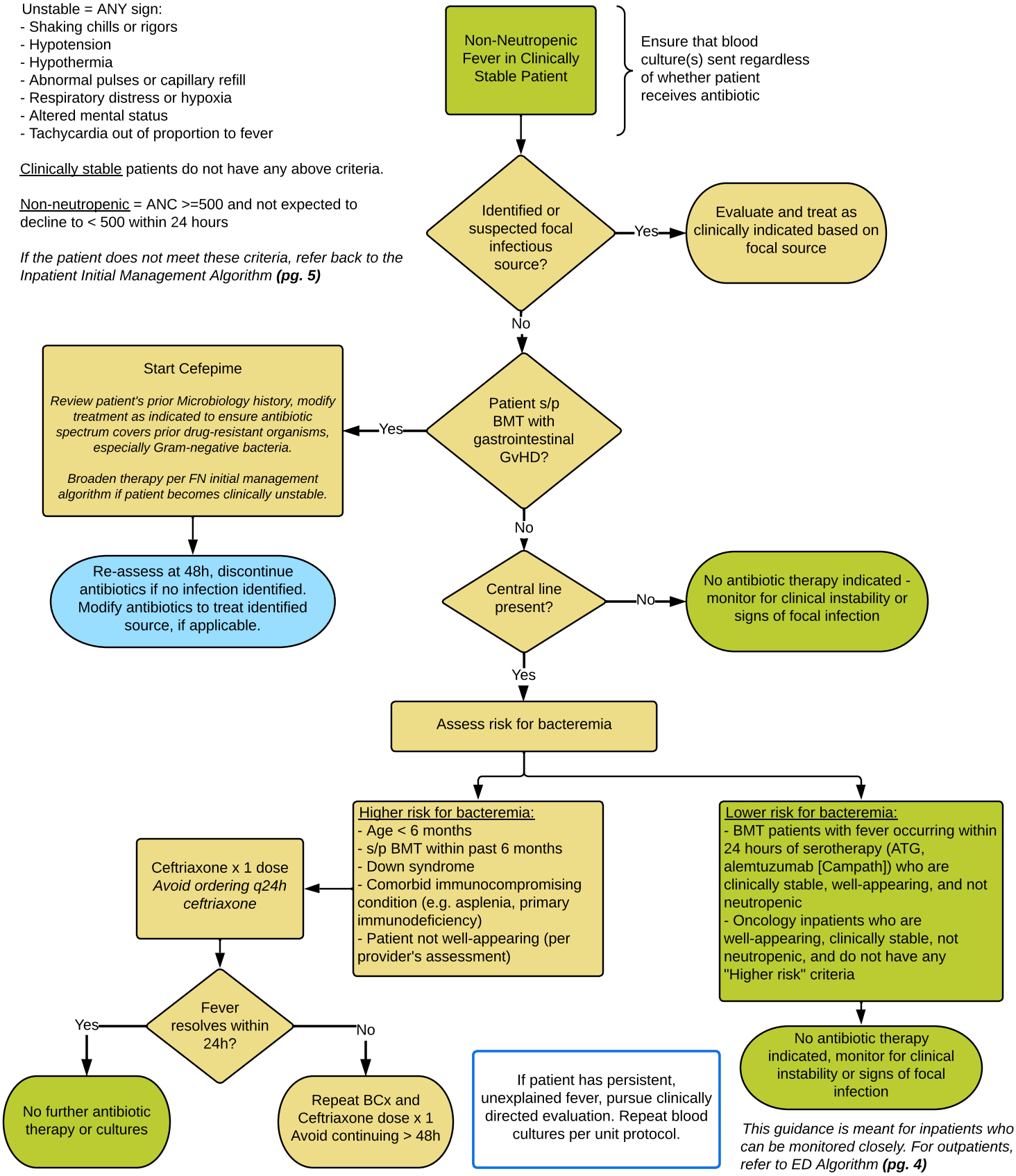
Refer to Table for Alternative Antibiotics in Patients with Penicillin or Cephalosporin Allergy (pg. 9)

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 >=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)***



This guidance is meant for inpatients who can be monitored closely. For outpatients, refer to ED Algorithm ***(pg. 4)***

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Fever in Patients Receiving Cancer Therapy and/or Hematopoeitic Transplant
Inpatient Re-assessment Algorithm

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

Inpatient on Oncology or BMT Service with Fever and Neutropenia
OR
Without Neutropenia but Clinically Unstable on Initial Evaluation

Re-assess for de-escalation of therapy at 48 hours, earlier for escalation of therapy if patient clinically unstable.

Clinically or microbiologically documented infection identified?

Yes → Optimize antimicrobial therapy to treat identified infection.
Consider ID consult.

If blood culture recovers gram-positive bacteria, repeat central blood cultures before adding vancomycin.
Refer to blood culture guideline: https://idmp.ucsf.edu/content/rapid-dx

No

Patient with Initial Severe Sepsis/Septic Shock
Started Meropenem + Vancomycin +/- Tobramycin +/- Micafungin

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

Patient with High-Risk FN (see ***pg. 5*** criteria)
Initially Clinically Stable OR Unstable but Without Severe Sepsis/Septic Shock
Started Cefepime (+ Vancomycin if Clinically Unstable)

Patient with Low-Risk FN (see ***pg. 5*** criteria)
Started Cefepime

Still unstable?
- Yes → ID consult recommended
Continue diagnostic evaluation to identify source
Further escalate therapy per Initial Management algorithm
- No → Discontinue Vancomycin
Discontinue Tobramycin if started
Discontinue Micafungin if started and no confirmation of invasive candidiasis (and not needed for prophylaxis)
→ Continue Meropenem for at least 7 days or until count recovery
Consider de-escalating to Cefepime if patient clinically stable with ongoing neutropenia after 7d
→ If fever persists > 96 hours, refer to Prolonged Fever Algorithm ***(pg. 8)***

Patient has become or remains unstable?
- Yes → ID consult recommended
Continue diagnostic evaluation to identify source
Further escalate therapy per Initial Management algorithm
- No → Discontinue Vancomycin if started
If patient broadened to Meropenem but did not have severe sepsis/septic shock, de-escalate to Cefepime
Do not broaden antibacterial coverage for fever alone

Patient remains clinically stable?
- No → Continue diagnostic evaluation to identify source
Escalate therapy per Initial Management algorithm (treating as High-Risk)
- Yes → Once patient has been afebrile x 24 hours, assess eligibility for early discharge per "Low-Risk FN Early Discharge" SOP (refer to Oncology service-specific SOP documents)
→ Continue antibiotic until count recovery
Cefepime if remaining inpatient
Levofloxacin if early discharge

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

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 service-specific SOP for "De-escalation of Antibiotics in Patients with Fever at Diagnosis of ALL"

Frequency of repeat blood cultures <u>if</u> 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
  --Intent to broaden antibiotic coverage
--Follow blood culture collection procedures per patient care unit standard

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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Fever in Patients Receiving Cancer Therapy and/or Hematopoeitic Transplant
Prolonged Fever with Ongoing Neutropenia Algorithm

Prolonged Fever (≥96 hours) and Neutropenia

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

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*

Meets the Invasive Fungal Disease (IFD) High-Risk Criteria?

Yes → **IFD High-Risk**

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 targed 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

Imaging consistent with possible invasive fungal disease (IFD)?
(e.g. pulmonary nodules with ground glass opacities)

No → **Antifungal Therapy:**
Start micafungin treatment dose or increase dose to treatment dose if patient has been receiving prophylaxis.

Continue until count recovery.

Yes → **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.

No → **Antifungal Therapy:**
Suggest not routinely starting empiric antifungal if patient has prolonged fever without other clinical evidence of IFD.

Diagnostic Evaluation:
1. Perform review of symptoms, physical exam, and assess for patient risk factors and targed 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

No → **IFD Low-Risk**

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 warrent immediate workup.
- **CVC exam**: visualize dressing and site for erythema, fluctuance, tendernesss, 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.

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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 *For patient age <5 years, prescribe second dose to give 12 hours later* OR Ceftriaxone by test dose procedure	Levofloxacin *For patient age <5 years, prescribe second dose to give 12 hours later*

*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.

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Content Reviewers

Pediatric Clinical Group	BCH OAK Reviewers	BCH SF Reviewers
Oncology	Anurag Agrawal Nahal Lalefar *(representing both services)*	Anuradha Banerjee Benjamin Huang
BMT		Sandhya Kharbanda
Clinical Pharmacy	Jelyn Evangelista Alia Yahya	Monica Huynh Tina Gu
Critical Care	Natalie Cvijanovich	Matt Zinter
Emergency Medicine	Lisa Hart Rajesh Daftary	Efrat Rosenthal
Infectious Diseases	Anders Newman *(both campuses)* Su Jin Joo *(both campuses)*	Tom Tarro