UNC Children's Clinical Practice Guideline
Pediatric Fever and Chemotherapy-Induced Neutropenia
Page 1: Overview

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Dates
Initial Final Version: 11/07/22
Last Updated: 02/06/23

Contents

How to use this guideline
This document provides guidance in management, including diagnostic evaluation and antimicrobial therapy, of children with chemotherapy-induced febrile neutropenia (FN). This document is not intended to replace clinician judgment in individual cases; however, these guidelines should apply to the vast majority of patients diagnosed with chemotherapy-induced FN.

Of note, patients undergoing chemotherapy may develop life threatening infections in the absence of a fever, emphasizing the need to rely on a complete range of clinical signs and symptoms, rather than placing full reliance on the temperature.

This guideline does NOT address management of pediatric patients with FN who are being evaluated in the Emergency Department or have aplastic anemia, previously received hematopoietic stem cell transplant, solid organ transplant, or other causes of neutropenia.

Population
Inclusion criteria: pediatric patients actively receiving cytotoxic chemotherapy or recovering from recent administration of cytotoxic chemotherapy with concern for FN and treated at UNC Children's Hospital.

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Page 2: Initial Antimicrobial Management

START
Concern for febrile neutropenia?

Yes → Is the patient septic or in septic shock?

Yes → **Initiate Pediatric Code Sepsis**
Begin cefepime and vancomycin (immediately after obtaining labs, if possible)

No → OFF algorithm

No → Obtain **STAT**:
1) CBC w/ differential (if not already done)
2) Blood cultures from all lumens of central line
3) Peripheral blood culture preferred to assist in determining ability for line salvage vs removal

DEFINITIONS

Fever = single temperature ≥38.3°C (101°F) or sustained >38°C (100.4°F) x1h

Neutropenia = ANC ≤ 500 or expected to be ≤ 500 within next 48 hours

What is the ANC?

- **ANC ≤ 500** → Does the patient have symptoms concerning for typhlitis?
- **ANC > 500** → Is the patient's ANC anticipated to be ≤ 500 in next 48-72h?

No → OFF algorithm

Yes → Continue with the algorithm

Does the patient have symptoms concerning for typhlitis?

No → Start cefepime

Yes → Start pip/tazo* (Don't combine with vanco)

*For patients with severe or IgE-mediated penicillin allergy, consider using aztreonam, levofloxacin, or meropenem

Metronidazole must be added to aztreonam and levofloxacin for anaerobic coverage.

Continue to assess patient's clinical status (Tables 1-2)

Repeat clinician assessment frequently during the first 6 hours following pathway initiation

Does the patient meet criteria for empiric vancomycin?
1) Mucositis
2) Skin or medical device site infection
3) AML patient
4) Induction, re-induction, or delayed intensification

YES → Is the patient on pip/tazo?

Yes → Change pip/tazo to cefepime AND metronidazole

No → ADD vancomycin

AND

NO → Return to Algorithm

Does the patient meet criteria for empiric acyclovir?
1) Cutaneous vesicular rash
2) Vesicular oral/perioral lesions
3) Other concerns for HSV/VZV

YES → ADD acyclovir IV

NO → Return to Algorithm

Continue to Page 3

Table 1: Clinical Status Assessment

Complete review of systems, with special focus on neuro, nose/sinuses, mouth, lower respiratory, GI, and skin
Detailed PE with particular focus on nose/sinuses, mouth, pulmonary, GI, and skin. Attention on sites of medical devices (e.g., CVC, G-tube), wounds, and perianal region.
Repeat vital signs every 4 hours for at least the first 24 hours

Table 2: Additional Workup based on Clinical Status Assessment

Respiratory Symptoms	Chest X-ray Full RPP-COVID
Genitourinary Symptoms	Urinalysis & urine culture
Significant Abdominal Pain	CT abdomen with contrast
Diarrhea	Defined as ≥3 loose stools/24h GIPP & *C diff*
Vesicular Oral/Perioral Lesions	HSV/VZV lesion swab(s) HSV/VZV blood PCRs
Cutaneous Vesicular Rash	HSV/VZV lesion swab(s)

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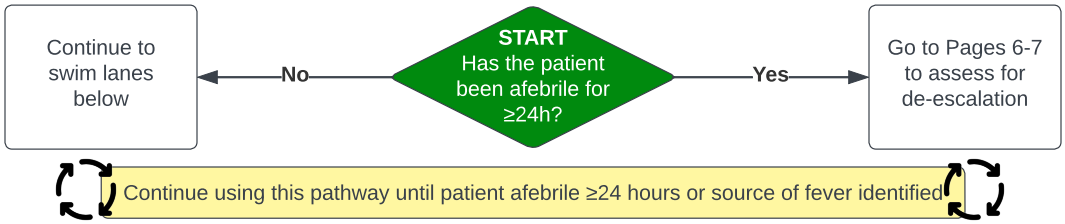
Page 3: Management of Continued Febrile Neutropenia



Time

	Antimicrobials	Lab Diagnostics	Imaging Diagnostics	Additional Considerations
Days 0-1 of Fever & Neutropenia	Continue empiric antimicrobial therapy as determined via algorithm on Page 2	Blood cultures at **time 0** (line & peripheral) and **24 hours** (line only; repeat peripheral if initial positive) Laboratory and imaging diagnostics based on clinical status assessment See Tables 1-2 on Page 2 for more details		Repeat clinician assessment frequently during the first 6 hours following pathway initiation Repeat vital signs every 4 hours while febrile
Days 2-4 of ongoing Fever & Neutropenia	Continue empiric antimicrobial therapy as determined via algorithm on Page 2 **Consider stopping empiric vancomycin** if no positive culture, clinical diagnosis (e.g., SSTI), or risk factors warranting need	Repeat blood cultures at **time 48 hours** OR if new concern for sepsis Blood cultures should not be repeated more than **every 48-72 hours** thereafter for persistent fever alone	Imaging diagnostics based on clinical status assessment See Table 2 on Page 2 for more details	If an infectious etiology is identified, consider targeting antimicrobial therapy Fever alone is not an indication for expanding gram-negative coverage
Days 5+ of ongoing Fever & Neutropenia	Continue empiric antimicrobial therapy as determined via algorithm on Page 2 Consider addition of empiric antifungal therapy upon initiating IFI work-up; see Page 4	Consider initiating invasive fungal infection (IFI) work-up for patients at high risk for IFI See Page 4 for algorithm		Patients at high risk of IFI include the following: Neutropenia >7 days Acute leukemia

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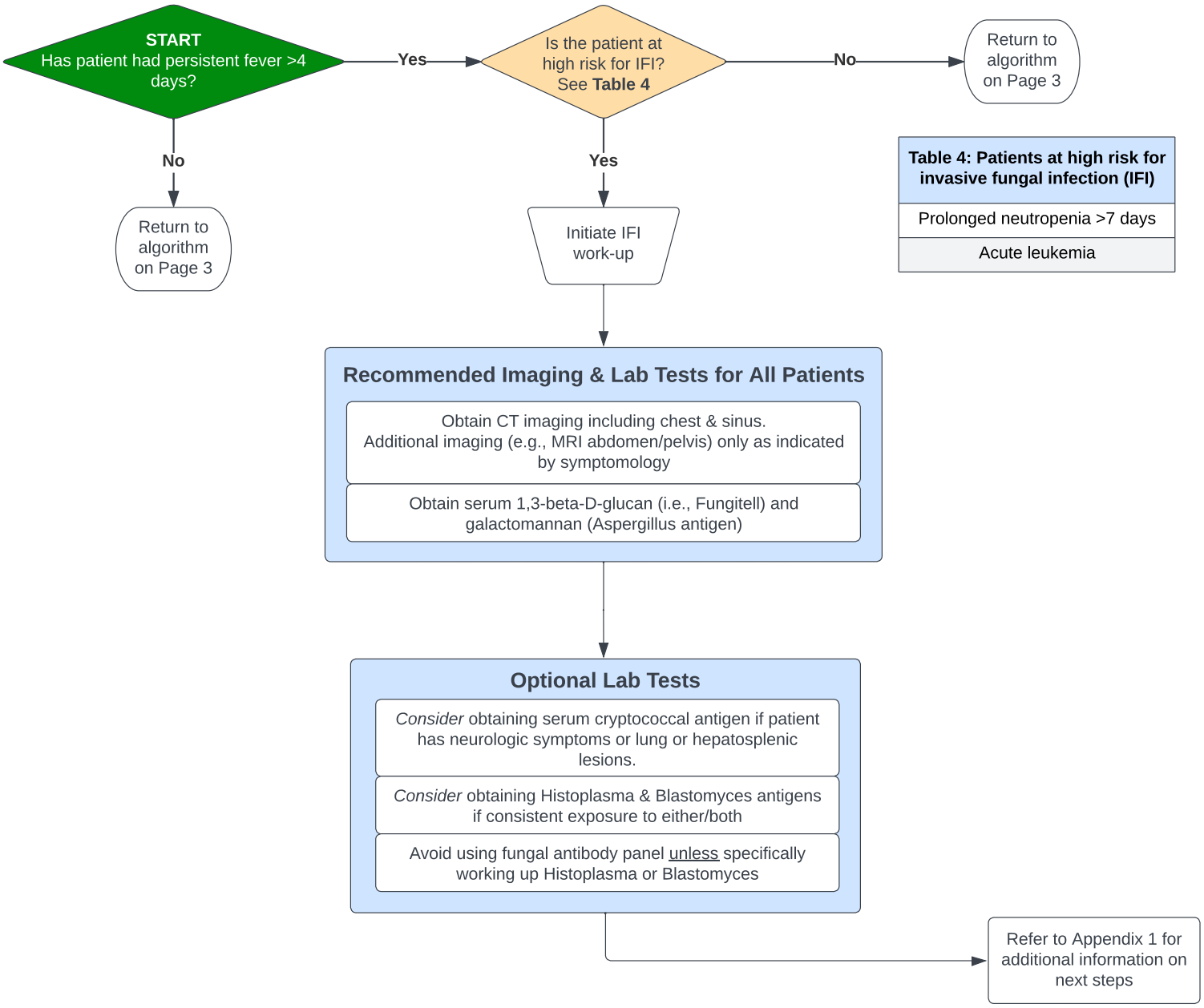
Page 4: Invasive Fungal Infection Work-up



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Page 5: Antimicrobial De-escalation Strategies for the Standard-Risk Neutropenic Patient

START
Does the patient meet ≥1 of the High-Risk Criteria? See Table 5

No → Patient considered **Standard-Risk** neutropenia

Yes → Patient considered **High-Risk** neutropenia
Return to Page 6

Has the patient been afebrile ≥48h?

No → Return to Page 3 for ongoing FN management

Yes → Assess level of suspicion for bacterial infection

Table 5. Criteria for High-Risk Neutropenia

Patient/Disease Factors	FN Episode Factors
AML	Hypotension
ALL (induction or delayed intensification)	Tachypnea or O2 <94%
Burkitt Leukemia OR Lymphoma	New chest X-ray changes suggestive of infection
Progressive or relapsed disease with marrow involvement	Altered mental status
Down Syndrome	Severe mucositis
	Vomiting or abdominal pain concerning for typhlitis

LOW suspicion for bacterial infection
- All bacterial cultures are negative OR respiratory virus identified without evidence of concomitant bacterial infection
- No suggestion of bacterial infection on imaging or physical examination

Treatment Recommendations
- De-escalate empiric ABX if patient is clinically stable and has remained afebrile ≥48 hours

De-escalation Strategy
- Discontinue empiric antibiotics, regardless of ANC

SUSPECTED bacterial infection
- All bacterial cultures are negative
- Possible bacterial infection based on imaging and/or physical examination (e.g., cellulitis, community acquired pneumonia, typhlitis, appendicitis, etc.)

Treatment Recommendations
- Tailor empiric ABX to target suspected infection if patient is clinically stable and has remained afebrile ≥48 hours

De-escalation Strategy & Duration
- Consider discontinuing targeted ABX after completion of an appropriate duration of therapy based on suspected infection, regardless of ANC

DOCUMENTED bacterial infection
- Positive bacterial culture AND/OR imaging or physical examination finding(s) consistent with infection

Treatment Recommendations
- Tailor empiric ABX to target infection if patient is clinically stable and has remained afebrile ≥48 hours

De-escalation Strategy & Duration
- Consider discontinuing targeted ABX according to duration of therapy recommended for documented infection

Continue daily monitoring for signs & symptoms of infection.
Re-initiate empiric antipseudomonal beta-lactam if:
- Fever: single temperature ≥38.3°C (101°F) or sustained >38°C x1h
- Newly positive bacterial cultures
- Physical examination or radiographic imaging findings consistent with probable or documented bacterial infection

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Page 6: Antimicrobial De-escalation Strategies for the High-Risk Neutropenic Patient

START
Does the patient meet ≥1 of the High-Risk Criteria? See Table 5

Yes → Patient considered **High-Risk** neutropenia

No → Patient considered **Standard-Risk** neutropenia Return to Page 5

Has the patient been afebrile ≥48h?

No → Return to Page 3 for ongoing FN management

Yes → 5 Evaluate patient with High-Risk neutropenia for empiric ABX de-escalation after receiving **FIVE** days of empiric ABX

Table 5. Criteria for High-Risk Neutropenia

Patient/Disease Factors	FN Episode Factors
AML	Hypotension
ALL (induction or delayed intensification)	Tachypnea or O2 <94%
Burkitt Leukemia OR Lymphoma	New chest X-ray changes suggestive of infection
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Down Syndrome	Severe mucositis
	Vomiting or abdominal pain concerning for typhlitis

LOW suspicion for bacterial infection
- All bacterial cultures are negative OR respiratory virus identified without evidence of concomitant bacterial infection
- No suggestion of bacterial infection on imaging or physical examination

Treatment Recommendations
- De-escalate empiric ABX if patient is clinically stable and has remained afebrile ≥48 hours

De-escalation Strategy
- Step-wise approach: stop vancomcyin (if receiving), *then* stop antipseudomonal ABX, regardless of ANC
- Non-step-wise approach: stop all empiric ABX at the same time, regardless of ANC
- May consider de-escalating to levofloxacin prophylaxis after stopping empiric ABX if patient remains neutropenic

SUSPECTED bacterial infection
- All bacterial cultures are negative
- Possible bacterial infection based on imaging and/or physical examination (e.g., cellulitis, community acquired pneumonia, typhlitis, appendicitis, etc.)

Treatment Recommendations
- Tailor empiric ABX to target suspected infection if patient is clinically stable and has remained afebrile ≥48 hours

De-escalation Strategy & Duration
- Consider discontinuing targeted ABX after completion of an appropriate duration of therapy based on suspected infection, regardless of ANC
- May consider de-escalating to levofloxacin prophylaxis after completion of targeted therapy if patient remains neutropenic

DOCUMENTED bacterial infection
- Positive bacterial culture AND/OR imaging or physical examination finding(s) consistent with infection

Treatment Recommendations
- Tailor empiric ABX to target infection if patient is clinically stable and has remained afebrile ≥48 hours

De-escalation Strategy & Duration
- Consider discontinuing targeted ABX according to duration of therapy recommended for documented infection, regardless of ANC
- May consider de-escalating to levofloxacin prophylaxis after completion of targeted therapy if patient remains neutropenic

Continue daily monitoring for signs & symptoms of infection.
Re-initiate empiric antipseudomonal beta-lactam if:
- Fever: single temperature ≥38.3°C (101°F) or sustained >38°C x1h
- Newly positive bacterial cultures
- Physical examination or radiographic imaging findings consistent with probable or documented bacterial infection

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Appendix 1: Invasive Fungal Infection Initial Management & Antifungal Agent Selection

Table 6. Scenario-based Management of Invasive Fungal Infection

Scenario	Interpretation	Additional Studies	Antifungal Management	Consults
Blood culture positive for yeast	Invasive candidiasis most likely; cryptococcus may be considered in the appropriate patient	Echocardiogram Eye exam Peripheral blood culture (repeat q24-48h until negative)	Initiate micafungin treatment	Peds ID Ophtho
Hepatosplenic lesions	Concerning for disseminated candidiasis or cryptococcosis in the appropriate patient	Cryptococcal antigen Consider liver biopsy	Initiate L-AMB 3-5mg/kg daily Micafungin is acceptable if confirmed as candidiasis	Peds ID Consider VIR
Imaging studies without significant findings; Fungal antigens negative; Patient stable.	Fungal infection unlikely	None	Targeted antifungal therapy may not be indicated; Consider initiating mold-active azole if clinically indicated	Consider Peds ID
Chest CT with nodular/ground-glass lesions. No cavities or true halo or reverse halo signs.	Possible mold infection (e.g., *Aspergillus*, dematiaceous); less likely mucormycosis	Consider bronchoscopy; if significant lesions, consider lung biopsy. Consider repeat imaging in 2wks	Initiate mold-active azole, such as posaconazole or voriconazole	Consider Peds ID
Sinus CT with erosive or invasive lesions	Concerning for fungal sinusitis. Needs immediate evaluation and biopsy due to significant risk of mucormycosis	Nasal endoscopy ASAP Low threshold for OR evaluation ?Role for CNS imaging?	Initiate L-AMB 5-10mg/kg daily Consider addition of mold-active azole pending identification of invasive mold species	STAT ENT consult Peds ID
Necrotizing cutaneous lesions	Concerning for mucormycosis or other virulent molds that requires urgent biopsy. If mucormycosis confirmed, aggressive debridement is necessary. Also consider ecthyma and mycobacterial	Biopsy with cultures (fungal, bacterial, AFB)	Initiate L-AMB 5-10mg/kg daily Consider addition of mold-active azole pending identification of invasive mold species	Surgery and/or Dermatology Peds ID

L-AMB: liposomal amphotericin B (Ambisome)

Table 7. Characteristics of IFI laboratory tests

	1,3-beta-D-glucan[1] (Fungitell)	**Galactomannan[1] (Aspergillus antigen)**	**Cryptococcal Antigen**
What it measures	Polysaccharide cell wall component found in a variety of fungi	Polysaccharide cell wall component primarily found in *Aspergillus* species	Polysaccharide cell wall component of *Cryptococcus* species
Reference value	< 60 pg/mL	< 0.5	Negative
Sensitivity	Invasive *Candida*: ~70% Lower for other IFI	Invasive *Aspergillus*: 50-70%	Serum: >95% CSF: >99% (for meningoencephilitis)
Specificity	~75%	>85%	>95%
Organisms to consider in setting of positive test[2]	*Candida, Aspergillus, Fusarium, Pneumocystis,* etc.	*Aspergillus, Penicillium*	*Cryptococcus neoformans* *Cryptococcus gattii*
Organisms NOT captured by laboratory test	*Mucorales, Rhizopus, Cryptococcus,* etc.	*Candida, Mucorales, Rhizopus, Cryptococcus,* etc.	All other fungi
Possible causes of false-positive lab test	Hemodialysis, use of blood products (e.g., IVIG, albumin), surgical gauze	*Penicillin agents no longer cause false positives due to improved manufacturing processes*	False-positives are rare
Possible causes of false-negative lab test	No commonly recognized causes	Patient receiving mold-active antifungal therapy	False-negatives are rare

[1] Results of these tests should be interpreted in setting of patient's entire clinical presentation; results alone should not be considered conclusive of invasive fungal disease.
[2] This list contains organisms more likely to produce either 1,3-beta-D-glucan or galactomannan and should not be considered an exhaustive list.

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Appendix 3: Characteristics of Select Antifungal Agents

Table 8. Characteristics of Selected Antifungal Agents

	Spectrum of Activity[1]	Adverse Effects	Monitoring	Notes
Micafungin	Yeast: *Candida* Mold: *Aspergillus* (not effective for treatment of aspergillosis)	Phlebitis; infusion reaction (e.g., rash, pruritis, vasodilation)	CBC/diff; SCr/BUN/K; ALT/AST/ALK/Tbili	Consider slowing infusion >60 minutes and/or use central line to reduce risk of infusion reaction
Fluconazole	Yeast: *Candida* (except *C krusei* & some *C glabrata*); *Cryptococcus* Mold: NONE	QTc prolongation; liver enzyme elevations	SCr/BUN; ALT/AST/ALK/Tbili; EKG	Check for CYP-mediated DDIs
Itraconazole	Yeast: *Candida* (except some *C glabrata*); *Cryptococcus* Mold: *Aspergillus, Histoplasma, Blastomyces*	QTc prolongation; liver enzyme elevations; CHF exacerbation	ALT/AST/ALK/Tbili Troughs 1-4	Check for CYP-mediated DDIs; drug of choice for histo/blasto infections; take capsule w food; take solution on empty stomach
Voriconazole	Yeast: *Candida* (except some *C glabrata*); *Cryptococcus* Mold: *Aspergillus, Fusarium*, *Scedosporium*, dematiaceous (pigmented) molds	QTc prolongation; liver enzyme elevations; visual disturbances; visual and/or audio hallucinations skin photosensitivity	ALT/AST/ALK/Tbili Troughs 1-5	Check for CYP-mediated DDIs; drug of choice for most dematiaceous mold infections
Posaconazole	Yeast: *Candida* (except some *C glabrata*); *Cryptococcus* Mold: *Aspergillus, Fusarium*, *Scedosporium,* mucormycosis	QTc prolongation; liver enzyme elevations	ALT/AST/ALK/Tbili TX trough >1000 PPX trough >700	Check for CYP-mediated DDIs; PO solution and tablets are NOT interchangeable, consult pharmacist
Isavuconazole	Yeast: *Candida* (except some *C glabrata*); *Cryptococcus* Mold: *Aspergillus, Scedosporium,* mucormycosis	QTc shortening; liver enzyme elevations	ALT/AST/ALK/Tbili Consider TDM[2]	Check for CYP-mediated DDIs
Liposomal Amphotericin B	Yeast: *Candida* (except *C lusitaniae*); *Cryptococcus* Mold: *Aspergillus* (except *A* terreus), Fusarium, *Histoplasma, Blastomyces,* mucormycosis	Transient infusion reaction (e.g., rash, pruritis, vasodilation); Electrolyte loss (K, Mg, Ca); renal dysfunction; anemia	CBC/diff; SCr/BUN/K/Mg/Ca; ALT/AST/ALK/Tbili	Consider pre-medicating with APAP and/or diphenhydramine if patient develops infusion reaction Consider fluid boluses before & after infusion to minimize nephrotoxicity

DDI: drug-drug interaction; CHF: congestive heart failure; TDM: therapeutic drug monitoring

[1] This is not an exhaustive list of fungi this agent may be active against. Consult Pediatric ID for additional information as needed.

[2] Consider obtaining isavuconazole trough levels in pediatric patients, especially those <12yo, receiving concomitant CYP3A4 inducing agents, or concern for compromised absorption.

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Appendix 4: Empiric Antibiotic De-escalation Checklist

These checklists are designed to facilitate the evaluation and management specifically for patients with fever and chemotherapy-induced chemotherapy with **LOW suspicion for bacterial infection**. Please refer to full guideline for management of those with SUSPECTED or DOCUMENTED bacterial infections.

Table 5 on the right can serve as a reminder of which patients fall into Standard or High-Risk febrile neutropenia. Any patient who has at least one patient/disease or febrile neutropenia episode is considered High-Risk.

Table 5. Criteria for High-Risk Neutropenia

Patient/Disease Factors	FN Episode Factors
AML	Hypotension
ALL (induction or delayed intensification)	Tachypnea or O2 <94%
Burkitt Leukemia OR Lymphoma	New chest X-ray changes suggestive of infection
Progressive or relapsed disease with marrow involvement	Altered mental status
Down Syndrome	Severe mucositis
	Vomiting or abdominal pain concerning for typhlitis

Standard-Risk Febrile Neutropenia ABX De-escalation Checklist

Date & time of initial BCx = ____/____/_____ @_____

Day 1 of antibiotics = ____/____/_____

Date & time of last fever = ____/____/_____ @_____

Date of de-escalation evaluation = ____/____/_____

- ○ Patient has been afebrile for ≥48 hours
- ○ Blood cultures no growth to date for ≥48 hours
- ○ There are no imaging or physical exam findings suggestive of infection
- ☆ If all boxes are checked, you may safely discontinue this patient's empiric antibiotics

High-Risk Febrile Neutropenia ABX De-escalation Checklist

Date & time of initial BCx = ____/____/_____ @_____

Day 1 of antibiotics = ____/____/_____

Date & time of last fever = ____/____/_____ @_____

Date of de-escalation evaluation = ____/____/_____

- ○ Patient has been afebrile for ≥48 hours
- ○ Patient has received at least 5 days of empiric ABX
- ○ Blood cultures no growth to date for ≥48 hours
- ○ There are no imaging or physical exam findings suggestive of infection
- ☆ If all boxes are checked, you may safely consider de-escalation or discontinuation of this patient's empiric antibiotics