Prolonged Fever and Neutropenia Pathway

Pathway Purpose: Standardize the evaluation and management of oncology and hematopoietic stem-cell transplant (HSCT) patients with prolonged febrile neutropenia at high risk for invasive fungal infection (IFI).

Each patient is unique. These are guidelines and should not replace clinical judgement.

Inclusion Criteria (all of the following):
- Oncology or HSCT patient
- Fever and neutropenia ≥ 4 days without identifiable source of infection
- One or more high-risk criteria: acute myeloid leukemia (AML), high-risk acute lymphoblastic leukemia (ALL), relapsed ALL, prolonged neutropenia >7-10 days, receiving high dose steroids (e.g. prednisolone 1mg/kg daily >7 days), HSCT in the first year after transplant without T-cell reconstitution, or HSCT on immunosuppressive agents for GVHD

Exclusion Criteria
- Non-oncology or immunocompetent patients with fever in the setting of neutropenia (e.g. presumed viral bone marrow suppression)

Initial Work-up

Based on Journal of Clinical Oncology's 2023 F&N Guidelines: https://ascopubs.org/doi/full/10.1200/JCO.22.02224

Exam

Comprehensive exam including:
- Palate
- Sinus
- Skin exam
- Central line site
- Perirectal

Lab Studies (blood)

- *Obtain* Mold panel PCR and *Candida* species PCR once
- *Obtain* LFTs and creatinine to evaluate for end organ dysfunction
- *Consider Aspergillus* galactomannan
- *Consider* viral testing (RPP/COVID, EBV, CMV, adenovirus, HSV) as appropriate
- *Consider* therapeutic drug monitoring for patients on azole antifungal prophylaxis
- Fungal blood cultures and 1,3-beta-D-glucan (Fungitell®) are not routinely recommended and require ID approval

Imaging Studies

- *Obtain* CT chest without contrast
- *Obtain* MRI Abdomen/Pelvis with and without contrast (25-min protocol) as better sensitivity for hepatic/splenic/renal lesions than CT
  - If severe renal dysfunction or unable to tolerate longer study: MRI without contrast (15 min protocol)
  - If uncooperative/unable to tolerate MRI: CT abdomen/pelvis with contrast
- *Add* CT sinus with and without contrast *only if* localizing signs/symptoms
- *Add* MRI brain with and without contrast *only if* any concern for CNS infection

Other

- Consult the Immunocompromised Pediatric Infectious Diseases (ID) team
  - Place consult order in Epic
  - Page on-call Immunocompromised Pediatric ID fellow/APP
- *See next page for additional considerations for specific patient populations*

Empiric Treatment

Based on Journal of Clinical Oncology's 2023 F&N Guidelines: https://ascopubs.org/doi/full/10.1200/JCO.22.02224

Concern for sepsis, hemodynamically unstable, or ill-appearing?

Yes
- Begin liposomal amphotericin B (ID approval required)
- Broaden antibiotics as appropriate

No

Begin caspofungin, voriconazole, or liposomal amphotericin B based on prophylaxis history, laboratory/imaging findings, and discussion with Immunocompromised Pediatric ID.*

*See the following pages for summary of antifungal options. **Consider existing prophylaxis agent when choosing treatment.**

Owner: Catherine Aftandilian, MD
Pathway Team: Lauren Kushner, MD; Hayden Schwenk, MD, MPH; Sean Green, PharmD
Pathway Liaison: Hannah Bassett, MD
Last Updated: 11/2024
Associated Order set: Prolonged fever and neutropenia
Prolonged Associated Policies: none

Feedback?

Prolonged Fever and Neutropenia Pathway

Additional evaluations to consider in certain patients

Diffuse lung process or rising oxygen requirement

Consider bronchoscopy with bronchoalveolar lavage (BAL)

- Consult Pulmonology as soon as clinical concern, prior to respiratory decline
- Studies (*see Bronchoscopy order set*): Gram stain/culture, KOH stain, fungal culture, AFB smear/culture, RVP/COVID, Mold panel PCR, Dimorphic fungi PCR, PJP PCR, ± *Aspergillus* galactomannan, ± *Legionella* PCR, ± *Mycoplasma pneumoniae* PCR, ± *Toxoplasma* PCR
- Data on diagnostic yield and complication rate of BAL and lung biopsy: Chellapandian, et al. JCO, 2015. https://ascopubs.org/doi/10.1200/JCO.2014.58.0480

New or suspicious skin lesions

Consider skin biopsy

- Consult Dermatology
- Routine studies: Pathology, Gram stain/culture, anaerobic culture, KOH stain, fungal culture, AFB smear/culture
- cfDNA fungal PCR assays and fungal sequencing available, but will *only* be performed if histopathology shows evidence of fungal elements

Lung or abdominal lesions on imaging

Consider biopsy of lung or intra-abdominal lesions if lesions are ≥1cm

- Consult IR or general surgery
- Routine studies: Gram stain/culture, anaerobic culture, KOH/fungal culture, AFB culture
- cfDNA fungal PCR assays and fungal sequencing available, but will *only* be performed if histopathology shows evidence of fungal elements

Other

Otolaryngology: Consult ENT promptly with any palatal or sinus findings concerning for IFI

Ophthalmologic evaluation and echocardiogram: Discuss with ID if/when appropriate

Specific Antifungal Recommendations

Condition	Recommendations
Candidemia (neutropenic)	i. Echinocandin is recommended for initial therapy ii. Liposomal amphotericin B can be considered, although risk for toxicity is higher iii. Continue minimum of 14d from last positive culture (and resolved neutropenia) iv. Central lines should be removed in accordance with guidelines from the Infectious Diseases Society of America (IDSA)
Disseminated (hepatosplenic) candidiasis	i. Echinocandin or liposomal amphotericin B is recommended for initial therapy ii. Use liposomal amphotericin B over echinocandin if there is concern for CNS involvement iii. Usual duration of therapy is weeks-months
Invasive aspergillosis	i. Voriconazole is the drug of choice for invasive *Aspergillus* infections ii. Isavuconazole and posaconazole are alternative treatment options iii. There is data in adults to suggest a survival benefit from initial combination therapy with an echinocandin. The addition of caspofungin to voriconazole for the first 2 weeks of therapy can be considered; discuss with ID.
Invasive mucormycosis	i. Treatment of mucormycosis generally requires *both* surgical and medical intervention ii. Liposomal amphotericin B is the drug of choice for the treatment of invasive mucormycosis iii. Posaconazole or isavuconazole can be considered as step-down therapy following a favorable clinical response to liposomal amphotericin B (usually after weeks-month of therapy)

Stanford MEDICINE Children's Health

Antifungal Characteristics

Drug	Formulations	CNS Penetration*	Urinary Penetration	Adverse Effects	Therapeutic Drug Monitoring[1]	Drug-drug Interactions
Fluconazole	IV, suspension, tab	Very high	Yes	Hepatotoxicity	No	Moderate
Voriconazole	IV, suspension, tab	High	No	Hepatotoxicity, vision, neuro, QTc, skin	Yes See guidance[1]	High
Posaconazole	IV, delayed release tab	Moderate	No	Hepatotoxicity, QTc (less than vori)	See guidance[1]	Moderate
Isavuconazole	IV, capsule	Low CNS, high brain	No	Hepatotoxicity, QTc shortening	See guidance[1]	Low
Caspofungin	IV	Poor	Poor	Mild hepatoxicity	No	Low
Liposomal amphotericin B	IV	Poor, but good data to support use	No	Nephrotoxicity, electrolyte wasting	No	Low

[1] See Azole Antifungal Therapeutic Drug Monitoring (TDM) Guidance on the intranet: Azole Antifungal TDM Guidance.pdf
*Talk to ID about ocular penetration

Antifungal Spectrum of Activity

Drug	*Candida spp*	*Aspergillus spp*	Mucorales	Other
Fluconazole	Yes (except *C. krusei* and some *C. glabrata*)	No	No	**Cryptococcus (first-line)**
Voriconazole	Yes (static)	**Yes (first-line)**	No	*Scedosporium**, *Fusarium**, *Trichosporon**, *Cryptococcus*
Posaconazole	Yes	Yes	Yes	*Scedosporium**, *Fusarium**, *Trichosporon**, *Cryptococcus*
Isavuconazole	Yes	Yes	Yes	*Fusarium**, *Trichosporon**, *Cryptococcus*
Caspofungin	**Yes (first-line)**	Yes (static)	No; some data support use as adjunct	None
Liposomal amphotericin B	Yes (except *C. lusitaniae*)	Yes (except *A. terreus*)	**Yes (first-line)**	*Fusarium**, *Trichosporon**, *Cryptococcus*

*Not reliably susceptible; therapy should be guided by culture and susceptibility data.

Additional details regarding cell-free DNA fungal PCR assays*

PCR Assay Type	Pathogens Included in Assay	Specimen Source
Mold panel PCR	• *Aspergillus* species: *A. fumigatus/A. flavus/A. niger*, *A. terreus*, *A. ustus*, and *A. nidulans* • Mucorales agents: *Rhizopus spp.*, *Mucor spp.*, and *Rhizomucor spp.* • *Fusarium* spp. • *Scedosporium* spp.	Plasma, bone marrow, CSF, sterile body fluids, fresh tissue from a sterile source, paraffin embedded tissue, BAL
Candida species PCR	*C. albicans*, *C. glabrata*, and *C. krusei*	Plasma, bone marrow, CSF, sterile body fluids, fresh tissue from a sterile source, paraffin embedded tissue *No* BAL: not a common pulmonary pathogen
Dimorphic fungi PCR	*Coccidioides immitis/posadasii*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Sporothrix schenckii*	Plasma, bone marrow, CSF, sterile body fluids, fresh tissue from a sterile source, paraffin embedded tissue, BAL
PJP PCR	*Pneumocystis jirovecii*	Plasma, BAL, induced sputum

*Additional Considerations:

- For pediatrics, a minimum of 2mL of whole blood is *acceptable* but sensitivity is improved with an optimal volume of 4mL.
- Only send in patients with clinical concern for IFI. Weekly "surveillance" screening is not recommended.
- The lab will reject repeat cfDNA fungal PCRs ordered from the same specimen type within 7 days.
- cfDNA fungal PCRs will only be performed on tissue specimens if histopathology shows evidence of fungal elements.
- For information on test development and performance, see https://pubmed.ncbi.nlm.nih.gov/33606010/, https://pubmed.ncbi.nlm.nih.gov/37450614/, and https://pubmed.ncbi.nlm.nih.gov/35387472/.

Stanford MEDICINE
Children's Health