Stony Brook University Hospital Treatment Guidelines:

Guidelines for Evaluation and Management of Cancer Patients with Neutropenic Fever and Suspected Invasive Fungal Infection

1.Evaluation of patients suspecting invasive fungal infection (see Figure below).

1.1. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be > 7 days.

1.2. Thorough review of systems and physical examinations focused on sinuses, oral cavity, skin (including catheter exit sites), lungs, abdomen, and any areas of concern by the patients should be performed.

1.3. Some risk factors for invasive fungal infection in cancer patients include

- Prolonged neutropenia (expected > 7 days)
- Mucositis
- Presence of central venous catheters
- Colonization with *Candida sp.* or mold e.g. *Aspergillus sp.*
- Prior mold infection
- Acute myeloid leukemia
- Allogeneic bone marrow or stem cell transplant recipients (day 01-100)
- Graft-versus-host disease receiving immunosuppressive therapy
- Prednisone > 1 mg/kg

1.3.1. In low-risk patients (expected neutropenia ≤ 7 days), the risk of invasive fungal infection is low, and routine use of empirical antifungal therapy is not recommended.

1.4. Diagnostic work up for invasive fungal infection includes

1.4.1. CT scan chest and sinuses (for suspected mold infection).
1.4.2. Serum *Aspergillus* galactomannan and/or 1,3-β-D-glucan
1.4.2.1. Both serum galactomannan and 1,3-β-D-glucan can give false positive or negative results and should not be used to screen for the invasive fungal infection without other appropriate testing modalities.
1.4.3. Symptoms or exam-guided studies or imaging, e.g.

- Abdomen US or CT scan
- Fungal blood cultures

- Sputum fungal cultures
- Biopsy suspected lesion (for histology and culture) if feasible
- Bronchoalveolar lavage if suspected invasive pulmonary fungal infection.

1.4.5. If the patient is receiving voriconazole or posaconazole prophylaxis, obtain serum drug level.

1.5. Consider Infectious Disease consult.

2. Empiric antifungal therapy (See Table 1 for recommended antifungal dosing)

2.1. In patients who are not receiving antifungal prophylaxis, invasive candida infection is most likely. The following antifungal agents can be used.

2.1.1. Micafungin

2.1.2. Fluconazole

2.2. In patients who receive fluconazole prophylaxis, they are at risk for fluconazole-resistant candida or mold infection, the following antifungal therapy can be considered.

2.2.1. Micafungin (preferred agent for fluconazole-resistant Candidiasis)

2.2.2. Voriconzole (preferred agents for Aspergillosis)

2.2.3 Posaconazole

2.2.4. Isavuconazole

Note: Isavuconazole is not approved for treatment of candidemia.

2.2.4. Liposomal amphotericin B

2.3. In patients who receive anti-mold azole prophylaxis, the therapeutic drug level should be obtained.

2.3.1. If the drug level is therapeutic, switching to a different class of mold-active antifungals (triazoles or liposomal amphotericin B) can be considered if work-up is suggesting the breakthrough invasive fungal infection.

Table 1. Antifungal Agents: Dosing in adults with normal renal and liver functions

Agents	Loading dose	Maintenance dose
Echinocandins: Micafungin	None	100 mg IV Q24 H
Triazoles*: Fluconazole[$]	None	400 mg IV/PO Q24H
Voriconazole[$]	6 mg/kg/twice daily IV/PO x 2 doses	4 mg/kg IV/PO Q12H
Posaconazole[$]	300 mg IV/PO (delayed-release tablets) twice daily x 2 doses	300 mg IV/PO (delayed-release tablets) Q24H
Isavuconazole	372 mg (isavuconazole 200 mg) IV/PO Q8H x 6 doses	372 (isavuconazole 200 mg) IV/PO Q24H
Liposomal amphotericin B	None	3-5 mg/kg/day (IV)

*Azoles inhibit cytochrome P450 isoenzymes that may lead to impaired clearance of other drugs metabolized by this pathway. Please carefully review and monitor for drug-drug interactions.
[$]Fluconazole, voriconazole and posaconazole can induce significant QT prolongation.

References:

1. Freifeld AG et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52: e56-e93.
2. Pappas P et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62: e1-e50.
3. Patterson T et al. Practice Guideline for the diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 63: e1-e60.
4. Prentice HG. et al. Towards a Targeted, Risk-based, Antifungal Strategy in Neutropenic Patients. Br J Haematol. 2000, 110: 273- 284.
5. Tissot F et al ECIL-6 Guidelines for the Treatment of Invasive Candidiasis, Aspergillosis and Mucormycosis in Leukemia and Hematopoietic stem cell transplant patients. Haematol 2017; 102: 433-444.
6. Zimmer AJ, Freifeld AG. Optimal Management of Neutropenic Fever in Patients with Cancer. J Oncol Pract. 2019; 15:19-24.
7. National Comprehensive Cancer Network (2022). NCCN Clinical Practice Guidelines in Oncology. Version 3.2022: Prevention and treatment of cancer related infections.

Stony Brook Medicine

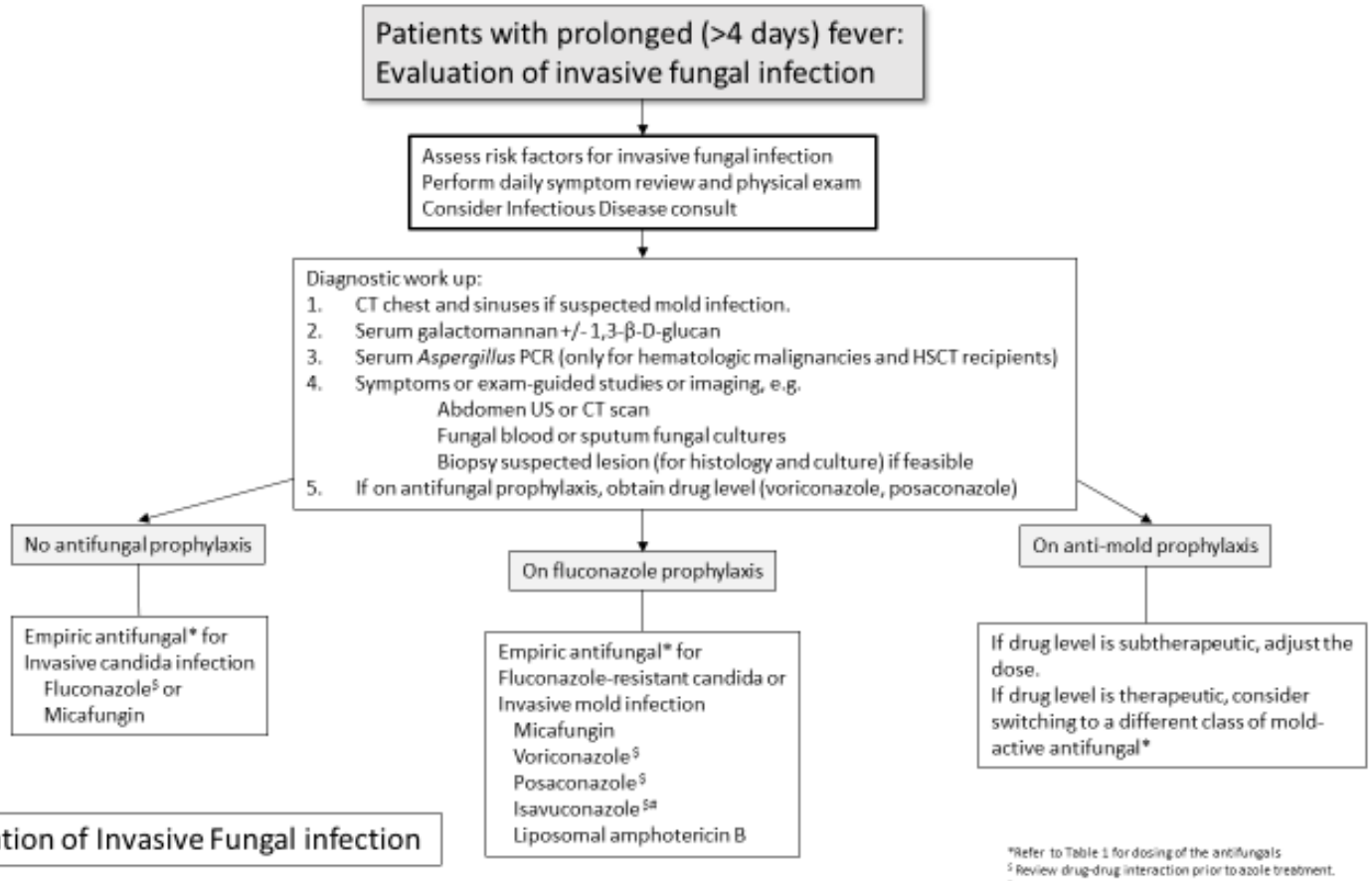

Figure 3: Evaluation of Invasive Fungal infection

*Refer to Table 1 for dosing of the antifungals
§ Review drug-drug interaction prior to azole treatment.
aIsavuconazole is not approved for treatment of candidemia.

This algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care.

Stony Brook University Hospital Antimicrobial Stewardship
Katherine De Jesus, PharmD; Sutthichai Sae-Tia, MD
Developed: 4/19/2023
Revised: 5/18/2023