MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

TREATMENT OF INVASIVE ASPERGILLOSIS AND MUCORMYCOSIS IN ADULTS

Clinical Setting	Therapy	Duration	Comments
Invasive Aspergillosis (IA) **Categories (see footnote for host and radiology criteria):** **Proven IA:** histopathology demonstrating invasive disease or culture of a sterile site **Probable IA:** a susceptible host with suggestive radiology who has either culture, cytopathology/ smear, or serum/BAL galactomannan positive. A (+) serum BDG test is supportive of, but not specific for a diagnosis of probable IA **Possible IA:** Negative microbiology (culture, pathology, or galactomannan assay), but radiographically suggestive in a susceptible host	**Infectious Disease Consult is STRONGLY recommended if Aspergillosis is suspected (i.e., positive biomarker or culture, radiologic findings)** Preferred: **Voriconazole** 6 mg/kg PO/IV q12h x2 doses, then 4 mg/kg PO/IV q12h (on an empty stomach). During voriconazole load and in severely ill patients, IV therapy is preferred. Preferred alternative in patients intolerant to voriconazole (see comments): **Isavuconazole** 372 mg q8h PO/IV x48 hours, then 372 mg PO/IV daily Preferred alternative in patients intolerant to voriconazole and isavuconazole or with refractory or breakthrough disease on voriconazole and isavuconazole, or unable to receive azoles due to interaction (see comments): **LAmB** (**liposomal amphotericin B**) 5 mg/kg IV daily Options for salvage therapy or in patients intolerant to above therapies (see comments): **Posaconazole** OR **Micafungin** OR Combination therapy **Voriconazole** + **Micafungin** Micafungin Dosing: *Monotherapy with micafungin should only be considered in possible disease if above options are not feasible. Use is not recommended as monotherapy for primary treatment.* **Micafungin** 150 mg IV daily	Minimum of 3-6 months; determined by clinical response, & radiological response, and patient's underlying disease or immune status.	**Dosing** • Dosing guidelines available here • Weight-based dosing recommendations for adult obese patients available here **Therapeutic drug monitoring** • Therapeutic drug monitoring is recommended for isavuconazole, posaconazole, and voriconazole. Please see Recommendations for Therapeutic Drug Monitoring of Antifungal Agents here **Drug Interactions** • Numerous significant drug interactions occur with azole antifungals. A review of the patient profile should be undertaken when these agents are initiated and discontinued (see footnote for specific notes). **Adverse Reactions** • Posaconazole and voriconazole have been associated with QTc prolongation. Isavuconazole is associated with dose-dependent decreases in QTc interval. As such, isavuconazole may be preferred in some patients experiencing issues with QTc prolongation (>500 msec). • Patients with a prolonged QTc or on select anti-arrythmics such as dofetilide should avoid voriconazole/posaconazole or perform EKG monitoring due to an increase risk of QT-prolongation and torsades • Unlike posaconazole and voriconazole, isavuconazole is water-soluble and thus does not require solubilization by cyclodextrin for an intravenous formulation. There are potential nephrotoxicity concerns with cyclodextrin in patients with pre-existing renal impairment. However, there is no strong clinical evidence suggesting an increased risk of worsening renal function with IV voriconazole use, so use of IV voriconazole may be considered, at the shortest duration possible, if deemed clinically appropriate. • Isavuconazole and posaconazole are associated with significantly less visual disturbances, hallucinations, and photosensitivity compared to voriconazole. Isavuconazole may be an option in patients intolerant to voriconazole. Of note, visual

	Posaconazole Dosing: **Posaconazole** delayed-release tablets 300 mg PO BID on Day 1 then 300 mg PO daily starting on Day 2 (cannot be crushed or divided) *In patients unable to tolerate whole tablets:* **Posaconazole** oral suspension 200 mg PO QID (should be given with fatty meals and acidic carbonated beverages to ensure adequate levels & use of acid suppression should be avoided) *In patients unable to tolerate oral medications:* **Posaconazole** intravenous solution 300 mg IV BID on Day 1 then, 300 mg IV daily starting on Day 2 Initial combination therapy (addition of micafungin to voriconazole x2 weeks) may be considered in patients with PROVEN or PROBABLE disease who meet ANY of the following: • *Have extensive multi-lobar involvement or disseminated infection* • *Have increasing oxygen requirements or respiratory distress with impending respiratory failure.* • *Expected long duration of neutropenia (>10 days) or extensive GVHD.*		hallucinations with voriconazole are usually transient (associated with loading dose) and/or associated with supra-therapeutic levels (>5.5 ug/mL). Visual disturbances, such as photopsia, are not dose dependent, may continue to occur, but have no long-term consequences. • Isavuconazole was associated with fewer hepatobiliary adverse effects than voriconazole (9% vs. 16%, respectively) in a trial of aspergillosis. However, hepatic adverse effects with voriconazole are generally both reversible and do not require discontinuation in clinical trials. As such, pre-existing hepatic impairment is not a contraindication to voriconazole and mild elevations during therapy are often multi-factorial and do not necessarily mandate a change in therapy. Patients with cirrhosis may have supratherapeutic levels on standard dosages of voriconazole. As such, therapeutic drug monitoring recommendations should be followed and ID Pharmacy (pagers 37689/2938/38272) should be contacted for dosing recommendations in patients with cirrhosis. **Breakthrough Infection and Salvage Treatment** • Patients with breakthrough infection on voriconazole/posaconazole prophylaxis may be at risk for azole resistance. If an isolate is available, susceptibilities should be performed. • Current and prior azole concentrations during prophylaxis/treatment should be reviewed when assessing breakthrough infection or need for salvage therapy. **Miscellaneous** • In patients with central nervous system involvement, voriconazole therapy is preferred. Liposomal Amphotericin B therapy is appropriate for patients intolerant or refractory to voriconazole. There is insufficient data regarding preference of other alternatives, and such decisions should be made on a case-by-case basis. • In patients with endophthalmitis, voriconazole (concomitant systemic and intravitreal) therapy is preferred.

Clinical Setting	Therapy	Duration	Comments
Proven or Probable Mucormycosis (e.g., *Rhizopus spp., Mucor spp., Rhizomucor spp., others)*	**Infectious Disease Consult is STRONGLY recommended if Mucormycosis is suspected** Primary Surgical debridement is generally necessary **LAmB** 5 mg/kg IV daily with consideration of escalation to a maximum of 10 mg/kg daily in patients with progressive or extensive disease or possible CNS disease Combination therapy should be discussed with ID Consultant Options for step-down therapy, salvage therapy, or in patients unable to take LAmB include isavuconazole or posaconazole. Consultation with ID is highly recommended	Generally prolonged (months). Until resolution of clinical signs and symptoms or treatment limiting adverse effects	• Please note that voriconazole IS NOT ACTIVE against mucormycosis • **See above (Invasive Aspergillosis) section for dosing recommendations**. Complete dosing guidelines available here • Weight-based dosing recommendations for adult obese patients available here • Therapeutic drug monitoring is recommended for isavuconazole and posaconazole. Please see Recommendations for Therapeutic Drug Monitoring of Antifungal Agents here

Specific Recommendations Regarding Drug Interactions with Azoles:

- Sirolimus, tacrolimus, and cyclosporine levels increase. Drug levels and dose adjustment may be necessary in consultation with transplant pharmacy
- Concomitant use of azoles with certain chemotherapeutic agents (vincristine, tyrosine-kinase inhibitors (e.g., imatinib, dasatinib, nilotinib, bosutinib, ponatinib), sorafenib, clofarabine, doxorubicin, or if mandated by clinical trial protocol (e.g., quizartinib) is not recommended and an alternative antifungal should be used (discuss with hematology)
- P-450 inducers (e.g., rifampin, phenobarbital, carbamazepine, St. John's wort) may result in subtherapeutic azole levels
- Complex drug interactions with antiretroviral agents exist and may alter serum azole and/or antiretroviral levels

Host and Radiologic Criteria for the Diagnosis of Invasive Fungal Infection (De Pauw B et al. Clin Infect Dis 2008;46:1813-21)

- Host factors:
  - Recent history of neutropenia (<500 neutrophils/mm3 for >10 days) temporally related to the onset of fungal disease
  - Receipt of an allogeneic stem cell transplant
  - Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
  - Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-a blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
  - Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
- Suggestive radiologic/clinical findings:
  - Lower respiratory tract fungal disease
    - The presence of 1 of the following 3 signs on CT:
      - Dense, well-circumscribed lesions(s) with or without a halo sign
      - Air-crescent sign
      - Cavity

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