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 (all three are therapeutically equivalent[4,5], choice dependent on drug interaction and toxicity considerations, as well as insurance coverage)[1]: **Isavuconazole** 372 mg q8h PO/IV x48 hours, then 372 mg PO/IV daily. Capsules may be opened and administered through feeding tube. OR **Posaconazole** 300 mg (PO/IV) BID on Day 1 then 300 mg PO daily starting on Day 2. Tablets may be crushed and administered through feeding tube. OR **Voriconazole** 6 mg/kg PO/IV q12h x2 doses, then 4 mg/kg PO/IV q12h (on an empty stomach). OR **May Consider** initial combination therapy (**Micafungin 150 mg** IV daily x2 weeks PLUS **voriconazole**, **posaconazole**, or **isavuconazole**) 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.* Alternative in patients intolerant to above azole agentsor with refractory or breakthrough disease, or unable to receive azoles due to interaction (see comments): **LAmB** (**liposomal amphotericin B**) 3-5 mg/kg IV daily	Minimum of 3-6 months; determined by clinical response, & radiological response, and patient's underlying disease or immune status.	See Page 2 for Dosing, Therapeutic Drug Monitoring, Drug-Drug Interactions, Adverse Reactions, Breakthrough Infection/Salvage Therapy, and Miscellaneous information for Aspergillosis Treatment

Invasive Aspergillosis Comments

Dosing

- Dosing guidelines available here
- Weight-based dosing recommendations for adult obese patients available here
- Loading doses are necessary to achieve more rapid attainment of therapeutic levels. As such, when switching from one azole to another, loading doses are recommended.

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 or sotalol 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, and so the benefit of using intravenous posaconazole or voriconazole outweigh any theoretical nephrotoxicity risks.
- Isavuconazole and posaconazole are associated with significantly less visual disturbances, hallucinations, and photosensitivity compared to voriconazole. Of note, visual 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 (pager 31888) should be contacted for dosing recommendations in patients with cirrhosis.

Breakthrough Infection and Salvage Treatment

- Patients with breakthrough infection on voriconazole/isavuconazole/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.
- Converting to LAmB is recommended. In select cases, changing to an alternative azole may be appropriate.

Miscellaneous

- Investigational agents may be available for patients intolerant/resistant/refractory to other therapies. Contact Infectious Diseases and/or Antimicrobial Stewardship to discuss.
- In patients with central nervous system and/or ocular 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. In patients with confirmed mucormycosis that is progressive, extensive, or involving the CNS, consideration can be given to escalation to a maximum of 10 mg/kg daily. 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 • Investigational agents may be available for patients intolerant/resistant/refractory to other therapies. Contact Infectious Diseases and/or Antimicrobial Stewardship to discuss.

Specific Recommendations Regarding Drug Interactions with Azoles:

- **Isavuconazole, Posaconazole, and voriconazole all inhibit CYP3A4, although isavuconazole is a more mild inhibitor than the other two agents. Voriconazole uniquely also inhibits CYP 2C9/2C19.**
- P-450 inducers (e.g., rifampin, phenobarbital, carbamazepine, St. John's wort) may result in subtherapeutic azole levels
- Sirolimus, tacrolimus, and cyclosporine levels increase. Drug levels and dose adjustment may be necessary in consultation with transplant pharmacy
- Concomitant use of azoles in hematology/oncology patients on chemotherapeutic agents or targeted therapies should be discussed with hematology
- 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

- Host factors:
  - Recent history of neutropenia (< 500 neutrophils/mm^3 for > 10 days) temporally related to the onset of fungal disease
  - Hematologic malignancy
  - 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 in past 60 days
  - Treatment with other recognized T cell immunosuppressants, such as calcineurin inhibitors, TNF-a blockers, lymphocyte-specific monoclonal antibodies (such as alemtuzumab), or immunosuppressive nucleoside analogues during the past 90 days

- Treatment with recognized B-cell immunosuppressants, such as Bruton'styrosine kinase inhibitors, e.g., ibrutinib
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
- Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

- Suggestive radiologic/clinical findings:
  - Lower respiratory tract fungal disease
    - The presence of 1 of the following 4 patterns on CT:
      - Dense, well-circumscribed lesions(s) with or without a halo sign
      - Air-crescent sign
      - Cavity
      - Wedge-shaped and segmental or lobar consolidation

References:

1. Patterson TF, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1–60.
2. Cornely OA, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019;19: e405–21.
3. Donnelly JP et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020;71:1367–76.
4. Maertens JA et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387:760-9.
5. Maertens JA et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet 2021; 397: 499–509.

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