C.S. MOTT CHILDREN'S HOSPITAL
MICHIGAN MEDICINE

GUIDELINES FOR TREATMENT OF INVASIVE ASPERGILLOSIS AND MUCORMYCOSIS IN PATIENTS ON PEDIATRIC SERVICES

Clinical Setting	Therapy	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 and a positive culture, cytopathology/ smear, or serum/BAL galactomannan A positive serum β-D-glucan 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, choice dependent on drug interactions, toxicity considerations, formulation, and insurance coverage): **Voriconazole** OR **Posaconazole** OR **Isavuconazole** **May consider** initial combination therapy (**Micafungin** PLUS voriconazole, posaconazole, or isavuconazole x 2 weeks) in patients with PROVEN or PROBABLE disease who meet ANY of the following criteria: • *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 agents, with refractory or breakthrough disease on an azole, or unable to receive azoles due to drug interactions (see comments): **Liposomal amphotericin B (LAmB)**	**Duration** • Minimum of 6-12 weeks, typically months; determined by clinical response, radiological response, and patient's underlying disease or immune status, in discussion with Pediatric Infectious Diseases. **CNS Infections** • 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. **Endophthalmitis** • In patients with endophthalmitis, voriconazole (concomitant systemic and intravitreal therapy) is preferred. **Please see table below for additional information on:** • Dosing and therapeutic drug monitoring • Drug interactions with azole antifungals Adverse reactions to consider for azole selection Breakthrough infection and salvage treatment
Proven or Probable Mucormycosis (e.g., *Rhizopus spp., Mucor spp., Rhizomucor spp.*)	**Infectious Disease Consult is STRONGLY recommended** if mucormycosis is suspected Primary **Surgical debridement is generally necessary** **Liposomal Amphotericin B (LAmB)** Combination therapy should be discussed with Pediatric Infectious Diseases. Options for step-down therapy, salvage therapy, or in patients unable to take LAmB include **isavuconazole** or **posaconazole**.	• Please note that voriconazole IS **NOT** ACTIVE against mucormycosis. **Duration** • Generally prolonged (months); until resolution of clinical signs and symptoms or treatment-limiting adverse effects.

Dosing

- See dosing table on page 3 below
- Please discuss dose adjustments with a Clinical Pharmacy Specialist.
- Loading doses for azole antifungals enable more rapid attainment of therapeutic levels. As such, when switching from one azole to another, loading doses are recommended if indicated based on patient's age and weight.
- Therapeutic drug monitoring is recommended for voriconazole, posaconazole, and isavuconazole. Please see Recommendations for Therapeutic Drug Monitoring of Antifungal Agents.

Drug Interactions with Azole Antifungals

- Numerous significant drug interactions occur with azole antifungals. A comprehensive review of the patient medication list should be undertaken when these agents are initiated or discontinued.
- Isavuconazole, posaconazole, and voriconazole all inhibit CYP3A4, although isavuconazole is a weaker inhibitor than the other two agents. Voriconazole also uniquely inhibits CYP2C9 and CYP2C19.
- P-450 inducers (e.g., rifampin, phenobarbital, carbamazepine, St John's wort) may result in subtherapeutic azole levels.
- Sirolimus, tacrolimus, and cyclosporine levels increase when given with azoles. 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/oncology.
- Complex drug interactions with antiretroviral agents exist and may alter serum azole and/or antiretroviral drug levels.

Adverse Reactions to Consider for Azole Selection

- Voriconazole and posaconazole have been associated with QTc prolongation. Patients with a prolonged QTc or who are receiving other QTc-prolonging medications should avoid voriconazole/posaconazole or receive EKG monitoring due to an increased risk of QTc prolongation or Torsades de Pointes.
- Isavuconazole is associated with dose-dependent decreases in QTc interval. As such, isavuconazole may be preferred in some patients experiencing issues with QTc prolongation.
- IV voriconazole and posaconazole require solubilization by cyclodextrin. There is no clinical evidence suggesting an increased risk of worsening renal function with IV voriconazole use, so the benefits of using IV voriconazole or posaconazole outweigh any theoretical nephrotoxicity risk in patients with preexisting renal impairment.
- Visual hallucinations with voriconazole are usually transient (associated with loading dose) and/or associated with supra-therapeutic levels (> 5.5 mcg/mL). Visual disturbances, such as photopsia, are not dose dependent, may continue to occur, but have no long-term consequences.
- Isavuconazole and posaconazole are associated with significantly fewer visual disturbances, hallucinations, and photosensitivity compared to voriconazole.
- Isavuconazole was associated with fewer hepatobiliary adverse effects than voriconazole (9% vs. 16%, respectively) in an aspergillosis trial. 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 AST/ALT elevations during therapy are often multi-factorial and do not necessarily mandate a change in therapy.

Breakthrough Infection and Salvage Treatment

- Patients with breakthrough infection on azole 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 potential breakthrough infection or need for salvage therapy.
- Converting to liposomal amphotericin B is recommended. In select cases, changing to an alternative azole may be appropriate.
- Investigational agents may be available for patients intolerant/resistant/refractory to other therapies. Contact Pediatric Infectious Diseases and/or Antimicrobial Stewardship to discuss.

Drug	Dosing for Aspergillosis or Mucormycosis Treatment
Voriconazole	< 16 years: 9 mg/kg PO/IV q12h (initial max 350 mg/dose) 16-17 years: 6 mg/kg PO/IV q12h (initial max 350 mg/dose) ≥ 18 years: 6 mg/kg PO/IV q12h x 2 doses, then 4 mg/kg PO/IV q12h (initial max 400 mg/dose) For obese (BMI ≥ 30) adults, dose should be calculated using adjusted body weight.

Drug	Dosing for Aspergillosis or Mucormycosis Treatment
Posaconazole	**Delayed-Release Tablet OR Intravenous Solution** < 13 years AND < 30 kg: 10 mg/kg PO/IV BID x 2 doses, then 10 mg/kg PO/IV daily (initial max: 300 mg/dose) - If using delayed-release tablet, round dose to the nearest 50 mg ≥ 13 years OR ≥ 30 kg: 300 mg PO/IV BID x 2 doses, then 300 mg PO/IV daily ** Posaconazole tablets may be crushed for enteral administration and are preferred over suspension. ** **Oral Suspension** • Two oral suspension formulations (delayed release [DR] and immediate release [IR]) are available, but have serious disadvantages. Contact Pediatric ID Clinical Pharmacist for guidance on appropriate use and dosing. • The IR oral suspension is NOT interchangeable with the DR oral suspension or DR tablets.
Isavuconazole	≥ 13 years AND ≥ 40 kg: 372 mg PO/IV q8h x 6 doses, then 372 mg PO/IV daily Contact Pediatric ID Clinical Pharmacist for dosing recommendations in patients < 13 years old. Isavuconazole capsules may be opened for enteral administration.
Liposomal Amphotericin B	5 mg/kg IV daily For obese (BMI ≥30) adults, dose should be calculated using adjusted body weight. Similar consideration may be given to obese adolescents.
Micafungin	5 mg/kg IV daily (max: 150 mg/dose)

Footnote: 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 the 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's tyrosine 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, randomized, 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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