



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

| Clinical Setting   | Therapy  | Comments   |
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| <p><b>Invasive Aspergillosis (IA)</b></p> <p><u>Categories</u> (see footnote for host and radiology criteria):</p> <p><u>Proven IA:</u><br/>histopathology demonstrating invasive disease or culture of a sterile site</p> <p><u>Probable IA:</u><br/>a susceptible host with suggestive radiology and a positive culture, cytopathology/sme ar, or serum/BAL galactomannan.</p> <p>A positive <math>\beta</math>-D-Glucan test is supportive of, but not specific for a diagnosis of probable IA</p> <p><u>Possible IA:</u><br/>Negative microbiology (culture, pathology, or galactomannan assay), but radiographically suggestive in a susceptible host</p> | <p><b>Infectious Disease Consult is STRONGLY recommended</b> if Aspergillosis is suspected (i.e., positive biomarker or culture, radiologic findings)</p> <p><u>Preferred - voriconazole:</u><br/>&lt;16 years:<br/><b>Voriconazole</b> 9 mg/kg IV/PO q12h<br/>16-17 years:<br/><b>Voriconazole</b> 6 mg/kg IV/PO q12h<br/><math>\geq</math>18 years:<br/><b>Voriconazole</b> 6 mg/kg IV/PO q12h x2 doses, then 4 mg/kg IV/PO q12h</p> <p><u>Preferred alternative in patients intolerant to voriconazole or with refractory or breakthrough disease on voriconazole (see comments):</u><br/><math>\geq</math>16 years AND <math>\geq</math>50 kg:<br/><b>Isavuconazole</b> 372 mg IV/PO q8h x6 doses, then 372 mg IV/PO daily<br/>&lt;16 years OR &lt;50 kg OR unable to tolerate azoles:<br/><b>LAmB (liposomal amphotericin B)</b> 5 mg/kg IV daily</p> <p><u>Preferred alternative in patients intolerant to azoles or with refractory or breakthrough disease on an azole (see comments):</u><br/><b>LAmB (liposomal amphotericin B)</b> 5 mg/kg IV daily</p> <p><u>Options for salvage therapy or in patients intolerant to above therapies (see comments):</u><br/><b>Micafungin</b><br/>OR<br/><b>Posaconazole</b></p> <p><u>Micafungin Dosing:</u><br/><i>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.</i><br/><b>Micafungin</b> 5 mg/kg IV daily (max: 150 mg/dose)</p> | <p><u>Dosing</u></p> <ul style="list-style-type: none"> <li>Please discuss dosing adjustments with a Clinical Pharmacy Specialist prior to changes in doses.</li> <li><a href="#">Weight-based dosing recommendations for adult obese patients</a> for voriconazole and Liposomal amphotericin B are available</li> </ul> <p><u>Duration</u></p> <ul style="list-style-type: none"> <li>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.</li> </ul> <p><u>Therapeutic Drug Monitoring</u></p> <ul style="list-style-type: none"> <li>Therapeutic drug monitoring is recommended for isavuconazole, posaconazole, and voriconazole. Please see <a href="#">Recommendations for Therapeutic Drug Monitoring of Antifungal Agents</a></li> </ul> <p><u>Drug Interactions</u></p> <ul style="list-style-type: none"> <li>Numerous significant drug interactions occur with azole antifungals. A comprehensive review of the patient profile should be undertaken when these agents are initiated and discontinued (see footnote for specific notes).</li> </ul> <p><u>Adverse Reactions</u></p> <ul style="list-style-type: none"> <li>Posaconazole and voriconazole have been associated with QTc prolongation. Patients with a prolonged QTc or on certain anti-arrhythmics should avoid voriconazole/posaconazole or perform EKG monitoring due to an increased risk of QTc-prolongation or torsades.</li> <li>Isavuconazole is associated with dose-dependent decreases in QTc interval. As such, isavuconazole may be preferred in some patients experiencing issues with QTc prolongation.</li> <li>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.</li> </ul> |

**Posaconazole Dosing:**  
*Delayed-release tablets are preferred over oral suspension due to better absorption. Tablets cannot be crushed or divided.*

<13 years:

**Posaconazole** delayed-release tablets 4 mg/kg (rounded to the nearest 100 mg) PO BID on Day 1 then 4 mg/kg (rounded to the nearest 100 mg) PO daily starting on Day 2 (initial max: 300 mg/dose)

≥13 years:

**Posaconazole** delayed-release tablets 300 mg PO BID on Day 1 then 300 mg PO daily starting on Day 2

*In patients unable to tolerate whole tablets (oral suspension should be given with fatty meals and acidic carbonated beverages to ensure adequate levels. Use of acid suppression should be avoided):*

<13 years:

**Posaconazole** oral suspension 4 mg/kg PO QID (initial max: 200 mg/dose)

≥13 years:

**Posaconazole** oral suspension 200 mg PO QID

*In patients unable to tolerate oral medications:*

<18 years:

**Posaconazole** intravenous solution 4 mg/kg IV q12h on Day 1; 4 mg/kg IV q24h starting on Day 2 (initial max: 300 mg)

≥18 years:

**Posaconazole** intravenous solution 300 mg IV q12h on Day 1; 300 mg IV q24h starting on Day 2

Initial combination therapy (addition of micafungin to voriconazole X 2 weeks) may be considered 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.*

- 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 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.
- 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.

**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 potential 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.

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|--|---|---|
| <u>Proven or Probable Mucormycosis</u><br>(e.g., <i>Rhizopus spp.</i> , <i>Mucor spp.</i> , <i>Rhizomucor spp.</i> , others) | <p><b>Infectious Disease Consult is STRONGLY recommended</b> if Mucormycosis is suspected</p> <p><u>Primary</u><br/><b>Surgical debridement is generally necessary</b></p> <p><b>LAmB</b><br/>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</p> <p>Combination therapy should be discussed with ID Consultant</p> <p>Options for step-down therapy, salvage therapy, or in patients unable to take LAmB include isavuconazole or posaconazole (see Invasive Aspergillosis section for dosing recommendations).</p> | <ul style="list-style-type: none"> <li>Please note that voriconazole <u>IS NOT ACTIVE</u> against mucormycosis</li> </ul> <p><b>Duration</b></p> <ul style="list-style-type: none"> <li>Generally prolonged (months). Until resolution of clinical signs and symptoms or treatment limiting adverse effects</li> </ul> <p><b>Therapeutic Drug Monitoring</b></p> <ul style="list-style-type: none"> <li>Therapeutic drug monitoring is recommended for isavuconazole and posaconazole. Please see <a href="#">Recommendations for Therapeutic Drug Monitoring of Antifungal Agents</a></li> </ul> |

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/mm<sup>3</sup> 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- $\alpha$  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

References:

- Patterson TF et al. [Clin Infect Dis 2016;63:e1-e60](#)
- Danion F et al. [Semin Respir Crit Care Med 2015;36:692-705](#).

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| Revision History:                        |                       |

The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider's professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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