# Table 1a. Pharmacology of Antifungal Agents Studied for Prophylaxis of Invasive Aspergillosis

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients | Absorption | Distribution | Metabolism | Half-life | Adverse events | Mechanism(s) of Resistance | Convenience feasibility and availability^ |
|---|---|---|---|---|---|---|---|---|---|---|
| **Class: AZOLES** | | | | | | | | | | |
| **Isavuconazole**<br><br>(isavuconazole 200 mg = isavuconazonium sulfate 375 mg) | Inhibits biosynthesis of ergosterol, an essential component of fungal cell membrane, through inhibition of the 14-alpha-demethylase enzyme | IV<br><br>PO: capsule | Loading 200 mg IV/PO Q8H x 6 doses, maintenance dose 200 mg IV/PO daily (Isavuconium prodrug dose is 372 mg) | Oral capsule: 98% bioavailable | >99% protein bound<br><br>Vd 6L/kg<br><br>Distributed into eye and brain | Hepatic: CYP 3A4 | 130h | Cardiac: Shortened QTc interval<br><br>Hepatobiliary: LFT elevation | *Cyp51A* mutations in the target enzyme<br><br>Non-*Cyp51A* mechanisms involve efflux pumps | Multiple daily dosing during the loading dose phase<br><br>Prophylaxis indication is off-label use<br><br>Ref: [1-8] |
| **Itraconazole** | | PO: Suspension<br><br>Conventional capsule<br><br>Super-bioavailable (SUBA) capsule | Suspension and conventional capsule: 200 mg TID x3 days, then 200 mg BID<br><br>SUBA capsule: 130 mg TID x 3 days, then 130 mg daily to BID depending on clinical response<br><br>*Conventional capsules and SUBA capsules | Absorption of oral suspension and conventional capsule is impacted by stomach pH<br><br>Solution: absorption is 55% on empty stomach; food decreases bioavailability<br><br>Conventional capsule: absorption is enhanced with food and gastric acid | Over 99% protein bound<br><br>Well-distributed into tissues, excluding the eye, brain.<br><br>Vd 11L/kg | Hepatic: CYP 3A4<br><br>Transporter protein: P-gp | 34-42h | Cardiac: congestive heart failure, cardiac arrhythmias and QTc prolongation, hypertension<br><br>GI: nausea, vomiting, diarrhea, all of which can be significant<br><br>Hepatobiliary: LFT elevation | Multiple point mutations involving the *Cyp51A* gene<br><br>Efflux transporter cdr1B involved in non-CYP-mediated mechanisms | Suspension requires an empty stomach for optimal absorption.<br><br>Conventional capsules should be taken with food or an acidic beverage.<br><br>SUBA capsule less impacted by food intake, with therapeutic level reached in both fed and fasting states<br><br>TDM indicated<br><br>Ref: [1, 4, 8-14] |

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients | Absorption | Distribution | Metabolism | Half-life | Adverse events | Mechanism(s) of Resistance | Convenience feasibility and availability^ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | are not inter-changeable | SUBA capsule: 81% bioavailable, less likely to be affected by food | | | | Neurology: peripheral neuropathy<br><br>Alopecia<br><br>Hyperaldos terolism | | |
| **Posaconazole** | Inhibition biosynthesis of ergosterol, an essential component of fungal cell membrane, through inhibition of the 14-alpha-demethylase enzyme | IV<br><br>PO: oral solution, delayed-release tablet | IV and DR tablet: loading 300 mg BID, maintenance 300 mg daily<br><br>Oral suspension: prophylaxis 200 mg TID; treatment 400 mg BID (or 200 mg QID) | DR tab ≥54% on fasting, improved if taken with food<br><br>Oral suspension: 8-47% and improved with high-fat meal | >98% protein bound<br><br>Well-distributed into eye and CNS tissue.<br><br>Vd 7-25L/kg | UGT 1A4<br><br>Transporter protein: P-gp | 26-31h | Endocrinology: pseudo-hyper-aldosteronism reported in cohort study.<br><br>Hypertension<br><br>Alopecia<br><br>Hyperaldoster onism | *Cyp51A* gene point mutations with substitution at G54 confers resistance to posaconazole | Oral suspension: absorption improves with high-fat food, liquid nutritional supplements or acidic carbonated beverage. High inter-patient variability.<br><br>DR tablet and DR oral suspension: not dependent on food for absorption<br><br>TDM indicated<br><br>Once daily dosing with DR tab and IV, multiple doses daily with oral solution<br><br>Ref: [1, 4, 8, 13, 15-18] |

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|---|---|---|---|---|---|---|---|---|---|---|
| **Voriconazole** | | IV<br><br>PO: tablet | IV and PO:<br><br>Prophylaxis 200 mg q12h<br><br>Treatment loading 6 mg/kg q12h x2 doses, maintenance 4 mg/kg q12h | >95% bioavailable with oral tablets or suspension | 58% protein bound<br><br>Well-distributed to CSF (60%), vitreous (38%), pleural fluid, bone<br><br>Vd 4.6L/kg | Hepatic, non-linear<br><br>CYP 3A4, 2C9, 2C19 | 6h | CNS: hallucinations and visual discoloration<br><br>Cardiac: QTc prolongation<br>GI: LFT abnormality | Elevated MIC through mutation of *cyp51A* most common, which encodes an enzyme involved in cell membrane synthesis; substitutions of TR34/L98H amino acids | TDM in first week of initiation, and as needed per side effects or potential new drug interactions<br><br>Ref: [1, 4, 8, 13, 16, 19-21] |

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients | Absorption | Distribution | Metabolism | Half-life | Adverse events | Mechanism(s) of Resistance | Convenience feasibility and availability^ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | For tablets, round off to nearest 50 or 200 mg increment.<br><br>In patients with ≥BMI 30 kg/$m^2$, consider dose by adjusted body weight. * | | | | | Skin: phototoxicity and cSCCA<br><br>Bone: periostitis | | |
| **Class: ECHINOCANDINS** | | | | | | | | | | |
| **Anidulafungin** | Blocks synthesis of β(1,3)-d-glucan of the fungal cell wall by non-competitive inhibition of the enzyme β(1,3)-d-glucan synthase | IV | Loading dose 200 mg x1 day, then 100 mg daily | Not applicable | 84% protein bound<br><br>Well-distributed to lung, liver, spleen<br><br>Minimal penetration to brain, eye and urinary tract system | No hepatic involvement<br><br>Spontaneous degradation in plasma<br><br><10% renal excretion | 40-50h | Generally well tolerated | Hotspot mutations in FKS1 gene, but much less common in *Aspergillus spp.* than in *Candida spp*. sphingolipid, cell wall remodeling | Only available in IV formulation<br><br>Once daily dosing<br><br>Ref: [22, 23] |
| **Caspofungin** | | | Treatment and prophylaxis: Loading 70 mg x1, maintenance 50 mg daily | | 97% protein bound<br><br>Well-distributed to lung, liver, spleen | Hydrolysis, N-acetylation | 9-11h | Generally well tolerated<br><br>GI: elevated LFT and bilirubin reported most commonly | | Only available in IV formulation<br><br>Once daily dosing<br><br>Ref: [8, 24-26] |

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients | Absorption | Distribution | Metabolism | Half-life | Adverse events | Mechanism(s) of Resistance | Convenience feasibility and availability^ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Liver cirrhosis (Child-Pugh B or C), may consider decreasing maintenance dose to 35 mg | | Minimal penetration to brain, eye and urinary tract system | | | | | |
| **Micafungin**<br><br>(does not have official indication for *Aspergillus* prophylaxis) | Blocks synthesis of β(1,3)-d-glucan of the fungal cell wall by non-competitive inhibition of the enzyme β(1,3)-d-glucan synthase | | Prophylaxis: 50-100 mg daily<br>Treatment: 100-150 mg daily<br><br>Some recommend dose escalation in setting of obesity | | >99% protein bound<br><br>Well-distributed to lung, liver, spleen<br><br>Minimal penetration to brain, eye and urinary tract system | Hydroxylation, methoxylation<br><br>Minor substrate of CYP 3A4 | 15-17h | Generally well tolerated<br><br>GI: elevated LFT and bilirubin reported most commonly | | Only available in IV formulation<br>Once daily dosing<br><br>Ref: [8, 27-30] |
| **Class: POLYENES** | | | | | | | | | | |
| **Amphotericin B, liposomal** | Binds to ergosterol in cell membrane causing ion leakage and cell death | IV<br><br>Nebulized for lung transplant patients | IV: 1-3 mg/kg daily<br><br>Nebulized: 10 mg twice weekly | Not applicable | Vd 0.16L/kg<br><br>Well-distributed into tissues, including brain | Not well understood | Initial 6–23 h, terminal 100–153h | Nephrotoxicity and infusion-related reactions; mechanism of toxicity is caused by amphotericin's | Mechanism of resistance toward *A. fumigatus* unknown<br><br>For non-*fumigatus Aspergillus*, efflux pumps, increased | Only available in IV formulation<br><br>Monitoring of kidney function, infusion- related reactions<br><br>ABLC manufacturing discontinued in US in 2025<br><br>Ref: [8, 25, 31-33] |
| **Amphotericin B, lipid complex** | | | IV: 5 mg/kg daily | | Vd 131 L/kg | | Initial 24h | | | |

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients | Absorption | Distribution | Metabolism | Half-life | Adverse events | Mechanism(s) of Resistance | Convenience feasibility and availability^ |
|---|---|---|---|---|---|---|---|---|---|---|
| **Amphotericin B deoxycholate** | | | IV: 0.1–1.5 mg/kg daily | | Well-distributed into tissues, including brain<br>Vd 5L/kg<br>Well-distributed into tissues | | terminal 173 h<br>Initial 10–24 h, terminal 15 days | affinity to human cholesterol, which is reduced by altering tissue distribution for the modified structures in lipid formulations | catalase activity, reduced ergosterol have been reported. | |
| **NEW ANTIFUNGAL AGENTS UNDERGOING CLINICAL TRIALS FOR PROPHYLAXIS** | | | | | | | | | | |
| **Class: AZOLES** | | | | | | | | | | |
| **Opelconazole** | By inhibiting lanosterol 14α-demethylase (CYP51A1), lanosterol conversion to ergosterol is inhibited | Inhaled | 5 mg single inhaled daily dosing (Dosages from 0.5 – 10 mg have been studied) | Only inhaled | After inhalation, opelconazole shows efficacy primarily in the lungs (systemic concentrations are minimal) | CYP 3A4/5 | No data | mild-to-moderate AEs (e.g., cough, throat tightness, headache, nausea, fatigue), which all resolved by the end of the study, no severe events have been observed | No data | Clinical trial safety study OPERA-S for prophylaxis or pre-emptive therapy in lung transplant (NCT05037851)<br>Ref: [8, 34-38] |
| **Class: ECHINOCANDINS** | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| **Rezafungin** | Blocks synthesis of β(1,3)-d- | IV | 400 mg/week first dose; 200mg-400 | N/A | Limited information, wisely | Fecal excretion is | 80h after first dose and 150h | Mild nausea and constipation. | Insufficient data; FKS mutation may be involved | Clinical trial ReSPECT study for prophylaxis of invasive fungal infection |

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients | Absorption | Distribution | Metabolism | Half-life | Adverse events | Mechanism(s) of Resistance | Convenience feasibility and availability^ |
|---|---|---|---|---|---|---|---|---|---|---|
| | glucan of the fungal cell wall by non-competitive inhibition of the enzyme β(1,3)-d-glucan synthase | | mg/weekly subsequent doses<br><br>No pediatric data | | distributed, minimal drug recovered in urine, studies have excluded endo/myocarditis and endophthalmitis. No information in CNS penetration | main route of elimination | after second/ third doses | | | in HCT population (NCT04368559)<br><br>Ref: [8, 34-38] |

Abbreviation Notes: AEs, adverse events; BID, twice daily dosing; CSF, cerebrospinal fluid; CNS, central nervous system; CYP, cytochrome P450 enzyme; DR, delayed-release; FKS, Forskolin gene involved in antifungal drug resistance; GI, gastrointestinal; h, hour; HCT, hematopoietic cell transplantation; ID, identifier; IV, intravenous; LFT, liver function test(s); MIC, minimum inhibitory concentration; N/A, not applicable; PO, per os; QTc, QT interval corrected for hemoglobin; SUBA, super bioavailability; TDM, therapeutic drug monitoring; TID, three times daily dosing; UGT, UDP- glycosyltransferase enzyme; Vd, volume of distribution.
*Adjusted body weight = ideal body weight + [(total body weight - ideal body weight) x0.4]

# Table 1b. Pharmacology of Antifungal Agents – Additional Information for Pediatric Patients

| Antifungal agents | Approved for IA Prophylaxis Indication in Children | Formulations | Pediatric Dosing* | Convenience feasibility and availability^ | Pediatric-specific information |
|---|---|---|---|---|---|
| **Class: AZOLES** | | | | | |
| **Isavuconazole** | No, but approved for treatment of IA and IM in pediatrics | IV: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole)/vial<br><br>PO: capsules as 74.5 mg isavuconazonium sulfate (equivalent to 40 mg of isavuconazole)/capsule *or* 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole)/capsule | IV<br>· Children ≥ 1 year old to < 3 years (and < 18 kg weight): Loading Dose (LD) 15 mg/kg IV q 8h x 6 doses followed by Maintenance Dose (MD) 15 mg/kg once daily.<br>· ≥ 3 to < 18 years old (and < 37 kg): LD 10 mg/kg IV q8h for 6 doses followed by MD 10 mg/kg once daily<br>Maximum: 372 mg/dose of isavuconazonium sulfate = 200 mg of isavuconazole per day<br><br>PO capsule<br>· Children 6 years to < 18 years old and:<br>· 16 kg to <18 kg weight, LD: two 74.5 mg capsules (149 mg) q 8h x 6 doses followed by MD: two 74.5 mg capsules (149 mg) once daily.<br>· 18 kg to < 25 kg weight, LD: three 74.5 mg capsules (223.5 mg) q 8h x 6 doses followed by MD: three 74.5 mg capsules (223.5 mg) once daily.<br>· 25 kg to < 32 kg weight, LD: four 74.5 mg capsules (298 mg) q 8h x 6 doses followed by MD: four 74.5 capsules (298 mg) once daily.<br>· ≥ 32 kg weight: LD 372 mg q 8h x 6 doses followed by MD: 372 mg once daily.<br>Maximum: 372 mg/dose of isavuconazonium sulfate = 200 mg of isavuconazole per day. | Multiple daily dosing during the loading dose phase only. | Maintenance dosing is to begin 12-24 hours after the last loading dose.<br><br>IV formulation approved in children ≥ 1 year of age. Capsules approved in children ≥ 6 years of age and ≥ 16 kg.<br><br>IV formulation may be administered via a nasogastric tube in children ≥ 6 years of age and ≥ 16 kg.<br><br>Moderate inhibitor of and substrate for CYP3A4, screen for drug-drug interactions<br><br>Ref: [39] |
| **Itraconazole** | No | PO:<br>Suspension | Dosing extrapolated from Suspension and conventional capsule: dose: 5 mg/kg/dose every 12 to 24h (maximum 200 mg/dose) 200 mg TID x3 days then 200 mg BID | Suspension has higher bioavailability than | Co-administration of CYP3A4 substrates is |

| Antifungal agents | Approved for IA Prophylaxis Indication in Children | Formulations | Pediatric Dosing* | Convenience feasibility and availability^ | Pediatric-specific information |
|---|---|---|---|---|---|
| | | Conventional capsule<br><br>Super-bioavailable (SUBA)<br><br>capsule | SUBA capsule: No data in pediatrics: 130 mg TID x 3 days then 130 mg daily to BID depending on clinical response<br><br>*Conventional capsules and SUBA capsules are not inter-changeable | capsule and requires an empty stomach for optimal absorption.<br><br>Conventional capsules should be taken with food or an acidic beverage.<br><br>SUBA capsule less impacted by food intake, with therapeutic level reached in both fed and fasting states | contraindicated with itraconazole.<br><br>High variability in absorption and differences in bioavailability among the oral formulations; TDM should be considered. When measured by high-pressure liquid chromatography, both the itraconazole and hydroxy-itraconazole metabolite concentrations should be considered.<br><br>SUBA formulation not studied in children.<br><br>Ref: [40, 41] |
| **Posaconazole** | Yes, in children ≥ 2 years of age | IV: 300 mg/vial<br><br>PO: delayed-release tablet (100 mg/tablet), delayed-release suspension (300 mg plus mixing liquid), oral suspension (40 mg/mL) | <u>IV</u><br>· 2 years to 12 years of age, LD: 6 mg/kg IV q12h for 2 doses, followed by MD: 6 mg/kg IV daily (Maximum of 300 mg/dose)<br>· ≥ 13 years old, LD: 300 mg IV q 12 h for 2 doses followed by MD: 300 mg IV once daily<br><br><u>Delayed-release tablets</u><br>≥ 2 years of age and weighing > 40 kg, LD: 300 mg BID for 2 doses, followed by MD: 300 mg once daily | Absorption improves with food<br><br>High inter-patient variability in absorption with oral solution | The immediate release oral suspension, delayed-release oral suspension, and delayed-release tablets are **<u>not</u>** interchangeable.<br><br>IV formulation approved in children ≥ 2 years of age. |

| Antifungal agents | Approved for IA Prophylaxis Indication in Children | Formulations | Pediatric Dosing* | Convenience feasibility and availability^ | Pediatric-specific information |
|---|---|---|---|---|---|
| | | | Delayed-release suspension<br>· 10 kg to < 12 kg weight, LD: 90 mg PO BID x 2 doses, followed by 90 mg once daily<br>· 12 kg to < 17 kg weight: 120 mg PO BID x 2 doses, followed by 120 mg once daily<br>· 17 kg to < 21 kg weight: 150 mg PO BID x 2 doses, followed by 150 mg once daily<br>· 21 kg to < 26 kg weight: 180 mg PO BID x 2 doses, followed by 180 mg once daily<br>· 26 kg to < 36 kg: 210 mg PO BID x 2 doses, followed by 210 mg once daily<br>· 36 kg to ≤ 40 kg: 240 mg PO BID x 2 doses, followed by 240 mg once daily<br>· > 40 kg: 300 mg PO BID x 2 doses, followed by 300 mg once daily<br><br>Immediate release oral suspension<br>≥ 13 years of age, LD: 200 mg PO three times a day, followed by 200 mg PO three times a day | Once daily dosing with DR tab and IV, multiple doses daily with oral solution | Delayed-release tablets approved in children ≥ 2 years of age and weigh 40kg.<br><br>Delayed-release oral suspension approved in children ≥ 2 years of age and weighing > 40kg. This formulation is contraindicated in children with hereditary fructose intolerance.<br><br>Immediate release oral suspension is approved in children ≥ 13 years of age. The oral suspension formulation requires intake with high-fat food and has poor biopharmaceutical characteristics. If prescribed, TDM should be considered, though there is no consensus of what concentration is necessary for prophylaxis in children.<br><br>Ref: [42-44] |

| Antifungal agents | Approved for IA Prophylaxis Indication in Children | Formulations | Pediatric Dosing* | Convenience feasibility and availability^ | Pediatric-specific information |
|---|---|---|---|---|---|
| **Voriconazole** | Yes, in HCT recipients ≥ 2 years of age. Also approved for treatment of IA in children ≥ 2 years of age. | IV: 200 mg/vial<br>PO: tablets (50 mg, 200 mg), oral suspension (200 mg/5 mL) | IV<br>· 2-12 yrs and weight < 50 kg: LD 9 mg/kg q12h x 2 doses; followed by MD: 8 mg/kg q12h<br>· ≥ 12-14 years of age and<br>· < 50 kg: LD 9 mg/kg q12h x 2 doses; followed by MD 8 mg/kg q12h<br>· ≥ 50 kg: LD 6 mg/kg q12h x 2 doses, followed by MD 4 mg/kg q12h<br>· ≥ 15 years of age: LD 6 mg/kg q12h x 2 doses, followed by MD 4 mg/kg q12h<br><br>Oral tablet:<br>· 2-12 yrs: LD 9 mg/kg q12h x 2 doses; followed by MD 9 mg/kg q12h<br>· ≥ 12-14 years of age and<br>· < 50 kg: LD 9 mg/kg q12h x 2 doses; followed by MD 9 mg/kg q12h (max 350 mg/dose)<br>· ≥ 50 kg: 200 mg q12h<br>· ≥ 15 years of age: LD 6 mg/kg q12h x 2 doses, followed by MD 4 mg/kg q12h (200 mg PO q12h)<br><br>Oral suspension:<br>· 2-12 yrs: 0.225 mL/kg q12h (max 8.75 mL (350 mg) every 12 hours)<br>· ≥ 12-14 years of age and<br>· < 50 kg: 0.225 mL/kg q12h (max 8.75 mL (350 mg) every 12 hours)<br>· ≥ 50 kg: 5 mL q12h<br>· ≥ 15 years of age and ≥ 50 kg: 5 mL q12h | TDM in first week of initiation, and as needed per side effects or potential new drug interactions | All voriconazole formulations are approved for the treatment of IA in children ≥ 2 years of age. Infants and children < 2 years of age: insufficient data.<br><br>The voriconazole prophylaxis dosing regimen is the same as for treatment in children 2-12y and approved for HCT recipients, beginning on the day of transplant and up to 100 days post-HCT; it may be continued up to 180 days post-HCT if receiving immunosuppression or with graft-versus-host disease diagnosis.<br><br>Frequency of voriconazole-associated phototoxicity is higher in children; photoprotection measures are warranted.<br><br>Ref: [45, 46] |

| Antifungal agents | Approved for IA Prophylaxis Indication in Children | Formulations | Pediatric Dosing* | Convenience feasibility and availability^ | Pediatric-specific information |
|---|---|---|---|---|---|
| **Class: ECHINOCANDINS** | | | | | |
| **Anidulafungin** | No | IV | For infants >1 month old and children, loading dose of 3 mg/kg (max 200 mg) followed by 1.5 mg/kg (max 100 mg) q24h | Only available in IV formulation | The compound does not interact with CYP450 isoenzymes, and no dose adjustment required for renal or hepatic insufficiency.<br><br>Ref: [47-50] |
| **Caspofungin** | No, but approved for treatment of IA in children ≥ 3 months of age. | IV | · 3 months – 17 years of age: 70 mg/m$^2$ x1 (max 70 mg), followed by MD: 50 mg/m$^2$ (max 70 mg) once daily<br>· ≥ 18 years of age: LD: 70 mg x1, followed by MD: 50 mg once daily | Only available in IV formulation<br><br>Once daily dosing | Pediatric dosing 3 months-≤ 17 years of age based on patient's body surface area (using Mosteller formula)<br><br>Ref: [51, 52] |
| **Micafungin** | No | IV | · Infants <4 months of age: 2 mg/kg/dose IV once daily<br>· Infants ≥4 months to adolescents: IV: 1 mg/kg/dose once daily<br><br>Non-controlled data with alternate dosing strategies:<br>· Alternate day dosing: Infants ≥7 months and Children ≤10 years: IV: 3 mg/kg/does every 48 hours (very limited data for antifungal prophy in pediatric HCT recipients) | Only available in IV formulation<br><br>Once daily dosing | Ref: [53-55] |

| Antifungal agents | Approved for IA Prophylaxis Indication in Children | Formulations | Pediatric Dosing* | Convenience feasibility and availability^ | Pediatric-specific information |
|---|---|---|---|---|---|
| | | | · Twice weekly dosing: 9 mg/kg/dose twice a week for IA prophylaxis in pediatric HCT recipients. | | |
| **Class: POLYENES** | | | | | |
| **Amphotericin B, liposomal** | No | IV<br><br>Nebulized for lung transplant patients | IV: 1-3 mg/kg daily<br>Alternatives: 1 mg/kg IV every other day; 2.5 mg/kg IV twice weekly<br><br>Nebulized: 10 mg twice weekly<br>Alternative: 25 mg nebulized three times a week for the first 60 days post-transplant, then 25 mg once weekly. | Only available in IV formulation<br><br>Monitoring of kidney function, infusion-related reactions | Optimal dosing for mold prophylaxis is not defined in pediatrics.<br><br>Ref: [56] |
| **Amphotericin B, lipid complex** | | | IV: 5 mg/kg daily | | |
| **Amphotericin B deoxycholate** | | | IV: 1–1.5 mg/kg daily | | |

*There are very few data to guide optimal dosing of antifungal prophylaxis in children.

Abbreviation Notes: HCT, hematopoietic cell transplantation; IA, invasive aspergillosis; ID, identifier; IM, invasive mucormycosis; IV, intravenous; LD, loading dose; MD, maintenance dose; PO, per os; SUBA, super bioavailability; TDM, therapeutic drug monitoring.

# Table 1c. Pharmacology of New Antifungal Agents NOT Studied for Prophylaxis of Invasive Aspergillosis

| Antifungal agents | Mechanism of action | Formulations | Dosing in Adult Patients[$] | Absorption | Distribution | Metabolism | Half-life | Adverse events[#] | Mechanism(s) of Resistance | Convenience feasibility and availability[^] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Class: DIHYROOROTATE DEHYDROGENASE ENZYME INHIBITOR** | | | | | | | | | | |
| **Olorofim** | Inhibition of pyrimidine biosynthesis by inhibiting dehydroorate dehydrogenase (DHODH) | Oral or IV | Oral: Loading of 4 mg/kg in 2 – 3 doses on day 1 followed by 2.5 mg/kg/day<br>IV dosing (0.5 – 4 mg/kg) has not been actively pursued; dose to target Cmin of 0.5 mg/ml<br><br>No pediatric data | Bioavailability 45% | Good distribution to tissues including kidney, liver, lung and found in brain at lower levels | Cleared by CYP450 enzymes; weak CYP3A4 inhibitor<br>99% protein bound | 20 – 30 hours | Infusion-related reactions (site pain and phlebitis)<br>Dizziness (67%) | Olorofim resistance in *Aspergillus fumigatus* is negligible but can be selected in laboratory conditions associated with mutations in *PyrE* gene.<br><br>Azoles may be antagonistic to olorofim (upregulation of pyrimidine biosynthetic factor). Azole olorofim cross resistance is possible by two transcription factors null mutants hapB and area. | Under clinical trial conditions, but in June 2023 it received orphan drug status by the US FDA for invasive mold infections including aspergillosis. Clinical trial OASIS for treatment of invasive aspergillosis (NCT05101187)<br><br>Ref: [34-38] |
| **Class: GEPIX** | | | | | | | | | | |
| **Fosmanogepix** | Inhibition of Gwt1 essential for transit and anchoring mannoproteins to fungal cell | IV and PO | Initial 1000mg IV x2/day on day 1 followed by 600 mg IV | 90% bioavailability | Most tissues including brain, liver, lung, kidneys, and eye | Converted by phosphatase to manogepix | 2.5h | Well tolerated, no dose limiting toxicities. Most common AE headache | Insufficient data | Phase Ib safety and PK study in patients with acute myeloid leukemia and neutropenia for prophylaxis where |

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| | membrane and wall | | once daily (all over 3 h) followed by 600 mg IV or 800 mg oral once daily.<br><br>No pediatric data | | | Elimination: primary biliary and fecal | | | | posaconazole was given for antifungal prophylaxis.<br><br>Ref: [34-38, 57, 58] |
| **Class: TRITERPENOID** | | | | | | | | | | |
| **Ibrexafungerp** | Disrupts fungal cell wall synthesis through inhibition of (1→3)-β-D-glucan | IV and oral | Oral tablets (loading dose of 500 mg BID on Days 1 and 2 followed by maintenance dose of 500 mg daily from Day 3 onwards)<br><br>No pediatric data | Oral bioavailability of 35%-50%. 99.6% protein bound | Concentration in multiple tissues including liver, spleen, lungs, bone marrow, kidney, and skin exceeds that of plasma. However, there is low distribution to CNS tissue | Ibrexafungerp is a substrate of CYP3A and P-glycoprotein, though it neither induces nor inhibits CYP3A | 20-30h | The most common AEs are mild-to-moderate and due to gastrointestinal tract symptoms, including nausea, diarrhea, abdominal pain, and vomiting, that may be dose limiting | Limited cross-resistance between ibrexafungerp and echinocandins in *Candida* species due to certain mutations in hot spots FKS1 and FKS2 may show resistance; insufficient data in *Aspergillus* | Clinical trial FURI included patients needing treatment for IA (NCT03059992).<br><br>Ref: [34-38, 59] |

Abbreviation Notes: AE, adverse event; BID, twice daily; CNS, central nervous system; CYP, cytochrome p450; FKS, Forskolin gene involved in antifungal drug resistance; Gwt, glucosaminyl-phosphatidylinositol O-acyltransferase enzyme; h, hour; ID, identifier; IV, intravenous; PK, pharmacokinetic; PO, per os; SUBA, super bioavailability; US FDA, United States Food and Drug Administration.

# Table 2. Involvement of Isoenzymes and Transporter Proteins Among Azole Antifungals [35]

| Azole antifungal agents | Isoenzymes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CYP 3A4 | | CYP 2C9 | | CYP 2C19 | | p-Glycoprotein | |
| | Inhibitor | Substrate | Inhibitor | Substrate | Inhibitor | Substrate | Inhibitor | Substrate |
| **Isavuconazole** | Moderate | Major | -- | -- | -- | -- | Weak | -- |
| **Itraconazole** | Strong | Major | Weak | -- | -- | -- | Strong | Minor |
| **Posaconazole** | Moderate | -- | -- | -- | -- | -- | Moderate | Moderate |
| **Voriconazole** | Strong | Minor | Moderate | Minor | Moderate | Major | -- | -- |

# Table 3. Drug-Drug Interactions Involving Antifungals [4]

| Antifungals agents | Drugs* that interact with the antifungal | Mechanism of interaction | Effect | Onset | Mitigation strategies: avoid vs. dose adjustment |
|---|---|---|---|---|---|
| **Voriconazole** | Letermovir [60] | Induction of 2C9, 2C19 | Decreased level of voriconazole | Within 7 days | Therapeutic drug monitoring and dose adjustment for voriconazole. |
| **All azoles** | Calcineurin inhibitors (cyclosporine, tacrolimus), sirolimus | Inhibition of 3A4 | Increased level of CNI and toxicity | Within 7 days | Therapeutic drug monitoring of CNI and dose adjustment, especially at commencement and cessation. Avoid combination with sirolimus. |
| **All azoles** | Vinca alkaloids, all-trans-retinoic acid, busulfan | Inhibition of 3A4 | Increased level of chemotherapy and toxicity | Within 7 days | Avoid while on the chemotherapy. |
| **All azoles** | Ventoclax, midostaurin, other small molecule targeted therapies | Inhibition of 3A4 | Increased level of the targeted therapies | Within 7 days | Dose adjust venetoclax and conduct therapeutic drug monitoring of azole if it cannot be avoided (for example, if venetoclax is administered with concomitant posaconazole, dose reduction of venetoclax by 75% is recommended [61-63]. Otherwise, select non-azole alternative for the duration of the venetoclax, midostaurin and other targeted therapies. |
| **All azoles** | Amiodarone | Inhibition of 3A4 | Increased azole, QTc prolongation | Within 7 days | Avoid |
| **All azoles (except isavuconazole)** | Quetiapine | | QTc prolongation | Within 7 days | Monitor QTc |
| **jAll azoles** | Rifamycins | Induction of 3A4 | Decreased azole | Within 7 days | Avoid |
| **All azoles** | Phenytoin | Induction of 3A4 | Decreased azole | Within 7 days | Avoid |
| **All azoles** | Carbamazepine | Induction of 3A4 | Decreased azole | Within 7 days | Avoid |
| **All azoles** | Macrolides | Induction of 3A4 | Increase azole | Within 7 days | TDM |

| | | | | | |
|---|---|---|---|---|---|
| **All azoles** | Steroids | Inhibit 3A4 | Increase steroid | Within 7 days | Monitor or dose adjust steroid (50% reduction) |

| Antifungals agents | Drugs* that interact with the antifungal | Mechanism of interaction | Effect | Onset | Mitigation strategies: avoid vs. dose adjustment |
|---|---|---|---|---|---|
| All azoles | Benzodiazepines | Inhibit 3A4 | Increase benzodiazepines | Within 7 days | Monitor or dose adjust |
| All azoles | Calcium channel blockers | Inhibit 3A4 | Increase Ca channel blocker | Within 7 days | Monitor or dose adjust |
| All azoles (except posaconazole) | Digoxin | Inhibit 3A4, transporter protein | Increase digoxin | Within 7 days | Monitor or dose adjust |
| All azoles | Inhaled steroid | Inhibit 3A4 | Increase steroid | Within 7 days | Reduced inhaled steroid 50% |
| All azoles | Atorvastatin/Simvastatin | Inhibit 3A4 | Increased stain | Within 7 days | Change to pravastatin or rosuvastatin |
| All azoles | Warfarin | Inhibit 3A4 | Increase warfarin | Within 7 days | Monitor INR and dose adjust warfarin |
| All azoles (isavuconazole least) | Apixaban class | Inhibit 3A4 | Increase apixaban | Within 7 days | Monitor and dose adjust apixaban |
| All azoles | Sulfonylureas | Inhibit 3A4 and 2C9 | Hypoglycemia | Within 1 week (PMID: 29784014) | Avoid |

Note: CNI, calcineurin inhibitor; INR, International normalized ratio; QTc, QT interval corrected for heart rate; TDM, therapeutic drug monitoring. This table is not intended to be an exhaustive list.

# Table 4. Therapeutic Drug Monitoring

| Antifungal agents | Concentration Target Range* (μg/ml) | | Earliest Timing | References |
|---|---|---|---|---|
| | **Efficacy** | **Toxicity** | | |
| **Isavuconazole** | >1<br>Targets have not been clearly established for prophylaxis. | <5** [59] | 5-7 days (with loading)<br>10-14 days (without loading) | [64-68] |
| **Itraconazole** | **HPLC orLC-MS** | | 5-7 days (with loading)<br>10-14 days (without loading) | [11, 12, 69-79] |
| | >0.5-1.0 (interpreted as sum of itraconazole and its active metabolite OH-itraconazole)<br>For prophylaxis, some experts recommend target of ≥0.5.<br>For treatment, some experts recommend target of >1-2 | <5 | | [80, 81] |
| | **Bioassay** | | | |
| | > 5 (measures total antifungal activity as a single combined value, reflecting the activity of both itraconazole plus OH-itraconazole ) | <17 | | |
| **Posaconazole** | >1<br>For prophylaxis, some experts recommend target of ≥0.5 to 0.7. | <4 | 5 days (with loading)<br>7-14 days (without loading) | [17, 82-95] |
| **Voriconazole** | >1-2<br>For prophylaxis, some experts recommend target of ≥0.5. | <5 | 2-3 days (with loading)<br>4-7 days (without loading) | [19, 96-110] |

Note: HPLC, high performance liquid chromatography; LC-MS: liquid chromatography-mass spectrometry

*Target range represents the lower and upper limits of drug levels.

**A retrospective study reported 5.86 μg/mL to be a threshold that balances sensitivity and specificity in the determination of toxicity risk for isavuconazole.

# Therapeutic drug monitoring

Therapeutic monitoring of drug concentrations is indicated in the setting of pharmacokinetic variability, the existence of either concentration efficacy or toxicity relationships, and the availability of reproducible concentration assays [106, 111]. Each of these factors have been demonstrated to some extent for the mold active triazole antifungals [17, 19, 65-78, 82, 85-88, 91-93, 96, 97, 99-105, 107, 108, 110]. The drug characteristics and clinical scenarios that impact achieving therapeutic concentrations vary among the individual drugs and even different formulations for the same antifungal [11, 71, 79, 83, 84, 89, 94, 95, 98, 109, 112-114]. Similarly, the therapeutic concentration range and strength of evidence supporting the range varies among drugs. The most compelling data supporting TDM exists for itraconazole and voriconazole. The clinical indications for monitoring include triazole initiation, change in dose, clinical worsening, suspected side effects, or addition of a new medication that may interact with the triazole. The associated toxic effects of these drugs are described above. The appropriate timing for therapeutic drug monitoring is designed to assess steady state trough concentrations. The optimal timing varies somewhat among compounds, but typically steady state can be approximated a week after initiation if a loading regimen is utilized and 10-14 days if not. Most laboratories utilize either high performance liquid chromatography or liquid chromatography-mass spectrometry methodology. However, some laboratories utilize a microbiologic assay for assessment of itraconazole [115]. The assay endpoints and range vary for the bioassay compared to chemical assays. In addition, the physical chemical assays will report both itraconazole and the primary metabolite, OH-itraconazole, both exhibit antifungal effects and the appropriate range is defined on the basis of the sum of these compounds. For the other antifungals, a single value is reported. The therapeutic concentration range and appropriate trough assay timing are reported in Table 4.

Dose reductions are typically indicated for concentrations in the toxic range, with repeat concentration monitoring after dose changes. Management options for subtherapeutic concentrations also vary among the individual drugs and formulations. For itraconazole and Posaconazole, the options include increase in dose or change to a more readily absorbed formulation or optimization of administration relative to food or gastric acidity [83, 114, 116-119]. For voriconazole, subtherapeutic concentrations can be remedied with an increase in dose or in rare situations altered by co-administration of an inhibitor of metabolism, such as omeprazole [120]. The pharmacokinetics of voriconazole are non-linear and the impact is difficult to predict [121]. Thus, repeat monitoring and consultation of an available dosing-nomogram or program is preferable [122]. Alternatively, changing to a different antifungal may be the most appropriate option. Formulation characteristics and dosing are discussed in more detail above. TDM may be considered in special populations, particularly in pediatric patients, which group very diverse populations based on age and maturing organs. Though typically > 80% of populations in which Pk studies have been conducted, often a large proportion are below target trough or area under the concentration [39, 42, 44, 123, 124].

# Table 5a. Dosing Adjustment for Liver Dysfunction

| Antifungal agents | Liver dysfunction Child-Pugh Class A and B (score 5 to 9) | Liver dysfunction Child-Pugh class C (score 10 to 15) | References |
|---|---|---|---|
| **Class: AZOLES** | | | |
| **Isavuconazole** | Dose adjustment not required | Use is not recommended unless benefits outweigh risks | [5, 125-127] |
| **Itraconazole** | No recommendations available. Use is discouraged unless benefits outweigh risks. Use with caution and under close monitoring, including therapeutic drug monitoring | | [126, 127] |
| **Posaconazole** | No dose adjustment is recommended. Therapeutic drug monitoring is recommended for oral suspension and should be considered for the other formulations. | | [126, 127] |
| **Voriconazole** | Dose reduction of 50% for maintenance dose with therapeutic drug monitoring. | No recommendations available. Use only if benefits outweigh the risk with therapeutic drug monitoring. One expert opinion suggested dose reduction to about one-third of maintenance dose could be considered, with therapeutic drug monitoring. | [126, 127] |
| **Class: ECHINOCANDINS** | | | |
| **Anidulafungin** | No dose adjustment required. | | [126-128] |
| **Caspofungin** | No dose adjustment required. | Reducing maintenance dose to 35 mg daily has been recommended in product monograph based on earlier data, but recent data suggest this may not be Necessary and may lead to underexposure in critically ill patients. | [126, 129] |
| **Micafungin** | No dose adjustment required. | US: no dose adjustment required<br>European Medicines Agency: use only if benefits outweigh risks. | [30, 130, 131] |
| **Class: POLYENES** | | | |
| **Amphotericin B, liposomal** | No dose adjustment required. | | [126, 127] |
| **Amphotericin B, lipid complex** | | | |
| **Amphotericin B, deoxycholate** | | | |

# Table 5b. Dosing Adjustment for Kidney Dysfunction

| Antifungal agents | GFR less than 50 mL/min | Reference |
|---|---|---|
| **Class: AZOLES** | | |
| **Isavuconazole** | No dose adjustment required | [5, 132] |
| **Itraconazole** | No dose adjustment required | [132] |
| **Posaconazole** | No dose adjustment required for posaconazole.<br>IV formulation contains the excipient sulfobutyl ether betacyclodextrin sodium (SBECD). Despite early concerns about accumulation of SBECD in patients with CrCL <50 mL/min, the topic has since been re-evaluated, such that short term use (e.g. 7 days) was deemed to be safe. It is possible that SBECD does not lead to kidney function deterioration, however, the data are conflicting | [132-134] |
| **Voriconazole** | No dose adjustment required for voriconazole. IV formulation contains the excipient sulfobutyl ether betacyclodextrin sodium (SBECD). Despite early concerns about accumulation of SBECD in patients with CrCL <50 mL/min, the topic has since been re-evaluated, such that short term use (e.g. 7 days) was deemed to be safe. It is possible that SBECD does not lead to kidney function deterioration, however, the data are conflicting | [132-135] |
| **Class: ECHINOCANDINS** | | |
| **Anidulafungin** | No dose adjustment required. | [132] |
| **Caspofungin** | | |
| **Micafungin** | | |
| **Class: POLYENES** | | |
| **Amphotericin B, liposomal** | No dose adjustment required.<br>Amphotericin B deoxycholate should be avoided in patients with kidney dysfunction due to concern of nephrotoxicity. | [32] |
| **Amphotericin B, lipid complex** | | |
| **Amphotericin B, deoxycholate** | | |

Note: GFR: glomerular filtration rate

# Table 5c. Dosing Considerations for Antifungals in Patients Receiving Extracorporeal Membrane Oxygenation (ECMO) or Renal Replacement Therapy (RRT)

| Antifungal agents | Dosing adjustment for ECMO* | Adjustment for RRT? | References |
|---|---|---|---|
| **Isavuconazole** | Standard dose | No | [136-139] |
| **Itraconazole** | No data | No | [136-138] |
| **Posaconazole** | Standard dose for prophylaxis | No | [136, 138] |
| **Voriconazole** | Moderate to significant loss to circuit<br>Increase loading dose duration to 48 hours suggested<br>Therapeutic drug monitoring to guide dosing | No | [136, 138] |
| **Anidulafungin** | Limited data | No | [22, 136, 138] |
| **Caspofungin** | Mixed data, increasing dose to 70 mg loading then 50-70 mg daily as maintenance dose suggested | No | [136, 138] |
| **Micafungin** | Mixed data. Increase to 150 mg daily suggested | No | [136, 138] |
| **Amphotericin B, liposomal** | Mixed data but given lipophilicity, increasing dose to 5-8 mg/kg daily suggested | No | [136, 137] |
| **Amphotericin B deoxycholate** | Standard dose | No | [136, 138] |
| **Amphotericin B, lipid complex** | No data | No data | -- |

*Dosing suggestions for ECMO and RRT are not specific to prophylaxis use of the antifungals unless specified

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