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Antifungal Azoles: Old and New  
Echinocandins in Children

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Antifungal Azoles: Old and New

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Management of fungal infections is complex with increasing choice of antifungals. Mortality and morbidity are significant despite treatment. Azoles are commonly used compounds which inhibit fungal lanosterol 14 $\alpha$  demethylase, thereby depleting ergosterol in the fungal cell membrane with the accumulation of lanosterol precursors. Imidazoles (miconazole, ketoconazole, clotrimazole) are used in topical preparations. Triazoles are used for prophylaxis, empirical and directed systemic antifungal therapy, and will be the focus of this review. There are important differences in structure, spectrum of activity, pharmacokinetics, drug interactions, and clinical indications.

FLUCONAZOLE

Fluconazole has activity against most *Candida* spp. (except *Candida krusei* and some *Candida glabrata* isolates), *Cryptococcus* spp., and many dimorphic fungi. Intravenous (IV) and oral formulations are avail-

able. The drug is well absorbed in children, has limited binding to plasma proteins, and penetrates into cerebrospinal fluid.<sup>1,2</sup> Fluconazole is cleared mainly unchanged in urine; clearance occurs more rapidly in children than adults. The recommended dose for neonates and children with invasive fungal infection (IFI) is 12 mg/kg/d.<sup>1,3,4</sup> Therapeutic concentrations may be achieved more rapidly with a loading dose.<sup>5</sup>

Efficacy data from 213 infants and children with IFI unresponsive or intolerant to therapy are published: responses were observed in 97% of infants (clinical/mycological response) and 73% (clinical) to 83% of children (mycological response).<sup>6,7</sup> Pathogens with decreased fluconazole susceptibility were infrequent in both the trials. As compared with placebo, fluconazole prophylaxis reduces the incidence of invasive candidiasis (IC) in preterm infants (birth weight <1500 g).<sup>8</sup> *Candida* infections are reduced in liver and hematopoietic stem cell transplant (HSCT) recipients receiving fluconazole prophylaxis.<sup>4,9</sup>

Fluconazole is well tolerated in children. Fluconazole-related adverse events occurred in only 6% of 213 infants/children: 3% discontinued therapy.<sup>6,7</sup> Gastrointestinal intolerance and elevated transaminases were most frequent.

Fluconazole is recommended for non-neutropenic patients with candidemia or IC, for maintenance/eradication therapy in cryptococcal meningitis, and for mucocutaneous candidiasis requiring systemic therapy.<sup>4,10</sup> Alternatives such as amphotericin B or echinocandins may be preferred, especially in children with severe illness, neonates, children with neutropenia, prior azole use, or at

risk for *C. krusei* or *C. glabrata* infection.<sup>4</sup> Prophylaxis should be considered in nurseries with a high incidence of IC.<sup>4,8</sup>

ITRACONAZOLE

Itraconazole is the first triazole with activity against filamentous fungi including *Aspergillus* spp. Capsules, oral solution, and IV formulations are available. Oral absorption is erratic: achlorhydria reduces and acidic beverages enhance capsule absorption.<sup>2</sup> The oral solution is better absorbed on an empty stomach. The drug is highly protein bound, extensively distributed into tissues and metabolized by the liver.<sup>2,11</sup> Drug interactions are frequent: itraconazole is a potent inhibitor of cytochrome CYP3A4 enzymes. More frequent dosing is required in children compared with adults (2.5–5 mg/kg twice daily).<sup>2</sup> No neonatal data for itraconazole exist. Therapeutic drug monitoring may assist in determining optimal dosing.

Prophylaxis with itraconazole solution is more effective than fluconazole in adults with hematological malignancy but may be limited by intolerance.<sup>9,12</sup> In 103 neutropenic children receiving itraconazole oral solution, 35% were noncompliant, intolerant, or developed adverse events on therapy. Nausea, vomiting, and diarrhea were most frequent.<sup>12</sup>

Itraconazole is recommended in mild-to-moderate infection or after amphotericin B therapy for severe/disseminated infection with dimorphic fungi including histoplasmosis, blastomycosis, and sporotrichosis.<sup>13–15</sup> Itraconazole is also recommended for allergic bronchopulmonary aspergillosis.<sup>16</sup>

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## VORICONAZOLE

Voriconazole is an extended-spectrum, second-generation azole, structurally similar to fluconazole with activity against most fluconazole-resistant yeasts, *Aspergillus* spp., *Penicillium* spp., *Scedosporium* spp., and *Fusarium* spp. It has no useful activity against zygomycetes. IV and oral preparations are available. The bioavailability of voriconazole is >90% in adults, yet reduced in children.<sup>17</sup> Absorption is reduced if taken with food. The drug has extensive distribution into tissues, including the central nervous system, and hepatically metabolized by CYP2C19, CYP2C9, and CYP3A4. Significant interpatient variability is observed.<sup>15</sup> This may be due to the factors including variable metabolism due to genetic polymorphism or elimination capacity, and/or drug interactions. Recent data suggest that  $\geq 7$  mg/kg of IV and 200 mg of oral voriconazole twice daily are required in children (2–12 years) to approximate adult levels.<sup>15,17</sup> Therapeutic drug monitoring may assist in optimizing dosing in children.

Voriconazole was administered (6 mg/kg load then 4 mg/kg twice daily) to 69 children with IFI, intolerant, or refractory to other therapies. Complete or partial responses were observed in 45% (aspergillosis; 43%; scedosporosis; 63%).<sup>18</sup> Improved survival has been demonstrated in adolescents and adults receiving voriconazole compared with amphotericin B deoxycholate.<sup>16</sup>

The most frequent adverse events with voriconazole are hepatotoxicity, visual disturbances, rash, and gastrointestinal intolerance.<sup>15,18</sup> Voriconazole-related adverse events occurred in 23 of 69 children (33%) yet only 3 discontinued therapy.<sup>18</sup>

Voriconazole is the drug of choice for invasive aspergillosis (IA).<sup>16</sup>

## POSACONAZOLE

Posaconazole is an extended-spectrum, second-generation azole, structurally similar to itraconazole. In addition to the spectrum of voriconazole, posaconazole has activity against zygomycetes. The drug is available in oral solution: an IV preparation is undergoing phase I trials. Optimum bioavailability is achieved with at least twice daily dosing with food or nutritional supplements.<sup>11</sup> Posaconazole is highly protein bound and has large volume of distribution. It is not significantly metabolized, but mostly excreted unchanged in the feces.<sup>11</sup> The drug inhibits cytochrome CYP3A4 and as such, drug interactions are observed. Limited pediatric pharmacokinetic data are available: trials are presently underway. Eleven children (10–17 years) receiving 800 mg/d had similar plasma levels to adults receiving the same dose.<sup>11</sup>

Pediatric safety and efficacy data are limited. Complete or partial responses were observed in 9 of 15 children receiving posaconazole salvage therapy for proven/probable IFI, including 4 of 7 with zygomycosis.<sup>19</sup> The median dose was 21 mg/kg (95% CI 17–25). This response rate was comparable to adults receiving therapy for aspergillosis and zygomycosis.<sup>19</sup> The drug was well tolerated; no children discontinued therapy with adverse events.

Posaconazole was compared with fluconazole or itraconazole in neutropenic adolescents and adults with acute myeloid leukemia (AML) or myelodysplastic syndrome. IFI was less frequent in those receiving posaconazole.<sup>20</sup> Posaconazole and fluconazole were administered to adolescents and adults with graft-versus-host disease. IA- and IFI-related mortality was less in those receiving posaconazole.<sup>21</sup>

Although prophylaxis with posaconazole is recommended in neutropenic patients with AML/myelodysplastic syndrome and HSCT recipients with graft-versus-host disease at high risk of IA, no pediatric dosing recommendations exist.<sup>16</sup>

## NEW TRIAZOLES

Three new extended-spectrum triazoles are in advanced stages of development: isavuconazole, ravuconazole, and albaconazole.<sup>22</sup> Isavuconazonium, the water soluble prodrug of isavuconazole, is available in oral or IV preparations. Unlike itraconazole and voriconazole, this drug does not require cyclodextrin to increase solubility. Absorption is minimally affected by food intake. Isavuconazole has a long elimination half life, large volume of distribution, and high protein binding. Less frequent drug interactions and comparable safety profile to licensed azoles are observed.<sup>22</sup> Isavuconazole has activity against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Paecilomyces* spp., and dermatophytes including many resistant species. Variable activity against zygomycetes and no activity against *Fusarium* spp. and *Scedosporium prolificans* are observed.<sup>22</sup> Phase III studies using isavuconazole prophylaxis in adults with AML and treatment in adults with IC and aspergillosis are being performed.

Ravuconazole and its prodrug E-1224 are structurally similar to isavuconazole.<sup>22</sup> Ravuconazole has a half life comparable to that of isavuconazole. Its absorption is increased with a high fat meal. In addition to the antifungal spectrum observed with isavuconazole, activity against *Histoplasma capsulatum* has been demonstrated.<sup>22</sup> Phase II studies using ravuconazole prophylaxis in adults undergoing HSCT are underway.

Albaconazole is a new potent triazole available as an oral preparation. The drug has excellent bioavailability and is widely distributed throughout body fluids.<sup>22</sup> It has activity against *Candida* spp., *Cryptococcus*

spp., *Malassezia* spp., dermatophytes, *Aspergillus* spp., and *Paecilomyces* spp. Phase II studies have been conducted in adults with vulvovaginitis and onychomycoses.

Further research is required to determine the optimal role of the new triazoles. Further studies in infants and children are required for these and some licensed agents to determine pediatric pharmacokinetics, optimal dosing, and safety.

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