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MINIREVIEW

Challenges in the Treatment of Invasive Aspergillosis in Immunocompromised Children

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ABSTRACT Invasive aspergillosis (IA) is associated with significant morbidity and mortality. Voriconazole remains the drug of choice for the treatment of IA in children; however, the complex kinetics of voriconazole in children make dosing challenging and therapeutic drug monitoring (TDM) essential for treatment success. The overarching goal of this review is to discuss the role of voriconazole, posaconazole, isavuconazole, liposomal amphotericin B, echinocandins, and combination antifungal therapy for the treatment of IA in children. We also provide a detailed discussion of antifungal TDM in children.

KEYWORDS invasive aspergillosis, voriconazole, isavuconazole, therapeutic drug monitoring, immunocompromised children, posaconazole

Invasive aspergillosis (IA) has been associated with high morbidity and mortality in immunocompromised children (1). There is a paucity of literature defining the comparative effectiveness of antifungal regimens in children. Additionally, the management of IA in children is further complicated by complex antifungal kinetics and the lack of established pediatric dosing, particularly for newer agents. However, the growing armamentarium of available antifungal agents, use of mold-active antifungal prophylaxis, and advances in novel cancer therapies to bridge chemotherapy cycles while sustaining neutrophil counts offers optimism that we can improve outcomes. Herein, we provide an overview on the role of voriconazole, posaconazole, isavuconazole, liposomal amphotericin B (L-AMB), echinocandins, and combination antifungal therapy for the treatment of IA in children, highlighting supportive literature, knowledge gaps, and the role of therapeutic drug monitoring (TDM) to optimize dosing in children.

PROPHYLACTIC VERSUS EMPIRIC VERSUS PREEMPTIVE ANTIFUNGAL THERAPY FOR INVASIVE ASPERGILLOSIS

Children at high risk of IA with an incidence ≥10% include those with acute leukemia, allogeneic hematopoietic cell transplant (allo-HCT) recipients (particularly those with graft versus host disease [GVHD]), chronic granulomatous disease (CGD), profound and prolonged neutropenia, and high-dose corticosteroid exposure (2, 3). A recent guideline provides a strong recommendation for providing mold-active antifungal prophylaxis (i.e., an echinocandin or a mold-active azole) to children receiving treatment for acute myeloid leukemia that is expected to result in profound and prolonged neutropenia, children undergoing allo-HCT during the pre-engraftment period, and children receiving immunosuppression for the treatment of GVHD (4). Certain solid organ transplant recipients, particularly lung transplant recipients, may also be at risk for IA, and targeted mold-active antifungal prophylaxis may be warranted in select patients (5).

In high-risk patients not receiving mold-active prophylaxis against IA, there should be a low threshold to initiate empirical antifungal therapy in settings of persistent

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neutropenic fever or when imaging demonstrates lesions suspicious for invasive fungal disease (IFD). Alternatively, some studies have employed a preemptive (diagnostic-driven) antifungal therapy approach where antifungals are withheld until additional predefined triggers for initiating antifungal therapy are met (e.g., in response to elevated fungal biomarkers such as the serum galactomannan or fungal PCR, with compatible radiographic findings). The intent of preemptive (diagnostic-driven) antifungal therapy is to reduce potentially unnecessary antifungal therapy.

The feasibility and safety of preemptive (diagnostic-driven) antifungal therapy has been studied in high-risk adult hematologic malignancy and HCT recipients. A meta-analysis of 9 studies found no difference in mortality between empirical and preemptive antifungal therapy and preemptive antifungal therapy was associated with a significant reduction in antifungal use (6). A randomized controlled trial (RCT) including 149 children with hematologic malignancy presenting with prolonged fever and neutropenia demonstrated no difference in 30-day mortality between empirical and preemptive therapy approaches (8% versus 5%, respectively). The preemptive approach resulted in a median of 5 fewer days of antifungal therapy (7). Given the limited data on this approach in children, the international guidelines on the management of fever and neutropenia in children with cancer do not endorse this approach (8); however, other guidelines on the management of IA and IFD in children recommend preemptive antifungal therapy as an option as long as rapid CT imaging and serial galactomannan screening are available (3, 9). In the setting of mold-active antifungal prophylaxis, the pretest probability of IA is reduced, which may limit the utility of a preemptive therapy approach that relies on biomarkers such as the serum galactomannan as a trigger for therapy initiation (10).

TREATMENT OPTIONS FOR DEFINITIVE THERAPY OF INVASIVE ASPERGILLOSIS IN CHILDREN

Voriconazole is considered standard of care for the definitive treatment of IA. This is based on a RCT including patients ≥12 years old with proven/probable IA that demonstrated superiority of voriconazole when compared to amphotericin B deoxycholate (AMB) (3, 11, 12). Clinical success at 12 weeks was 53% with voriconazole versus 32% with AMB (11). Patients randomized to AMB were more likely to discontinue therapy due to excessive nephrotoxicity. This intolerance to AMB therapy may have contributed to the poorer outcomes of AMB recipients in the modified intention-to-treat analysis. Voriconazole pharmacokinetics and dosing are well established for children 2 years and older; however, children metabolize voriconazole faster than adults, resulting in difficulty achieving therapeutic troughs (13, 14).

In situations precluding the use of voriconazole, alternative therapies include L-AMB (15), posaconazole (16), isavuconazole (17), and echinocandins (18). L-AMB is less nephrotoxic compared to AMB (19% versus 34%) (19) as the lipid formulation is minimally renally eliminated (20). Posaconazole has been compared to voriconazole in a RCT including patients ≥13 years old with proven/probable/possible IA and was found to be noninferior to voriconazole (at a fixed adult dose without TDM (16)). However, use of posaconazole in children is limited due to the lack of established dosing for the newer delayed-release (DR) tablet formulation, which offers enhanced bioavailability. A new DR oral suspension of posaconazole recently received FDA approval and is anticipated to be available for clinical use in the near future for children ≤40 kg in weight.

Isavuconazole is the most recently approved triazole for the treatment of IA. A recent RCT including patients ≥18 years old with proven/probable/possible IA or other filamentous fungi found isavuconazole to be noninferior to voriconazole (at a fixed adult dose without TDM) (17). Isavuconazole was also associated with fewer adverse drug events. At this time, there is limited pediatric pharmacokinetic data available and very little clinical experience using isavuconazole in children.

Definitive therapy with an echinocandin (e.g., micafungin, caspofungin, anidulafungin) has not been directly compared to voriconazole in a randomized trial. Therefore,

echinocandins are discouraged as first line options (3, 12, 21, 22) but can be considered as salvage therapy in situations where other antifungal options are contraindicated (18).

Prospective comparative studies of antifungals for the treatment of IA are lacking in children. Data supporting the use of these agents in children for the treatment of IA are largely limited to observational studies. Voriconazole (23) and L-AMB (24) have been assessed as primary therapy for IA in children, whereas posaconazole (25) and echinocandins (18) have been assessed as salvage therapy. Patient-specific variables also need to be factored in when selecting an antifungal for the treatment of IA such as baseline liver dysfunction, QTc prolongation, allergies, drug-drug interactions, and risk of increasing toxicities of concomitant medications, e.g., increased vincristine and vinblastine neurotoxicity with voriconazole and posaconazole.

VORICONAZOLE

Voriconazole is a triazole antifungal that inhibits 14α-demethylase-mediated ergosterol synthesis in the fungal cell membrane, which arrests growth and causes eventual cell death (26). It is a structural analog of fluconazole with an extra α-*O*-methyl group that confers activity against *Aspergillus* spp. and other filamentous fungi (26). Voriconazole penetrates well into most sites including the cerebrospinal fluid (CSF) and vitreous humor but does not penetrate into the urine. It is hepatically metabolized by CYP2C19, CYP2C9, and CYP3A4 and is also an inhibitor of these enzymes, leading to many clinically relevant drug-drug interactions. Due to its insolubility, the intravenous formulation of voriconazole contains sulfobutyl ether β-cyclodextrin, which can accumulate in patients with renal impairment.

Voriconazole pharmacokinetics in children 2 to <12 years old. Voriconazole dosing in children varies from adults due to differences in body weight, absorption, and developmental changes in drug metabolizing enzyme expression (i.e., ontogeny of drug metabolizing enzymes) (27). Children can metabolize voriconazole three times faster than adults due to higher expression and catalytic efficiency of hepatic enzyme CYP2C19 as well as a higher contribution of the drug metabolizing enzyme flavin-containing monooxygenase 3 toward *N*-oxidation (13, 14). This results in a higher capacity to eliminate voriconazole (28) and metabolism that becomes saturated (nonlinear) at higher doses compared to adults (29, 30). Additionally, when administered enterally, voriconazole's bioavailability is lower in children (45-75%) (29, 31, 32) versus adults (46–94%) (33, 34). This is potentially due to increased intestinal first-pass metabolism where the drug concentration is greatly reduced before it reaches the systemic circulation (35).

The combination of the enhanced metabolism and decreased enteral bioavailability results in the need for higher mg/kg doses of voriconazole in children to achieve exposures comparable to adults (Table 1) (28). Children prescribed the recommended initial doses in Table 1 are predicted to have a mean trough of 1.04 μg/mL with intravenous (i.v.) dosing and 0.48 μg/mL with enteral (p.o.) dosing (28). As the goal trough is at least 1 μg/mL, i.v. therapy is preferred over p.o. at the time of therapy initiation.

Voriconazole pharmacokinetics in adolescents ≥12 years old. Young adolescents with low body weight exhibit lower exposures when prescribed standard adult doses, suggesting their metabolism is more similar to that of children (36). Therefore, adolescents 12 to <15 years old weighing <50 kg should be dosed like children, whereas adolescents 12 to <15 years old weighing ≥50 kg or adolescents ≥15 years old should start with adult dosing (Table 1) (28).

Voriconazole pharmacokinetics in infants and children <2 years old. There is currently no approved voriconazole dosing recommendation for children <2 years old, and there are limited pharmacokinetic data in this age group. Children <2 years old generally require higher mg/kg doses and often require the total daily dose to be divided every 8 h (q8h) (37–39). This may be due to the ontogeny of CYP2C19, where enzyme activity rises rapidly after birth and is ~2-fold higher than adults during the first year of life and remains elevated during the second year of life (40). The enzyme activity gradually declines to about 1.5-fold the adult value by 6 to 7 years of life (40). In a study that included 11 children <2 years old, only 14% of those prescribed the

TABLE 1 Antifungal agents for the treatment of invasive aspergillosis in immunocompromised children

Antifungal	Route	Pediatric dose and frequency	Empiric dosage adjustments	Therapeutic drug monitoring and subsequent dosage adjustments

Voriconazole	Intravenous (i.v.)	2 to <12 yr old or 12 to <15 yr old weighing <50 kg:
		• 9 mg/kg/dose i.v. q12h × 2 on day 1, then 8 mg/kg/dose i.v. q12h
		12 to <15 yr old weighing ≥50 kg or ≥15 yr old:
		• 6 mg/kg/dose i.v. q12h × 2 on day 1, then 4 mg/kg/dose i.v. q12h
			Obesity:
			• Use adjusted body wt
			• Adjusted body wt (kg) = (ideal body wt + 0.4 (actual wt – ideal body wt)
			Hepatic impairment:
			• Child-Pugh class A or B: reduce maintenance dose to 50% of usual dose
			• Child-Pugh class C: use not recommended; if no alternatives, limited data suggests reducing maintenance dose to 33% of usual dose
				• Obtain steady-state trough after 5–7 days of therapy
				• Target trough 1–6 mcg/mL (some target 2–6 mcg/mL)
				• If subtherapeutic, increase by 1–2 mg/kg/dose or in 50-mg increments
				• Infants and young children may require q8h dosing
				• i.v. to p.o. switch: round dose up as p.o. bioavailability is suboptimal in children
				• Repeat troughs:
				  • Once weekly after therapeutic trough achieved
				  • After dose changes
				  • i.v. to p.o. switch
				  • Change in hepatic function
				  • Suspected toxicity/failure
				  • Starting/stopping CYP450 2C19, 2C9, or 3A4 inhibitors or inducers

	Enteral (per os [p.o.])	2 to <12 yr old or 12 to <15 yr old weighing <50 kg: • 9 mg/kg/dose p.o. q12h (max 350 mg/dose p.o.) 12 to <15 yr old weighing ≥50 kg or ≥15 yr old: • 6 mg/kg/dose p.o. q12h × 2 on day 1, then 4 mg/kg/dose p.o. q12h		

Posaconazole	p.o. immediate-release (IR) suspension	<13 yr old:
		• 18–24 mg/kg/day p.o. divided q6h (max 200 mg p.o. q6h)
		≥13 yr old:
		• 200 mg p.o. q6h
			None	• Obtain steady-state trough after 7 days of therapy
				• Target troughs ≥1 mcg/mL for treatment
				• p.o. IR suspension: if subtherapeutic, escalate mg/kg dose until maximum dose of 400 mg p.o. q6h
				• p.o. DR tablet: increase in 100-mg increments, or can alternate dosing if need "fractions" of a dose (Note: doses >400 mg daily and q12h maintenance dosing have not been well studied)
				• p.o. DR suspension: the maximum dose that can be accurately withdrawn from the mixing cup after reconstitution is 240 mg/dose
				• Repeat troughs:
				  • Once weekly after therapeutic trough achieved
				  • After dose changes
				  • i.v. to p.o. switch
				  • Change in hepatic function
				  • Suspected toxicity/failure
				  • Starting/stopping UGT inhibitors or inducers

	p.o. delayed-release (DR) tablets	Delayed-release tablets have not been formally studied in children <13 yr old; doses below are based on unpublished experience Children <13 yr old who are able to swallow tablets: • 10–19 kg: 100 mg p.o. q12h × 2 on day 1, then 100 mg p.o. q24h • 20–29 kg: 200 mg p.o. q12h × 2 on day 1, then 200 mg p.o. q24h • ≥30 kg: 300 mg p.o. q12h × 2 on day 1, then 300 mg p.o. q24h ≥13 yr old: 300 mg p.o. q12h × 2 on day 1, then 300 mg p.o. q24h		
	i.v.	2 to <18 yr old: • 6 mg/kg/dose i.v. q12h on day 1, then q24h thereafter (max 300 mg/dose) ≥18 yr old: • 300 mg i.v. q12h × 2 on day 1, then 300 mg i.v. q24h		
	p.o. delayed-release (DR) PowderMix suspension	2 to <18 yr old: • 10 to <12 kg: 90 mg p.o. q12h on day 1, then q24h thereafter • 12 to <17 kg: 120 mg p.o. q12h on day 1, then q24h thereafter • 17 to <21 kg: 150 mg p.o. q12h on day 1, then q24h thereafter • 21 to <26 kg: 180 mg p.o. q12h on day 1, then q24h thereafter • 26 to <36 kg: 210 mg p.o. q12h on day 1, then q24h thereafter • 36 to 40 kg: 240 mg p.o. q12h on day 1, then q24h thereafter		

(Continued on next page)

TABLE 1 (Continued)

Antifungal	Route	Pediatric dose and frequency	Empiric dosage adjustments	Therapeutic drug monitoring and subsequent dosage adjustments
Isavuconazole (doses are expressed in mg/kg of the pro-drug isavuconazonium sulfate)	i.v./p.o.	6 mo to <1 yr old: • 6 mg/kg/dose of isavuconazonium sulfate i.v./p.o. q8h × 6 loading doses on days 1–2, then 6 mg/kg/dose i.v./p.o. q24h, to start 12–24 h after last loading dose 1 to <18 yr old: • 10 mg/kg/dose of isavuconazonium sulfate i.v./p.o. q8h × 6 loading doses on days 1–2, then 10 mg/kg/dose i.v./p.o. q24h (max 372 mg of isavuconazonium sulfate/dose), to start 12–24 h after last loading dose • Doses as high as ~20 mg/kg/day of isavuconazonium sulfate (max 744 mg of isavuconazonium/day) have been described in case reports, and some have divided the maintenance dose q12h	Hepatic impairment: • Child-Pugh class A or B: usual dose • Child-Pugh class C: use not recommended; limited data suggest a dose reduction is necessary	• Obtain weekly troughs at day 7, 14, 21, and 28 (steady state is approximately day 21–28) • Target trough 2–4 mcg/mL or area under the curve of 60–233 mcg* h/mL • Repeat troughs: • Once weekly after therapeutic trough achieved • After dose changes • i.v. to p.o. switch • Change in hepatic function • Suspected toxicity/failure • Starting/stopping CYP450 3A4, 3A5, or UGT inhibitors or inducers
Liposomal amphotericin B (L-AMB, Ambisome)	i.v.	• 3 to 5 mg/kg/dose i.v. q24h	None	None
Micafungin	i.v.	≥4 mo old: • 3 to 4 mg/kg/dose i.v. q24h (max 150 mg/dose)	None	None
Caspofungin	i.v.	≥3 mo old: • 70 mg/m^2/dose i.v. loading dose × 1 (max 70 mg/dose load), then 50 mg/m^2/dose i.v. q24h maintenance dose (max 50 mg/dose) (may increase maintenance dose to 70 mg/m^2/dose i.v. q24h (max 70 mg/dose) if clinical response inadequate)	Hepatic impairment: • Child-Pugh class A: no adjustment • Child-Pugh class B: decrease maintenance dose to 70% of usual dose • Child-Pugh class C: avoid use; if no alternatives, consider same dose adjustment as Child-Pugh class B	None
Anidulafungin	i.v.	≥1 mo old: • 3 mg/kg/dose i.v. loading dose × 1 (max 200 mg/dose load), then 1.5 mg/kg/dose i.v. q24h maintenance dose (max 100 mg/dose)	None	None

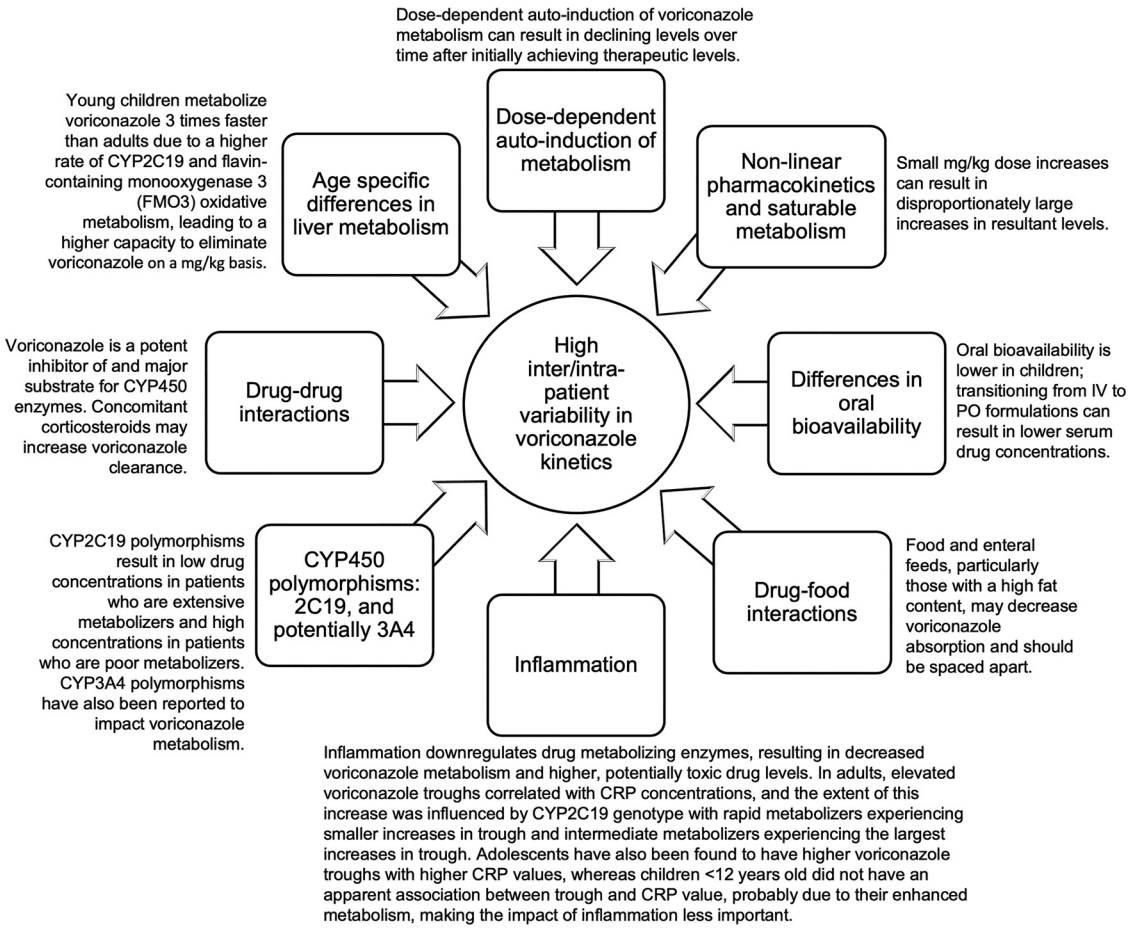

FIG 1 Causes of inter- and intrapatient variability in voriconazole pharmacokinetics. CRP, C-reactive protein; IV, intravenous; PO, per os (enteral).

2- to <12-year-old dose reached an initial therapeutic steady-state trough (37). The median total daily dose required to reach troughs ≥1 μg/mL was 31.5 (range: 12 to 71) mg/kg/day i.v., and the median time to therapeutic troughs was 11.5 days (range: 8 to 21 days). Doses >40 mg/kg/day were divided q8h. In another case series, all children <2 years old required q8h dosing to achieve troughs ≥2 μg/mL; doses ranged from 8.5 to 17.7 mg/kg/dose q8h (38). The time to therapeutic troughs ranged from 10 to 36 days. Finally, one study found that young age was significantly associated with voriconazole treatment failure (41).

Collectively, these data highlight the challenges with dosing and inability to achieve therapeutic troughs in a timely manner, which can potentially contribute to voriconazole failure. As such, significant caution should be taken when prescribing voriconazole in this age group; a second antifungal agent should be used until therapeutic levels of voriconazole are reached. Alternative antifungals should be considered in this age group (e.g., L-AMB).

Voriconazole therapeutic drug monitoring. TDM is essential for the optimization of voriconazole therapy (42). The pharmacokinetic variability observed is due to multiple factors including cytochrome (CYP) P450 2C19 polymorphisms (43–45), CYP3A4 polymorphisms (46–48), CYP450 drug-drug interactions (49–51), age-specific differences in liver metabolism (13, 14, 28), autoinduction of metabolism (52, 53), nonlinear pharmacokinetics and saturable metabolism (29, 30), age-dependent differences in oral bioavailability (29, 31, 32), drug interactions with high-fat foods (54, 55), inflammatory states (56–59), and drug interactions with corticosteroids (60) (Fig. 1).

Controversy exists as to when steady state is achieved with voriconazole as the half-life is dose-dependent due to nonlinear pharmacokinetics (43). Most suggest that steady state is reached in 4 to 7 days (12) or 5 to 7 days (34, 61), whereas others suggest that with loading doses, it is reasonable to obtain a trough as early as day 3 (3).

Guidelines for the treatment of IA provide a general recommendation to target troughs $\geq$1 μg/mL (9, 12); however, some suggest targeting troughs $\geq$2 μg/mL for disseminated and central nervous system infections (3). Additionally, achieving a trough/MIC ratio of $\sim$2 has been associated with improved rates of successful outcome (62–64). For *A. fumigatus* with an epidemiologic cutoff value (ECV) of 1 μg/mL (65), a trough of 2 μg/mL or higher will achieve a trough/MIC ratio of at least 2. *Aspergillus* spp. with higher ECVs of 2 μg/mL (e.g., *A. flavus*, *A. niger*, *A. terreus*) would require higher troughs to achieve a trough/MIC ratio of 2.

Subtherapeutic voriconazole troughs are associated with poor clinical outcomes in both adults (42, 66, 67) and children (23, 32, 68) with IA. In a meta-analysis of 24 studies (including 5 pediatric studies), a trough value of 1 μg/mL or higher was associated with an almost 2-fold higher odds of successful outcome compared to lower troughs (42). In an observational study of 46 children with proven/probable/possible IFD, 75% of children who died had at least one low voriconazole trough versus 20% of those who survived (32). Each additional voriconazole trough $<$1 μg/mL was associated with a 6.3-fold increase in the risk of death (32). Of note, there may have been confounding variables in these studies where those who were critically ill had difficulty achieving therapeutic troughs.

Toxicities classically associated with voriconazole include hepatotoxicity, neurotoxicity (e.g., encephalopathy, myoclonus, hallucinations), and visual disturbances (e.g., abnormal vision, photophobia, chromatopsia) (69). Patients with supratherapeutic levels have at least a 3-fold higher likelihood of hepatotoxicity and at least a 5-fold higher likelihood of neurologic or visual disturbances. Trough values $\geq$6 μg/mL are most concerning for precipitating clinical or laboratory evidence of toxicity (42).

Other serious and relatively common adverse events include QTc prolongation (70, 71) and phototoxicity (72–74); a clear correlation between these toxicities and supratherapeutic levels is lacking. There is increasing concern regarding the long-term phototoxic effects of voriconazole, particularly the risk of developing squamous cell carcinoma (SCC) (73). In one study, those who developed SCC had received a median of 35 months of voriconazole (73). These patients experienced a multistep malignant process with erythema of the skin in the first year, actinic keratosis in the second or third year and then SCC in the third or fourth year.

Voriconazole dosage adjustments based on therapeutic drug monitoring. Most children prescribed voriconazole will have subtherapeutic initial steady-state troughs, necessitating further dosage adjustments. In a study that included 31 children 2 to 12 years old prescribed the dosing outlined in Table 1, only 32% reached a therapeutic initial steady-state trough (37). The median total daily dose required to reach therapeutic troughs was 15.5 (range: 13 to 55) mg/kg/day, i.v. and 22 (range: 14 to 30) mg/kg/day p.o., and the median time from start of therapy to therapeutic troughs was 6 (range: 4 to 41) days. Doses $>$40 mg/kg/day were divided q8h.

Dosage adjustments should be approached with caution as voriconazole exhibits saturable and nonlinear kinetics; small increases in the milligram-per-kilogram dose may result in substantially large increases in the resultant trough. For example, a 50% increase in dose from 4- to 6-mg/kg/dose could result in an increase in trough from 0.75 to 1.8 μg/mL, which is a 240% relative increase in trough (32). Dosage adjustments can be made in 1- to 2-mg/kg increments for i.v. or p.o. suspension dosing of voriconazole, or in 50-mg increments for p.o. tablet dosing (28, 61). These increments generally translate to a 20% to 25% dose increase. If multiple dose escalations are not achieving target troughs, q8h dosing should be considered, especially in infants and younger children.

Even after achieving a therapeutic trough, some centers recommend checking weekly troughs due to the high intrapatient variability in kinetics and potential for autoinduction of metabolism (37, 52). Autoinduction can occur after 1 week on therapy or months later, and the magnitude of the decrease in troughs can range from a 1.6- to 12-fold decrease (52).

Dosing voriconazole in the setting of organ dysfunction. Although voriconazole does not require renal dosage adjustment, the cyclodextrin vehicle in the i.v. formulation can accumulate in patients with renal impairment, potentially causing further nephrotoxicity (43, 75, 76). The FDA (54) and European Medicines Agency (EMA) (77) labeling recommend avoiding i.v. voriconazole in patients with a creatinine clearance $<$50 mL/min; however, there is increasing literature suggesting that patients with baseline renal impairment prescribed i.v. voriconazole do not experience further worsening of their renal function (78, 79). These data suggest that i.v. voriconazole can remain a treatment option in patients with renal dysfunction. This is particularly important when the p.o. bioavailability of voriconazole is suboptimal (31) or when patients cannot tolerate p.o. medications.

Since voriconazole is extensively metabolized by the liver, dosage adjustments are recommended in hepatic impairment (Table 1) (54). Although the FDA (54) and EMA (77) labeling recommend avoiding voriconazole in Child-Pugh class C hepatic impairment, some data suggest reducing the maintenance dose to 33% of the usual dose to maintain troughs $\leq$5 μg/mL in this population (80–82).

Precision medicine strategies to dose voriconazole. Voriconazole is primarily metabolized by CYP2C19 (43), which is known to exhibit genetic polymorphisms (Table S1). Decreased CYP2C19 function is associated with higher voriconazole levels and potential drug toxicity, whereas increased CYP2C19 function is associated with subtherapeutic voriconazole levels and potential treatment failure (44, 83). Genotype-directed voriconazole dosing in children is outlined in Table S1 (45, 84–90). Preemptive CYP2C19 genotype testing in patients at high risk of developing IA, before voriconazole initiation, allows for early dose optimization (84). In a study of children who underwent HCT, the median time to reach therapeutic voriconazole troughs was 29 days with usual dosing followed by TDM versus 6.5 days with preemptive genotype-guided dosing (91). For allo-HCT recipients, CYP2C19 genotyping should occur prior to transplant, as genotype testing performed after successful engraftment reflects the donors' genotype (92).

POSACONAZOLE

Posaconazole is a triazole antifungal agent with broad antifungal activity including *Aspergillus* spp. and Mucormycetes (26). It is a derivative of ketoconazole with an additional nonpolar side chain that enhances binding to the 14α-demethylase apoprotein, resulting in enhanced mold activity. Posaconazole has poor penetration into the CSF, vitreous humor, and urine. It is primarily metabolized by uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes (especially UGT1A4) and is a substrate of P-glycoprotein (P-gp) (93). Posaconazole is also a strong CYP3A4 inhibitor. Similar to voriconazole, due to its insolubility, the i.v. formulation of posaconazole also contains cyclodextrin.

Posaconazole exhibits significant interpatient variability due to issues related to absorption. The three commercially available formulations (immediate-release [IR] p.o. suspension, delayed-release [DR] p.o. tablet, i.v. formulation) are not bioequivalent and therefore not interchangeable. Saturable absorption has been demonstrated with the IR p.o. suspension where dosing multiple times per day (e.g., 4 times per day) increases exposure more than increasing the milligram dose of posaconazole (94). Additionally, increasing beyond 800 mg/day of the IR posaconazole suspension does not result in increased exposure (95, 96). Absorption can be unpredictable in hematologic malignancy and HCT patients due to the presence of diarrhea, mucositis, colitis, or GVHD (97, 98). The IR p.o. suspension has the poorest bioavailability (8 to 47%) (99) and requires an acid environment for absorption; therefore, H2-receptor antagonists and proton pump inhibitors will decrease absorption (100). Taking the IR p.o. suspension with a high-fat meal ($>$50% calories from fat) or an acidic beverage (e.g., cola, fruit juice) increases absorption (100).

The DR tablets were designed to have enhanced bioavailability ($\sim$54% under fasted conditions) that is not affected by acid suppressants and less impacted by food when compared to the IR p.o. suspension (93). The tablets were produced by hot-melt extrusion

technology where posaconazole is mixed with a pH-sensitive polymer to produce a molecularly dispersed drug-polymer combination that is designed to release the entire dose of posaconazole in the small intestine (101, 102). A novel powder for oral suspension was FDA approved in May of 2021 that may offer the same bioavailability as the DR tablet because it consists of the same hot-melt extrudate intermediate of posaconazole and pH-sensitive polymer found in the DR tablet (103). This DR p.o. suspension is expected to be commercially available in 2022 for use in children ≤40 kg who are unable to swallow the DR tablets, and the FDA approved dosing is outlined in Table 1.

Posaconazole pharmacokinetics in children. A recent prospective multicenter sequential dose-escalation study of 136 neutropenic children 3 months to <18 years old found unacceptably high rates of subtherapeutic troughs with posaconazole IR p.o. suspension dosed at 12 to 18 mg/kg/day divided q12h or q8h (104). Other studies have also found that in children <13 years old, target exposures are difficult to achieve (105–108), and doses as high as 49 mg/kg/day have been used (106). It is unclear if there is a maximal mg/kg dose that would result in saturable absorption in children.

For children who are able to swallow tablets, the DR tablets are preferred over IR p.o. suspension due to the enhanced bioavailability and higher likelihood of achieving target posaconazole concentrations. In a retrospective study of 63 pediatric HCT recipients, steady-state posaconazole troughs on day 7 were significantly higher with DR tablets versus IR p.o. suspension (median trough 0.874 versus 0.252 μg/mL, respectively) (109). Suggested dosing for the DR tablets is outlined in Table 1.

A phase 1 clinical trial evaluating the pharmacokinetics and safety of i.v. posaconazole in 118 immunocompromised children 2 to 17 years old with neutropenia was recently published (103). Intravenous posaconazole at 6 mg/kg/dose q12h on day 1 and then q24h thereafter resulted in a mean steady-state trough of 0.626 μg/mL in the 2- to <7 year-old-group and 1.16 μg/mL in the 7- to 17-year-old group (110). Other studies have found the need for higher doses of i.v. posaconazole (~10 mg/kg/dose q12h on day 1, then q24h thereafter) to achieve troughs >1 μg/mL (111, 112).

Posaconazole therapeutic drug monitoring. For the treatment of IFD, a trough target of ≥1 μg/mL is suggested by most experts (3) based on an open label multicenter study using the IR p.o. suspension for the salvage treatment of proven/probable IA (113). The highest response rates (75%) were observed in the group of patients with average posaconazole concentrations (C_{avg}) ≥1.25 μg/mL (113). For the prevention of IFD, a trough target of ≥0.7 μg/mL is suggested by most experts (3) based on a *post hoc* analysis of two randomized controlled trials evaluating posaconazole IR p.o. suspension for the prevention of IFD (114). C_{avg} ≥0.7 μg/mL was associated with less breakthrough proven/probable IFD (114).

An upper trough threshold associated with toxicity has yet to be established for posaconazole; this is potentially secondary to the inability to achieve high concentrations with the IR p.o. suspension. With the DR tablet and i.v. formulations, higher concentrations are achievable, and some retrospective studies have noted increased rates of adverse events with higher posaconazole doses (115) or exposures (116, 117), while others have not identified a toxicity-exposure relationship (118, 119).

Posaconazole has a long elimination half-life (~30 h), and it takes ~7 to 10 days to reach steady state (93). Therefore, levels should be measured after at least 7 days of therapy. Some studies have suggested that pre-steady-state troughs obtained between days 3 to 5 are strongly correlated with steady-state troughs obtained between days 7 to 8 and may provide an early predictor of subtherapeutic troughs and allow for earlier intervention (120). Implementation of antifungal stewardship programs with a TDM component have been shown to significantly increase therapeutic levels of posaconazole (121).

ISAVUCONAZOLE (ISAVUCONAZONIUM SULFATE)

Isavuconazonium sulfate is a prodrug, which is rapidly converted in the bloodstream to the active compound isavuconazole (122). It is structurally similar to voriconazole except for an additional side chain that broadens its antifungal activity (123). It is highly water soluble and therefore does not require cyclodextrin in the i.v.

TABLE 2 Summary of dosing and concentrations achieved in case reports of isavuconazole use in children

Reference	Patient case	Dose expressed in mg of isavuconazonium sulfate	Isavuconazole trough achieved
De Leonardis et al. (134)	3-yr-old girl with acute lymphoblastic leukemia (ALL) receiving isavuconazole for cerebral and pulmonary invasive aspergillosis (IA)	12.4 mg/kg/dose of isavuconazonium sulfate q8h for 2 days, followed by 12.4 mg/kg/dose of isavuconazonium sulfate q24h	Trough 2.9 mcg/mL on day 7; subsequent troughs remained between 2 and 4 mcg/mL throughout the course of therapy
Pomorska et al. (135)	7-yr-old girl with ALL receiving isavuconazole plus amphotericin B lipid complex plus caspofungin for disseminated mucormycosis	372 mg of isavuconazonium sulfate q8h × 2 days, followed by 372 mg of isavuconazonium sulfate q24h	Troughs between 2 and 3 mcg/mL on days 3, 5, 7, and 28
		The maintenance dose was subsequently doubled to 744 mg of isavuconazonium sulfate q24h	Troughs between 3 and 6 mcg/mL on days 7, 14, 21, and 28 of higher dose
Cornu et al. (136)	3-yr-old girl with ALL with disseminated mucormycosis	167 mg of isavuconazonium sulfate i.v. q12h	Troughs consistently above 2 mcg/mL on q12h dosing
		Dose changed to 186 mg of isavuconazonium sulfate p.o. q12h (186-mg capsule of isavuconazonium was opened and administered via nasogastric tube)	
Barg et al. (137)	Case series of 3 children (ages 4, 5, and 19 yr old) with invasive mucormycosis	372 mg of isavuconazonium sulfate q24h administered to all children (for the 4- and 5-yr-old patients, this dose was ~20 mg/kg/dose of isavuconazonium sulfate q24h)	Troughs generally remained between 2 and 4 mcg/mL

formulation (122). It has an oral bioavailability of 98% in adults and absorption is not dependent on food nor is it impacted by gastric acid suppressants (122). Despite having poor CSF penetration (124), isavuconazole penetrates well into the brain parenchyma (125) and has been successfully used to treat cerebral aspergillosis (126). It does not achieve measurable quantities in the urine (122). It is hepatically metabolized by CYP450 3A4, 3A5, and UGT and is also an inhibitor of CYP3A4/5, UGT, P-gp, and organic cation transporters (OCT 1 and 2), subjecting it to drug-drug interactions (122, 127). Isavuconazole has served as a therapeutic option in patients with voriconazole or posaconazole induced toxicity (128–130). Specifically, hepatobiliary, skin, and eye disorders appear to be less frequent with isavuconazole compared to voriconazole (17). Interestingly, isavuconazole is associated with QT interval shortening while all other triazoles are associated with QT prolongation (131, 132).

Isavuconazole pharmacokinetics in children. A phase I pharmacokinetic study of isavuconazole in 45 immunocompromised children was recently published predicting that >80% of children receiving i.v. and >76% of children receiving p.o. isavuconazole at the doses listed in Table 1 are expected to achieve the area under the curve target exposures seen in adults (133). Published case reports of isavuconazole use in children (134–138) (Table 2) report targeting troughs of 2 to 4 μg/mL to achieve exposures similar to adult participants in the SECURE trial (17) where mean isavuconazole troughs were 2.6 μg/mL on day 7, 3 μg/mL on day 14, and 3.6 μg/mL at steady state (139). In younger children, higher doses (~20 mg/kg/dose of isavuconazonium sulfate q24h) may be required to achieve target isavuconazole troughs (140).

Isavuconazole therapeutic drug monitoring. Currently, TDM is not recommended for adult patients receiving isavuconazole. This recommendation is supported by a lack of correlation observed between isavuconazole troughs and clinical response (e.g., overall response or mortality) in clinical trials (139) and a lack of correlation between isavuconazole exposure and adverse events (139, 141). However, some observational studies have noted more adverse events in patients with higher isavuconazole troughs (142–144). In a study of 45 nonimmunocompromised adults prescribed long-term isavuconazole, troughs ≥4.6 μg/mL were found to be independently predictive of treatment emergent adverse effects, most commonly hepatotoxicity and neuropathy (144). If treatment emergent adverse effects are suspected, TDM should be considered.

In adults, steady state is reached between day 21 (145) and day 35 (146) due to the long elimination half-life of isavuconazole (~130 h) (147). Children may have enhanced clearance of isavuconazole based on the ontogeny of CYP3A4 where activity of this enzyme in children >1 year old exceeds the enzyme activity seen in adults (40, 148). Obtaining weekly levels before steady state may be beneficial to ensure that initial doses prescribed are adequate after the loading dose and to detect poor metabolism early on before supratherapeutic concentrations develop. Thus far, isavuconazole appears to exhibit linear pharmacokinetics, where the percent increase in trough is proportional to the percent increase in dose. Doses up to 744 mg of isavuconazonium sulfate q24h have been safe and well tolerated in a phase 2 dose escalation study in adults (149). Lastly, due to the long elimination half-life of isavuconazole (~130 h), there may be a role for a 5-day per week dosing regimen as opposed to daily dosing in patients who are unable to absorb the enteral formulation and need to receive IV isavuconazole in the clinic setting (150); however, additional investigation would be necessary to determine the efficacy of a 5-day per week regimen for isavuconazole.

Dosage adjustments are not required in renal impairment (151) or in Child-Pugh class A or B hepatic impairment even though patients with liver disease have higher drug concentrations when receiving standard doses of isavuconazole (152, 153). Isavuconazole has not been formally studied in Child-Pugh class C disease, and a case report suggests potentially toxic levels even with a dosage reduction to every 48 h maintenance dosing (154).

Clinical experience with isavuconazole in children. A retrospective study reported an overall complete/partial response rate of 71% in 24 pediatric hematologic malignancy/HCT patients with proven/probable/possible IFD (83% with IA) treated with isavuconazole (138). Patients in this case series received isavuconazole as either salvage treatment (69%) after failure of/intolerance to other antifungals or as part of combination antifungal therapy (29%). Adverse events (elevated liver enzymes or serum creatinine) during isavuconazole treatment were noted in 21% of the patients. A phase II trial is under way evaluating the efficacy and safety of isavuconazole for the treatment of IA or invasive mucormycosis in children (ClinicalTrials.gov identifier: NCT03816176).

LIPOSOMAL AMPHOTERICIN B

L-AMB is a polyene antifungal that binds to ergosterol in the fungal cell membrane, causing the formation of pores and leakage of intracellular contents (26). Polyenes exhibit broad-spectrum antifungal activity against yeasts and molds. AMB is primarily renally eliminated, and accumulation in the renal tubules can result in dose-dependent nephrotoxicity (26). Infusion reactions (e.g., fevers, rigors, chills) are also common with AMB. Reformulation of AMB into lipid formulations (L-AMB) results in reduced distribution of the drug to the kidneys (20) and therefore less nephrotoxicity (19). Despite having minimal CSF penetration, L-AMB is a preferred antifungal for the treatment of fungal meningitis. L-AMB penetrates well into most other sites except the urine. Unlike the triazoles, there are minimal drug-drug interactions with polyenes.

L-AMB has not been compared to voriconazole in a RCT like AMB but is a reasonable alternative to voriconazole for the treatment of IA (24). Suggested dosing for L-AMB is described in Table 1. Escalating the L-AMB dose to 10 mg/kg/day compared to 3 mg/kg/day did not improve response rate or survival and resulted in higher rates of nephrotoxicity in a RCT including 201 immunocompromised patients with proven/probable invasive mold disease, 97% of which was IA (15).

ECHINOCANDINS

Caspofungin has been studied for the primary treatment of IA in noncomparative trials in immunocompromised adults (21, 22). Caspofungin has also been investigated as salvage therapy for IA in both adults (155, 156) and children (18, 157, 158). In settings where triazoles and L-AMB are contraindicated, echinocandins may be considered. Additionally, echinocandins can be considered as adjunctive therapy to voriconazole in select clinical situations discussed below (12, 159).

COMBINATION ANTIFUNGAL THERAPY

The goal of combination antifungal therapy is to target different metabolic pathways to achieve additive or synergistic activity and improve patient outcomes (160, 161). Azole-echinocandin, polyene-azole, and polyene-echinocandin combinations have been extensively evaluated in *in vitro* and animal models of IA (Table 3). The results of these studies vary from synergy to indifference to antagonism for each combination and the applicability of these findings to clinical decision-making is not known. There are limited well-designed clinical trials comparing combination therapy versus monotherapy (162). RCTs comparing combination therapy to monotherapy have not been conducted in children (1).

Azole-echinocandin combination therapy. Concurrent inhibition of ergosterol synthesis in the fungal cell membrane by an azole and inhibition of (1→3)-beta-D-glucan synthesis in the fungal cell wall by an echinocandin is an attractive combination; however, preclinical (163–167) and observational studies have demonstrated conflicting results with some favoring voriconazole-echinocandin combination therapy over voriconazole monotherapy (168), while others did not (162, 169, 170). An adult RCT comparing voriconazole plus anidulafungin (for at least 2 weeks) versus voriconazole plus placebo found no significant difference in 6-week mortality (159) (Table 3). In a *post hoc* analysis limited to patients with positive galactomannan indices, 6-week mortality was significantly lower in the combination therapy group (16 versus 27%). This has led to guidelines recommending to consider voriconazole-echinocandin combination therapy for the primary treatment of IA in select patients, such as those with severe IA in the setting of profound and prolonged neutropenia (3, 12). In the setting of primary treatment failure, the guidelines also suggest to consider voriconazole-echinocandin combination therapy for salvage treatment (3, 12). The clinician should recognize, however, that combination therapy has the potential to induce more adverse events as such as hepatobiliary toxicity (13% versus 8%) (159).

Polyene-azole combination therapy. There is a mechanistic concern that azole exposure could limit formation of ergosterol in the fungal cell membrane, which is the target for polyene (L-AMB) activity, leading to antagonism and potentially negative outcomes (171, 172). Antagonism has been demonstrated in some (171, 172), but not in all *in vitro* studies (173–176). Some animal studies have suggested that sequential azole followed by polyene therapy was associated with higher mortality compared to either simultaneous administration or sequential polyene followed by azole therapy (177, 178), but this has not been observed in human clinical trials (179). There are no RCTs comparing polyene-azole combination therapy versus monotherapy for the treatment of invasive molds; observational studies have not demonstrated a benefit with this combination when compared to polyene monotherapy (180, 181). In a cohort study of adult and pediatric patients with fungal CNS infections, voriconazole-L-AMB combination therapy had numerically higher response rates compared to those receiving other combinations (71 versus 55%) (182).

Polyene-echinocandin combination therapy. Preclinical studies have shown conflicting results for polyene-echinocandin combinations (183–187). Observational studies of salvage therapy have not demonstrated a benefit with this combination when compared to polyene (188) or echinocandin monotherapy (189). In a small RCT of L-AMB 3 mg/kg/day plus caspofungin versus L-AMB 10 mg/kg/day alone, combination therapy resulted in more favorable overall responses at end of therapy (~day 17 to 18) compared to monotherapy (67 versus 27%); however, by week 12, response and survival were similar between the groups (190). Based on these data, guidelines do not support L-AMB plus an echinocandin combination therapy as a first line option but suggest this combination can be considered as an alternative to voriconazole monotherapy for primary treatment or salvage treatment of IA (3).

Combination antifungal therapy to bridge to therapeutic voriconazole levels. Although voriconazole monotherapy is generally supported as the first line therapy for IA, achieving therapeutic troughs can be difficult in children and can take several dose escalations (191). Given these challenges, a reasonable approach is to initially prescribe a second antifungal agent that is continued until therapeutic voriconazole troughs are

TABLE 3 Combination antifungal therapy for the treatment of invasive aspergillosis[a]

Combination	*In vitro* and *in vivo* data	Clinical data			Recommendation
		Study design	Comparison	Results	
Azole-echinocandin	Indifference to synergy at standard doses of voriconazole and echinocandin Indifference to antagonistic effect when higher echinocandin doses were combined with voriconazole Synergy demonstrated with isavuconazole-echinocandin and posaconazole-echinocandin combinations	Randomized controlled trial (RCT) of allogeneic hematopoietic cell transplant (HCT) and hematologic malignancy patients ≥16 yr old with proven/probable IA (159)	Primary treatment with voriconazole plus anidulafungin (for at least 2 wk) versus voriconazole plus placebo	No difference in all-cause 6-wk mortality: 20% in combination vs. 28% in monotherapy group, ($P = 0.087$) Reduced successful global response at 6 wks in combination therapy vs. monotherapy group (33 vs. 43%) (may have been influenced by large no. of "not evaluable" patients at 6 wk in combination therapy group due to missing data) *Post hoc* analysis of galactomannan-positive patients: all-cause 6-wk mortality 16% in combination vs. 27% in monotherapy group ($P = 0.037$)	IDSA: combination can be considered for the primary treatment of IA in select patients, particularly in the setting of severe disease in hematologic malignancy patients and in patients with profound and prolonged neutropenia; combination may also be considered for salvage therapy of progressive or refractory IA ESCMID-ECMM: combination can be considered as alternative to voriconazole monotherapy for primary treatment of IA; can also be considered for salvage therapy
Polyene-azole	Antagonism or indifference observed at higher polyene concentrations, whereas synergy observed at lower polyene concentrations when combined with either itraconazole or voriconazole Synergy demonstrated with posaconazole-polyene combination Sequential azole followed by polyene therapy associated with higher mortality compared to either simultaneous administration or sequential polyene followed by azole therapy	*Post hoc* analysis of 201 patients receiving 3 vs. 10 mg/kg/day of L-AMB for the treatment of proven/probable invasive mold disease (179)	Azole therapy exposure within 30 days prior to study enrollment vs. no prior azole therapy exposure	No difference in favorable overall response (49% vs. 46%) or 12-wk survival (64% vs. 66%)	L-AMB frequently used to bridge to therapeutic voriconazole troughs in children
		Retrospective cohort study of 192 patients with fungal central nervous system infections treated with voriconazole; 37 received combination antifungal therapy (182)	Combination therapy containing L-AMB vs. combination therapy that did not contain L-AMB	Response rate 71% with L-AMB combination therapy vs. 55% with other combinations ($P = 0.5$)	

(Continued on next page)

TABLE 3 (Continued)

Combination	*In vitro* and *in vivo* data	Clinical data			Recommendation
		Study design	Comparison	Results	
Polyene-echinocandin	Synergy, indifference and antagonism demonstrated with combination therapy Conflicting data on sequential therapy; some studies showed sequential polyene followed by echinocandin therapy resulted in improved survival compared to echinocandin followed by polyene therapy, however, antagonism also observed with certain sequential therapy regimens (regardless of which agent was administered first)	RCT of patients ≥10 yr old with hematologic malignancies receiving primary treatment for proven/probable IA (190)	L-AMB 3 mg/kg/day plus caspofungin vs. L-AMB 10 mg/kg/day	Combination therapy resulted in more favorable overall responses at end of therapy (~day 17–18) compared to monotherapy (67% vs. 27%, $P = 0.028$); however, 12-wk favorable overall response (80% vs. 67%) as well as 12-wk survival (100% vs. 80%) were not significantly different between groups	ESCMID-ECMM: combination therapy can be considered as an alternative to voriconazole monotherapy for primary treatment of IA; it can also be considered for salvage therapy

[a]IA, invasive aspergillosis; ESCMID-ECMM, European Society for Clinical Microbiology and Infectious Diseases-European Confederation of Medical Mycology; IDSA, Infectious Diseases Society of America.

documented. The ideal choice of the second agent in this clinical situation is not known, but L-AMB or an echinocandin is often used. Continuation of combination therapy for the entire treatment course is likely unnecessary and has been associated with increased adverse events (1, 159, 169).

TREATMENT OPTIONS FOR AZOLE RESISTANT INVASIVE ASPERGILLOSIS IN CHILDREN

The prevalence of azole-resistance among *Aspergillus* spp. has increased over the last few decades globally; however, frequency varies significantly by region (192). Patients with voriconazole-resistant IA empirically started on voriconazole have a 23% higher mortality rate on day 42 when compared to patients with voriconazole-susceptible IA who are empirically initiated on voriconazole (193). Most experts would suggest discontinuing voriconazole as soon as azole-resistance is detected, and to switch to another drug class, i.e., polyene or echinocandin (194), as cross-resistance with other azoles occurs (195). Although, the utility of azole-echinocandin combination therapy for the treatment of azole-resistant IA has not been adequately studied, this combination may be considered as an alternative to echinocandin monotherapy in situations where polyenes cannot be used (194, 196). There are a number of novel antifungal agents in the pipeline with activity against voriconazole-resistant *Aspergillus* spp. (i.e., olorofim, fosmanogepix, ibrexafungerp, rezafungin) providing optimism for enhanced options for azole-resistant *Aspergillus* spp. in the future. Unfortunately, accessibility to children <18 years old is limited as clinical trials are restricted to adults (197). The availability of compassionate access for children varies, thus clinicians should consider engaging with industry providers of these agents when necessary.

TREATMENT DURATION FOR INVASIVE ASPERGILLOSIS IN CHILDREN

Guidelines recommend 6 to 12 weeks of antifungal therapy for IPA (12); however, this is based on expert opinion as there are limited data to define the optimal duration of therapy in both adults and children. An adult observational study found treatment durations <9 weeks to be independently associated with relapse of IPA (adjusted hazard ratio [aHR]:

3.7; 95% confidence interval [CI]: 1.1 to 12.3) (198). Radiographic nonresponse at the time of initial treatment termination (aHR: 4.6; 95% CI: 1.2 to 17.5) and Charlson comorbidity index score (aHR: 1.8; 95% CI: 1.2 to 2.6) were also independently associated with relapse of IPA. While these adult data cannot be directly extrapolated to children, they do highlight the importance of considering radiographic and clinical response in duration of therapy decisions. Ultimately, in determining duration of therapy, clinicians should assess degree of immunosuppression, site(s) of disease, and clinical/radiographic evidence of disease resolution (3, 9). Longer durations should probably be considered in children without resolution of clinical/radiographic findings or in those with continuous immunosuppression (199).

CONCLUSION

There are significant challenges with the treatment of IA in children but recent published literature has helped to broaden the therapeutic options for these invasive infections. Given the accumulated experience with TDM and more optimal CNS penetration, voriconazole remains a preferred option among many clinicians for IA in children. However, the availability of pediatric specific pharmacokinetic data and comparative trial results in adults has made posaconazole a reasonable initial therapeutic choice for non-CNS IA. L-AMB or an echinocandin represent alternative options in clinical scenarios that preclude the use of voriconazole or posaconazole. Importantly, all these agents have their respective limitations for use in children and thus data on novel agents are anxiously anticipated. For example, more data are needed to endorse the routine use of isavuconazole in children. The existing literature does not support the routine use of combination antifungal therapy for the primary treatment of IA, although combination therapy can be considered until therapeutic azole troughs are achieved.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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