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Pharmacokinetics and Pharmacodynamics of Antifungals in Children and their Clinical Implications

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Abstract

Invasive fungal infections are a significant cause of morbidity and mortality in children. Successful management of these systemic infections requires identification of the causative pathogen, appropriate antifungal selection, and optimisation of its pharmacokinetic and pharmacodynamic properties to maximise its antifungal activity and minimise toxicity and the emergence of resistance. This review highlights salient scientific advancements in paediatric antifungal pharmacotherapies and focuses on pharmacokinetic and pharmacodynamic studies that underpin current clinical decision making. Four classes of drugs are widely used in the treatment of invasive fungal infections in children, including the polyenes, triazoles, pyrimidine analogues and echinocandins. Several lipidic formulations of the polyene amphotericin B have substantially reduced the toxicity associated with the traditional amphotericin B formulation. Monotherapy with the pyrimidine analogue flucytosine rapidly promotes the emergence of resistance and cannot be recommended. However, when used in combination with other antifungal agents, therapeutic drug monitoring of flucytosine has been shown to reduce high peak flucytosine concentrations, which are strongly associated with toxicity. The triazoles feature large inter-individual pharmacokinetic variability, although this pattern is less pronounced with fluconazole. In clinical trials, posaconazole was associated with fewer adverse effects than other members of the triazole family, though both posaconazole and itraconazole display erratic absorption that is influenced by gastric pH and the gastric emptying rate. Limited data suggest that the clinical response to therapy may be improved with higher plasma posaconazole and itraconazole concentrations. For voriconazole, pharmacokinetic studies among children have revealed that children require twice the recommended adult dose to achieve comparable blood concentrations. Voriconazole clearance is also affected by the cytochrome P450 *(CYP) 2C19* genotype and hepatic impairment. Therapeutic drug monitoring is recommended as voriconazole pharmacokinetics are highly variable and small dose increases can result in marked changes in plasma concentrations. For the echinocandins, the primary source of pharmacokinetic variability stems from an age-dependent decrease in clearance with increasing age. Consequently, young children require larger doses per kilogram of body weight than older children and adults. Routine therapeutic drug monitoring for the echinocandins is not recommended. The effectiveness of many systemic antifungal agents has been correlated with pharmacodynamic targets in in vitro and in murine models of invasive candidiasis and aspergillosis. Further study is needed to translate these findings into optimal dosing regimens for children and to understand how these agents interact when multiple antifungal agents are used in combination.

1 Introduction

Invasive fungal infections are a leading cause of mortality among immunocompromised and critically ill children [1]. The most common aetiological agents of invasive fungal infections

are *Candida* and *Aspergillus*, which despite prompt antifungal therapy have mortality rates of 30–80 % [2–6]. It is therefore desirable to consider antifungal pharmacokinetics and pharmacodynamics, which have the potential to inform the development of dosing regimens that can improve antifungal activity and minimize toxicity [7].

Currently, four broad classes of systemic antifungal agents are used in the treatment of invasive fungal infections, including the polyenes, triazoles, pyrimidine analogues, and echinocandins [8]. The polyenes and triazoles target key components of the fungal cell membrane (Fig. 1) [9]. The pyrimidine analogue flucytosine inhibits DNA and RNA synthesis, which disrupts protein synthesis and cellular division [10]. The echinocandins are a recently discovered class of antifungal agents that interfere with cell wall biosynthesis [11]. Each of these classes exhibits unique pharmacokinetic and pharmacodynamic characteristics, which have been the subject of varying degrees of scientific investigation.

Pharmacokinetic and pharmacodynamic relationships have been defined for several antifungal agents that have been used to predict responses to treatment [12, 13]. In evaluating these pharmacodynamic relationships, three patterns of antifungal activity have been defined: (1) concentration-dependent activity, where antifungal activity increases with higher drug concentrations (e.g. polyenes and echinocandins); (2) time-dependent activity with little to no post-antifungal effect, where higher antifungal concentrations do not increase the rate or extent of antifungal activity and there is negligible antifungal activity when drug concentrations fall below the minimum inhibitory concentration (MIC) (e.g. flucytosine); and (3) time-dependent activity with prolonged post-antifungal effects, where fungal growth is suppressed for a period of time after the drug concentration falls below the MIC (e.g. triazoles) [14, 15]. However, it must be noted that post-antifungal effects are often pathogen specific [16, 17]. To define the pharmacodynamic pattern that best describes the antifungal activity of a given drug dose fractionation studies are often performed, in which a variety of doses are administered at multiple dosing intervals (Fig. 2). If regimens with shorter dosing intervals are more efficacious, then the time-dependent pharmacodynamic parameter ($T >$ MIC) is the most important parameter, as in the case of flucytosine [12]. When large, infrequently administered doses are the most efficacious, then the ratio of the maximum concentration (C_{max}) to the MIC (C_{max}/MIC) is the most important pharmacodynamic parameter, as in the case of the polyenes and echinocandins [15, 18, 19]. Lastly, when antifungal activity is comparable for each of the dosing intervals, then the clinical outcome is most dependent on the total dose or the area under the plasma concentration–time curve (AUC) in relation to the MIC (AUC/MIC) [20]. Dose fractionation studies have found that this pattern of activity is correlated with the clinical response to therapy for the triazoles [13, 21]. Both in vivo and in vitro experiments have shown that the pharmacodynamic parameter that is best correlated with the response to treatment and its relative magnitude are comparable for drugs within the same class, when unbound drug concentrations are evaluated [22]. Additionally, extensive studies conducted with antibacterials have demonstrated that the correlation between pharmacodynamic target attainment and clinical outcomes is remarkably conserved across species, dosing intervals and infection foci [22, 23]. This may reflect the fact that the targets of antimicrobial therapies are within the infecting organism and thus do not vary as a consequence of differing host species [24]. Additionally, pharmacodynamic targets are often formulated as a

function of the unbound drug concentration and therefore account for inter- and intra-species pharmacokinetic differences [24].

For well-studied conditions, such as disseminated candidiasis, a bridging approach has proven effective in extending results obtained from studies conducted in animal models to the clinic [25]. For children, this often involves extrapolation of efficacy from studies in adults [26]. Recent guidelines from the US FDA and the European Medicines Agency (EMA) have recognised that this approach may be considered in cases where the drug is to be used for the same indication(s), the disease process is similar, and the outcome of therapy is comparable. Successful examples can be found in the field of antifungal pharmacology with respect to the development of caspofungin and micafungin [27, 28]. These drugs were licensed for paediatric use following a series of systematic investigations in phase I–III clinical trials, which established age-specific population pharmacokinetics, determined appropriate paediatric doses, and collected limited safety and efficacy data needed to support the feasibility of extrapolating data from large randomised trials conducted in adults [29–31]. Despite these and other recent successes, many of the older antifungal agents have never been licensed for paediatric use and remain understudied. A list of antifungal agents that have been approved by the FDA for the treatment of invasive fungal infections is featured in Table 1.

Understanding the pharmacokinetics and pharmacodynamics of antifungal agents used across the paediatric age spectrum represents a major challenge as human growth during the first two decades of life is dynamic and nonlinear [32]. For the safe and effective treatment of invasive fungal infections it is necessary to evaluate drug absorption, distribution, metabolism and elimination throughout childhood [33]. In this review, we comprehensively evaluate the pharmacokinetic and pharmacodynamic literature describing the four most common classes of antifungal agents and describe paediatric-specific considerations in their pharmacokinetics, pharmacodynamics and therapeutic drug monitoring. Each section concludes with an evaluation of current knowledge gaps and highlights areas for future research. Published reports were systematically identified using the search terms ‘paediatric’ or ‘pediatric’ or ‘children’ and the generic and trade names for each antifungal agent in PubMed and EBSCOhost. When no paediatric studies were identified, the query was modified to remove the paediatric-specific search terms. Identified articles were then reviewed and evaluated by at least two authors and duplicate publications were excluded from further review. The literature search was finalised on 1 November 2013 and no limits were applied on the basis of publication date.

2 Polyenes

Polyene macrolides are the oldest class of antifungal agents and have been used for more than 50 years, primarily due to their broad spectrum of activity [34–36]. The most common systemically administered drug in this class is amphotericin B deoxycholate [37]. Amphotericin B binds to fungal membrane ergosterols, which results in increased cell permeability and ultimately cell death [38]. Although amphotericin B binds to fungal membrane sterols with high affinity, it also binds to cholesterol components of mammalian cells and therefore is commonly associated with toxic adverse events [36].

In an effort to alleviate concerns regarding toxicity, several lipid-based formulations of amphotericin B have been developed [39]. The reformulation of amphotericin B into a liposomal carrier (liposomal amphotericin B) or a lipid complex with a ribbon-like (amphotericin B lipid complex) or disk-like (amphotericin B colloidal dispersion) shape alters the pharmacokinetic and pharmacodynamic properties of these drugs. Critically, in comparison to conventional amphotericin B deoxycholate, these three commercially produced lipidic formulations are associated with less toxicity [37].

2.1 Pharmacokinetics and Pharmacodynamics

Amphotericin B deoxycholate is administered parenterally as it exhibits negligible gastrointestinal absorption [38]. Upon entering the bloodstream, amphotericin B rapidly dissociates from the deoxycholate, where >90 % of the drug binds to serum proteins [38]. Amphotericin B distributes widely into tissues, particularly the liver and spleen (Table 2) [40]. In adults, amphotericin B features a distribution phase of 15–48 h and a terminal elimination half-life of approximately 15 days [41]. Similar distribution phase kinetics have been reported for pre-term neonates, infants, and children 4 months to 14 years of age [42, 43]. Among children, the terminal elimination phase half-life of amphotericin B has been reported to range from weeks to months [42]. Amphotericin B poorly penetrates into the cerebrospinal fluid (CSF), vitreous humour or amniotic fluid [44]. Excretion into the urine is also negligible [38].

The clinical utility of amphotericin B deoxycholate is limited due to the drug's narrow therapeutic window, which requires clinicians to carefully balance efficacy and toxicity [39]. Adverse events commonly include acute infusion-related toxicity and nephrotoxicity [45, 46]. Within the last 10 years, several studies demonstrated that continuous infusion of amphotericin B deoxycholate may reduce the incidence of nephrotoxicity and infusion-related adverse reactions [47–51]. However, amphotericin B has been shown to feature concentration-dependent antifungal activity in vitro, which suggests that infrequent administration of large amphotericin B doses may optimise its pharmacodynamic activity [15]. Moreover, amphotericin B exhibits non-linear, concentration-dependent protein binding in plasma and tissues [52]. Few pharmacokinetic and pharmacodynamic studies have accounted for the influence of physiologically relevant concentrations of human serum albumin when comparing amphotericin B dosing regimens. However, in the single study conducted to date, Lewis et al. [53] developed an in vitro pharmacodynamic model to compare continuous versus rapid infusion strategies with varying concentrations of human serum albumin. The authors found that the antifungal activity of amphotericin B was dramatically reduced or completely ablated in the presence of human serum albumin concentrations ranging from 4 to 8 %. The authors further reported no difference in the rate or extent of amphotericin B antifungal activity with rapid or continuous infusion regimens. These findings suggest that extended or continuous infusion strategies may reduce the incidence of toxic adverse events, although such regimens are unlikely to optimise amphotericin B pharmacodynamics and may result in treatment failure.

For patients who are refractory to or intolerant of conventional amphotericin B deoxycholate, several lipidic formulations may be considered. The pharmacokinetic

properties of these lipid-based formulations differ markedly when compared to amphotericin B deoxycholate [38].

Amphotericin B lipid complex pharmacokinetics have been extensively studied in mice, rats, rabbits and dogs [54, 55]. Following administration of a single dose of amphotericin B lipid complex, amphotericin B concentrations were substantially lower in the liver, spleen and lungs than concentrations measured following administration of amphotericin B deoxycholate [55]. Comparable concentrations were measured in the kidneys [55]. In plasma, amphotericin B lipid complex achieved higher amphotericin B concentrations than conventional amphotericin B deoxycholate [55]. As the dose of amphotericin B lipid complex is increased, amphotericin B concentrations in the liver, spleen and lung tissue increase markedly; however, no change is observed in amphotericin B concentrations in the kidneys or in the plasma [55]. In a murine model system, the half-maximal lethal dose (LD_{50}) following a single intravenous dose of amphotericin B deoxycholate was determined to be 3 mg/kg, whereas the LD_{50} of amphotericin B lipid complex was established at 40 mg/kg [56]. In multiple-dose studies, amphotericin B lipid complex continued to exhibit significantly reduced toxicity in mice and rabbits when compared to amphotericin B deoxycholate [56, 57]. In humans, the pharmacokinetics of amphotericin B lipid complex are similar to those reported in animal studies [58].

Amphotericin B colloidal dispersion pharmacokinetics have also been extensively studied in animal models [59–61]. Following a single intravenous bolus, amphotericin B colloidal dispersion resulted in significantly lower plasma amphotericin B concentrations than dosing with amphotericin B deoxycholate in rats [59]. The terminal elimination half-life is also longer and the volume of distribution is considerably larger [59]. In dogs, administration of amphotericin B colloidal dispersion resulted in increased amphotericin B concentrations in the liver, comparable concentrations in the plasma and decreased concentrations in the kidney when compared with dosing with amphotericin B deoxycholate [60]. In further single- and multiple-dose experiments across several species, amphotericin B colloidal dispersion consistently demonstrated less toxic effects than amphotericin B deoxycholate [61]. As yet, few human trials have investigated the pharmacokinetics of amphotericin B colloidal dispersion; however, safety and efficacy trials have demonstrated that amphotericin B colloidal dispersion displays comparable antifungal activity and less nephrotoxicity than amphotericin B at clinically relevant doses [62].

The pharmacokinetics of liposomal amphotericin B have been studied in mice, rats and rabbit models of invasive fungal infection [63, 64]. Liposomal amphotericin B is negatively charged and considerably smaller than the two lipid complex formulations of amphotericin B (amphotericin B lipid complex and amphotericin B colloidal dispersion), which may retard its uptake within the reticuloendothelial system [65]. This may explain, in part, why liposomal amphotericin B achieves far higher peak amphotericin B plasma concentrations and features a prolonged circulation time when compared to amphotericin B lipid complex and amphotericin B colloidal dispersion [65]. In mice and rats, liposomal amphotericin B is less nephrotoxic, with an LD_{50} 50-fold lower than that of amphotericin B deoxycholate [63]. However, slight elevations in liver transaminases have also been reported following the administration of multiple doses of liposomal amphotericin B [63]. In a small human

autopsy study, liposomal amphotericin B achieved the highest amphotericin B concentrations in the liver and the spleen, which is consistent with previous findings from animal models [66]. Using a two-compartment model, liposomal amphotericin B pharmacokinetic parameters were established for a cohort of 44 immunocompromised adults [67]. The authors found that liposomal amphotericin B exhibits a non-linear dose-response relationship that was consistent with reticuloendothelial uptake and redistribution [67]. Hong et al. [68] evaluated the population pharmacokinetics of liposomal amphotericin B among 39 children with neoplastic disease and found that weight exerted a significant influence upon both clearance and the volume of distribution in the central compartment. In simulations, the authors found that weight-related changes in liposomal amphotericin B pharmacokinetic parameters alter drug exposure, such that children <20 kg require a higher dose to achieve peak amphotericin B concentration targets.

2.2 Intra- and Inter-Individual Variability

The disposition of amphotericin B deoxycholate is more variable among neonates and young children than in adolescents and adults [69]. Serum half-lives were reported to be longer in four of five neonates than in older children [69]. Following 5 days of therapy, inter-individual variability in amphotericin B clearance was high among 13 neonates [42]. Pharmacokinetic evaluations conducted with amphotericin B lipid complex also revealed evidence of substantial inter-individual variability in clearance and volume of distribution (35 and 43 %, respectively) [70]. These data suggest that younger children have a greater potential for drug accumulation and heightened inter-individual variability than adults [37]. Additionally, amphotericin B deoxycholate CSF concentrations are 2–4 % of serum concentrations in adults; however, CSF penetration may be as high as 40 % among pre-term neonates [42, 71].

2.3 Dosing Optimisation

Amphotericin B features a broad spectrum of activity and is an established agent in the treatment of endemic and opportunistic invasive fungal infections; however, up to 80 % of patients experience infusion-related toxicity or nephrotoxicity [36, 72]. Although nephrotoxicity is typically less severe in infants and children, efforts are needed to optimise the dosing of amphotericin B to improve its tolerability [37]. To this end, several studies have administered amphotericin B deoxycholate by continuous infusion, as opposed to traditional 2–6 h infusions [49, 51, 73, 74]. These studies reported a decrease in the rate of nephrotoxicity and fewer infusion-related reactions when compared with a 4-h infusion at the same daily dose [51]. Despite these promising findings, however, continuous infusion of amphotericin B has not been widely adopted due to challenges in obtaining venous access solely for the purpose of administering the drug and pharmacodynamic data that suggest that amphotericin B is most efficacious when higher daily doses are administered less frequently [15, 24, 51].

In an effort to enhance the efficacy of amphotericin B dosing regimens, the randomised multicentre AmBiLoad trial evaluated a high loading dose of liposomal amphotericin B at 10 mg/kg/day for the first 14 days of therapy as compared with standard dosing regimens of 3 mg/kg/day [75]. At the end of study drug treatment, the primary endpoint was assessed as

complete or partial response to therapy, along with secondary survival and safety outcomes. The authors found that liposomal amphotericin B at 3 mg/kg/day yielded a response rate of 50 % and a 12-week survival rate of 72 %. The high loading dose regimen did not improve clinical outcomes and resulted in higher rates of nephrotoxicity.

2.4 Therapeutic Drug Monitoring

Therapeutic drug monitoring for amphotericin B deoxycholate is of limited utility due to the absence of a well-defined correlation between measured amphotericin B concentrations and clinical efficacy [76]. Moreover, at doses that are routinely administered clinically, plasma concentrations rarely exceed 1–2 μg/mL [77]. On the basis of these findings, in 1991 the Working Party of the British Society for Antimicrobial Chemotherapy concluded that therapeutic drug monitoring of amphotericin B deoxycholate is unnecessary [78]. More recent studies have sought to determine whether plasma or serum amphotericin B concentrations correlate with nephrotoxicity [79, 80]. These studies concluded that amphotericin B-induced nephrotoxicity was correlated with the total cumulative dose, rather than serum concentrations. To date, amphotericin B plasma or serum concentrations have not been correlated with clinical efficacy or toxicity, such that therapeutic drug monitoring cannot be recommended. Limited paediatric pharmacokinetic data suggest that the intra-individual variability observed with the lipidic formulations of amphotericin B may be larger than the inter-individual variability, confounding dose individualisation efforts through therapeutic drug monitoring [68, 81].

2.5 Drug Resistance

Despite more than 50 years of widespread clinical use, fungal resistance to amphotericin B is rare [82]. In a recent study of more than 9,000 *Candida albicans* isolates, 99.8 % remained sensitive to amphotericin B [83]. Resistance is most frequently encountered in isolates of *Candida lusitaniae, Aspergillus terreus* and *Aspergillus nidulans* [84]. In in vitro experiments, mutant isolates that display resistance to amphotericin B and nystatin develop compensatory mechanisms to replace ergosterol with precursor sterols [85]. Due to the relative scarcity of polyene-resistant fungal strains, it has been speculated that the fitness cost incurred by developing this adaptive form of resistance attenuates the pathogenicity of ergosterol-deficient mutants [86].

2.6 Clinical Recommendations and Prospects for Future Research

As equally effective, less toxic antifungal agents have been developed, it is now unlikely that further characterisation of amphotericin B deoxycholate pharmacokinetics and pharmacodynamics will occur [87]. However, further evaluation of lipidic formulations of amphotericin B is warranted due to their improved toxicity profile and equivalent efficacy [88, 89]. These agents are typically employed as salvage therapies for patients who are refractory to or intolerant of amphotericin B deoxycholate, primarily owing to their high cost. Consequently, few studies have sought to establish correlations between pharmacokinetic profiles and clinical outcomes. As the costs of these agents decrease, such studies will be invaluable in guiding clinical decision making.

3 Pyrimidine Analogues

Flucytosine (5-fluorocytosine, 5-FC) is a pro-drug that is actively transported into fungal cells by cytosine permease [90]. Cytosine deaminase converts flucytosine to 5-fluorouracil, which can subsequently be converted to 5-fluorouridine triphosphate for incorporation within fungal RNA (thereby inhibiting protein synthesis), or be converted to 5-fluorodeoxyuridine monophosphate and inhibit thymidylate synthetase (thereby inhibiting DNA synthesis) [10, 91, 92].

3.1 Pharmacokinetics and Pharmacodynamics

Flucytosine is administered orally with >70 % absorption, although absorption can be delayed by renal insufficiency, antacids and food [93, 94]. Flucytosine is not highly bound by serum proteins, is highly water soluble, and penetrates well into the CSF, vitreal humour, peritoneal fluid as well as the synovial fluid of inflamed joints [93, 95–98]. Peak concentrations are reached within 1–2 h post-administration and it is recommended that serum concentrations be maintained between 40 and 80 μg/mL [93, 99]. Flucytosine is primarily eliminated by the kidneys via glomerular filtration, such that its clearance is closely correlated with serum creatinine concentrations [93, 97, 100].

Flucytosine is rarely used as a monotherapy due to the emergence of rapid antifungal resistance during treatment [101–105]. However, flucytosine is thought to be synergistic with amphotericin B, which facilitates its penetration into fungal cells [106]. Concentrations of amphotericin B are increased in the CSF, heart valves and the vitreal body when coadministered with flucytosine [101]. There are sparse pharmacokinetic data on flucytosine in paediatric patients. In adults, the serum half-life of flucytosine is 3–6 h in patients with normal renal function, but is extended in patients with impaired renal function (up to 85 h) [97]. A neonatal pharmacokinetic study demonstrated that the half-life was twice that reported in adults, although peak concentrations were comparable [42]. Additionally, the volume of distribution of flucytosine approximates the volume of total body water due to its high solubility [103]. In a retrospective study of 391 paediatric patients, 65 % of flucytosine trough concentrations exceeded the normal reference range in children 1–30 days of age [107]. These data suggest that the standard dose of 100 mg/kg/day may not be appropriate and that further studies are needed to establish optimal age-appropriate dosing regimens.

3.2 Intra- and Inter-Individual Variability

High inter-individual variability exists with paediatric patients. Baley et al. [42] reported that three infants had an extended half-life up to 35 h, which they attributed to immature kidney function.

3.3 Dosing Optimisation

Due to the prolonged half-life of flucytosine in paediatric patients, it has been suggested that dosing intervals can be as long as 24 h without compromising its fungistatic activity, despite adult recommendations for 6-hourly dosing [42]. Additionally, the synergistic effect of amphotericin B and flucytosine achieves the same therapeutic target with lower doses [10, 108].

3.4 Therapeutic Drug Monitoring

When using flucytosine, it is important to monitor plasma concentrations to avoid toxicity. High peak serum concentrations have resulted in hepatic injury, bone marrow suppression and gastrointestinal disturbances [109–112]. In addition, renal insufficiency can be induced by amphotericin B co-treatment and commonly leads to toxicity as a consequence of decreased renal clearance.

3.5 Drug Resistance

Resistance is common with flucytosine and typically occurs through mutations in cytosine permease (decreases drug uptake into fungal cells), increased synthesis of pyrimidines (decreases competitive inhibition) or, most commonly, through mutations in uridine monophosphate pyrophosphorylase, which decrease the metabolism of flucytosine to its active antimetabolite [94, 113, 114]. Both high and low flucytosine concentrations have been demonstrated to incur resistance [114]. Nearly 8 % of C. *albicans* and *Torulopsis glabrata* strains are intrinsically resistant, whereas only 1–2 % of *Candida neoformans* strains are resistant [115]. Between 8 and 44 % of non-*albicans Candida* species have been reported to be resistant to flucytosine [116].

3.6 Clinical Recommendations and Prospects for Future Research

Flucytosine monotherapy is not recommended due to the rapid emergence of resistance and therefore it is unlikely that feature studies will evaluate flucytosine pharmacokinetics in isolation. However, further studies are needed in children to understand the mechanism and effects of flucytosine and amphotericin B synergy. Pharmacokinetic and pharmacodynamic studies will be vitally important in establishing an optimal dosing regimen for these two agents [104]. Further investigation of combination therapies with triazoles is also warranted.

4 Triazoles

The triazoles feature broad antifungal activity and are well-tolerated [117]. These agents interfere with fungal-specific cytochrome P450 (CYP) activity (lanosterol 14-α-demethylase), which then inhibits cell membrane ergosterol synthesis [118]. Ergosterol synthesis is essential to maintain normal membrane permeability [119]. Triazole-mediated inhibition of ergosterol synthesis alters fungal membrane permeability and results in cell death.

The most commonly prescribed triazole agents include fluconazole, itraconazole, voriconazole and posaconazole [120]. Collectively, these drugs represent a major advance in paediatric antifungal therapy, although historically their use has been marked by the emergence of resistance and drug-drug interactions [117]. Fluconazole features activity against many *Candida* species, but has little or no activity against *Candida krusei, Candida glabrata* and most filamentous fungi, including *Aspergillus* [121]. Newer triazole agents, such as posaconazole, display potent in vitro activity against pathogenic yeasts and moulds, including fluconazole-resistant strains of *Candida* and Zygomycetes [122].

4.1 Pharmacokinetics and Pharmacodynamics

Fluconazole is available for parenteral and oral administration and is well-absorbed from the gastrointestinal tract (Table 3)[123]. Fluconazole is a hydrophilic drug and 11–13 % of the drug binds to serum proteins [124, 125]. In adults, fluconazole distributes into a volume similar to that of total body water (approximately 0.71 L/kg) [126]. However, the apparent volume of distribution in immunocompromised paediatric patients varies by age, with the largest volume of distribution reported among neonates, which decreases with increasing age until adult levels are reached in adolescence [127]. Fluconazole is widely distributed to nearly all organs and tissues, including the central nervous system (CNS) [119]. Fluconazole also undergoes minimal metabolism and is primarily excreted unchanged in the urine [125, 128]. The longest half-life has been observed among neonates, which then declines to 21–23 h among children 3 months to 16 years of age and rises again to approximately 30 h among adults [127, 129, 130]. These age-specific pharmacokinetic differences suggest that the increased volume of distribution in children will result in lower systemic fluconazole concentrations than in adults who receive a proportional dose [127]. Additionally, the shorter half-life among children (with the exception of neonates) has the potential to result in reduced drug accumulation if adult once-daily dosing regimens are extrapolated to children [127].

Itraconazole is available in a capsular, oral and intravenous formulation [131]. The capsular formulation is characterised by erratic absorption and variable plasma concentrations [132]. More recently developed oral and intravenous formulations display less variable pharmacokinetics [117]. Itraconazole is a highly lipophilic drug that is nearly insoluble in water [133]. Gastric emptying rates affect itraconazole dissolution in the stomach and its absorption from the small intestine [133]. Upon entering the bloodstream itraconazole rapidly binds to red blood cells and circulating plasma proteins [134]. Consequently, unbound concentrations of itraconazole in the CSF, vitreal fluid and saliva are markedly lower than unbound plasma concentrations [134]. Following a single dose, peak concentrations are reached within 2–3 h post-administration and the terminal elimination half-life is approximately 25 h [135]. Itraconazole is extensively metabolised in the liver, primarily by CYP3A4, for which itraconazole is both a substrate and an inhibitor [136]. Due to CYP3A4 auto-inhibition, the half-life of itraconazole has been found to increase to more than 30 h in patients following a week of therapy [137].

Due to the highly variable absorption profile of the capsular formulation of itraconazole, most paediatric studies have characterised the pharmacokinetics of the oral and intravenous formulations of itraconazole [135, 138, 139]. de Repentigny and colleagues [138] administered oral itraconazole at 5 mg/kg once daily for 2 weeks to 26 infants and children 6 months to 12 years of age who were at risk for invasive fungal infections. The authors reported lower C_{max} and AUC from time zero to 24 h (AUC_{24}) values among children 6 months to 2 years of age on the first day of therapy, although these differences resolved by day 14. When compared to repeated-dose pharmacokinetic studies among adults who received oral itraconazole at 5 mg/kg, the C_{max} and AUC_{24} among children were approximately one third of the values measured among adults [138, 140, 141]. Similar results were reported in a subsequent study conducted among 26 HIV-infected children and

adolescents 5–18 years of age [135]. More recently, the single-dose pharmacokinetics of an intravenous formulation of itraconazole were evaluated among 33 children 7 months to 17 years of age [139]. Itraconazole C_{max} and AUC_{24} values were higher in children who received the intravenous formulation than in previous studies conducted using the oral formulation. However, as itraconazole undergoes significant first-pass hepatic inactivation (approximately 50 %), this was not unexpected [142]. The authors found no evidence that age influenced itraconazole pharmacokinetics, suggesting that weight-based dosing of intravenous itraconazole may be employed irrespective of the age of the child being treated [139].

Voriconazole is available in both an oral and an intravenous formulation [143]. In healthy volunteers, the oral formulation of voriconazole displays high bioavailability (>90 %) and moderate protein binding (58 %) [144]. Unlike itraconazole, pharmacokinetic studies in adults have revealed evidence of high inter-individual variability with both voriconazole formulations [145, 146]. A non-linear dose-exposure relationship has been reported that may be attributable to saturation of hepatic metabolizing enzymes [143]. Pharmacogenetic studies have demonstrated that genetic differences in *CYP2C19* expression contributes to the inter-individual variability observed in voriconazole pharmacokinetics [147–150]. Genetic variants in *CYP2C19* are common and are known to alter voriconazole metabolism [151]. Using adult doses, paediatric pharmacokinetic studies have described a linear non-saturable dose-exposure profile for children <5 years of age [152]. However, at higher recommended doses, children exhibit non-linear voriconazole pharmacokinetics in the majority of children [153]. As a consequence of differences in the degree of non-linearity in voriconazole pharmacokinetics between children and adults, paediatric patients require more than twice the adult dose to achieve comparable blood concentrations [154]. Recently, several paediatric studies have reported an association between improved patient outcomes and a voriconazole trough concentration > 1 μg/mL [155–157]. However, high inter-individual variability makes it challenging to reliably attain this trough target in clinical practice. Michael et al. [153] reported trough concentrations < 0.1 μg/mL and as high as 16.3 μg/mL in two toddlers who received the same 7 mg/kg intravenous dose.

Posaconazole is the most recently developed member of the triazole class and is currently available as an oral suspension and a delayed-release tablet [158, 159]. The oral absorption of posaconazole is variable (8–47 %) and may be altered in patients with poor appetite, nausea, diarrhoea, gastrointestinal disorders, and in patients receiving concurrent acid-suppressive therapies [160]. However, the bioavailability of the posaconazole suspension can be greatly enhanced when it is administered after a high-fat meal [161]. Administration every 6 or 8 h with food has been shown to increase posaconazole exposure by 180 % when compared with once-daily dosing [162]. Notably, the recently approved delayed-release tablet formulation of posaconazole features improved bioavailability, no food effect and decreased inter-individual variability when compared with the oral suspension [159, 163, 164]. Similar to the other members of the triazole family, posaconazole inhibits CYP3A4; however, unlike voriconazole, CYP2C9, CYP2C19 and other CYP isoenzymes are not affected [165, 166]. Posaconazole has a large volume of distribution at steady state and has been reported to feature high alveolar penetration with concentrations in pulmonary alveoli that are approximately 35-fold higher than plasma concentrations [167]. However, the extent

to which posaconazole crosses the blood–brain barrier is unknown. Up to 20–30 % of the posaconazole dose is metabolised by uridine diphosphate (UDP)-glucuronosyltransferase UGT1A4 (the glucuronide conjugates possess minimal antifungal activity) [168] and the remaining 70–80 % is eliminated unchanged in the faeces [158, 169]. To date, the few studies available report no obvious pharmacokinetic differences between children and adults [170].

4.2 Intra- and Inter-Individual Variability

Triazole pharmacokinetics are influenced by pathophysiologic considerations, including small bowel resection, graft versus host disease, fluid overload and gastroenteritis [76]. Although specific pharmacokinetic differences exist in certain patient populations, fluconazole pharmacokinetics are generally less variable than those in other triazole agents [77, 129]. However, the volume of distribution of fluconazole among children is larger and marked by increased variability when compared with adult patients [171].

Itraconazole is an extremely weak base and is only ionised in acidic environments [172]. For this reason, the capsular formulation of itraconazole features variable dissolution in the stomach before being absorbed from the small bowel [133]. Additionally, itraconazole is both an inhibitor and a substrate of the drug transporter P-glycoprotein (P-gp) [173]. The expression level of P-gp expression found on the apical membrane of mature enterocytes may play a significant role in itraconazole absorption. This is especially relevant in critically ill children where P-gp expression has been found to vary up to tenfold [174]. Similarly, itraconazole is both a substrate and an inhibitor of CYP3A4 [173]. Itraconazole-induced inhibition of CYP3A4 may result in increased plasma concentrations of other medications that are metabolised by CYP3A4, including: midazolam, atazanavir, ritonavir, tacrolimus, cyclosporine (ciclosporin) and others (Table 4) [175].

The factors contributing to the high inter- and intraindividual variability in voriconazole pharmacokinetics are poorly understood in children [176]. A multicentre retrospective review evaluated voriconazole pharmacokinetics among 139 children with invasive aspergillosis and found that published doses ranged from 3.4 to 23 mg/kg/day [177]. Despite this wide range in administered voriconazole doses, target troughs >1 μg/mL were rarely achieved [155, 178, 179]. Moreover, among those children who did achieve target trough concentrations, the weight-adjusted doses varied widely. In two additional studies recently conducted among paediatric haematopoietic stem cell transplant patients, less than half of the patients studied achieved and sustained a therapeutic trough concentration without individualised voriconazole concentration monitoring and dose adjustment [157, 180]. To better elucidate the factors affecting voriconazole pharmacokinetics in children, Karlsson et al. [181] conducted a population pharmacokinetic analysis using data from three studies conducted among children 2–11 years of age who received a range of single or multiple intravenous and/or oral voriconazole doses. The authors reported that the *CYP2C19* genotype and blood ALT concentration significantly influenced voriconazole clearance [181]. Similar to other triazole agents, drug-drug interactions can significantly alter voriconazole exposure [154]. In one such study, the coadministration of phenobarbital caused a 50 % reduction in the voriconazole C_{max} [182].

Variability in posaconazole pharmacokinetics occurs primarily as a consequence of altered absorption [170]. This phenomenon is more pronounced in critically ill patient populations, including those with gastric mucosal alterations such as chemotherapy-associated mucositis [143]. In one adult study, allogeneic bone marrow transplant recipients had posaconazole concentrations that were 52 % lower than those measured among non-transplanted febrile neutropenic patients [183]. The authors also reported a larger inter-individual coefficient of variation (71–82 %). In a study of 12 children and 194 adults, mean posaconazole plasma concentrations were comparable [170]. The youngest study participant was 8 years old and had a mean steady-state posaconazole plasma concentration of 227 ng/mL, which was comparable with the mean steady-state concentration measured among the oldest paediatric participant (238 ng/mL) [170]. This finding suggests that posaconazole pharmacokinetics are similar among older children and adults; however, posaconazole pharmacokinetics have not been studied among children <8 years of age.

4.3 Dosing Optimisation

As invasive fungal infections often occur in immunocompromised patients or those with concomitant bacterial infections, it is challenging to evaluate the clinical response to antifungal therapy [184]. However, in a study of 28 adult cancer patients with presumed or proven mould infections, the total daily dose of fluconazole was increased to 1,200, 1,600 and 2,000 mg, which was associated with C_{max} values of 51.8, 74.4 and 91.8 mg/L, respectively [185]. Less than one third of the patients in each dosing group responded to therapy, implying that the clinical response is not dose—and therefore concentration—dependent. However, in this study rates of adverse events were observed to increase with larger doses [185]. Dosages up to 1,600 mg/day were well-tolerated, although larger doses were associated with neurotoxicity [185].

Guidelines from the Infectious Disease Society of America (IDSA) recommend that adults with candidaemia who receive treatment with fluconazole be given a loading dose on the first day of therapy [186, 187]. In the only paediatric study to date, Piper et al. [188] evaluated the pharmacokinetics and safety of a 25 mg/kg loading dose among eight infants <60 days of age with serial fluconazole serum concentration measurements. The authors found that five of eight (63 %) infants achieved the therapeutic exposure target (AUC_{24} > 400 mg·h/L) and 100 % achieved a 24-h trough concentration > 8 μg/mL. The three infants who did not achieve the AUC target were receiving extracorporeal membrane oxygenation (n = 1), were severely oedematous (n = 1) or immunocompromised (n = 1). Larger loading doses may be warranted for these special patient populations.

There are no published itraconazole pharmacodynamic studies among children with invasive fungal infections. However, a single study examined the pharmacodynamics of oral itraconazole among HIV-infected children and adolescents with oropharyngeal candidiasis [135]. As predicted from murine dose fractionation studies, the pharmacodynamic parameter that was most closely correlated with the response to treatment was the AUC_{12} (r = 0.595; P = 0.01) [135].

In vivo experiments in animal models of invasive candidiasis have demonstrated a strong relationship between voriconazole exposure and treatment efficacy [21]. Similar to other

triazoles, the unbound voriconazole AUC/MIC needed to produce a half-maximal antifungal effect was approximately 25 [21]. For adults with disseminated candidiasis, a voriconazole AUC/MIC <25 was associated with treatment failure in 40–50 % of the patients studied [189]. Among patients with invasive aspergillosis, a trough voriconazole concentration > 0.5 μg/mL was associated with a trend toward a higher odds of treatment success (odds ratio 1.5; 95 % CI 0.6–3.4) [190]. In a more recent study of 52 patients who received more than 2,000 days of voriconazole therapy for the treatment of invasive fungal infections, trough concentrations < 1 μg/mL were associated with a positive outcome in approximately 50 % of cases as compared to 90 % among patients with troughs ≥1 μg/mL [156]. In a recent paediatric study, a trough voriconazole concentration < 1 μg/mL was associated with a 2.6-fold increased odds of death (95 % CI 1.6–4.8; $P = 0.002$) [155]. In Monte-Carlo simulations, the authors found that an intravenous dose of 7 mg/kg or an oral dose of 200 mg every 12 h would be predicted to achieve a trough > 1 μg/mL in 66 % of patients, although predicted trough concentrations were highly variable [155]. In another paediatric study, the clinical outcomes of 30 immunocompromised patients who received a combined 2,135 days of voriconazole therapy were evaluated [191]. No statistically significant relationship was found between voriconazole concentrations and overall mortality; however, a higher percentage of subtherapeutic plasma concentrations was observed in those who died [191]. Among children < 5 years of age, the median dose that yielded trough concentrations > 1 μg/mL was 19 mg/kg every 12 h, which is more than double the current recommended dose for this age group [155, 191].

Few studies have examined the relationship between posaconazole exposure and clinical efficacy in adults and none have been conducted in children. However, pharmacodynamic exposure studies have been conducted in murine models of invasive candidiasis and demonstrated that posaconazole efficacy is maximised with an unbound AUC_{24}/MIC >20–25 [192]. In one adult study, 67 patients with refractory invasive aspergillosis received posaconazole and were evaluated for their clinical response to therapy [193]. An exposure-response relationship was defined, where 80 % of patients in the lowest mean plasma concentration quartile (< 0.13 μg/mL) experienced treatment failure as compared with 30 % of patients with steady-state posaconazole concentrations ≥1.25 μg/mL [193]. Further research is needed to determine if this exposure-response relationship exists in children.

4.4 Therapeutic Drug Monitoring

Therapeutic drug monitoring is rarely performed for fluconazole, largely owing to its relatively low pharmacokinetic variability and the lack of studies establishing a correlation between fluconazole concentrations and clinical outcomes [76, 77, 129]. If therapeutic drug monitoring for fluconazole is conducted, its extended half-life suggests that the timing of the sample does not influence the measured concentration once steady state has been reached [76]. A target AUC_{24} >400 mg·h/L is recommended to achieve an AUC/MIC > 25 for *Candida* species with an MIC at which 90 % of bacteria are inhibited (MIC90)of 8 μg/mL [194–196].

Numerous itraconazole pharmacodynamic studies have demonstrated strong links between drug concentrations and clinical efficacy for adult patients with superficial and invasive

fungal infections [134, 197–200]. Three studies have thus far investigated the utility of itraconazole therapeutic drug monitoring [197, 199, 201]. In a rabbit model of invasive pulmonary aspergillosis, Berenguer et al. [197] reported a strong inverse correlation between itraconazole plasma concentrations and *Aspergillus fumigatus* tissue density. Moreover, plasma concentrations <6 μg/mL resulted in a considerable loss of in vivo antifungal activity. This parallels reports from a study of 21 adults with invasive aspergillosis in which the mean itraconazole trough measured among patients who responded to therapy was 6.5 μg/mL, as compared with 4.2 μg/mL among those who did not respond to therapy [199]. In another study, itraconazole trough concentrations > 1 μg/mL were associated with therapeutic success among all HIV-infected adult patients who received treatment for cryptococcal meningitis [201]. In aggregate, these findings suggest that itraconazole therapeutic drug monitoring should be considered for immunocompromised patients and that trough concentrations > 1 μg/mL should be targeted.

Therapeutic drug monitoring for voriconazole is recommended for children with invasive fungal infections owing to high inter-individual variability and the lack of a well-defined dose-exposure relationship [202]. In several case series and case reports, voriconazole plasma concentrations were often reported to be subtherapeutic despite successive dose increases [154, 176]. Conversely, other children had dramatic increases in their measured voriconazole concentrations following small dose increases [154]. In a previously mentioned study conducted among 30 children with immunosuppressive conditions, plasma concentrations were found to vary widely and 73 % of the children required a dose adjustment [191]. The authors also reported that elevated trough concentrations (≥5.5 μg/mL) were associated with dermatological and neurological adverse events, although a similar relationship was not demonstrated for hepatotoxicity [191]. Similarly, Neely et al. [155] reported that the risk of hepatotoxicity was not significantly associated with voriconazole dose, AUC, mean plasma concentration, C_{max} or minimum plasma concentration. In aggregate, these findings suggest that target voriconazole trough concentrations should be> 1 μg/mL to maximise therapeutic effectiveness and<5.5 μg/mL to minimise the development of toxicity in children.

Several studies have reported a link between higher steady-state and trough posaconazole concentrations and improved clinical outcomes [193, 203]. Less than one in four adults who received posaconazole as salvage therapy for the treatment of invasive aspergillosis responded to therapy when their mean plasma concentration was < 0.15 μg/mL [193]. In contrast, three of four patients with a mean posaconazole concentration ≥1.25 μg/mL responded to therapy [193]. The optimal steady-state, peak or trough posaconazole target is unclear; however, Andes et al. [143] suggested that a steady-state plasma concentration of at least 0.5–1.5 μg/mL may be a reasonable target for patients with invasive fungal infections. Limited data suggest that there is not an association between elevated posaconazole plasma concentrations and toxicity [170]. In clinical trials, posaconazole was generally well-tolerated and associated with fewer adverse drug–drug interactions than other members of the triazole family [204, 205].

4.5 Drug Resistance

A major complicating factor in the use of fluconazole is the emergence of resistant fungal organisms. Multiple epidemiological studies have demonstrated that increased fluconazole use, both as a therapeutic and as a prophylactic, is associated with increased rates of *non-albicans Candida* bloodstream infections [206, 207]. Additionally, several reports have suggested that the annual incidence of fluconazole-resistant oropharyngeal candidiasis in patients with AIDS has risen to approximately 5–10 % [208, 209]. Two randomised controlled trials evaluated prophylactic posaconazole versus fluconazole or itraconazole for immunocompromised patients at risk for invasive fungal disease and reported an increase in the frequency of fluconazoleresistant *C. albicans* during long-term prophylaxis but not in those who received posaconazole or itraconazole [210]. This differential resistance pattern among the triazoles may be attributable to a single point mutation in the gene that encodes the triazole-target lanosterol 14-α-demethylase *(ERG11)*, which has been shown to confer fluconazole resistance [211]. In contrast, multiple mutations are required to affect posaconazole and itraconazole susceptibility [121]. Molecular dynamic studies have demonstrated that the long side chain present on posaconazole and itraconazole stabilises the binding affinity of these agents to regions surrounding the haeme cofactor CYP51 [212]. Consequently, more mutations are required to destabilise the long side chains of posaconazole and itraconazole, which are necessary to confer resistance to *Candida* species [212]. In the last decade, *Aspergillus* resistance to the triazole class has increased [213]. A point mutation in the *CYP51A* gene has been associated with posaconazole and itraconazole *A. fumigatus* resistance [214]. Additionally, a recent study from The Netherlands evaluated *A. fumigatus* isolates obtained from eight university hospitals and identified a new CYP51A-mediated voriconazole resistance mechanism in 21 isolates obtained from 15 patients [215]. Eight patients were diagnosed with voriconazole-resistant invasive aspergillosis. At 12 weeks after isolation of the highly resistant *A. fumigatus* strain, four of eight (50 %) patients had died and two (25 %) had persisting infections. All of the patients who died had received primary therapy with voriconazole, whereas three of three (100 %) patients with invasive aspergillosis who received initial treatment with liposomal amphotericin B were alive at 12 weeks. Perhaps most concerning, the authors recovered these highly resistant strains from the air of the hospital paediatric ward as well as the patients' homes and backyards [215]. As voriconazole yields response rates 15–20 % higher than non-triazole-containing regimens, it is currently the first-line antifungal agent for invasive aspergillosis, although monitoring for the spread of these highly resistant strains must be undertaken to ensure that changes in antifungal selection are guided by local epidemiology [216, 217].

4.6 Clinical Recommendations and Prospects for Future Research

The triazoles display time-dependent, concentration-independent fungistatic activity in mice, although further study is needed to assess whether a clinical relationship between adult pharmacodynamic targets (e.g. AUC/MIC >25) and clinical outcomes can be defined for children [24]. Based on limited in vitro and clinical data, fungicidal agents may be preferable to fungistatic drugs when treating invasive fungal infections in severely immunocompromised patients [202]. However, definitive randomised trials are needed to answer this question. There is also a pressing need to evaluate the efficacy of fluconazole

loading doses in children [188]. Lastly, very few studies have examined the pharmacokinetics of triazole-based combination therapies [218, 219]. In vitro studies have demonstrated that the combination of posaconazole and the echinocandin caspofungin exhibit synergistic antifungal activity against Zygomycetes [218]. Clinically, synergistic effects have also been described among adult patients treated concurrently with voriconazole and anidulafungin [219]. Further research is needed to define the pharmacokinetics and pharmacodynamics of triazole-based combination antifungal therapies in children, as no such studies currently exist.

5 Echinocandins

The first prospective trials to evaluate the echinocandins in children began in the early 2000s and since that time there has been a substantial increase in their use [27, 28, 220]. This is likely a consequence of their comparable efficacy and improved side effect profile when compared with other systemic antifungal agents [220]. These drugs exert their antifungal effects by inhibiting the ß-(1,3)-D-glucan synthase complex, which disrupts cell membrane permeability. The favourable side effect profile of the echinocandins is attributed to the absence of a mammalian ortholog of the glucan synthase complex and limited interaction with phase I/II metabolic enzymes [221].

Three echinocandin agents are approved for the treatment of invasive fungal infections in adults, including caspofungin, micafungin and anidulafungin. More recently, caspofungin and micafungin were approved for use in children [222, 223]. The echinocandins feature fungicidal activity against many *Candida* species and fungistatic activity against *Aspergillus* [224]. Additionally, the echi-nocandins have been used to successfully treat triazole-resistant *Candida* strains and have been reported to feature antifungal activity against biofilms [225, 226]. These agents display similar clinical efficacy for a broad spectrum of invasive yeasts and moulds, are highly protein bound (97–99 %), are widely distributed (with the exception of the CSF and urine), and are well-tolerated. Despite these pharmacokinetic and pharmacodynamic similarities, age-specific metabolic differences influence dosing requirements for young children. The echinocandins are only available for parenteral administration, although they feature long half-lives and may be dosed once per day [221].

5.1 Pharmacokinetics and Pharmacodynamics

As large lipopeptides, the echinocandins exhibit poor oral bioavailability and must be administered parenterally [224]. The echinocandins exhibit linear pharmacokinetic profiles post-infusion and are slowly eliminated in the bile and faeces with varying degrees of degradation products found in the urine. Distribution occurs to most tissues with the exception of the CSF and the urine [224]. The activity of the echinocandins is attributed to concentration-dependent (e.g. AUC/MIC or C_{max}/MIC) rather than time-dependent killing against *Candida* species [221]. Despite glycan synthase expression in other clinical opportunistic yeasts and moulds, echinocandins are not active against Zygomycetes, *Fusarium* species or *Scedosporium* species. Additionally, they are inactive against *Trichosporon* species due to the production of 1,6-D-glucan linkages [221]. None of the echinocandins are robust substrates for the CYP family or P-gp system, nor do they require

dosing adjustments in the setting of renal insufficiency [187]. While the echinocandins share many similarities in their pharmacokinetic and pharmacodynamic profiles, differences do exist. Caspofungin is subject to hydrolysis or N-acetylation, whereas micafungin is metabolised by catechol-*O*-methyltransferase and anidulafungin is chemically degraded [11].

For caspofungin, true pharmacokinetic steady state is estimated to require 2–3 weeks of dosing, although the majority of accumulation will occur within the first few days of administration [27]. After initial administration, caspofungin distributes to the kidney, lung, spleen and liver, with 35 % of the total dose residing hepatically at 24 h post-infusion [227]. A weight-based dosing regimen of caspofungin in children 2–11 years and two adolescents was found to be inadequate, leading to a significantly lower AUC_{24} and half-life than in adults receiving 50 mg/day [27]. However, using a body surface area (mg/m^2) dosing regimen generated very similar AUC_{24} values when compared with adults after multiple doses (i.e. steady state). For both children and adolescents, dosing scaled to body surface area effectively controls for the variation in caspofungin clearance across the paediatric age range. However, it is not possible to achieve an identical AUC_{24}, peak and trough profile to that of adults as the half-life of caspofungin is 30–40 % shorter in children. This may be driven by higher intrinsic transporter expression, increased blood flow and/or relative liver size [28].

Similar to caspofungin, the pharmacokinetic profile of micafungin is influenced by age [31, 228]. Children ≤8 years of age exhibit higher micafungin clearance (up to 150 %), have an increased volume of distribution at steady state, and significantly shorter half-life than older children [28]. These findings were corroborated in a recent analysis of paediatric patients from a double-blind, randomised, multinational non-inferiority trial [228]. Micafungin and caspofungin exhibit similar C_{max} and half-life profiles in children.

Compared to the FDA-approved echinocandins, relatively little is known about anidulafungin. From the few studies of anidulafungin in children, there are some notable differences in comparison with caspofungin and micafungin. Anidulafungin has a lower capacity for protein binding, a larger volume of distribution and a longer half-life [229]. Additionally, a dose-escalation study in children (2–11 years of age) and adolescents (12–17 years of age) found that dosing by weight generated similar pharmacokinetic parameters to those in adults [229]. Additionally, anidulafungin rapidly reaches steady-state concentrations (after two doses) as compared with the other echinocandins [11].

The echinocandins exhibit a concentration-dependent post-antifungal effect, which appears to be inversely related to the duration of exposure [223]. This seems to be a corollary to the ‘paradoxical effect’ where *Candida* species survive and continue to grow when exposed to high echinocandin concentrations. However, this has been demonstrated in vitro and the clinical relevance is not yet known [230, 231].

5.2 Intra- and Inter-Individual Variability

For the two FDA-approved echinocandins, the main source of pharmacokinetic variability in children is their decreasing clearance with increasing age [221]. Additionally, the underlying

disease status of the patient and concomitant medications also contribute to inter- and intra-individual variability. Relatively small sample sizes in published paediatric studies make it difficult to assess differences in treatment outcomes by age, sex and race/ethnicity [232].

5.3 Dosing Optimisation

Current paediatric indications and dosing recommendations for the FDA-approved echinocandins are listed in Table 1. The echinocandins do not require dosing adjustments for patients with renal failure. However, in patients with severely compromised hepatic function a decrease in dosage is recommended for caspofungin and may be considered for micafungin [187, 221].

Micafungin has recently been approved for the treatment of candidaemia and antifungal prophylaxis in children ≥4 months of age [222]. For the treatment of oesophageal candidiasis among patients <30 kg, 3 mg/kg (2.5 mg/kg if < 30 kg) with a daily maximum of 150 mg is recommended. For other sites (not including the CNS) of infection, 2 mg/kg with a maximum daily dose of 100 mg is recommended. This latest recommendation parallels experience from previous studies that used weight-based dosing and similar amounts of micafungin [221, 233]. However, the recommended dose for non-oesophageal candidaemia (2 mg/kg) results in a 25 % lower C_{max} and 50 % lower AUC for children < 5 years of age [234]. However, Undre et al. [234] caution that no children failed therapy due to a lack of efficacy and their sample size prohibited their ability to establish definitive paediatric dosing recommendations. Additionally, the authors hypothesised that younger children are likely to have a higher free fraction of micafungin due to developmental changes in protein binding [235]. In an open-label study assessing micafungin safety and pharmacokinetics, micafungin was well-tolerated in infants with suspected invasive CNS candidiasis who received up to 10 mg/kg/day [236, 237]. This finding is in agreement with 2009 IDSA guidelines, which recommend paediatric micafungin doses of 2–4 mg/kg/day [187].

As with micafungin, early studies of caspofungin indicated that children and adolescents require higher doses than adults [27]. Dosing caspofungin based on body surface area rather than weight led to consistent achievement of plasma concentrations that correlated with efficacy in adults [187]. Unlike the other echinocandins, the pharmacokinetics of caspofungin necessitate a loading dose. FDA dosing recommendations for children ≥3 months are based on body surface area. The loading dose is 70 mg/m^2 on day 1 with a maintenance dose of 50 mg/m^2 up to a maximum of 70 mg/m^2 if required.

Anidulafungin is not approved for use in paediatric patients in the USA or Europe and limited data exist regarding its use in children. However, like micafungin and caspofungin, its safety and efficacy profiles appear promising [238, 239]. Dosing by weight has led to similar pharmacokinetic profiles as found in adults and, in contrast to the other echinocandins, anidulafungin clearance does not depend on age [223].

Small sample sizes among paediatric studies have made assignation of echinocandin-specific adverse drug reactions imprecise. Many of the reported side effects are consistent with adult data, including gastrointestinal disturbances (vomiting, diarrhoea, fever, nausea, abdominal pain) and transaminase elevation. Discontinuation due to these side effects is infrequent

(3.8 % in a substudy of micafungin use in paediatric patients < 16 years of age) relative to other classes of antifungals and infusion-related hypersensitivity reactions are rare [233].

5.4 Therapeutic Drug Monitoring

At present, therapeutic drug monitoring is not recommended for the echinocandins due to a lack of evidence that suggests that routine plasma concentration monitoring provides utility in clinical practice [202, 240]. Nonetheless, in a case of neonatal meningitis, therapeutic monitoring of caspofungin concentrations in the CSF was found to be useful in establishing caspofungin concentrations that were sufficient to sterilise the CSF [241]. Additionally, monitoring may be considered when cyclosporine is coadministered, which has been reported to increase caspofungin and anidulafungin plasma concentrations due to diminished hepatic uptake [242]. Conversely, cyclosporine concentrations may become elevated when administered with micafungin. A similar pattern has been reported for sirolimus and nifedipine, which also occurs as a consequence of mild CYP3A inhibition [243]. Tacrolimus concentrations may be decreased with the concurrent use of caspofungin; however, this has not been reported to cause toxicity [244]. Agents known to induce hepatic metabolism, such as rifampin (rifampicin), can lead to significant decreases in caspofungin plasma concentrations [242].

5.5 Drug Resistance

Echinocandin resistance is rare and has been reported in <1.2 % of *Candida* species isolated in a recent global surveillance study [245, 246]. However, evidence of clinically resistant *Candida* with MICs within the susceptible and intermediate breakpoints has prompted a reassessment of echinocandin susceptibilities [247]. Although multiple potential mechanisms of resistance have been demonstrated in vitro, clinically relevant echinocandin resistance for *Candida* species is driven primarily by 'hot spot' mutations in the β-1,3-D-glucan synthase (encoded by the *fks1/fks2* genes) target enzyme [248, 249]. The former breakpoint MIC of ≤2 deemed as 'susceptible' for all *Candida* species and the echinocandin class has been revised [247]. Currently, MICs >0.5 μg/mL are considered resistant for anidulafungin, caspofungin and micafungin against *C. albicans, C. tropicalis* and *C. krusei* and >0.4 μg/mL for *C. parapsilosis. C. glabrata* resistance may be on the rise and is defined at values >0.12 μg/mL for micafungin and > 0.25 μg/mL for anidulafungin and caspofungin. Clinical breakpoints have not been defined for *Aspergillus* species [245]. Cross-resistance with the polyenes or triazoles has not been reported. Rather, the echinocandins are considered first-line agents for the treatment of fluconazole-resistant strains of *Candida* [221]. Resistance to one echinocandin can generally be interpreted as resistance to the entire class [246, 247].

5.6 Clinical Recommendations and Prospects for Future Research

The use of echinocandins in paediatric patients has substantially increased over the last 5 years [220, 232]. The echinocandins offer comparable efficacy, an improved safety profile, and advantages in treating resistant fungal infections and refractory biofilms. However, the evolving story of drug-drug interactions and uncertainties regarding pharmacodynamic exposure-response relationships are two key areas where there are still many unanswered questions. A recent survey of prescribing practices among Japanese physicians in paediatric

patients with invasive fungal infections found that physicians were more likely to use antifungals based on perceptions of potency rather than on safety. Micafungin was the most frequently prescribed [250]. More research is needed to ensure that paediatric echinocandin dosing regimens are optimised for therapeutic effectiveness without compromising patient safety or tolerability.

6 Summary and Conclusions

The introduction of several new systemic antifungal agents in the last two decades has expanded our therapeutic arsenal for the treatment of invasive fungal infections. However, with these new agents comes a pressing need to understand their pharmacokinetic properties, clinical effects and associated toxicities.

The pharmacokinetic and pharmacodynamic characteristics of systemic antifungal agents have been well-studied in adults; however, paediatric-specific data are limited. Extensive in vitro and animal model studies have demonstrated strong relationships linking antifungal exposure to treatment efficacy. Our understanding of these principles is increasing and has highlighted the utility of therapeutic drug monitoring for flucytosine, itraconazole, voriconazole and posaconazole. However, further research is needed to define the pharmacokinetics, pharmacodynamics and clinical utility of combination antifungal therapies in children.

From all of the studies discussed in this review, it must be concluded that—in the absence of data—antifungal pharmacokinetics in children cannot be assumed to mirror adult pharmacokinetic parameters. However, antifungal pharmacodynamic targets are remarkably similar among all age groups, different drugs within the same class, and even across species. These pharmacodynamic targets provide clinicians the opportunity to predict treatment efficacy.

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Key Points

The development of dosing recommendations for children with invasive fungal infections is complicated by non-linear growth and the maturation of organ function.

Pharmacokinetic and pharmacodynamic relationships established in vitro and in murine models have been confirmed in paediatric clinical trials for several antifungal agents.

Therapeutic drug monitoring should be considered for antifungal agents that exhibit high inter-individual variability and a strong association between plasma concentrations and efficacy and/or toxicity (e.g. voriconazole).

Further research is need in the design and optimisation of combination antifungal regimens.

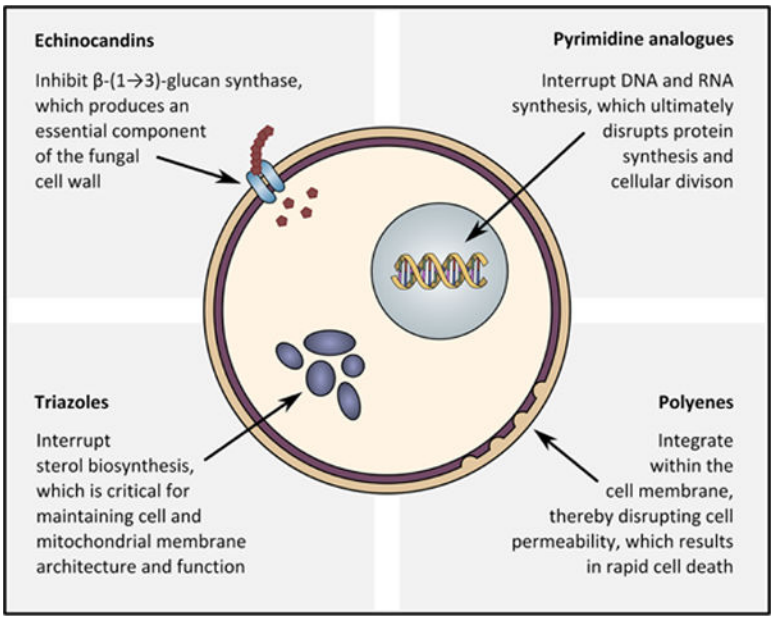

Fig. 1.

The four most common classes of systemic antifungal agents used in the treatment of invasive fungal infections and their mechanisms of action

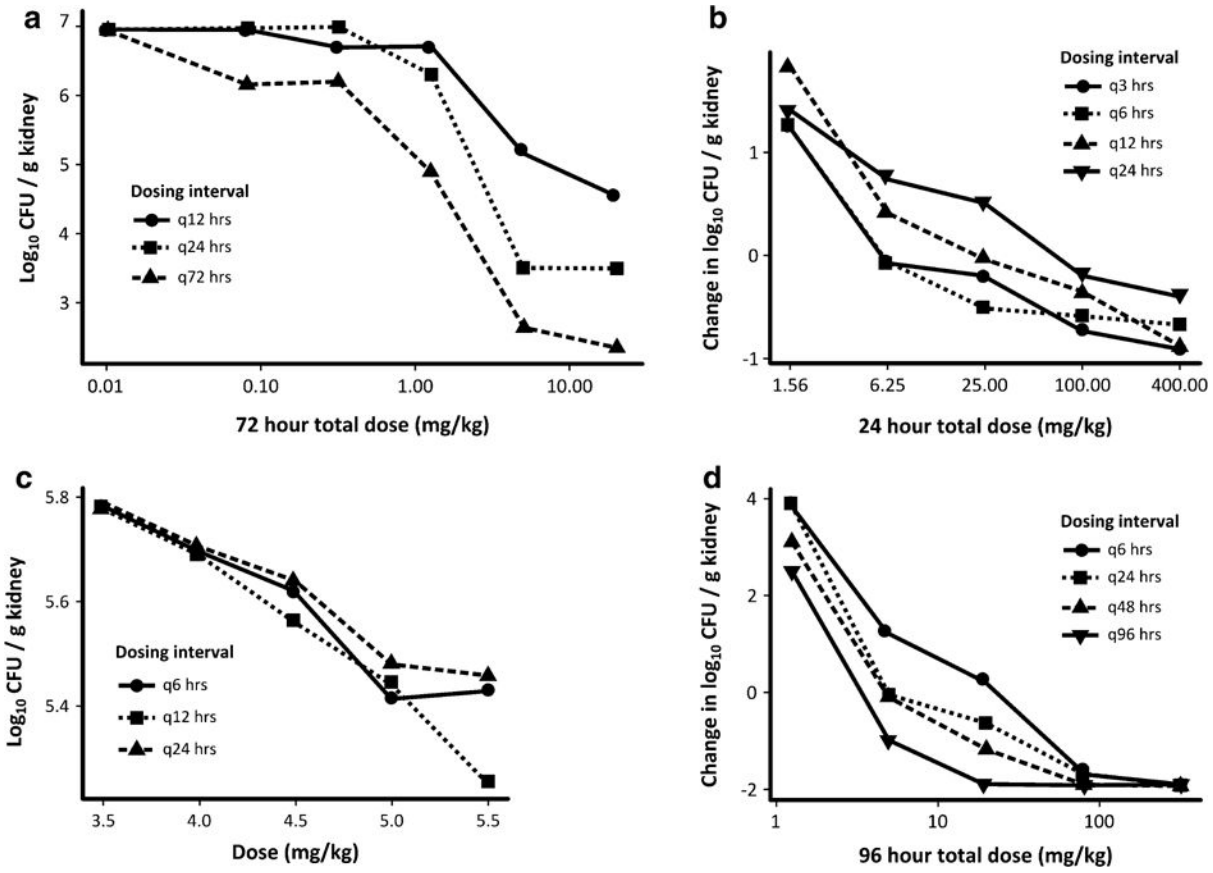

Fig. 2.

Antifungal pharmacodynamics in murine models of invasive candidiasis. **a** Amphotericin B dose fractionation studies for three dosing intervals and the $\log_{10}$ colony-forming units per gram of kidney in a neutropenic mouse model of disseminated candidiasis (data from Andes et al. [15]). **b** Flucytosine dose fractionation studies for four dosing intervals and the mean *Candida* density in the kidneys of neutropenic mice (data from Andes and van Ogtrop [12]). **c** Fluconazole dose fractionation studies for three dosing intervals and mean fungal density in the kidneys of mice with invasive candidiasis (data from Louie et al. [13]). **d** Anidulafungin dose fractionation studies for four dosing intervals and the mean change in *Candida* density in the kidneys of neutropenic mice with invasive candidiasis (data from Andes [24]). *CFU* colony-forming units, *qx hrs* every *x* hours

Table 1

US FDA-approved agents for the treatment of invasive fungal infections in children

Pharmacological agent	Approved indication	Approved dose
Azoles		
Fluconazole	Treatment of oropharyngeal and oesophageal candidiasis and cryptococcal meningitis	Initial: 6 mg/kg/dose od Maintenance: 3–12 mg/kg/dose od Maximum daily dose: 600 mg/day
Itraconazole	Treatment of blastomycosis (pulmonary and extrapulmonary), histoplasmosis (including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis) and aspergillosis (pulmonary and extrapulmonary) in patients who are intolerant of or who are refractory to amphotericin B therapy	3–5 mg/kg/dose od
Posaconazole	Treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole	400 mg bid
Voriconazole	Treatment of invasive aspergillosis; candidaemia in non-neutropenic patients; disseminated *Candida* infections in skin, the abdomen, kidney, bladder wall and wounds; oesophageal candidiasis; and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, in patients intolerant of or refractory to other therapies	9 mg/kg/dose bid Maximum single dose: 350 mg/dose
Echinocandins		
Caspofungin	Empirical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidaemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections; treatment of oesophageal candidiasis; and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies	Initial: 70 mg/m^2/dose od Maintenance: 50 mg/m^2/dose od Maximum daily dose: 70 mg/m^2/day
Micafungin	Treatment of patients with candidaemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; treatment of patients with oesophageal candidiasis	2 mg/kg od Maximum daily dose: 100 mg/day
Polyenes		
Amphotericin B deoxycholate	Treatment of potentially life-threatening invasive fungal infections: aspergillosis, cryptococcosis, North American blastomycosis, systemic candidiasis, coccidioido-mycosis, histoplasmosis, zygomycosis, including mucormycosis due to susceptible species of the genera *Absidia, Mucor* and *Rhizopus*, and infections due to related susceptible species of *Conidiobolus* and *Basidiobolus*, and sporotrichosis	Initial: 0.25–0.5 mg/kg/dose od Maintenance: 0.25–1 mg/kg/dose od Maximum daily dose: 1.5 mg/kg/day
Liposomal amphotericin B (AmBisome)	Empirical therapy for presumed fungal infection in febrile, neutropenic patients; treatment of cryptococcal meningitis in HIV-infected patients; treatment of patients with *Aspergillus, Candida* and/ or *Cryptococcus* infections refractory to amphotericin B deoxycholate, or in patients in whom renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate; and treatment of visceral leishmaniasis	3–5 mg/kg/dose od
Amphotericin B lipid complex (Abelcet®)	Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy	3–5 mg/kg/dose od
Amphotericin B colloidal dispersion (Amphotec®)	Treatment of invasive aspergillosis in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses, and in patients with invasive aspergillosis where prior amphotericin B deoxycholate therapy has failed	3–1 mg/kg/dose od
Pyrimidine analogues		
Flucytosine	Treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*	50–150 mg/kg qid

bid twice daily, *od* once daily, *qid* four times daily

Table 2

Structural and pharmacokinetic properties of amphotericin B formulations among adults with invasive fungal infections

Property	Amphotericin B deoxycholate	Lipidic formulations		
		Amphotericin B lipid complex	Amphotericin B colloidal dispersion	Liposomal amphotericin B
Formulation properties				
Size (nm)	0.035	1,600–11,000	120–140	80
Structure	Micelles	Ribbon-like	Disk-like	Liposomes
Plasma pharmacokinetic properties				
Dose (mg/kg)	1.0	5.0	5.0	5.0
Maximum plasma concentration (mg/L) [mean ± SD]	5.36 ± 0.82	1.58 ± 0.32	7.66 ± 4.51	46.7 ± 2.81
Minimum plasma concentration (mg/L) [mean ± SD]	0.34 ± 0.07	0.24 ± 0.08	0.37 ± 0.12	26.4 ± 4.99
Area under the concentration–time curve from time 0 to 24 h (mg·h/L) [mean ± SD]	17.4 ± 1.21	11.8 ± 3.09	20.4 ± 4.10	887 ± 59
Apparent volume of distribution at steady state (L/kg) [mean ± SD]	0.81 ± 0.10	6.35 ± 1.25	3.61 ± 0.64	0.10 ± 0.01
Total plasma clearance (L/kg/h) [mean ± SD]	0.041 ± 0.00	0.315 ± 0.11	0.187 ± 0.04	0.001 ± 0.00
Pulmonary pharmacokinetic properties				
Dose (mg/kg)	1.0	5.0	5.0	5.0
Concentration in lung tissue (μg/g) [mean ± SD]	2.71 ± 1.22	16.26 ± 1.62	6.29 ± 1.17	6.32 ± 0.57
Concentration in epithelial lining fluid (mg/L) [mean ± SD]	0.44 ± 0.13	0.90 ± 0.28	0.68 ± 0.27	2.28 ± 1.43
Concentration in pulmonary alveolar macrophages (mg/L) [mean ± SD]	8.92 ± 2.84	89.1 ± 37.0	5.43 ± 1.75	7.52 ± 2.50
Tissue penetration properties				
Plasma concentration (mg/L) [mean ± SD]	1.82 ± 0.07	0.93 ± 0.03	0.85 ± 0.01	62.90 ± 0.99
CSF concentration (mg/L) [mean ± SD]	0.023 ± 0	0.022 ± 0	0.014 ± 0.007	0.024 ± 0.001
Brain concentration (μg/g) [mean ± SD]	0.18 ± 0.03	0.27 ± 0.02	0.22 ± 0.02	1.99 ± 0.33

Data from Hiemenz and Walsh [251], Groll et al. [252, 253]

CSF cerebrospinal fluid

Table 3

Pharmacokinetic properties of fluconazole, itraconazole, voriconazole and posaconazole in adults

Property	Fluconazole	Itraconazole[a]	Voriconazole	Posaconazole
Dose	6–12 mg/kg/day	200 mg bid	6 mg/kg q12 h for 2 doses, then 4 mg/kg q12 h	600–800 mg/day in divided doses
Formulation properties				
Route of administration	IV infusion, PO capsules, PO solution	IV infusion, PO capsules, PO solution	IV infusion, PO capsules, PO suspension	PO suspension
Oral bioavailability (%)	>80	50	90	
Protein binding (%)	11–13	>99	58	98–99
Pharmacokinetic properties				
Maximum concentration (μg/L)	6–20	0.5–2.3	3.0–4.6	1.5–2.2
Area under the concentration– time curve (mg·h/L)	400–800	29.2	20.3	8.9
Terminal elimination half-life (h)	22–35	24–42	6	25
Unchanged drug in urine (%)	80	1–10	<2	<2
Primary route of metabolism	Hepatic (minor)	Hepatic	Hepatic	Hepatic (moderate)
Primary route of elimination	Renal	Hepatic	Renal	Faeces
Bodily fluid penetration properties				
CSF penetration (%)	80	<10	60	–
Vitreous penetration (%)	28	10	38	26

Data from Lewis [117] and Lipp [158]

bid twice daily, *CSF* cerebrospinal fluid, *IV* intravenous, *PO* oral, *q12 h* every 12 h

[a] Data are for the oral solution formulation of itraconazole

Table 4

Fluconazole, itraconazole, voriconazole and posaconazole drug–drug interactions

Property	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Decreased absorption of azoles				
Antacids		X		
Didanosine, oral	X	X	X	X
Histamine H_2 receptor antagonists		X		
Omeprazole	X	X	X	X
Sucralfate		X	X	X
Increased metabolism of azoles				
Carbamazepine	X	X	X	X
Isoniazid		X	X	
Phenobarbital	X	X	X	
Phenytoin	X	X	X	X
Rifampin (rifampicin)	X	X	X	X
Increased plasma concentration of coadministered drug				
Ado-trastuzumab emtansine		X	X	X
Alfuzosin		X	X	X
Aliskiren		X		
Alprazolam		X		
Apixaban		X	X	X
Astemizole			X	
Atazanavir			X	
Atorvastatin				X
Avanafil		X	X	X
Axitinib		X	X	X
Barbiturates			X	
Bosutinib	X	X	X	X
Cabozantinib		X	X	X
Cisapride	X	X	X	X
Citalopram	X			
Conivaptan	X	X	X	X
Crizotinib		X	X	X
Darunavir			X	
Dihydroergotamine		X	X	X
Dofetilide	X	X	X	X
Dronedarone		X	X	X
Efavirenz				X
Eletriptan			X	X
Eplerenone		X	X	X
Ergoloid mesylates		X	X	X
Ergonovine		X	X	X

Property	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Ergotamine		X	X	X
Everolimus		X	X	X
Halofantrine		X	X	X
Imatinib		X	X	X
Ivabradine	X	X	X	X
Lapatinib		X	X	X
Lomitapide	X	X	X	X
Lopinavir			X	
Lovastatin		X	X	X
Lurasidone			X	X
Macitentan		X	X	X
Methadone		X		X
Methylergonovine		X	X	X
Midazolam		X		
Mifepristone	X		X	
Nevirapine		X		
Nilotinib		X	X	X
Nisoldipine		X	X	X
Ospemifene	X			
Pimozide	X	X	X	X
Pomalidomide		X	X	X
Proton pump inhibitors				X
Quinidine	X	X	X	X
Ranolazine	X	X	X	X
Regorafenib		X	X	X
Rifamycin derivatives			X	
Ritonavir			X	
Rivaroxaban		X	X	X
Salmeterol		X	X	X
Silodosin		X	X	X
Simvastatin		X	X	X
Sirolimus			X	X
St John’s wort			X	
Tamsulosin		X	X	X
Terfenadine			X	
Ticagrelor		X	X	X
Tolvaptan	X	X	X	X
Topotecan		X		
Toremifene		X	X	X
Triazolam		X		
Ulipristal	X	X	X	X
Vemurafenib		X	X	X

Property	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Vincristine, liposomal		X	X	X

Data from Hoesley and Dismumkes [254], Dismukes [255], Katz [256] and the Lexi-Comp *Drug Interactions Handbook and Drug Interactions Software* [257]