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New and emerging options for management of invasive fungal diseases in paediatric patients

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Abstract

Invasive fungal diseases (IFDs) play an important role in the supportive care of paediatric patients with acute leukaemia and those undergoing allogeneic haematopoietic cell transplantation, and they are associated with significantly decreased overall survival rates in affected individuals. Relative to adults, children and adolescents are distinct in terms of host biology, predisposing conditions, presentation and epidemiology of fungal diseases, and in the pharmacology of antifungal agents. The paediatric development of antifungal agents has moved forward in a coordinated manner, and major advances have been made regarding concepts and recommendations for the prevention and treatment of IFDs. However, antifungal therapy is increasingly complex, and a solid knowledge of the available options is needed more than ever for successful management. This narrative review provides a summary of the paediatric development of agents that have been recently approved (anidulafungin, posaconazole) or are in advanced stages of development (isavuconazole). It also reviews the emerging evidence for the efficacy of echinocandins for prophylaxis of invasive aspergillosis, presents new data on alternative dosing regimens of echinocandins and voriconazole, and provides a brief overview of new antifungal agents in clinical development that are expected to be developed for paediatric patients.

KEYWORDS
antifungal agents, children, mycoses, prevention, treatment

1 | INTRODUCTION

Invasive fungal diseases (IFDs) are important causes of morbidity and mortality in children and adolescents with acute leukaemia or undergoing allogeneic haematopoietic cell transplantation. Estimated natural incidence rates in these populations range from 10% to 25%[1] and recent outcome analyses covering the span of the past 20 years have shown that the diagnosis of probable or proven IFDs is linked to a significantly decreased event-free and overall survival.[2,3] Despite the still unsatisfactory outcome of IFDs, considerable advances have been made in the diagnosis of IFDs, the development of robust in vitro susceptibility testing, the concepts of antifungal interventions, and the design and *conduct* of clinical trials.[1,4,5] In addition, the advent of new antifungal classes and new antifungal agents in the early 2000s has increased our options for prophylaxis and treatment of these infections and has made antifungal therapy safer, and more effective, but also more complex.[6–8] In this narrative review, we provide an update on current developments and trends in the medical management of IFDs in children and adolescents with acute leukaemia or allogeneic

haematopoietic cell transplantation. We review the clinical trials that resulted in the paediatric approval of anidulafungin and posaconazole and their approved indications, provide an update on the paediatric development of isavuconazole, discuss new data on caspofungin and voriconazole and present novel antifungal agents that are expected to be developed for paediatric patients.

2 | ANTIFUNGAL AGENTS RECENTLY APPROVED IN PAEDIATRIC PATIENTS

2.1 | Anidulafungin

The echinocandins are a class of intravenous lipopeptides that inhibit the synthesis of 1,3-*beta*-D-glucan, an important component of the cell wall of many pathogenic fungi that does not exist in mammalian cells. They are active in vitro and effective in vivo against *Candida*- and *Aspergillus* spp., and have a favourable safety profile and favourable pharmacokinetics. For management of invasive fungal diseases, three agents are currently available: Anidulafungin, caspofungin and micafungin. These agents are pharmacologically not principally different and are currently the recommended first-line options for invasive candidiasis.[6–8] Whereas caspofungin and micafungin are licensed in paediatric patients of all age groups for some years now, the paediatric development of anidulafungin has been completed just recently.[9]

In the United States and the European Union, anidulafungin is approved for primary therapy of candidemia and other forms of invasive *Candida* infections and oesophageal candidiasis in patients ≥18 years of age since 2006. Licensing for paediatric patients ≥1 year of age occurred in 2020 (Table 1).[10,11] Anidulafungin has linear pharmacokinetics, low intersubject variability, a long half-life permitting once-daily dosing and is eliminated by chemical degradation. The compound does not interact with CYP450 isoenzymes, and no dose adjustments are required for renal or hepatic insufficiency. Anidulafungin is well tolerated, and there have been no safety concerns in paediatric patients except for the IV carrier polysorbate 80 in neonates.[6–9]

Early studies in paediatric patients have demonstrated that following weight-based dosing, pharmacokinetic parameters are similar across age—and dosage cohorts and overall similar to those of adults: In phase I/II study of the pharmacokinetics and safety of anidulafungin in 19 granulocytopenic children with cancer, two age cohorts (2–11 and 12–17 years) and two sequential dosing regimens (0.75 or 1.5 mg/kg/day) were studied.[12] No serious drug-related adverse events were noted. Pharmacokinetic parameters of distribution and elimination were independent of age and dosage and similar relative to those in adults. Following single and repeat daily doses of 0.75 and 1.5 mg/kg, concentration data in plasma corresponded to those in adults given a daily 50 and 100 mg dose, respectively. In a second study, intravenous anidulafungin (1.5 mg/kg/day) was investigated in 15 infants and neonates at risk for invasive candidiasis over up to 5 days. Drug exposures were similar between neonates and infants; no drug-related serious adverse events were observed. Following a dose of 1.5 mg/kg and day, neonates and infants showed similar exposure

TABLE 1 Formulations and dosages of anidulafungin, posaconazole and isavuconazole in paediatric patients.

Antifungal agent (brand name)	Formulation	Adult dose	Paediatric dosage
Anidulafungin (U.S.: Eraxis®; E.U.: Ecalta®)	*Anidulafungin*		*≥1 months of age*
	Intravenous solution	100 mg once daily (day 1: 200 mg)	1.5 mg/kg (not to exceed 100 mg) of anidulafungin once daily (day 1: 3.0 mg/kg; not to exceed 200 mg)
Posaconazole (Noxafil®)	*Posaconazole*		*≥2 years of age*
	Intravenous solution	300 mg once daily (day 1: twice daily)	6 mg/kg once daily (max. 300 mg; day 1: twice daily)
	Delayed-release tablets	300 mg once daily (day 1: twice daily)	>40 kg: 300 mg once daily (day 1: twice daily)
	Oral suspension	200 mg three times daily (≥13 years [FDA])	Not approved (EMA)
	Powder for delayed release oral suspension	Not approved	≤40 kg: weight-based once-daily dosing (day 1: twice daily). For details, see SPC
Investigational			
Isavuconazole (Cresemba®)	*Isavuconazonium sulfate*		*≥1 year of age*
	Oral capsules Intravenous solution	372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily (days 1 and 2: three times daily)	10 mg/kg of isavuconazonium sulfate once daily (days 1 and 2: three times daily)

as children receiving the identical weight-based dosing and in adult patients receiving 100 mg/day.[13] In a later population pharmacokinetic study of these and two further studies across the full range of adult and paediatric ages, relationships between anidulafungin exposure and key efficacy and safety endpoints were evaluated. Estimated anidulafungin exposures again were similar across age groups (neonates to adults) at the weight-based doses studied in paediatric patients, and no associations were noted between exposure and efficacy or safety endpoints.[14]

The safety and efficacy of anidulafungin were ultimately studied in an international phase II prospective cohort study (NCT00761267) of first-line therapy of invasive candidiasis (ICC) including candidemia in 49 children and adolescents 2 to <18 years old. Anidulafungin was administered for 10–35 days at 1.5 mg/kg with a loading dose of 3 mg/kg on day 1. Efficacy, assessed by global (clinical and microbiologic) response, was evaluated at the end of intravenous treatment (EOIVT), the end of all treatment, at the 2 and 6 weeks follow-up and safety was assessed through week 6 follow-up. In all patients, at least one treatment-emergent adverse event was recorded, with diarrhoea (22.4%), vomiting (24.5%) and pyrexia (18.4%) as the most frequent entities. Five patients discontinued treatment due to adverse events, of which four were considered study drug-related (8.2%). All-cause mortality was 8.2% (4/49) by EOIVT and 14.3% (7/49) by week 6 follow-up. None of the seven deaths during the study period was considered treatment-related. The global response success rate was 70.8% at EOIVT.[15] Of note, in a further 19 patients 1 month to <2 years of age with invasive candidiasis ($n = 16$) or considered at high risk of ($n = 3$) invasive candidiasis, most treatment-emergent adverse events were mild to moderate and no treatment-related deaths occurred. The global response rate at the end of intravenous treatment was 68.8%, and separately assessed pharmacokinetics were congruent with those in adult patients.[16]

On the grounds of these data, anidulafungin has been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of invasive candidiasis in paediatric patients aged 1 month to <18 years (Table 1). A waiver has been given to study neonates because of the need for two to three times increased dosages to cover hematogenous *Candida* meningoencephalitis (HCME) and the potential toxicity of the polysorbate 80 solvent at these dosages in the neonates.[10,11] Given the documented efficacy and safety in paediatric patients, the superior clinical and microbiological outcomes of anidulafungin in the randomised, double-blind phase III registration trial in adults that compared anidulafungin 100 mg once daily with fluconazole 400 mg once daily in a total of 245 mostly nonneutropenic patients with invasive candidiasis[17]; additional data from a patient-level pooled analysis of six clinical trials including 536 patients with candidemia and invasive candidiasis who received anidulafungin[18]; and the absence of safety signals in the paediatric trials, anidulafungin is a new and important option for echinocandin-based treatment of candidemia and other forms of invasive candidiasis in paediatric patients ≥1 month of age.

2.2 | Posaconazole

The triazoles have become essential to our antifungal arsenal. Despite their potential for drug–drug interactions, agents of this class are overall well-tolerated, possess—with the exception of fluconazole—a broad spectrum of antifungal activity and have clinical efficacy in a broad range of indications which depend on the fungal isolate, the clinical situation, and the detailed approval status of the individual agent. They act through inhibition of the CYP-450-dependent conversion of lanosterol to ergosterol, which leads to a depletion of ergosterol, formation of toxic sterols and inhibition of cell growth and replication. Whereas fluconazole, itraconazole and voriconazole are approved in paediatric patients for many years, posaconazole has been approved only recently and the paediatric development of isavuconazole is currently in its final stages (Table 1).[6–9]

Posaconazole has potent and broad-spectrum in vitro activity against a wide array of medically relevant yeast and moulds, including many of the so-called rare fungal pathogens. The available formulations include an intravenous (IV) solution in cyclodextrin and three different oral formulations (oral suspension; gastro-resistant/delayed-release tablets; and the novel gastro-resistant/delayed-release powder for oral suspension). Independent of the formulation, posaconazole has a large volume of distribution and an elimination half-life of close to 20 h. It does not undergo metabolisation by the CYP P450 enzyme system but is excreted primarily in unchanged form in the faeces. It is an inhibitor of CYP3A4, but has no effects on other CYP450 enzymes, resulting in a limited spectrum of drug–drug interactions. Posaconazole is generally well tolerated; the most frequently reported adverse events include gastrointestinal disturbances, headaches and abnormal liver function tests. Current evidence indicates no need for altered dosages based on differences in age, gender, race, renal or hepatic function.[6–9,19] Based on two pivotal phase III clinical trials in adult patients that demonstrated preventative efficacy of the oral suspension in particular against invasive aspergillosis and a significant survival advantage in one of the two studies,[20,21] posaconazole is approved since 2006 for antifungal prophylaxis in high-risk adult patients with acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) and allogeneic haematopoietic cell transplantation (HCT) and graft-versus-host diseases (GVHD). In 2021, posaconazole has also been approved in adults for first-line treatment of invasive aspergillosis. In a randomised, controlled phase III, non-inferiority clinical trial comparing posaconazole with voriconazole in the primary treatment of invasive aspergillosis, posaconazole was similar to voriconazole in all-cause mortality at 6 weeks after diagnosis in patients with proven or probable invasive aspergillosis. Posaconazole was well-tolerated and associated with fewer treatment-related adverse events.[22]

The paediatric development of posaconazole was initiated first in 2007 with a multicenter sequential dose-escalation trial of the oral suspension. Patients were enrolled into three age groups and three dosage cohorts and received 7–28 days of posaconazole oral

suspension and pharmacokinetic sampling at fixed time points. The dosing target was set as ~90% of subjects with C_{avg} (AUC/dosing interval) between 500 and 2500 ng/mL, with an anticipated mean steady state plasma concentration (C_{avg}) of ~1200 ng/mL. While no safety signals were observed up to 18 mg/kg/day divided thrice daily, the proportion of subjects reaching the dosing target was <90% across all age- and dosage cohorts (range: 31%–80%). High variability in exposure was noted in all groups, and the study and the development of oral suspension in paediatric patients were discontinued after 8 years in 2015. The observed absence of a dose-exposure relationship and the high variability in exposure were likely due to absorption issues.[23] In addition to this formal dose-finding trial conducted by the manufacturer of posaconazole, a larger number of cohort studies from around the world have reported similar observations and lend support to the recommendation to preferentially not use the oral suspension for dosing in children.[23,24]

Following approval of the intravenous solution and the gastro-resistant/delayed-release tablets with improved oral bioavailability in adults, a novel gastro-resistant/delayed-release powder for oral suspension (PFS) was developed and then investigated together with the intravenous solution in a phase 1b, sequential dose-escalation trial in children aged 2–17 years with documented or expected neutropenia.[25] Study participants received posaconazole intravenously at 3.5, 4.5 or 6.0 mg/kg/day for at least 10 days with the option to de-escalate to posaconazole PFS at the same dose for ≤18 days. In this study, the target exposure of ~90% of participants with a $C_{avg} \geq 500$ ng/mL and an average C_{avg} of ~1200 ng/mL was met following oral and intravenous doses of 4.5 and 6.0 mg/kg/day. PFS yielded lower posaconazole exposures than intravenous posaconazole across age groups at all doses. Both formulations were well-tolerated and had similar safety profiles as reported for adults: Among 115 evaluable patients, four (3.5%) discontinued the study drug due to drug-related adverse events, and there was no apparent correlation between drug-related adverse events and exposure.[25]

On grounds of this pivotal dose-finding trial, posaconazole was approved for paediatric patients 2 years and older for prophylaxis of invasive fungal diseases in high-risk patient populations (haematopoietic stem cell transplant [HSCT] recipients with graft-versus-host disease [GVHD]) or those with hematologic malignancies with prolonged neutropenia from chemotherapy by the FDA; and high-risk patients with acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) and those with allogeneic haematopoietic cell transplantation (HCT) and graft-versus-host diseases (GVHD) by the EMA (Table 1).[26,27]

Of note, approval for treatment of invasive aspergillosis has been postponed by both agencies until completion of a phase II clinical trial in paediatric patients >2 years of age. A phase I/II clinical trial of the pharmacokinetics and safety of the intravenous solution and the PFS in neonates, infants and young children <2 years with proven/probable invasive fungal diseases is part of the Paediatric Investigation Plan so that, pending completion, approval of the compound in these population can also be expected.

3 | ANTIFUNGAL AGENTS IN ADVANCED STAGES OF PAEDIATRIC DEVELOPMENT

3.1 | Isavuconazole

Isavuconazole is a newer intravenous and oral antifungal triazole that is administered as the water-soluble prodrug isavuconazonium sulfate. On the grounds of two pivotal clinical trials,[28,29] it is approved in adults for first-line treatment of invasive aspergillosis and for treatment of mucormycosis. Isavuconazole has broad-spectrum antifungal activity including yeast and moulds, linear pharmacokinetics, a long elimination half-life and high oral bioavailability. Its potential for CYP450-dependent drug–drug interactions and its safety profile is overall similar to other triazoles with some advantages in direct comparisons to voriconazole.[6–9]

The initial dose finding in paediatric patients was explored through a population pharmacokinetic model developed in adults, allometric scaling and Monte-Carlo simulations. Using this approach, a dose of 10 mg/kg isavuconazonium sulfate (max. 372 mg), administered intravenously every 8 h for the first 2 days and every 24 h thereafter was predicted to yield potentially safe and effective exposures in paediatric patients 2–17 years of age.[30] The pharmacokinetics, safety and tolerability of this dose were then studied in a phase 1 clinical trial in 46 immunocompromised children and adolescents, stratified by age (1 to <6, 6 to <12 and 12 to <18 years) following either intravenous or oral dosing. Using a population pharmacokinetic model incorporating the paediatric data plus intravenous dosing data from a phase 1 study in adults and stepwise covariate modelling, age, sex, race and body mass index had no significant impact on any of the pharmacokinetic parameters. Prediction of the area under the concentration-time curve at steady state by Monte Carlo simulations and assessment of target attainment revealed plasma drug exposures within the target range observed in adults for >80% and >76% of simulated paediatric patients following intravenous and oral administration, respectively. At the studied dosage of 10 mg/kg, isavuconazonium sulfate was well-tolerated with five adverse events (10.9%) leading to study drug discontinuation.[30]

A non-comparative, phase 2 multicenter study to evaluate the safety and tolerability, efficacy and pharmacokinetics of isavuconazonium sulfate for the treatment of invasive aspergillosis or invasive mucormycosis in children and adolescents 1 to <18 years of age (9766-CL-0107) has been completed as part of the commitments of the paediatric investigation plan of isavuconazole. Results from this study may be expected to be presented this year along with the submission of the paediatric data to the regulatory authorities. Favourable assessments and recommendations provided, isavuconazole may soon become available for paediatric patients in the indications approved in adults (Table 1).[9] Of note, development in neonates and infants less than 1 year of age has been waived on the grounds that isavuconazole does not represent a relevant therapeutic advantage over existing treatment options in this population.

4 | EMERGING EVIDENCE FOR EFFICACY OF ECHINOCANDINS IN PREVENTING INVASIVE ASPERGILLOSIS

Based on epidemiological data, current paediatric-specific international guidelines recommend antifungal prophylaxis against *Candida*- and *Aspergillus* spp. in patients with acute and recurrent leukaemia and following allogeneic cell transplantation. Recommendations are founded on the existence of pharmacokinetically defined, safe and approved paediatric doses and the extrapolation of efficacy from large randomised adult clinical trials. Since evidence from appropriately designed, randomised phase III clinical trials for prophylactic efficacy against yeast and mould organisms has been restricted to posaconazole, voriconazole and itraconazole, the current recommendations are essentially azole-based with the use of amphotericin B or echinocandins as secondary alternatives.[1,31,32]

The second-line use of echinocandins has been challenged by a recently published clinical trial that, for the first time, demonstrated the preventative efficacy of an echinocandin against invasive aspergillosis in a population at high risk to develop invasive fungal diseases (Table 2).[33] In a multicenter, open-label trial, patients between 3 months and 30 years with newly diagnosed or relapsed acute myeloid leukaemia were enrolled from April 2011 to November 2016. Patients were randomised during the first chemotherapy cycle to receive prophylaxis with either caspofungin ($n=257$) or fluconazole ($n=260$) during granulocytopenia following each chemotherapy cycle. The primary endpoint was a diagnosis of proven or probable invasive fungal disease; secondary endpoints included the occurrence of invasive aspergillosis, use of empirical antifungal therapy and overall survival. Because a scheduled interim analysis of efficacy and an unscheduled futility analysis based on 394 enrolled patients suggested futility, patient enrolment was stopped and the study closed. Five hundred and eight of the 517 participants (median age, 9 years [range, 0–26 years]; 44% female) who were randomised until study closure completed the trial. A total of 23 proven or probable invasive fungal diseases were diagnosed after a blinded central review, six in the caspofungin and 17 in the fluconazole arm, including14 moulds, seven yeasts and two not further categorised fungi. The cumulative incidence of proven or probable invasive fungal disease at 5 months was 3.1% in the caspofungin and 7.2% in the fluconazole arm ($p=.03$ by log-rank test). The cumulative incidence of proven or probable invasive aspergillosis was 0.5% with caspofungin versus 3.1% with fluconazole ($p=.046$). There were no significant differences in the use of empirical antifungal therapy (71.9% vs. 69.5%, $p=.78$) or two-year overall survival (68.8% vs. 70.8%, $p=.66$).[33] With the potential limitation of early termination upon the suggestion of futility, the results of this study suggest that, beyond prevention of invasive candidiasis, caspofungin may also be an option for prophylaxis in patients at high risk for invasive aspergillosis.

In a second multicentre, randomised, open-label trial conducted by the same consortium of investigators, 560 children and adolescents (3 months to <21 years) undergoing allogeneic HCT were planned to be enrolled between April 2013 and September 2016 (Table 2).[34] Patients were randomised to caspofungin or a centre-specific comparator (fluconazole or voriconazole), to be administered as prophylaxis from day 0 of transplantation to day 42 or hospital discharge. The primary endpoint of the study was the diagnosis of proven or probable invasive fungal diseases at day 42 following a blinded central review. Similar to the other study, enrolment in this trial was also terminated early following a scheduled

TABLE 2 Summary of clinical trials investigating the efficacy of caspofungin for antifungal prophylaxis in paediatric patients at high risk.

First author and year of publication	Study characteristics	Most relevant observations
Fisher et al. (2019)[33]	Multicenter, randomised, open-label trial investigating prophylaxis with caspofungin ($n=257$) or fluconazole ($n=260$) in patients 3 months to 30 years with acute myeloid leukaemia. Participants were randomised between April 2011 and November 2016 during the first chemotherapy cycle. Prophylaxis was administered during the following each chemotherapy cycle during neutropenia The primary outcome was proven or probable IFD as adjudicated by a blinded central review	517 patients were randomised (median age, 9 years [range, 0–26 years]; 44% female), and 508 completed the trial. The 5-month cumulative incidence of proven or probable IFD was 3.1% in the caspofungin group vs. 7.2% in the fluconazole group (overall $p=.03$ by log-rank test) and was 0.5% vs. 3.1% for proven or probable invasive aspergillosis, respectively (overall $p=.046$). There were no differences in empirical antifungal therapy and 2-year (overall survival). No safety signals were observed
Dvorak et al. (2021)[34]	Multicenter, randomised, open-label trial planned to enrol 560 children and adolescents 3 months to <21 years undergoing allogeneic HCT between April 2013 and September 2016. Eligible patients were randomised to prophylaxis with caspofungin or a centre-specific comparator (fluconazole or voriconazole). Prophylaxis was administered from day 0 of HCT to day 42 or discharge The primary outcome was proven or probable IFD at day 42 as adjudicated by blinded central review	The study was closed early as a planned futility analysis showed a low rate of IFD in the comparator triazole arm. 290 eligible patients (median 9.5, range 0.3–20.7 years) were randomised to caspofungin ($n=144$) or a triazole ($n=146$; fluconazole, $n=100$; voriconazole, $n=46$). The day 42 cumulative incidence of proven or probable IFD was 1.4% in the caspofungin group vs. 1.4% in the triazole group ($p=.99$, log-rank test). There was no significant difference in proven or probable IFD at day 42

Abbreviations: HCT, haematopoietic cell transplantation; IFD, invasive fungal disease.

futility analysis that showed a low rate of invasive fungal diseases in the comparator arm. Altogether 290 patients (median age 9.5, range 0.3–20.7 years) were randomised to caspofungin ($n=144$) or, center-specific, either fluconazole ($n=100$) or voriconazole ($n=46$). The cumulative incidence of proven or probable invasive fungal diseases at day 42 was 1.4% in the caspofungin versus 1.4% in the triazole study arm ($p=.99$). No difference was noted between caspofungin versus fluconazole (1.0%, $p=.78$) or caspofungin versus voriconazole (2.3%, $p=.69$).[34] With a rate of invasive fungal diseases of 1.4%, caspofungin was similar to voriconazole in preventing invasive fungal diseases and invasive aspergillosis, although later periods of risk (i.e. the time until immune recovery) were not considered in this trial due the need for daily intravenous administration of caspofungin. Of note, the prophylactic potential of echinocandins against invasive *Aspergillus* infections may be further supported by a large randomised study of micafungin versus fluconazole in patients in mostly autologous HCT patients that had shown a significant benefit against invasive *Candida* infections, but also a trend toward preventing invasive *Aspergillus* infections.[35]

5 | NEW DATA ON ALTERNATIVE DOSING REGIMENS

5.1 | Extended dosing regimens of echinocandins

Current echinocandins require intravenous dosing on a daily basis, which limits their usefulness in the outpatient setting. While not approved, extended dosing regimens of antifungal prophylaxis with these compounds are a reasonable option, as the echinocandins have suitable pharmacological properties, including dose-proportional, linear pharmacokinetics, exposure-dependent pharmacokinetic/pharmacodynamic relationships, a prolonged elimination half-life and a wide therapeutic window. Indeed, a number of small non-comparative cohort studies of the pharmacokinetics, safety and explorative efficacy of extended dosing of echinocandins exist and have provided evidence for the principal feasibility of this approach (Table 3).[36]

In a prospective observational cohort study, the pharmacokinetics of micafungin at a dose of 9 mg/kg (maximum: 300 mg) twice a week were studied in 61 paediatric patients 1–17 years of age undergoing induction chemotherapy for acute lymphoblastic leukaemia (Table 3).[37] For analysis, nonlinear mixed-effects modelling was used and existing adult data were used to supplant the paediatric data. Monte Carlo simulations were done with dosing regimens of 5, 7 and 9 mg/kg administered twice weekly as well as a fixed dosing per body weight band. Time-normalised simulated exposures were compared with those after dosing with the 100 mg regimen in adults. A two-compartment model best fits the data. In comparison to adults, clearance and central volume of distribution were lower ($p<.01$) in paediatric patients. Predicted exposures as measured by the area under the concentration versus time curve (from 0 to 168 h) for the 5, 7 and 9 mg/kg twice weekly and fixed dosing per weight band regimens were higher than the adult reference exposure. The authors concluded that these findings provide evidence for the pharmacokinetic equivalence of twice weekly and once daily regimens and that the higher micafungin exposures may be caused by a slower-than-anticipated plasma clearance in the complex situation of paediatric leukaemia patients undergoing induction chemotherapy. The clinical experience with the 9 mg/kg twice a week has been reported in the form of an abstract (Table 3).[38] One hundred sixty-nine children with acute lymphoblastic leukaemia received micafungin as prophylaxis during the first 5 weeks of induction chemotherapy, where azoles are contraindicated due to the use of vincristine. A historical cohort of patients ($n=643$), which did not receive antifungal prophylaxis during the induction course, served as control. The primary endpoints of the study were the percentage of proven and probable *Aspergillus* infections and their cumulative incidence during the induction and first consolidation course through week 11 of antileukemic chemotherapy. In contrast to 36 of the 643 historical control patients (5.6%), only two of the 169 patients (1.2%) receiving twice weekly micafungin developed proven of probable invasive aspergillosis ($p=.013$ by Fisher's exact test and $p=.014$ Grey's test, respectively). While this study suggests the preventative efficacy of micafungin in a high-risk setting, the interpretation is limited by the historical control arm and even more so, the absence of information on the occurrence of non-*Aspergillus* invasive fungal diseases during the study.

Extended dosing regimens were also explored for caspofungin (Table 3). For this purpose, raw data from children aged 3 months to 17 years enrolled in registration trials of the manufacturer and provided by the manufacturer were used to develop a structured population pharmacokinetic model. With the final model, Monte Carlo simulations were done to explore the dose that would be needed for adequate drug exposure in a twice-weekly setting. Mean weekly $AUC_{0-24h/MIC}$ values and reported AUC_{0-24h} values from published paediatric and adult trials with caspofungin were used to assess adequate exposure. A two-compartment pharmacokinetic model with linear elimination and allometric scaling using fixed exponents was found to best describe the data. Monte Carlo simulations revealed that a 200 mg/m^2 twice-weekly extended dosing regimen, with a maximum total dose of 200 mg should result in average weekly exposures that match those obtained following the approved once-daily dosing. While no accepted PK/PD targets for invasive aspergillosis exist, the proposed regimen also would cover the PK/PD targets proposed for the treatment of invasive *candidiasis*.[39]

Taken together, these studies provide a sound pharmacokinetic and pharmacodynamics rationale for extended dosing regimens of caspofungin and micafungin and their further study in preferentially large and controlled clinical trials.

5.2 | Three times daily dosing of voriconazole

Voriconazole is an oral and intravenous broad-spectrum triazole with important antifungal indications. It is approved in the United States

TABLE 3 Summary of studies investigating alternative dosing regimens for micafungin, caspofungin and voriconazole in paediatric patients.

First author and year of publication	Study characteristics	Most relevant observations
Bury et al. (2022)[37]	Phase II study of the pharmacokinetics and safety of twice-a-week micafungin at a dose of 9 mg/kg (maximum 300 mg) during ALL induction therapy. Nonlinear mixed-effects modelling was used for analysis with model building supported by existing adult data. Monte Carlo simulations were performed with twice-a-week dosing regimens of 5, 7 and 9 mg/kg and flat dosing per weight band. Simulated exposures were compared with the exposure in adults after a once-daily 100 mg regimen	Sixty-one paediatric patients were included (median 4.0, range 1.0–17 years; and median 19.5, range 8.60–182 kg), respectively. A two-compartment model best fitted the data. Clearance and central Volume of Distribution were lower ($p < .01$) in paediatric patients compared to adults. Predicted plasma exposures (AUC_{0-168h}) for the 5, 7 and 9 mg/kg and flat dosing per weight band regimens exceeded the adult reference exposure after a once-daily 100 mg regimen. No safety signals were observed
Bury et al. (2022)[38]	Phase II study of 169 children (median age, 4 years) with ALL who received micafungin prophylaxis at a dose of 9 mg/kg (maximum 300 mg) twice weekly during the first 5 weeks of induction therapy. This cohort was compared to historical control patients ($n = 643$; median age, 5 years), which did not receive antifungal prophylaxis during the induction course	Two of the 169 patients (1.2%) receiving micafungin developed proven or probable invasive aspergillosis in comparison to 36 out of the 643 patients (5.6%) of the historical control ($p = .013$). No information was provided on the occurrence of non-Aspergillus invasive fungal diseases during the study. Of note, similar to the pharmacokinetic study, no safety signals were noted
Gastine et al. (2022)[39]	Development of a population pharmacokinetic model based on previously published data from children aged 3 months to 17 years to assess twice-weekly dosing for antifungal prophylaxis with caspofungin. Monte Carlo simulations were performed based on the final model to assess the dose needed for adequate exposure in a twice-weekly setting. Mean weekly AUC_{0-24h}/MIC together with reported AUC_{0-24h} from previously reported paediatric trials were used to guide adequate exposure	A two-compartment model with linear elimination and allometric scaling using fixed exponents was most adequate to describe the given paediatric population. Monte Carlo simulations showed that a 200 mg/m^2 twice-weekly regimen with a maximum 200 mg total dose should result in exposures matching registered daily dosing as well as commonly used pharmacokinetic/pharmacodynamic exposure targets. A clinical validation of this dosing approach, however, is pending
Gastine et al. (2017)[42]	Development of a population pharmacokinetic model to explore voriconazole exposure in plasma after alternative dosing regimens during the first days of treatment. Concentration data were obtained from a paediatric phase II study in allogeneic HCT patients. Nonlinear mixed effects modelling was used to develop the model. Monte Carlo simulations were then performed to test an array of TID intravenous dosing regimens in children 2 to 12 years of age	A two-compartment model with first-order absorption, nonlinear Michaelis–Menten elimination and allometric scaling best described the data. Monte Carlo simulations of a regimen of 9 mg/kg of body weight TID simulated for 24, 48 and 72 h followed by 8 mg/kg BID resulted in improved early target attainment relative to that with the currently recommended BID dosing regimen but no increased rate of accumulation thereafter. A clinical validation of this dosing approach, however, is pending

Abbreviations: ALL, acute lymphoblastic leukaemia; AUC, area under the concentration-versus-time curve; BID, twice daily; MIC, minimum inhibitory concentration; TID, three times daily.

and the European Union for the treatment of invasive aspergillosis, fusariosis and scedosporiosis; treatment of oesophageal candidiasis; and primary treatment of candidemia and certain forms of invasive candidiasis in non-neutropenic adults and paediatric patients 2 years of age and older. In the European Union, voriconazole also is approved for prophylaxis of invasive fungal infections in high-risk allogeneic haematopoietic stem cell transplant recipients of identical age categories. In subjects ≥12 years of age, the recommended intravenous dosage is 4 mg/kg twice daily (day 1, 6 mg/kg twice per day) and the oral dosage is 200 mg twice daily (day 1, 400 mg twice per day). In children ≥2 to 11 years of age and those 12–14 years of age weighing <50 kg, an intravenous dose of 8 mg/kg twice daily (day 1, 9 mg/kg twice per day) and an oral dose of the suspension of 9 mg/kg twice daily are recommended.[40,41]

The pharmacokinetics of voriconazole are complex, and, in particular in children, still not completely understood. In addition to a considerable intrasubject variability in exposure, there is a large inter—subject variability that is not fully explained by CYP2C19 polymorphisms.[42] Based on the significant correlations between exposure and effect,[43] and the significant impact of therapeutic drug monitoring on treatment responses and adverse effects,[44,45] therapeutic drug monitoring of voriconazole is strongly recommended.[1,46] Nevertheless, the high fraction of patients with insufficient exposure after recommended doses[47,48] and the delay in achieving sufficient exposure through drug monitoring stand in stark contrast to the imperative of administering effective treatment with the first doses.[49,50] Indeed, pharmacokinetic models continue to explore optimised dosing regimens,[51,52] including three times daily dosing.[42]

In this context, a population pharmacokinetic model was created to investigate voriconazole exposure in plasma after administration of alternative dosing regimens (Table 3).[42] For this purpose, concentration data were obtained from a paediatric phase II study of voriconazole for antifungal prophylaxis in allogeneic haematopoietic cell transplantation. Nonlinear mixed effects modelling was used to build the model, and Monte Carlo simulations were carried out to test a spectrum of three-times-daily intravenous dosing regimens in children aged 2–12 years. A two-compartment model with first-order absorption, nonlinear Michaelis–Menten elimination and allometric scaling best fit the observed concentration data (maximal kinetic velocity for nonlinear Michaelis–Menten clearance [V_{max}] = 51.5 mg/h/70 kg, central volume of distribution [V_1] = 228 L/70 kg, intercompartmental clearance [Q] = 21.9 L/h/70 kg, peripheral volume of distribution [V_2] = 1430 L/70 kg, bioavailability [F] = 59.4%, K_m = fixed value of 1.15 mg/L, absorption rate constant = fixed value of 1.19/h). Interindividual variabilities for V_{max}, V_1, Q and F were 63.6%, 45.4%, 67% and 1.34% on a logit scale, respectively, and residual variability was 37.8% (proportional error) and 0.0049 mg/L (additive error). Monte Carlo simulations of an intravenous regimen of 9 mg/kg three times daily simulated for 24, 48 and 72 h followed by 8 mg/kg twice daily yielded an improved early target attainment in comparison to the recommended twice daily dosing regimen without increased accumulation thereafter.[42]

The results of this in silico modelling study indicate that upfront intravenous three times daily dosing at 9 mg/kg per dose for up to 72 h may result in a substantially higher proportion of children having adequate exposure to VCZ early during treatment. However, further validation of exposure, safety and tolerability in a carefully designed clinical trial will be needed before a broader implementation of this regimen in children 2–12 years of age may be considered.

5.3 | Alternative dosing regimens of posaconazole and isavuconazole

In contrast to voriconazole, exposures after administration of the new oral and the intravenous formulations of posaconazole and those after administration of isavuconazole are dose-dependent and less variable, which may allow for exploration of extended dosing regimens. Along these lines, data have been published on a patient in whom a dosing scheme with administration of isavuconazole from Monday through Friday apparently yielded sufficient exposures throughout Saturday and Sunday under conditions of steady state.[53] At present, such dosing modifications have to be carefully interpreted and should only be used in conjunction with drug monitoring and definitely not in routine patient care, as alternative options exist and the benefit for the patient is limited.

6 | NOVEL ANTIFUNGAL AGENTS IN CLINICAL DEVELOPMENT

New populations at risk, the increased demand for antifungal treatment, the emergence of drug-resistant pathogens in the hospital and the environment, and the inherent limitations of existing antifungal classes and agents provide a continuous need to expand our options for antifungal prophylaxis and treatment.[9] Whereas there has been a perceived standstill in the identification and development of new agents after the approval of the second-generation triazoles and the echinocandins two decades ago, a number of new antifungal compounds with novel targets or certain improved pharmacological features have emerged from the preclinical setting and have entered advanced stages of clinical development (Figure 1). These compounds include rezafungin (an intravenous modification of anidulafungin with an extended half-life, once weekly dosing and developed for invasive candidiasis and antifungal prophylaxis); ibrexafungerp (a first-in-class oral and intravenous triterpenoid targeting [1→3]-β-D-glucan synthesis with some cross-resistance to echinocandins and similar projected indications); fosmanogepix (a novel oral and intravenous Gwt1 enzyme/GPI Anchor Protein inhibitor with broad-spectrum antifungal activity including common and rare mould species), and olorofim (an oral and intravenous inhibitor of dihydroorotate dehydrogenase involved in pyrimidine synthesis with strong activity against filamentous and dimorphic fungi, including rare mould organism without current treatment options). The preclinical data and the detailed description of completed and ongoing clinical trials performed in adults are beyond the scope of this article, and the reader is referred to current state-of-the-art expert review articles.[54,55] Paediatric investigation plans (PIPs) are an integral part of the clinical development for all of these compounds and paediatric phase I/II clinical trials are currently in the process

Antifungal Agents	*Candida* spp.	*Aspergillus* spp	Mucorales	Rare molds	Dimorphic Fungi
Rezafungin					
Ibrexafungerp					
Fosmanogepix					
Olorofim					

FIGURE 1 In vitro activity of antifungal agents in clinical development against the most relevant invasive fungal pathogens. Green, activity against most isolates; yellow, variable or marginal activity and red, no relevant activity (modified from Lamoth et al. [54]).

of planning. Thus, there is a reasonable likelihood that these compounds will complement the paediatric antifungal armamentarium within the next 5–10 years.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

Children and adolescents with acute leukaemia or undergoing allogeneic haematopoietic cell transplantation exhibit differences in host biology, concomitant conditions, presentation and epidemiology of invasive fungal diseases and the pharmacology of antifungal agents. During the past three decades, medical mycology has witnessed a tremendous evolution, including the advent of better-tolerated formulations of amphotericin B, new antifungal triazoles providing effective treatment and prophylaxis for invasive aspergillosis, and the class of echinocandins that has changed the management of invasive candidiasis. Whereas the paediatric development of some agents has been slower than we would consider reasonable, all except isavuconazole currently have a paediatric label, allowing for their safe use at appropriate doses for approved indications. In addition, after some years of perceived standstill in antifungal drug development, several new agents are in advanced clinical development. With two decades of experience within regulatory authorities, industry and paediatric academia, we should be optimistic that these compounds will soon complement the paediatric antifungal armamentarium.

Considering the evolution of medicine and the emergence of resistant fungal pathogens, the current threat by invasive fungal diseases in immunocompromised paediatric patients will rather increase than decline. The availability of more than one or two treatment options clearly is an important asset; at the same time, however, antifungal prevention, diagnosis and management are becoming more and more complex. In addition to information on prior antifungal treatments, microbiological data, co-morbidities and co-medications, a solid and detailed knowledge of the pharmacology of available antifungal agents and clinical trial results is needed more than ever and calls for dedicated antifungal stewardship programs in paediatric centres that care for patients at high risk.[56,57] On a broader level, established fungal disease-centred international networks such as the International Paediatric Fungal Network (IPFN)[58] or the PENTA Fungal Infections Network,[59] and the inclusion of paediatric patients in important large international guideline consortia such as the European Conference on infections in Leukaemia (ECIL)[60] and the European Confederation of Medical Mycology (ECMM)[61] are to be commended for their contributions and offer further hope for substantial advancements in paediatric antifungal supportive care in the future.

AUTHOR CONTRIBUTIONS

Andreas H. Groll: Conceptualization; writing – original draft; writing – review and editing; data curation; methodology; investigation; formal analysis. **Katharina Körholz:** Methodology; writing – review and editing; investigation; data curation; conceptualization. **Malcolm Holterhus:** Investigation; methodology; writing – review and editing; data curation; conceptualization. **Thomas Lehrnbecher:** Conceptualization; investigation; methodology; writing – review and editing; data curation.

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CONFLICT OF INTEREST STATEMENT

A. H. Groll has received grants from Gilead, Merck, Sharp & Dohme and Pfizer; has served as consultant to Amplyx, Astellas, AstraZeneca, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Scynexis and Mundipharma; and has been in the speaker bureau of Gilead Sciences, Merck Sharp and Dohme and Astra Zeneca. T. Lehrnbecher served as a consultant to Gilead Sciences, Pfizer, Merck/MSD, Mundipharma and Roche and has been in the speaker's bureau of Gilead Sciences, Merck/MSD, EUSA Pharma, Pfizer and Sanofi Pasteur. K. Koerholz has been in the speaker bureau of Merck Sharp and Dohme. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov/.

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