EXPERT OPINION

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Advances in the treatment of invasive neonatal candidiasis

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Introduction: Invasive candidiasis is responsible for ~ 10% of nosocomial sepsis in very-low-birth-weight infants and is associated with substantial morbidity and mortality. Over the last two decades, the antifungal armamentarium against *Candida* spp. has increased; however, efficacy and safety studies in this population are lacking.

Areas covered: We reviewed the medical literature and extracted information on clinical and observational studies evaluating the use of antifungal agents in neonates with invasive candidiasis.

Expert opinion: Efficacy and safety data for antifungals in neonates are lacking, and the majority of studies conducted to date have concentrated on pharmacokinetic/pharmacodynamic evaluations. Unlike other anti-infective agents, efficacy data in the setting of neonatal candidiasis cannot be extrapolated from adult studies due to differences in the pathophysiology of the disease in this population relative to older children and adults. Data for amphotericin B deoxycholate, fluconazole, and micafungin suggest that these are the current agents of choice for this disease in neonates until data for newer antifungal agents become available. For prophylaxis, data from fluconazole randomized controlled trials will be submitted to the regulatory agencies for labeling. Ultimately, the field of therapeutics for neonatal candidiasis will require multidisciplinary collaboration given the numerous challenges associated with conducting clinical trials in neonates.

Keywords: antifungal agents, *Candida*, echinocandin, invasive candidiasis, neonates, polyene, triazole

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1. Introduction

The epidemiology and devastating outcomes of invasive candidiasis in neonates have been a strong driver for laboratory studies, clinical research, and development of new antifungal agents. *Candida* spp. infections are responsible for ~ 10% of nosocomial sepsis in very-low-birth-weight (VLBW, < 1500 g birth weight) infants [1], with a cumulative incidence of 1 – 4% among all neonatal intensive care unit (NICU) admissions [2]. In spite of decreasing rates of invasive neonatal candidiasis over the last decade [1,2], mortality related to the disease remains considerably high (20 – 30%), with high rates (59 – 73%) of long-term neurodevelopmental impairment in survivors [2-4]. These rates are two to sixfold higher in neonates with invasive candidiasis relative to peers without the disease [2].

Among *Candida* species, *Candida albicans* is the most prominent pathogen in neonates; however, the incidence of cases due to *C. parapsilosis* accounts for ~ 25% of invasive candidiasis in VLBW infants [5]. *C. glabrata* and *C. krusei*, recognized for their resistance to azoles, are of less concern in the NICU [6]; among ~ 131,000 infants admitted to 128 NICUs between 1995 and 2004, *C. glabrata* and *C. krusei* represented only 2 and 1% of all cases, respectively [6].

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Article highlights.

- The majority of studies of antifungal agents in neonates are limited to pharmacokinetics/pharmacodynamic studies.
- Because the pathophysiology of invasive candidiasis in neonates is different from older children and adults, efficacy and safety trials in this population are needed to support labeling.
- Results from ongoing safety and efficacy clinical trials in neonates are expected in the next 3 – 5 years for newer triazoles and echinocandins.
- Amphotericin B deoxycholate, fluconazole, and micafungin are the agents of choice for treatment of neonatal invasive candidiasis.

This box summarizes key points contained in the article.

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Amphotericin products and fluconazole have been the mainstays of therapy against neonatal invasive candidiasis, but several new antifungal agents (e.g., echinocandins) have emerged as therapeutic alternatives in neonates [7]. This antifungal drug class is attractive because the drugs can be used as monotherapy, have an acceptable safety profile, have experimental activity against *Candida* biofilm, and possess an extended activity spectrum against *C. glabrata, C. tropicalis*, and *C. krusei* [8].

Invasive candidiasis in the nursery represents a significant burden in terms of morbidity and mortality. The first stage of this pathologic process starts with *Candida* colonization acquired either by vertical transmission during vaginal delivery or postnatally from contact with maternal skin or skin of health care providers. Once colonization is established, the likelihood of development of invasive neonatal candidiasis depends on the combination of host risk factors and organism virulence. The most important host risk factors include: i) extreme prematurity, with invasive candidiasis developing in 2 – 5% of VLBW infants compared to 4 – 16% of extremely low-birth-weight (ELBW) [1,2,9-11]; ii) site providing medical care, with incidence variation of invasive candidiasis ranging from 2.4 to 20.4% among ELBWs [9] – empirical use of broad-spectrum antibiotics, use of antifungal prophylaxis, central catheter management, and hand-washing practices can contribute to this incidence variation among different NICUs; and iii) exposure to broad-spectrum antibiotics (e.g., third-generation cephalosporins) as the strongest modifiable risk factor [12]. Other risk factors include use of indwelling catheters, steroid therapy, histamine-2-receptor antagonists use, neutropenia, endotracheal intubation, cardiac or abdominal surgery, and necrotizing enterocolitis [13-15]. Organism virulence factors that increase risk include species (*C. albicans* is the most pathogenic), filament formation, adhesins, and biofilm formation [16].

The most common clinical presentation of *Candida* infection in the NICU is candidemia with end organ involvement [17]. *Candida* has great affinity for specific organs (e.g., kidneys, eyes, heart, CNS); therefore, neonates might develop a variety of clinical presentations such as urinary obstruction, renal insufficiency, endophthalmitis, endocarditis, and meningitis [16]. Data from single-center, retrospective observational studies reporting prevalence of end organ involvement are heterogeneous, likely due to the lack of sensitivity of end organ culture in isolating disseminated disease; however, estimates of 4 – 70% were reported [17]. In contrast to older children and adults, a differentiating feature of the pathophysiology of *Candida* infections in neonates is involvement of the CNS or hematogenous *Candida* meningoencephalitis (HCME) with an incidence that exceeds 15% in neonates with invasive candidiasis [2,12]. However, diagnosing HCME is challenging. Only 37% of infants with proven candidal meningitis also had positive blood cultures for *Candida*. In addition, normal cerebrospinal fluid (CSF) parameters are present in almost half of infants with candidal meningitis [18]. As a result, antifungal therapy in this population should be optimized to the most efficacious dose with penetration to treat CNS disease [19].

2. Polyenes

The polyene class includes amphotericin B deoxycholate (AmB) and the lipid-based formulations: amphotericin B liposomal complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AmB). The mechanism of action of polyenes involves binding to ergosterol, a fungal cell wall component, which leads to increased membrane permeability and cell death [20]. All these amphotericin formulations have been used to treat invasive candidiasis in neonates [21-23] despite not having specific guidance for this population on the FDA label [24-26]. The European Medicines Agency (EMA) has only approved L-AmB as one of the first-line therapeutic options for the treatment of candidemia and deeply invasive candidiasis [27,28]. Currently, ABCD manufacturing is suspended [29].

The use of polyenes in the nursery requires several considerations: i) amphotericin B formulations penetrate the CNS (but not the CSF) and therefore are good candidates for neonatal candidiasis characterized by HCME [2]; ii) treatment of candiduria and renal fungal infection is likely effective due to penetration into renal tissue [17]; and iii) given the extremely variable pharmacokinetics (PK) of AmB in neonates, there is a chance for treatment failures or unwanted toxicities [30].

2.1 Amphotericin B deoxycholate

Over the last 5 decades, AmB has played a major role as a main agent for the treatment of invasive candidiasis in neonates.

Several PK/pharmacodynamic (PD) studies including premature infants and children have shown extreme inter-patient variability for the half-life, volume of distribution, and clearance of amphotericin B, with an overall supported dose of 1.0 – 1.5 mg/kg/day [30,31]. However, a population PK study

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of amphotericin B products in 57 children 9 months to 16 years of age with malignancies suggested that younger and lighter infants may be underexposed with doses of 1 mg/kg/day, whereas older and heavier children may be overdosed at the same dose [32]. Penetration into the CSF seems to be associated with age. Whereas in adults, CSF values are 2 – 4% of serum concentrations [33], in a small series of premature infants born at 27.4 (± 5) weeks gestational age (GA) (n = 5), amphotericin B concentrations in CSF were ~ 40% of simultaneously collected serum concentrations [30]. It is unclear if the CSF concentrations are due to meningeal inflammation, immaturity of the blood–brain barrier characteristic of premature infants, or a combination of both.

The efficacy of AmB has been assessed in several studies that included a limited number of neonates, most of whom presented with candidemia or meningitis [34]. Clinical response rates were > 75% in the majority of the studies [35-37], with AmB doses of 0.5 – 1 mg/kg/day often co-administered with flucytosine [34].

A single-center retrospective observational study of 36 infants with documented candidemia (mean GA of 28 weeks and mean birth weight of 988 g) treated with AmB for a total of 10 doses (0.5 – 1 mg/kg/day) reported a mortality of about ~ 17% [37]. In another single-center, 10-year retrospective observational study (1989 – 1999), 23 of 106 neonates (0.4% of admissions) had candidal meningitis (median GA of 26.2 weeks and median birth weight of 820 g) and were treated with AmB (median cumulative dose of 30 mg/kg, median of treatment duration 31 days). The *Candida*-related mortality was 26% (6/23) [35].

Only one published prospective randomized controlled trial (RCT) evaluated the efficacy of AmB versus fluconazole in 23 neonates with candidemia from two medical centers. Eleven neonates received AmB (1 mg/kg/day for 162 days), and 12 neonates received fluconazole (5 mg/kg/day for 75 days). Of the fluconazole group, 67% (8 of 12 patients) survived versus 55% (6 of 11 infants) for the amphotericin group. Additionally, infants receiving amphotericin B had significantly higher values of total and direct bilirubin and alkaline phosphatase compared with fluconazole recipients [36].

The safety of AmB in infants has not been evaluated in RCTs. However, several observational studies have reported the safety of these agents in infants and children [30,31,38,39]. Although infusion-related toxicity and nephrotoxicity are common safety findings in adults [40], the results of the observational studies suggest that the frequency of nephrotoxicity is lower in infants and children. However, data from a single-center observational study including 92 infants (median GA of 26 weeks and median birth weight of 863 g) who received at least three doses of AmB (mean daily dose of 0.9 mg/kg) showed that 15 infants (16%) had elevation of serum creatinine and 16 (17%) developed hypokalemia [39]. The increase in serum creatinine values was transient for most infants, and values returned to baseline by the end of therapy, suggesting that AmB did not play an important role in this change of laboratory parameter [39]. Another observational study including 753 ELBW (birth weight < 1250 g) infants reported that the combination of conventional AmB with adequate hydration and higher sodium intakes of > 4 mEq/kg/day may provide protection against nephrotoxicity in this population [41].

2.2 Lipid-based amphotericin B preparations

Three lipid-based formulations are associated with less toxicity [20] and are primarily used for neutropenic patients with persistent fever and patients with systemic mycoses refractory to AmB [42]. Compared with AmB, they require higher doses for equivalent antifungal efficacy *in vitro* and in animals models, but these lipid formulations have the same mechanism of action and antifungal spectrum as AmB [43]. Interestingly, the PK and PD of these formulations are poorly characterized in both children and neonates [44,45]. To date, animal models have demonstrated that different amphotericin B lipid formulations show variations in PK and PD. A population PK analysis of ABLC in 28 neonates with invasive candidiasis (GA of 24 – 41 weeks) showed that a dose of 2.5 – 5 mg/kg/day provided therapeutic exposures [46].

Efficacy data of lipid amphotericin B formulations in neonates are limited to open-label studies or individual case reports; prospective randomized trials comparing these formulations with AmB have not been conducted [34]. A study of 40 preterm infants with candidiasis (mean GA of 28.4 weeks and mean birth weight of 1090 g) treated with L-AmB (cumulative dose of 45.2 mg/kg) reported clinical cure of 72% [23]. A prospective multicenter study including 118 neonates with systemic candidiasis demonstrated 94% efficacy for L-AmB and 86% for ABLC [47]. Additional observational studies in < 25 neonates showed clinical cure in > 80% of neonates treated with lipid formulations of amphotericin B [34].

The safety of amphotericin lipid formulations in neonates has been evaluated in some observational uncontrolled studies. The results of these studies combined (n = 124 infants) showed a favorable safety profile for L-Amb with mild increases in liver enzymes (0 – 37%) and serum creatinine (0 – 5%), and a decrease in potassium (0 – 5%) [23,48]. No serious adverse events (AEs) were reported in these studies. Two large safety studies for ABLC were conducted in children [49,50]. One of these involved 111 children (21 days – 16 years of age) who received ABLC (5 mg/kg/day) and demonstrated no drug-related AEs [49]. The other study included 548 children (aged 0 – 20 years) who received 5 mg/kg/day of ABLC and showed an increase of serum creatinine of 2.5× baseline in 8.8% of children [50]. A recent study in a large cohort including 730 infants < 120 days of age showed both increased mortality and treatment failure for neonates with confirmed *Candida* infection treated with lipid formulations compared with AmB [51]. These results may be explained by lower exposures in the CNS and urinary tract achieved by the amphotericin lipid formulations; both anatomic compartments

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are considered preferred targets for *Candida* infections in neonates [46]. However, appropriate dosing of these formulations in neonates to reach therapeutic exposure in those compartments has not been studied. These results combined suggest that if amphotericin lipid formulations are used in the nursery, documentation of urine sterilization after treatment is necessary.

3. Triazoles

The mechanism of action for triazole agents involves the fungal cytochrome P-450-dependent enzyme lanosterol 14-α-demethylase, causing accumulation of aberrant and toxic sterols in the cell membrane [52,53].

3.1 First-generation triazoles

This class includes fluconazole and itraconazole, both available as oral and parenteral formulations. Their activity spectrum covers several *Candida* species [54], such as *C. albicans*, *C. dubliniensis*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitanie*.

3.1.1 Fluconazole

Fluconazole represents the only triazole agent that has been extensively used in NICUs, where *C. albicans* and *C. parapsilosis* are the predominant pathogens [55]. However, in recent years, resistance to fluconazole has appeared, with some centers reporting ~ 8% of resistance among *Candida* isolates [56]. *C. krusei* is inherently resistant to fluconazole, and *C. glabrata* has resistance rates > 50% [57]. Other than limited PK information, fluconazole does not have an FDA indication for neonatal use [58]. The EMA has labeled fluconazole use in term newborn infants and children 0 – 17 years of age for the treatment of invasive candidiasis, mucosal candidiasis, cryptococcal meningitis, and prophylaxis of invasive candidiasis in immunocompromised children [59].

Fluconazole has a very high bioavailability (> 90%) and excellent CSF penetration (~ 80%), and clearance is mainly renal. However, neonates and infants display important PK differences relative to older children and adults, including a greater volume of distribution and reduced systemic clearance. For treatment, this requires the use of a loading dose (25 mg/kg) [53] followed by daily maintenance doses (12 mg/kg) [60]. For prophylaxis, the PK differences require the use of 6 mg/kg twice per week [60,61].

Several efficacy studies in neonates with invasive candidiasis have shown the clinical and microbiological efficacy of fluconazole [7]. The oldest report is a non-randomized prospective study across nine countries that included 40 neonates and infants (2 days to 3 months of age) who received fluconazole with an average daily dose of 5.3 mg/kg (range of 1 – 16 mg/kg) and exhibited 97% clinical and mycological response [62]. A two-center RCT (n = 23 infants) comparing AmB with fluconazole for the treatment of fungal septicemia resulted in no difference in outcomes and a trend toward fewer side effects in the fluconazole group. The study was not powered, however, to show differences in mortality or neurodevelopmental outcomes [53].

The use of fluconazole as a *prophylactic* agent, has been more extensively studied in neonates and infants. To date, the efficacy of fluconazole prophylaxis in this population has been evaluated in eight retrospective observational studies [63-70], six RCTs [71-76], and one meta-analysis [77]. Based on the results of these studies, the routine use of fluconazole prophylaxis should be limited to NICUs with a significant incidence of invasive candidiasis (≥ 15%) [71,74,76]. Results from these RCTs are being submitted to regulatory agencies for labeling.

In a prospective, randomized, double-blind trial of 100 infants over a 30-month period, Kauffman *et al.* demonstrated a decrease in fungal colonization (22 vs 60%) as well as in the development of invasive candidiasis compared with placebo (0 vs 20%) in patients with birth weights < 1000 g who received fluconazole for 6 weeks (3 mg/kg every 24 – 72 h) [71]. Additionally, these investigators conducted a follow-up prospective, randomized, double-blind study (N ~ 80) comparing two different fluconazole dosing regimens (regimen from the prior study and a twice-weekly regimen), which did not show significant difference in fungal colonization ($p = 0.83$) or invasive disease ($p = 0.68$) [72].

Manzoni *et al.* conducted an RCT including 322 infants with birth weight < 1500 g from eight NICUs in Italy who received a fluconazole prophylaxis regimen of 3 – 6 mg/kg several times per week for 4 – 6 weeks. The study showed a reduction in the incidence of invasive candidiasis (incidence of 2.7% in the 6 mg group [$p = 0.005$], 3.8% in the 3 mg group [$p = 0.02$], and 13.2% in the placebo group) and *Candida* colonization (incidence of 9.8% in the 6 mg group, 7.7% in the 3 mg group, and 29.2% in the placebo group [$p < 0.001$]) [74].

The most recent RCT [76] to evaluate the safety and efficacy of fluconazole in preventing death or invasive candidiasis in ELBW infants included 361 infants with birth weight < 750 g from 32 NICUs in the United States randomly assigned to receive 6 mg/kg twice weekly for 42 days or placebo. The primary end point was a composite of death or definite or probable invasive candidiasis prior to study day 49 (1 week after completion of study drug). Secondary outcomes included invasive candidiasis and neurodevelopmental outcomes, the latter evaluated in surviving infants at 18 – 22 months corrected age. The results showed that 42 days of fluconazole compared with placebo among infants of birth weight < 750 g did not result in a lower incidence of death or invasive candidiasis (16% [95% CI, 11 – 22%] vs 21% in the placebo group [95% CI, 0.43 – 1.23%]; $p = 0.24$). Invasive candidiasis occurred less frequently in the fluconazole group (3% [95% CI, 1 – 6%]) vs the placebo group (9% [95% CI, 5 – 14%]; $p = 0.02$), and neurodevelopmental impairment did not differ between the groups (fluconazole, 31% [95% CI, 21 – 41%] vs placebo, 27% [95% CI, 18 – 37%]; $p = 0.60$).

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A meta-analysis of five RCTs [77] (excluding the most recent one) showed a considerably lower incidence of invasive fungal infection in neonates receiving prophylactic fluconazole (relative risk 0.48 [95% CI, 0.31 – 0.73]; number needed to treat: 11 [95% CI, 7 – 33]). A difference in mortality between the fluconazole prophylaxis and placebo groups was observed.

The fluconazole safety profile in neonates was also evaluated in the first five efficacy RCTs previously mentioned. Specifically, the effect of fluconazole on liver function tests [71-75] was evaluated in two of these RCTs, which included a total of 223 infants combined. No clinically significant increases in aspartate aminotransferase and alanine aminotransferase were found, and all the values returned to baseline after discontinuation of fluconazole.

3.1.2 *Itraconazole*

This antifungal agent has fungicidal activity against filamentous fungi [78], and fungistatic activity against *Candida* species [79]. Itraconazole use is approved for the treatment of oropharyngeal and esophageal candidiasis in adult HIV patients or other immunocompromised patients by the FDA [80] and the EMA [27], but is not labeled for pediatric populations.

Itraconazole's PK characteristics include high protein-binding, extensive hepatic metabolism, and variable oral absorption that can be enhanced by acidic gastric environment, food, and oral formulations administration [80]. The bioavailability of itraconazole is dose-dependent; therefore, dividing the daily dose in two doses per day appears to be more suitable to achieve similar exposures in adults and children [81,82]. Similar PK parameters are seen in children > 5 years of age and adults [82].

There is not much knowledge about the use of itraconazole in neonates; thus, efficacy data are limited. However, two different case reports, one about a VLBW neonate treated with itraconazole for invasive candidiasis [83], and the other about a preterm newborn treated with oral itraconazole due to hepatic candidiasis [84], showed that this antifungal agent was effective and well-tolerated.

The most common AEs of itraconazole are gastrointestinal symptoms (8 – 12%), and it appears well tolerated in children [82]. Nevertheless, the potential drug–drug interactions due to inhibition of CYP3A enzymes are the most important safety risk [85], especially the well-documented enhanced vincristine neurotoxicity when the interaction with itraconazole occurs in both children and adults [86].

We would not recommend itraconazole use in neonates and children given the erratic, nonlinear oral bioavailability, high PK variability, and the lack of efficacy and safety data from clinical trials in these patient populations [54].

3.2 Second-generation triazoles

This class of antifungal agents includes voriconazole, posaconazole, and ravuconazole. They have a broad spectrum of activity against medically important yeasts [54], including *C. albicans, C. dubliniensis*, *C. tropicalis* [87], *C. lusitanie* [88], and *C. parapsilosis* [89]. *C. krusei* is often susceptible to voriconazole and almost always susceptible to posaconazole [90]. For *C. glabrata* [7], cross-resistance among the azoles is common: *C. glabrata* isolates that are resistant to fluconazole are usually also resistant to voriconazole.

3.2.1 *Voriconazole*

Voriconazole is indicated for *Candida* infections in non-neutropenic patients and severe invasive *Candida* infections resistant to fluconazole in children 2 – 12 years of age in the United States and the European Union [91,92].

Voriconazole is available in both intravenous (i.v.) and oral formulations with ~ 90% oral bioavailability. PK characteristics include a considerable percentage of protein binding (58%), a large volume of distribution, and good penetration into the CSF. It is extensively metabolized by the liver, with < 5% excreted unchanged in the urine [53]. In children, the PK of voriconazole is linear at lower doses; body weight is the principal contributor to drug exposure. The linear kinetics at lower voriconazole doses can be partially explained by the higher rates of elimination found in children when compared with adults. Voriconazole metabolism in children is also affected by genetic polymorphisms in the CY2C19 gene as occurs in adults [53].

Efficacy studies of voriconazole in the neonatal population are limited to case reports [53]. Kohli *et al.* [93] reported successful use of oral voriconazole (4 mg/kg/dose twice a day) in two newborns with *Candida* infection and concomitant severe cardiac disease. Administration of i.v. voriconazole (4 mg/kg/day) to two ELBW infants to treat primary cutaneous aspergillosis [94] and in a preterm infant with fluconazole-resistant *C. albicans* infection [95] resulted in successful outcomes.

In adults and older children, the side effects reported for voriconazole include reversible dose-dependent visual disturbances (increased brightness, blurred vision) [96] and occasional photosensitization skin reactions [97]. Future clinical trials to evaluate voriconazole safety in premature infants are unlikely given its known ocular side effects and concern about how it might affect the developing retina [53].

In the setting of alternative therapies, we discourage the use of voriconazole in the neonatal population because PK and safety in infants still need to be characterized [54].

3.2.2 *Posaconazole*

Posaconazole is active against most of the yeasts and azole-resistant *Candida* spp. It is approved in the United States in adults for prophylaxis and treatment of disseminated candidiasis and aspergillosis in severely immunocompromised patients, and for the treatment of oropharyngeal candidiasis [53], but not for its use in infants [98]. This antifungal is not licensed for patients < 18 years of age by the EMA [27].

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This agent is orally available with a well-established efficacy and tolerability in adults. Additionally, a gastro-resistant tablet to overcome some oral suspension-related PK limitations as well as an i.v. solution for patients who are unable to receive oral formulations have been developed [99]. It has a high plasma protein binding (98%), and it is primarily eliminated through feces with minimal renal clearance [100]. Posaconazole is not a substrate of the cytochrome P-450 enzymatic system [53].

In spite of poor PK characterization in children, the use of posaconazole for prophylaxis [101] and treatment [102] has been reported in children with chronic granulomatous disease. The PK of the drug have been described in a small cohort of 12 children with chronic granulomatous disease and suggest that doses of 120 – 300 mg/kg/day may result in exposure similar to adults [101]. A trial to evaluate the safety, tolerance, and PK of posaconazole in immunocompromised children with neutropenia due to malignancies is ongoing (ClinicalTrials.gov #NCT01716234) [54]. Gastrointestinal symptoms are the most common side effects reported for posaconazole (25% of juvenile and adult patients) [102,103].

There are no reports on the use of posaconazole in neonates. We would only consider its use as salvage therapy in neonates with refractory disease to other agents [53].

3.2.3 *Isavuconazole*

This agent is a novel broad-spectrum triazole. Isavuconazole has shown good *in vitro* activity against most of the *Candida* species, including *C. glabrata* and *C. krusei* [104]. Likewise, its *in vitro* activity against *Candida* spp. has demonstrated superior potency when compared to fluconazole, itraconazole, and amphotericin B, and similar to that of voriconazole and posaconazole [105]. Currently, isavuconazole is not available for commercial use and is under review by the FDA and the EMA for the treatment of invasive aspergillosis and mucormycosis in adults [106].

Isavuconazole PK/PD studies in adults [107] showed high bioavailability, long half-life, large volume of distribution, and reduced clearance with predominantly hepatic metabolism. The efficacy of isavuconazole in disseminated candidiasis has been assessed in murine models [108]. Isavuconazole antifungal activity was impressive in these models, and against *C. krusei* was superior to voriconazole and fluconazole. Interestingly, a reduction in the burden of *C. krusei* in the brain was another efficacy finding.

A Phase III, double-blind, randomized study to evaluate the safety and efficacy of isavuconazole versus caspofungin followed by voriconazole in the treatment of candidemia and other invasive candida infections (NCT00413218) was recently completed, and primary data are anticipated for the second-half of this year [106].

To date, we do not recommend the use of isavuconazole in children as clinical trials to evaluate PK/PD, efficacy, and safety in the pediatric population have not been completed, and the clinical experience knowledge is still limited for adults [54].

4. Echinocandins

The echinocandin class includes caspofungin, micafungin, and anidulafungin. These drugs are only available in parenteral form [54]. The mechanism of action is based on the inhibition of (1,3)-β-D-glucan synthase, a fungus-specific enzyme required for the biosynthesis of glucan, a sugar in the fungal cell wall [109]. They have a broad spectrum of coverage consisting of fungicidal activity against most *Candida* spp., including fluconazole-resistant species (*C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, and C. krusei*) [110]. *C. parapsilosis* has an intrinsically reduced susceptibility to echinocandins *in vitro*, which has not correlated with therapeutic failures *in vivo* [27]. The unique mechanism of action of echinocandins offers some advantages over azole antifungal agents, including low toxicity and minimal drug–drug interactions [54].

The use of echinocandins in the nursery hinges on several considerations: i) they do not penetrate the CSF, but animal models suggest brain parenchyma penetration, which is critical for the treatment of neonates with assumed HCME [111]; ii) there is a theoretical concern related to the reduced susceptibility of echinocandins for the treatment of *C. parapsilosis* infection *in vitro* and the increasing predominance of this pathogen in the nursery, but clinical studies in adults with infections due to *C. parapsilosis* treated with an echinocandin have shown outcomes comparable with other antifungal agents [27]; iii) preclinical associations between high-dose and prolonged micafungin administration and development of hepatic tumors prompted the EMA to issue a warning suggesting the use of micafungin as a second-line agent in the presence of other alternatives [27]; iv) echinocandins may not be effective for the treatment of candiduria because they do not achieve therapeutic concentrations in the urine [112]; and v) the PK of some echinocandins have been extensively studied in neonates and premature infants.

4.1 Caspofungin

Caspofungin demonstrates *in vitro* fungicidal activity against *Candida* spp. with a concentration-dependent effect and prolonged post-antifungal effect (12 h) [113]. This antifungal agent is approved by the FDA for children 3 months to 17 years of age and by the EMA for children 12 months to 17 years of age for the treatment of candidemia [114,115].

This drug displays a linear PK and hepatic metabolism, with a terminal half-life of about ~ 10 h [116]. In infants < 3 months of age, caspofungin (25 mg/m^2/day) achieved exposures similar to adults [117].

The efficacy of caspofungin for invasive candidiasis in infants < 3 months of age is limited to small cohorts and case reports. A retrospective observational study of 13 infants (median GA 27 weeks and median birth weight 727 g) with persistent candidemia despite conventional antifungal therapy (amphotericin B and/or fluconazole or flucytosine) who

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received add-on therapy with i.v. caspofungin (1 mg/kg/day) had blood culture sterilization within 3 days [118]. A case series of caspofungin administration as a rescue therapy for refractory invasive candidiasis in 10 neonates (mean GA 33 weeks and mean birth weight 1500 g) showed clearance of blood cultures in 3 – 7 days [119].

The most common AEs reported for caspofungin in five clinical trials in children 3 months to 17 years of age included fever, rash, hypokalemia, and elevated liver enzymes [117,120-123]. Drug concentration was not associated with incidence of AEs [120]. Safety studies have not been conducted in neonates.

An ongoing trial will address the safety, tolerability, and efficacy of caspofungin compared with AmB in the treatment of invasive candidiasis in neonates and infants (ClinicalTrials.gov #NCT01945281).

4.2 Micafungin

Micafungin is the only antifungal agent for which an age-specific exposure target has been proposed for neonates. Likewise, dosing is well-defined in infants and children, the FDA has labeled its use in children and infants > 3 months of age, and the EMA and Japanese regulatory agencies have included neonates in their labels [124,125].

Micafungin is highly bound to protein and has good distribution into tissues including lung, liver, and spleen. Neonatal animal models of HCME [126] have shown success with high-dose micafungin in spite of reported limited penetration into the CNS of adults. It undergoes only limited Phase I metabolism, with the parent drug excreted mainly via the biliary system. Micafungin has concentration-dependent fungicidal killing activity [127].

An age effect represented by an inverse relationship between weight and clearance has been demonstrated in different PK studies in children, such that as body weight decreases, higher dosages of micafungin (on an mg/kg basis) are required to achieve equivalent drug exposure [128]. Hence, younger infants (GA of 24 – 40 weeks and postnatal age of 2 – 119 days) in four PK studies demonstrated higher systemic clearance (normalized by body weight) and therefore a need for higher dosing (in mg/kg) relative to older children and adults [129]. A population PK study in infants showed that a dose of 10 mg/kg/day achieved therapeutic CNS exposures in > 80% of neonates [126].

The efficacy of micafungin was evaluated in a clinical trial including 106 children < 16 years of age with invasive candidiasis and compared with L-Amb. Both drugs had equivalent efficacy, but micafungin showed better tolerance [130]. These results are consistent with data from a large adult study [131], which demonstrated non-inferiority of micafungin relative to L-Amb.

Micafungin has a favorable safety profile as evidenced by pooled data from six pediatric studies including 296 children [132]. Transient liver enzyme elevations and decreased potassium (3%) were the most commonly reported treatment-related AEs [132]. High doses (15 mg/kg) have been evaluated in a small cohort of premature neonates; however, a maximum tolerated dose has not been identified [133].

A Phase III RCT comparing the safety and efficacy of micafungin versus AmB in neonates and infants is currently ongoing (NCT00815516) [54].

4.3 Anidulafungin

Anidulafungin has a fungicidal effect against *Candida* spp. including fluconazole-resistant strains [134]. Ratios of C_{max} to MIC and of AUC to MIC strongly predict successful treatment of systemic candidiasis in neutropenic murine models [134]. This drug is not FDA or EMA approved in children [27,135].

Anidulafungin is highly protein-bound (> 99%) [136], demonstrates linear PK, and has a longer half-life than other echinocandins (20 h) [137]. An anidulafungin dose of 1.5 mg/kg/day in a small cohort of infants and neonates provided exposures similar to adults receiving 100 mg/day [138]. In the same PK study (n = 15), no serious drug-related AEs were observed, and adequate tolerance was reported [54].

There are no additional trials evaluating the safety and efficacy of anidulafungin in neonates. Given the limited data available for anidulafungin, this drug should not be used in this population.

5. Nucleoside analogs

5-Flucytosine (5-FC), a pyrimidine analog, inhibits the fungal nucleic acid synthesis [139]. It is active against *Candida* spp. and *Cryptococcus neoformans* [140]. Flucytosine should always be used in combination with other antifungal agents because of the rapid development of resistance when given as monotherapy [27]. Other than PK data included in the FDA label, 5-FC is not approved for use in neonates [141].

A fungistatic activity against yeasts with concentration-independent PD and a post-antifungal effect up to 10 h have been demonstrated by *in vitro* and *in vivo* testing [142]. General PK characteristics consist of minimal protein-binding and adequate distribution into tissues and body fluids. The main route of elimination is through urine as an active form, and the elimination half-life is 3 – 5 h [143]. PK information in children is limited, but drug clearance appears slower in children compared with adults [30,144]; therefore, the adult dose of 100 mg/kg/day might lead to overexposure. Moreover, in neonates, a suggestion that the dosing interval should be longer (8 – 24 h) is supported by the longer elimination half-life when compared with adults (4 vs 7 h) [30,144]; however, the drug has a narrow therapeutic index.

The attractiveness of flucytosine's pharmacological profile relies in its extensive penetration into tissues and fluids such as CSF and urine, which makes it a suitable adjunct for other first-line agents, especially for treatment of cryptococcal meningitis or comparable infections at restricted sites due to *Candida* (e.g., CNS candidiasis and urinary candidiasis) [145-147].

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Table 1. Summary of antifungal agents in neonates.

Drug	Neonates (0 – 30 days)			Labeled in neonates by FDA/EMA	Ref.
	Dosing	Efficacy	Safety		
Polyenes					
Amphotericin B	0.6 – 1 mg/kg i.v. q24 h	No	Yes	No/No	[27,30-32,38]
ABLC	2.5 – 5 mg/kg q24 h	No	Uncertain	No/No	[27,49]
ABCD	Unknown	No	Uncertain	No/No	
L-AmB	Unknown	No	Uncertain	No/Yes	[23,27,28]
Triazoles					
Fluconazole	Treatment: Loading dose 25 mg/kg; maintenance dose 12 mg/kg q72 h* 12 mg/kg q48 h‡ 12 mg/kg q24 h§ Prophylaxis: 6 mg/kg twice weekly	Yes for prophylaxis	Yes	No/Yes	[59,60,77]
Itraconazole	Unknown	Uncertain	No	No/No	[27,54,80]
Voriconazole	Unknown	Uncertain	No	No/No	[27,54]
Posaconazole	Unknown	Uncertain	No	No/No	[27]
Isavuconazole	Unknown	Uncertain	No	No/No	[54,106,107]
Echinocandins					
Caspofungin	25 mg/m^2 i.v. q24 h	No	No	No/No	[27,115,117,120-122]
Micafungin	10 mg/kg i.v. q24 h¶	No	Limited	No/Yes	[27,132]
Anidulafungin	Load with 3 mg/kg i.v. once, then 1.5 mg/kg i.v. q24 h	No	No	No/No	[27,137,138,149]

*≤ 29 weeks gestation, postnatal age 0 – 14 days.

‡≤ 29 weeks gestation, postnatal age > 14 days, or 30 – 36 weeks gestation, postnatal age 0 – 14 days.

§≥ 30 weeks gestation, postnatal age > 14 days, or > 36 weeks gestation.

¶Micafungin – EMA approved dose for treatment of invasive candidiasis in neonates (body weight < 40 kg): 2 mg/kg/day.

ABCD: Amphotericin B colloidal dispersion; ABLC: Amphotericin B lipid complex; EMA: European Medicines Agency; i.v.: Intravenous; L-AmB: Liposomal amphotericin B; q: Every.

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Additionally, combined administration of flucytosine with amphotericin B for cryptococcal meningitis treatment decreases the necessary MIC of amphotericin B to inhibit *in vitro* growth of *Candida*, and reduces the required amphotericin B dosage and the relapse rate [148]. Consequently, flucytosine has been reportedly used in neonates for disseminated candidiasis and CNS and/or urinary tract infections with uncertainty about a beneficial role in HCME [2]. Known side effects are related to severe gastrointestinal disturbances, which can impair the oral feeding process in neonates [27].

We discourage the use of 5-FC in infants given the limited PK, safety, and efficacy data [54]; safe target plasma concentrations are not well-established in children as opposed to adults [149].

6. Conclusion

Newer antifungals have been developed, giving clinicians more options in the treatment of invasive candidiasis. However, due to the paucity of studies in neonates, most of the data have been extrapolated from older children and adult studies (**Table 1**). Dedicated neonatal safety/efficacy studies will bridge that knowledge gap.

7. Expert opinion

Efficacy and safety data for antifungals in neonates are lacking, and the majority of studies conducted to date have concentrated on PK/PD evaluations. Although this is a positive step, these studies are limited because efficacy and safety studies will still be required in this patient population.

Unlike other anti-infective agents for which efficacy data can be extrapolated from well-controlled adult studies for the same indication, this is not possible in the setting of neonatal candidiasis. This is due to differences in the pathophysiology of the disease in this population relative to older children and adults. In neonates, invasive candidiasis is characterized by invasion of the CNS. Therefore, therapies targeted for neonatal invasive candidiasis should target not only the bloodstream but also this difficult-to-reach compartment. Estimation of drug CNS penetration in neonates is challenging because sampling from this compartment is often not available to confirm PK predictions; CSF concentrations may not reflect CNS exposures where the disease is occurring; the role of meningeal inflammation and development of the blood–brain barrier is not fully characterized in premature infants; and there is substantial variability in drug disposition in this population.

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For some antifungal agents such as micafungin, novel methods bridging animal CNS drug penetration data with dose ranging PK studies in neonates and population PK/PD methodologies have been used to overcome these challenges and allow identification therapeutic targets at the site of drug action (e.g., CNS). These efforts have allowed the development of micafungin doses specific for neonates to be evaluated in RCTs. Similar models should be replicated when planning drug development programs for this indication in this patient population. This will allow for the maximum likelihood of selecting the most efficacious and safest dose for neonates with invasive candidiasis and will result in informative controlled trials. This is particularly important in the setting of the legislative environment in the United States and European Union encouraging clinical trials in neonates.

Data for AmB, fluconazole, and micafungin suggest that these are the current agents of choice for this disease in neonates until data for newer antifungal agents become available. For prophylaxis, data from fluconazole RCTs will be submitted to the regulatory agencies for labeling. This will allow for a risk-based approach to prophylaxis of invasive candidiasis in neonates.

Another challenge to overcome in the treatment of neonatal candidiasis is the use and development of diagnostic tests allowing for early organism identification. Because neonates with invasive candidiasis present with non-specific signs of sepsis, improving the sensitivity and specificity of diagnostic tests in blood and target-organ samples will allow for early initiation of treatment and by extension improved mortality and neurodevelopmental outcomes. Blood culture remains the gold standard for diagnosis of neonatal candidiasis, but it has very poor sensitivity (< 30%) and takes about 3 – 5 days for specific identification. However, newer techniques such as matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry, peptide nucleic acid fluorescent *in situ* hybridization, and polymerase chain reaction hold great promise for earlier identification of *Candida* species from positive blood cultures. Fungal antigen (e.g., mannan and 1-3-β-D-glucan) diagnostic tests have shown some promise in adults (high specificity [> 90%], low sensitivity [30 – 60%]), but age-specific characterization of these tests is still needed for children and neonates. Therefore, the use of these tests for neonatal candidiasis is limited.

The field of therapeutics for neonatal candidiasis will require the collaboration of government, academia, and industry to select the most accurate experimental models, perform dosing optimization prior to starting clinical trials, and conduct clinical trials that will yield necessary information to improve public health. Given the numerous challenges associated with conducting clinical trials in neonates, it will be virtually impossible to move the field forward without this collaboration.

Declaration of interest

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