Published in final edited form as:

Expert Opin Pharmacother. 2015 May ; 16(7): 1035–1048. doi:10.1517/14656566.2015.1031108.

Advances in the treatment of invasive neonatal candidiasis

Lorena Botero-Calderon, MD,

Universidad del Valle, calle 4B # 36-00, Cali, Colombia

Daniel K. Benjamin Jr., MD, PhD, and

Kiser-Arena Professor of Pediatrics, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705, USA

Michael Cohen-Wolkowicz, MD, PhD

Associate Professor of Pediatrics, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705, USA

Abstract

Introduction—Invasive candidiasis is responsible for approximately 10% of nosocomial sepsis in very-low-birth-weight (VLBW) infants and is associated with substantial morbidity and mortality. Over the last 2 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 collected thus far or data submitted to regulatory agencies 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

Corresponding author: Daniel K. Benjamin Jr., MD, PhD, Duke Clinical Research Institute, 2400 Pratt St., Durham, NC 27705, USA; phone: +1-919-668-7081; danny.benjamin@duke.edu.

Lorena Botero-Calderon has no disclosures to report.

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 2- to 6-fold higher in neonates with invasive candidiasis relative to peers without the disease [2].

Among *Candida* species, *C. 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].

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% to 5% of VLBW infants compared to 4% to 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, central nervous system [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 Food and Drug Administration (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 amphotericin B deoxycholate 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, with an overall supported dose of 1.0–1.5 mg/kg/day [30, 31]. However, a population PK study 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, while older and heavier children may be overdosed at the same dose [32]. Penetration into the CSF seems to be associated with age. While in adults, CSF values

are 2–4% of serum concentrations [33], in a small series of premature infants born at 27.4 ($\pm$ 5) weeks gestational age ($n=5$), 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 include 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 gestational age 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 gestational age 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 1 published prospective randomized controlled study evaluated the efficacy of AmB vs. fluconazole in 23 neonates with candidemia from 2 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 vs. 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 randomized controlled trials (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 gestational age of 26 weeks and median birth weight of 863 g) who received at least 3 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 (gestational age [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 gestational age 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 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. lusitaniae*.

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 a 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 9 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 2-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, however, has been more extensively studied in neonates and infants. To date, the efficacy of fluconazole prophylaxis in this population has been evaluated in 8 retrospective observational studies [63–70], 6 RCTs [71–76], and 1 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 hours) [71]. Additionally, these investigators conducted a follow-up prospective, randomized, double-blind study (N~80) comparing 2 different fluconazole dosing regimens

(regimen from 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 8 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% confidence interval [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%]; $p=0.60$).

A meta-analysis of 5 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 [NNT]: 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 5 efficacy RCTs previously mentioned. Specifically, the effect of fluconazole on liver function tests [71–75] was evaluated in 2 of these RCTs, which included a total of 223 infants combined. No clinically significant increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 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 2 doses per day appears

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 interaction with itraconazole occurs in both children and adults [86].

We would not recommend itraconazole use in neonates and children given the erratic, non-linear 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. lusitaniae* [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 (IV) and oral formulations with approximately 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 less than 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 CYP2C19 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 2 newborns with *Candida* infection and concomitant severe cardiac disease. Administration of IV voriconazole (4 mg/kg/day) to 2 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].

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 pharmacokinetics limitations as well as an IV 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 per 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](https://clinicaltrials.gov/ct2/show/study/NCT01716234) #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 a 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 3, double-blind, randomized study to evaluate the safety and efficacy of isavuconazole vs. 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 since 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 hours) [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 hours [116]. In infants <3 months of age, caspofungin (25 mg/m²/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 gestational age 27 weeks and median birth weight 727 g) with persistent candidemia despite conventional antifungal therapy (amphotericin B and/or fluconazole or flucytosine) who received add-on therapy with IV 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 gestational age 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 5 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](https://clinicaltrials.gov/ct2/show/study/NCT01945281) #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 1 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 a mg/kg basis) are required to achieve equivalent drug exposure [128]. Hence, younger infants (gestational age of 24–40 weeks and postnatal age of 2–119 days) in 4 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 6 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 3 RCT comparing the safety and efficacy of micafungin vs. 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 maximum concentration (C_{max}) to minimal inhibitory concentration (MIC) and of area under the curve (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 hours) [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 analogue, 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 pharmacodynamics and a post-antifungal effect up to 10 hours 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 hours [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 hours to 24 hours) is supported by the longer elimination half-life when compared with adults (4 hours vs. 7 hours) [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]. Additionally, it is well documented the synergistic role of flucytosine when combined administration with amphotericin B is given for cryptococcal meningitis treatment by decreasing the necessary MIC of amphotericin B to inhibit *in vitro* growth of *Candida*, and also reducing 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.

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 randomized controlled trials. 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 collected thus far or data submitted to regulatory agencies 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 it takes about 3 to 5 days for specific identification. However, newer techniques such as matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS), peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), and polymerase chain reaction (PCR) 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.

Acknowledgments

Daniel K. Benjamin Jr. receives support from the United States government for his work in pediatric and neonatal clinical pharmacology (2K24HD058735-06, UL1TR001117, NICHD contract HHSN275201000003I, and NIAID contract HHSN272201500006I); he also receives research support from Cempra Pharmaceuticals (subaward to HHSO100201300009C) for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp).

Michael Cohen-Wolkowicz receives support for research from the NIH (1R01-HD076676-01A1), the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the National Institute of Allergy and Infectious Disease (HHSN272201500006I and HHSN272201300017I), the National Institute for Child Health and Human Development of the NIH (HHSN275201000003I), the Food and Drug Administration (1U01FD004858-01), the Biomedical Advanced Research and Development Authority (BARDA) (HHSO100201300009C), the nonprofit organization Thrasher Research Fund (www.thrasherresearch.org), and from industry (CardioDx and Durata Therapeutics) for drug development in adults and children (www.dcri.duke.edu/research/coi.jsp).

List of Abbreviations

5-FC	5-Flucytosine
ABCD	amphotericin B colloidal dispersion
ABLC	amphotericin B liposomal complex
AE	adverse event
ALT	alanine aminotransferase
AmB	amphotericin B deoxycholate
AST	aspartate aminotransferase
AUC	area under the curve
CI	confidence interval
C_{MAX}	maximum concentration
CNS	central nervous system
CSF	cerebrospinal fluid
ELBW	extremely low birth weight
EMA	European Medicines Agency
FDA	Food and Drug Administration
HCME	hematogenous <i>Candida</i> meningoencephalitis
IV	intravenous
L-AmB	liposomal amphotericin B
MIC	minimal inhibitory concentration
NICU	neonatal intensive care unit
NNT	number needed to treat
PD	pharmacodynamics
PK	pharmacokinetics
RCT	randomized controlled trial
VLBW	very low birth weight

Bibliography

1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002; 110(2 Pt 1):285–291. [PubMed: 12165580]
2. Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics*. 2006; 117:84–92. [PubMed: 16396864]
3. Friedman S, Richardson SE, Jacobs SE, O'Brien K. Systemic *Candida* infection in extremely low birth weight infants: short-term morbidity and long term neurodevelopmental outcome. *Pediatr Infect Dis J*. 2000; 19:499–504. [PubMed: 10877162]
4. Lee BE, Cheung PY, Robinson JL, et al. Comparative study of mortality and morbidity in premature infants (birth weight < 1250 g) with candidemia or candidal meningitis. *Clin Infect Dis*. 1998; 27:559–565. [PubMed: 9770157]
5. Clerihew L, Lamagni TL, Brocklehurst P, McGuire W. *Candida parapsilosis* infection in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92:F127–F129. [PubMed: 17337658]
6. Fridkin SK, Kaufman D, Edwards JR, et al. Changing incidence of *Candida* bloodstream infections among NICU patients in the United States: 1995–2004. *Pediatrics*. 2006; 117:1680–1687. [PubMed: 16651324]
7. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 48:503–535. [PubMed: 19191635]
8. Manzoni P, Benjamin DK, Hope W, et al. The management of *Candida* infections in preterm neonates and the role of micafungin. *J Matern Fetal Neonatal Med*. 2011; 24(Suppl 2):24–27. [PubMed: 21749182]
9. Cotten CM, McDonald S, Stoll B, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics*. 2006; 118:717–722. [PubMed: 16882828]
10. Benjamin DK Jr, DeLong ER, Steinbach WJ, et al. Empirical therapy for neonatal candidemia in very low birth weight infants. *Pediatrics*. 2003; 112:543–547. [PubMed: 12949281]
11. Aliaga S, Clark RH, Laughon M, et al. Changes in the incidence of candidiasis in neonatal intensive care units. *Pediatrics*. 2014; 133:236–242. [PubMed: 24446441]
12. Kelly MS, Benjamin DK Jr, Smith PB. The epidemiology and diagnosis of invasive candidiasis among premature infants. *Clinics Perinatol*. 2015; 42:105–117.
13. Benjamin DK Jr, Garges H, Steinbach WJ. *Candida* bloodstream infection in neonates. *Semin Perinatol*. 2003; 27:375–383. [PubMed: 14626501]
14. Benjamin DK Jr, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics*. 2010; 126:e865–e873. [PubMed: 20876174]
15. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in neonatal intensive care unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr Infect Dis J*. 2000; 19:319–324. [PubMed: 10783022]
16. Bendel CM. Nosocomial neonatal candidiasis. *Pediatr Infect Dis J*. 2005; 24:831–832. [PubMed: 16148852]
17. Benjamin DK Jr, Poole C, Steinbach WJ, et al. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. *Pediatrics*. 2003; 112(3 Pt 1): 634–640. [PubMed: 12949295]
18. Greenberg RG, Benjamin DK Jr. Neonatal candidiasis: diagnosis, prevention, and treatment. *J Infect*. 2014; 69(Suppl 1):S19–S22. [PubMed: 25129318]
19. Hsieh E, Smith PB, Jacqz-Aigrain E, et al. Neonatal fungal infections: when to treat? *Early Hum Dev*. 2012; 88(Suppl 2):S6–S10. [PubMed: 22633516]
20. Cohen-Wolkowicz M, Moran C, Benjamin DK Jr, Smith PB. Pediatric antifungal agents. *Curr Opin Infect Dis*. 2009; 22:553–558. [PubMed: 19741525]

21. Linder N, Klinger G, Shalit I, et al. Treatment of candidemia in premature infants: comparison of three amphotericin B preparations. *J Antimicrob Chemother.* 2003; 52:663–667. [PubMed: 12972450]
22. Jeon GW, Koo SH, Lee JH, et al. A comparison of AmBisome to amphotericin B for treatment of systemic candidiasis in very low birth weight infants. *Yonsei Med J.* 2007; 48:619–626. [PubMed: 17722233]
23. Scarcella A, Pasquariello MB, Giugliano B, et al. Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J.* 1998; 17:146–148. [PubMed: 9493812]
24. Bristol-Meyers Squibb. Fungizone (amphotericin B deoxycholate) [package insert]. 2009
25. Astellas Pharmaceuticals. [[Last accessed 15 December 2014]] AmBisome (liposomal amphotericin B) [package insert]. Available at: <http://www.astellas.us/docs/ambisome.pdf>
26. Sigma-Tau Pharmaceuticals. [[Last accessed 21 December 2014]] Abelcet (amphotericin B Lipid Complex) [package insert]. Available at: http://www.sigmatau.com/products/abelcet_rx.asp
27. Lestner J, Smith PB, Cohen-Wolkowicz M, et al. Antifungal agents and therapy for infants and children with invasive fungal infections: a pharmacological perspective. *Br J Clin Pharmacol.* 2012;1381–1395.
28. Groll AH, Tragiannidis A. Update on antifungal agents for paediatric patients. *Clin Microbiol Infect.* 2010; 16:1343–1353. [PubMed: 20678177]
29. ABCD. [[Last accessed 20 February 2015]] Johns Hopkins Antibiotic (ABX) Guide. Available at: http://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540020/all/Amphotericin_B_cholesteryl_sulfate_complex_ABCD_
30. Baley JE, Meyers C, Kliegman RM, et al. Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr.* 1990; 116:791–797. [PubMed: 2329429]
31. Koren G, Lau A, Klein J, et al. Pharmacokinetics and adverse effects of amphotericin B in infants and children. *J Pediatr.* 1988; 113:559–563. [PubMed: 3411404]
32. Nath CE, McLachlan AJ, Shaw PJ, et al. Population pharmacokinetics of amphotericin B in children with malignant diseases. *Br J Clin Pharmacol.* 2001; 52:671–680. [PubMed: 11736878]
33. Luna B, Drew RH, Perfect JR. Agents for treatment of invasive fungal infections. *Otolaryngol Clin North Am.* 2000; 33:277–299. [PubMed: 10736404]
34. Almirante B, Rodriguez D. Antifungal agents in neonates. *Pediatr Drugs.* 2007; 9:311–321.
35. Fernandez M, Moylett EH, Noyola DE, Baker CJ. Candidal meningitis in neonates: a 10-year review. *Clin Infect Dis.* 2000; 31:458–463. [PubMed: 10987705]
36. Driessen M, Ellis JB, Cooper PA, et al. Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. *Pediatr Infect Dis J.* 1996; 15:1107–1112. [PubMed: 8970221] *This study is the only published prospective randomized controlled study evaluating the efficacy of AmB vs. fluconazole in 23 neonates with candidemia from 2 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). Results showed superior efficacy in the fluconazole group, 67% (8 of 12 patients) survived vs. 55% (6 of 11 infants) in the amphotericin group.
37. Glick C, Graves GR, Feldman S. Neonatal fungemia and amphotericin B. *South Med J.* 1993; 86:1368–1371. [PubMed: 8272913]
38. Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. *Antimicrob Agents Chemother.* 1989; 33:1989–1993. [PubMed: 2610508]
39. Le J, Adler-Shohet FC, Nguyen C, Lieberman JM. Nephrotoxicity associated with amphotericin B deoxycholate in neonates. *Pediatr Infect Dis J.* 2009; 28:1061–1063. [PubMed: 19935267]
40. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. *Rev Infect Dis.* 1990; 12:308–329. [PubMed: 2184499]
41. Holler B, Omar SA, Farid MD, Patterson MJ. Effects of fluid and electrolyte management on amphotericin B-induced nephrotoxicity among extremely low birth weight infants. *Pediatrics.* 2004; 113:e608–e616. [PubMed: 15173544]
42. Dismukes WE. Introduction to antifungal drugs. *Clin Infect Dis.* 2000; 30:653–657. [PubMed: 10770726]

43. Andes D, Safdar N, Marchillo K, Conklin R. Pharmacokinetic-pharmacodynamic comparison of amphotericin B (AMB) and two lipid-associated AMB preparations, liposomal AMB and AMB lipid complex, in murine candidiasis models. *Antimicrob Agents Chemother*. 2006; 50:674–684. [PubMed: 16436726]
44. Groll AH, Giri N, Petraitis V, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental *Candida albicans* infection of the central nervous system. *J Infect Dis*. 2000; 182:274–282. [PubMed: 10882607]
45. Groll AH, Lyman CA, Petraitis V, et al. Compartmentalized intrapulmonary pharmacokinetics of amphotericin B and its lipid formulations. *Antimicrob Agents Chemother*. 2006; 50:3418–3423. [PubMed: 17005824]
46. Wurthwein G, Groll AH, Hempel G, et al. Population pharmacokinetics of amphotericin B lipid complex in neonates. *Antimicrob Agents Chemother*. 2005; 49:5092–5098. [PubMed: 16304177]
47. Lopez Sastre JB, Coto Cotallo GD, Fernandez Colomer B. Grupo de Hospitales C. Neonatal invasive candidiasis: a prospective multicenter study of 118 cases. *Am J Perinatol*. 2003; 20:153–163. [PubMed: 12802715]
48. Cetin H, Yalaz M, Akisu M, et al. The efficacy of two different lipid-based amphotericin B in neonatal *Candida* septicemia. *Pediatr Int*. 2005; 47:676–680. [PubMed: 16354223]
49. Walsh TJ, Seibel NL, Arndt C, et al. Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J*. 1999; 18:702–708. [PubMed: 10462340]
50. Wiley JM, Seibel NL, Walsh TJ. Efficacy and safety of amphotericin B lipid complex in 548 children and adolescents with invasive fungal infections. *Pediatr Infect Dis J*. 2005; 24:167–174. [PubMed: 15702047]
51. Ascher SB, Smith PB, Watt K, et al. Antifungal therapy and outcomes in infants with invasive *Candida* infections. *Pediatr Infect Dis J*. 2012; 31:439–443. [PubMed: 22189522] *This study included a large cohort of 730 infants <120 days of age and showed both increased mortality and treatment failure for neonates with confirmed *Candida* infection treated with lipid formulations compared with AmB. The results of this study warrant reconsideration of the use and role of lipid amphotericin formulations in the nursery.
52. Frattarelli DA, Reed MD, Giacoia GP, Aranda JV. Antifungals in systemic neonatal candidiasis. *Drugs*. 2004; 64:949–968. [PubMed: 15101785]
53. Watt K, Manzoni P, Cohen-Wolkowicz M, et al. Triazole use in the nursery: fluconazole, voriconazole, posaconazole, and ravuconazole. *Curr Drug Metab*. 2013; 14:193–202. [PubMed: 22935068]
54. Autmizguine J, Guptill JT, Cohen-Wolkowicz M, et al. Pharmacokinetics and pharmacodynamics of antifungals in children: clinical implications. *Drugs*. 2014; 74:891–909. [PubMed: 24872147]
55. Saxen H, Virtanen M, Carlson P, et al. Neonatal *Candida parapsilosis* outbreak with a high case fatality rate. *Pediatr Infect Dis J*. 1995; 14:776–781. [PubMed: 8559627]
56. Cleveland AA, Farley MM, Harrison LH, et al. Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011. *Clin Infect Dis*. 2012; 55:1352–1361. [PubMed: 22893576]
57. Pfaller MA, Messer SA, Boyken L, et al. Variation in susceptibility of bloodstream isolates of *Candida glabrata* to fluconazole according to patient age and geographic location. *J Clin Microb*. 2003; 41:2176–2179.
58. Roerig. [[Last accessed 15 December 2014]] Diflucan (fluconazole) [package insert]. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=575>
59. Turner K, Manzoni P, Benjamin DK, et al. Fluconazole pharmacokinetics and safety in premature infants. *Curr Med Chem*. 2012; 19:4617–4620. [PubMed: 22876898]
60. Wade KC, Wu D, Kaufman DA, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother*. 2008; 52:4043–4049. [PubMed: 18809946]
61. Wade KC, Benjamin DK Jr. Kaufman DA, et al. Fluconazole dosing for the prevention or treatment of invasive candidiasis in young infants. *Pediatr Infect Dis J*. 2009; 28:717–723. [PubMed: 19593252]

62. Fasano C, O'Keeffe J, Gibbs D. Fluconazole treatment of neonates and infants with severe fungal infections not treatable with conventional agents. *Eur J Clin Microbiol Infect Dis*. 1994; 13:351–354. [PubMed: 8070446]
63. Healy CM, Baker CJ, Zaccaria E, Campbell JR. Impact of fluconazole prophylaxis on incidence and outcome of invasive candidiasis in a neonatal intensive care unit. *J Pediatr*. 2005; 147:166–171. [PubMed: 16126043]
64. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant *Candida* species. *Pediatrics*. 2008; 121:703–710. [PubMed: 18381534]
65. Aghai ZH, Mudduluru M, Nakhla TA, et al. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. *J Perinatol*. 2006; 26:550–555. [PubMed: 16940972]
66. Bertini G, Perugi S, Dani C, et al. Fluconazole prophylaxis prevents invasive fungal infection in high-risk, very low birth weight infants. *J Pediatr*. 2005; 147:162–165. [PubMed: 16126042]
67. Manzoni P, Arisio R, Mostert M, et al. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. *Pediatrics*. 2006; 117:e22–e32. [PubMed: 16326690]
68. McCrossan BA, McHenry E, O'Neill F, et al. Selective fluconazole prophylaxis in high-risk babies to reduce invasive fungal infection. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92:F454–F458. [PubMed: 17460023]
69. Uko S, Soghier LM, Vega M, et al. Targeted short-term fluconazole prophylaxis among very low birth weight and extremely low birth weight infants. *Pediatrics*. 2006; 117:1243–1252. [PubMed: 16585321]
70. Weitkamp JH, Ozdas A, LaFleur B, Potts AL. Fluconazole prophylaxis for prevention of invasive fungal infections in targeted highest risk preterm infants limits drug exposure. *J Perinatol*. 2008; 28:405–411. [PubMed: 18185518]
71. Kaufman D, Boyle R, Hazen KC, et al. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med*. 2001; 345:1660–1666. [PubMed: 11759644]
72. Kaufman D, Boyle R, Hazen KC, et al. Twice weekly fluconazole prophylaxis for prevention of invasive *Candida* infection in high-risk infants of <1000 grams birth weight. *J Pediatr*. 2005; 147:172–179. [PubMed: 16126045]
73. Kicklighter SD, Springer SC, Cox T, et al. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. *Pediatrics*. 2001; 107:293–298. [PubMed: 11158461]
74. Manzoni P, Stolfi I, Pugni L, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med*. 2007; 356:2483–2495. [PubMed: 17568029] **This RCT including 322 infants with birth weight <1500 g from 8 NICUs in Italy was conducted to evaluate 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 and *Candida* colonization.
75. Parikh TB, Nanavati RN, Patankar CV, et al. Fluconazole prophylaxis against fungal colonization and invasive fungal infection in very low birth weight infants. *Indian Pediatr*. 2007; 44:830–837. [PubMed: 18057479]
76. Benjamin DK Jr, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. *JAMA*. 2014; 311:1742–1749. [PubMed: 24794367] **This is the most recent RCT to evaluate the safety and efficacy of fluconazole in preventing death or invasive candidiasis in ELBW infants and included 361 infants with birth weight <750 g from 32 NICUs in the United States randomly assigned to receive 6 mg/kg of body weight twice weekly for 42 days or placebo. 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. Based on these results, the routine use of fluconazole prophylaxis should be limited to NICUs with moderate-to-high incidence of invasive candidiasis.
77. Clerihew L, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. *Cochrane Database Syst Rev*. 2007; (4):CD003850. [PubMed: 17943803]

78. Manavathu EK, Cutright JL, Chandrasekar PH. Organism-dependent fungicidal activities of azoles. *Antimicrob Agents Chemother*. 1998; 42:3018–3021. [PubMed: 9797246]
79. Fung-Tomc JC, White TC, Minassian B, et al. In vitro antifungal activity of BMS-207147 and itraconazole against yeast strains that are non-susceptible to fluconazole. *Diagn Microbiol Infect Dis*. 1999; 35:163–167. [PubMed: 10579098]
80. Janssen Pharmaceuticals. [[Last accessed 30 October 2013]] SPORANOX - itraconazole solution [package insert]. Available at: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=ae50721d-ee15-4ee7-9fe7-afd98c56461b>
81. Groll AH, Wood L, Roden M, et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. *Antimicrob Agents Chemother*. 2002; 46:2554–2563. [PubMed: 12121932]
82. Schmitt C, Perel Y, Harousseau JL, et al. Pharmacokinetics of itraconazole oral solution in neutropenic children during long-term prophylaxis. *Antimicrob Agents Chemother*. 2001; 45:1561–1564. [PubMed: 11302829]
83. Bhandari V, Narang A, Kumar B, et al. Itraconazole therapy for disseminated candidiasis in a very low birthweight neonate. *J Paediatr Child Health*. 1992; 28:323–324. [PubMed: 1323317]
84. Sciacca A, Betta P, Cilauro S, et al. [Oral administration of itraconazole in a case of neonatal hepatic candidiasis]. *Med Surg Pediatr*. 1995; 17:173–175.
85. Bermudez M, Fuster JL, Llinares E, et al. Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. *J Pediatr Hematol Oncol*. 2005; 27:389–392. [PubMed: 16012330]
86. Moriyama B, Henning SA, Leung J, et al. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. *Mycoses*. 2012; 55:290–297. [PubMed: 22126626]
87. Pasquale T, Tomada JR, Ghannoun M, et al. Emergence of *Candida tropicalis* resistant to caspofungin. *J Antimicrob Chemother*. 2008; 61:219. [PubMed: 18024953]
88. Hawkins JL, Baddour LM. *Candida lusitanae* infections in the era of fluconazole availability. *Clin Infect Dis*. 2003; 36:e14–e18. [PubMed: 12522762]
89. Pfaller MA, Diekema DJ, Gibbs DL, et al. Geographic and temporal trends in isolation and antifungal susceptibility of *Candida parapsilosis*: a global assessment from the ARTEMIS DISK Antifungal Surveillance Program, 2001 to 2005. *J Clin Microbiol*. 2008; 46:842–849. [PubMed: 18199791]
90. Pfaller MA, Messer SA, Boyken L, et al. Selection of a surrogate agent (fluconazole or voriconazole) for initial susceptibility testing of posaconazole against *Candida* spp.: results from a global antifungal surveillance program. *J Clin Microbiol*. 2008; 46:551–559. [PubMed: 18094129]
91. European Medicines Agency. Vfend: EPAR, product information. 2013
92. Roerig. Vfend (voriconazole) [package insert]. 2013
93. Kohli V, Taneja V, Sachdev P, Joshi R. Voriconazole in newborns. *Indian Pediatr*. 2008; 45:236–238. [PubMed: 18367773]
94. Frankenbusch K, Eifinger F, Kribs A, et al. Severe primary cutaneous aspergillosis refractory to amphotericin B and the successful treatment with systemic voriconazole in two premature infants with extremely low birth weight. *J Perinatol*. 2006; 26:511–514. [PubMed: 16871222]
95. Muldrew KM, Maples HD, Stowe CD, Jacobs RF. Intravenous voriconazole therapy in a preterm infant. *Pharmacotherapy*. 2005; 25:893–898. [PubMed: 15927909]
96. Tan K, Brayshaw N, Tomaszewski K, et al. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J Clin Pharmacol*. 2006; 46:235–243. [PubMed: 16432276]
97. Denning DW, Griffiths CE. Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. *Clin Exp Dermatol*. 2001; 26:648–653. [PubMed: 11722447]
98. Merck. Noxafil (posaconazole) [package insert]. 2012
99. McKeage K. Posaconazole: a review of the gastro-resistant tablet and intravenous solution in invasive fungal infections. *Drugs*. 2015 published online 17 January 2015.

100. Courtney R, Sansone A, Smith W, et al. Posaconazole pharmacokinetics, safety, and tolerability in subjects with varying degrees of chronic renal disease. *J Clin Pharmacol*. 2005; 45:185–192. [PubMed: 15647411]
101. Welzen ME, Bruggemann RJ, Van Den Berg JM, et al. A twice daily posaconazole dosing algorithm for children with chronic granulomatous disease. *Pediatr Infect Dis J*. 2011; 30:794–797. [PubMed: 21772229]
102. Segal BH, Barnhart LA, Anderson VL, et al. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis*. 2005; 40:1684–1688. [PubMed: 15889369]
103. Krishna G, Sansone-Parsons A, Martinho M, et al. Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. *Antimicrob Agents Chemother*. 2007; 51:812–818. [PubMed: 17210771]
104. Seifert H, Aurbach U, Stefanik D, Cornely O. In vitro activities of isavuconazole and other antifungal agents against *Candida* bloodstream isolates. *Antimicrob Agents Chemother*. 2007; 51:1818–1821. [PubMed: 17307977]
105. Guinea J, Pelaez T, Recio S, et al. In vitro antifungal activities of isavuconazole (BAL4815), voriconazole, and fluconazole against 1,007 isolates of zygomycete, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species. *Antimicrob Agents Chemother*. 2008; 52:1396–1400. [PubMed: 18212101]
106. Pharmaceutica, B. [[Last accessed 18 February 18 2015]] Basilea announces that FDA's Anti-Infective Drugs Advisory Committee recommends approval of isavuconazole for the treatment of invasive aspergillosis and mucormycosis. Available at: <http://www.basileacom/chameleon/public/86a99c56-37ce-f80c-b8c5-76337f55e395/668590pdf>
107. Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. *Infect Drug Resist*. 2013; 6:163–174. [PubMed: 24187505]
108. Majithiya J, Sharp A, Parmar A, et al. Efficacy of isavuconazole, voriconazole and fluconazole in temporarily neutropenic murine models of disseminated *Candida tropicalis* and *Candida krusei*. *J Antimicrob Chemother*. 2009; 63:161–166. [PubMed: 19008255]
109. Hatano K, Morishita Y, Nakai T, Ikeda F. Antifungal mechanism of FK463 against *Candida albicans* and *Aspergillus fumigatus*. *J Antibiot (Tokyo)*. 2002; 55:219–222. [PubMed: 12003006]
110. Ikeda F, Wakai Y, Matsumoto S, et al. Efficacy of FK463, a new lipopeptide antifungal agent, in mouse models of disseminated candidiasis and aspergillosis. *Antimicrob Agents Chemother*. 2000; 44:614–618. [PubMed: 10681327]
111. Groll AH, Mickiene D, Petraitiene R, et al. Pharmacokinetic and pharmacodynamic modeling of anidulafungin (LY303366): reappraisal of its efficacy in neutropenic animal models of opportunistic mycoses using optimal plasma sampling. *Antimicrob Agents Chemother*. 2001; 45:2845–2855. [PubMed: 11557479]
112. Wynn JL, Tan S, Gantz MG, et al. Outcomes following candiduria in extremely low birth weight infants. *Clin Infect Dis*. 2012; 54:331–339. [PubMed: 22144537]
113. Ernst EJ, Klepser ME, Pfaller MA. Postantifungal effects of echinocandin, azole, and polyene antifungal agents against *Candida albicans* and *Cryptococcus neoformans*. *Antimicrob Agents Chemother*. 2000; 44:1108–1111. [PubMed: 10722525]
114. Merck. Cancidas (caspofungin) [package insert]. 2013
115. European Medicines Agency. [[Last accessed 20 February 20 2015]] Cancidas: EPAR - product information. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000379/WC500057186pdf.
116. Stone JA, Holland SD, Wickersham PJ, et al. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agents Chemother*. 2002; 46:739–745. [PubMed: 11850256]
117. Saez-Llorens X, Macias M, Maiya P, et al. Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrob Agents Chemother*. 2009; 53:869–875. [PubMed: 19075070]

118. Natarajan G, Lulic-Botica M, Rongkavilit C, et al. Experience with caspofungin in the treatment of persistent fungemia in neonates. *J Perinatol*. 2005; 25:770–777. [PubMed: 16222348]
119. Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J*. 2004; 23:1093–1097. [PubMed: 15626944]
120. Li CC, Sun P, Dong Y, et al. Population pharmacokinetics and pharmacodynamics of caspofungin in pediatric patients. *Antimicrob Agents Chemother*. 2011; 55:2098–2105. [PubMed: 21300834]
121. Walsh TJ, Adamson PC, Seibel NL, et al. Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother*. 2005; 49:4536–4545. [PubMed: 16251293]
122. Zaoutis TE, Jafri HS, Huang LM, et al. A prospective, multicenter study of caspofungin for the treatment of documented *Candida* or *Aspergillus* infections in pediatric patients. *Pediatrics*. 2009; 123:877–884. [PubMed: 19255017]
123. Franklin JA, McCormick J, Flynn PM. Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J*. 2003; 22:747–749. [PubMed: 12938676]
124. Astellas Pharmaceuticals. Mycamine [package insert]. 2013
125. European Medicines Agency. Mycamine: EPAR, product information. 2013
126. Hope WW, Mickiene D, Petraitis V, et al. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous *Candida meningoenkephalitis*: implications for echinocandin therapy in neonates. *J Infect Dis*. 2008; 197:163–171. [PubMed: 18171300]
127. Petraitis V, Petraitiene R, Groll AH, et al. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. *Antimicrob Agents Chemother*. 2002; 46:1857–1869. [PubMed: 12019101]
128. Hope WW, Seibel NL, Schwartz CL, et al. Population pharmacokinetics of micafungin in pediatric patients and implications for antifungal dosing. *Antimicrob Agents Chemother*. 2007; 51:3714–3719. [PubMed: 17638696]
129. Lepak AJ, Marchillo K, VanHecker J, et al. Isavuconazole pharmacodynamic target determination for *Candida* species in an in vivo murine disseminated candidiasis model. *Antimicrob Agents Chemother*. 2013; 57:5642–5648. [PubMed: 24002092]
130. Queiroz-Telles F, Berezin E, Leverger G, et al. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. *Pediatr Infect Dis J*. 2008; 27:820–826. [PubMed: 18679151]
131. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidiasis: a phase III randomised double-blind trial. *Lancet*. 2007; 369:1519–1527. [PubMed: 17482982]
132. Arrieta AC, Maddison P, Groll AH. Safety of micafungin in pediatric clinical trials. *Pediatr Infect Dis J*. 2011; 30:e97–e102. [PubMed: 21378595]
133. Smith PB, Walsh TJ, Hope W, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J*. 2009; 28:412–415. [PubMed: 19319022]
134. Pfaller MA, Boyken L, Hollis RJ, et al. In vitro activities of anidulafungin against more than 2,500 clinical isolates of *Candida* spp., including 315 isolates resistant to fluconazole. *J Clin Microbiol*. 2005; 43:5425–5427. [PubMed: 16272464]
135. [[Last accessed 15 December 2014]] Roerig. Eraxis (anidulafungin) [package insert]. Available at: <http://medlibrary.org/lib/rx/meds/eraxis/>
136. Damle B, Stogniew M, Dowell J. Pharmacokinetics and tissue distribution of anidulafungin in rats. *Antimicrob Agents Chemother*. 2008; 52:2673–2676. [PubMed: 18443124]
137. Benjamin DK Jr, Driscoll T, Seibel NL, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother*. 2006; 50:632–638. [PubMed: 16436720]
138. Cohen-Wolkowicz M, Benjamin DK Jr, Piper L, et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. *Clin Pharmacol Ther*. 2011; 89:702–707. [PubMed: 21412233]

139. Denning DW, Hope WW. Therapy for fungal diseases: opportunities and priorities. *Trends Microbiol.* 2010; 18:195–204. [PubMed: 20207544]
140. Johnson E, Espinel-Ingroff A, Szekely A, et al. Activity of voriconazole, itraconazole, fluconazole and amphotericin B in vitro against 1763 yeasts from 472 patients in the voriconazole phase III clinical studies. *Int J Antimicrob Agents.* 2008; 32:511–514. [PubMed: 18790613]
141. Valeant. [[Last accessed 21 December 2014]] Ancobon (flucytosine) [package insert]. Available at: <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=2352>
142. Lewis RE, Klepser ME, Pfaller MA. In vitro pharmacodynamic characteristics of flucytosine determined by time-kill methods. *Diagn Microbiol Infect Dis.* 2000; 36:101–105. [PubMed: 10705051]
143. Schonebeck J, Polak A, Fernex M, Scholer HJ. Pharmacokinetic studies on the oral antimycotic agent 5-fluorocytosine in individuals with normal and impaired kidney function. *Chemotherapy.* 1973; 18:321–336. [PubMed: 4741211]
144. Soltani M, Tobin CM, Bowker KE, et al. Evidence of excessive concentrations of 5-flucytosine in children aged below 12 years: a 12-year review of serum concentrations from a UK clinical assay reference laboratory. *Int J Antimicrob Agents.* 2006; 28:574–577. [PubMed: 17085019]
145. Johnson KC, Barone JG. Management of obstructing fungal pyelonephritis in infants. *Urology.* 2006; 67 424.e7-e9.
146. Wald M, Lawrenz K, Kretzer V, et al. A very low birth weight infant with *Candida* nephritis with fungus balls. Full recovery after pyelotomy and antifungal combination therapy. *Eur J Pediatr.* 2003; 162:642–643. [PubMed: 12827511]
147. Bryant K, Maxfield C, Rabalais G. Renal candidiasis in neonates with candiduria. *Pediatr Infect Dis J.* 1999; 18:959–963. [PubMed: 10571429]
148. Utz JP, Garriques IL, Sande MA, et al. Therapy of cryptococcosis with a combination of flucytosine and amphotericin B. *J Infect Dis.* 1975; 132:368–373. [PubMed: 1185007]
149. Francis P, Walsh TJ. Evolving role of flucytosine in immunocompromised patients: new insights into safety, pharmacokinetics, and antifungal therapy. *Clin Infect Dis.* 1992; 15:1003–1018. [PubMed: 1457631]

Highlights

- The majority of studies of antifungal agents in neonates are limited to PK/PD 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.

Table 1

Summary of Antifungal Agents in Neonates

Drug	Neonates (0–30 days)			Labelled in neonates by FDA/EMA	References
	Dosing	Efficacy	Safety		
Polyenes					
Amphotericin B	0.6–1 mg/kg IV q24h	No	Yes	No/No	27, 30–32, 38
ABLC	2.5–5 mg/kg q24h	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 q72h ^a	Yes for prophylaxis	Yes	No/Yes	59, 60, 77
	12 mg/kg q48h ^b				
	12 mg/kg q24h ^c				
	Prophylaxis: 6 mg/kg twice weekly				
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 IV q24h	No	No	No/No	27, 115, 117, 120–122
Micafungin	10 mg/kg IV q24h ^d	No	Limited	No/Yes	27, 132
Anidulafungin	Load with 3 mg/kg IV once, then 1.5 mg/kg IV q24h	No	No	No/No	27, 137, 138, 149

ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin B lipid complex; EMA = European Medicines Agency; FDA = Food and Drug Administration; IV = intravenous; L-AmB = liposomal amphotericin B; q = every.

^a 29 weeks gestation, postnatal age 0–14 days.

^b 29 weeks gestation, postnatal age >14 days, or 30–36 weeks gestation, postnatal age 0–14 days.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^c 30 weeks gestation, postnatal age >14 days, or >36 weeks gestation.

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