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Management of Neonatal Candidiasis

Michael Cohen-Wolkowiez[1], **Daniel K Benjamin Jr**[2], and **P Brian Smith**[2]
[1]Duke University Department of Pediatrics, Durham, NC, USA
[2]Duke Clinical Research Institute, Durham, NC, USA

Abstract

Invasive candidiasis (IC) is common and often fatal in extremely premature neonates. In the last decade, the therapeutic armamentarium for IC has markedly expanded; however, the pharmacokinetics, safety and efficacy of most antifungal agents in premature neonates are unknown. We will review the major systemic antifungal agents in clinical use.

Documented invasive candidiasis (IC) is defined as a positive culture from normally sterile body fluid. The most common source (approximately 70% of neonatal cases) is the bloodstream. Other sources include urine (15%) and the cerebrospinal fluid (CSF; approximately 10%).

The cumulative incidence of invasive candidiasis is inversely proportional to birth weight at <1% in neonates born >1500 g, 1% in neonates born 1001–1500 g, 4% in neonates born 751–1000 g, and 12% in neonates born 401–750 g [1–3]. Nearly 80% of cases diagnosed in premature neonates occur in the first 42 days of life [1]. Birth weight and age at time of infection also predict subsequent mortality: up to 40% of neonates <750 g die as compared with <20% in neonates born 1000–1500 g [1]. The associated mortality with IC is three times higher than that of uninfected neonates of similar gestational age and birth weight [4] and morbidity is substantial with both end-organ damage [5] and neurodevelopmental impairment [1,6]. The prevalence of end-organ damage outside of the central nervous system is approximately 10% (Benjamin et al SPR 2008); central nervous system disease is difficult to diagnose, but is thought to be common based on animal model, clinical and autopsy studies.

Antifungal agents currently used in clinical practice include polyenes (amphotericin B deoxycholate and lipid formulations), azoles (fluconazole, voriconazole, and posaconazole), and echinocandins (caspofungin, micafungin, and anidulafungin). In neonates, these products are most commonly prescribed in three different settings:

- Prophylaxis of neonatal candidiasis.
- Empirical therapy of suspected invasive fungal infections.
- Treatment of confirmed candidiasis.

Although these agents are used extensively in neonates, none are US Food and Drug Administration (FDA) approved for use in neonates <3 months of age. Table 1 summarizes important studies addressing the pharmacokinetics and dosing of antifungal agents in neonates and children.

Address for correspondence: Daniel K Benjamin, Associate Professor, Duke University, Pediatrics, 2400 Pratt Street, Duke Clinical Research Institute, Durham, NC 27715, USA. danny.benjamin@duke.edu.

Antifungal therapy

There is a paucity of randomized trials evaluating treatment options in neonatal candidiasis, and a well-powered efficacy trial has yet to be completed. Although duration of antifungal therapy has not been established, because of the frequency of central nervous system involvement, a minimum of 21 days of systemic therapy should be considered. End organ involvement, assessment of neonates with candidemia should include an ultrasound of the head and abdomen, urine culture, lumbar puncture, ophthalmologic exam, and an echocardiogram.

As in older patients, removal (or replacement) of central venous catheters within 24 h of a positive blood culture is an important component of treatment [7]. Although obtaining new central vascular access is often difficult in preterm neonates, delayed removal or replacement of central venous catheters in candidemic neonates has been associated with increased mortality and morbidity, including worse neurodevelopmental outcomes [1,7,8]. We suggest that if central access is required for supportive care, replacement of the central catheter with a new catheter at a different anatomic site be performed.

Amphotericin B deoxycholate

A polyene antifungal, amphotericin B deoxycholate, is the most frequently used agent for IC in the neonatal population [9]. Despite the long history of amphotericin B deoxycholate use, there are limited pharmacokinetic data in neonates and some noticeable differences in adult versus pediatric patients. Two studies involving a total of 17 neonates demonstrated a longer half-life of the drug compared with adults [10,11]. The dose of amphotericin B deoxycholate is 0.5–1.0 mg/kg once daily over 2–4 h [12]. CSF penetration, which is only 5–10% of serum levels in adults, may reach 40% of serum levels in preterm neonates [13]. Side effects observed in neonates include electrolyte abnormalities and nephrotoxicity [14]. Close monitoring of potassium and magnesium levels, and renal function, is important during therapy [15].

Amphotericin B deoxycholate is effective against most *Candida* spp. that cause disease in neonates, with the exception of *C lusitaniae* [16]. Resistance has also been noted in some isolates of *C glabrata* and *C krusei* [17].

Lipid preparations of amphotericin B

Inability to tolerate amphotericin B deoxycholate due to renal insufficiency may provoke the need for alternate therapies for invasive candidiasis [18]. Three lipid formulations of amphotericin B are available: amphotericin B lipid complex (ABLC or Abelcet®), amphotericin B colloidal dispersion (ABCD or Amphotec®), and liposomal amphotericin B (L-amB or AmBisome®). A potential advantage of these drugs is the ability to administer increased doses of the parent drug with less associated renal toxicity. Published experience with these drugs in neonates is limited [19]. The lipid preparations may not be optimal to clear renal infections because the drugs concentrate in lower amounts in the kidney than does amphotericin B deoxycholate [20]. A population pharmacokinetics study of ABLC (2.5–5 mg/kg/day) conducted in 28 neonates with IC (median weight 1060 g [range 480–4900 g]; median gestational age 27 weeks [24–41 weeks]) showed that weight was the only factor influencing clearance [21]. The disposition of ABLC in these infants did not differ from older children.

ABCD and L-AmB were compared with amphotericin B deoxycholate in 56 candidemic neonates, including 36 extremely low birth weight neonates (birth weight <1000 g) [18]. Neonates with creatinine level <1.2 mg/dL were given amphotericin B deoxycholate (n=34)

while the remaining patients were randomized to either ABCD (n=16) or L-AmB (n=6). No differences in mortality rate or time to clear infection were observed.

In another study, L-AmB was evaluated in 40 preterm and four term neonates with candidiasis [15]. The only side effect noted was hypokalemia, which occurred in 16 (36%) of the neonates; 32 neonates (73%) responded to therapy, including five of six (83%) with meningo-encephalitis. A series of 41 episodes of candidiasis in neonates (69% were extremely low birth weight [ELBW]) identified and treated prospectively with L-AmB, noted successful treatment in 39 (95%) of cases [19]. The authors noted that eradication of infection occurred earlier when the target dose of 5–7 mg/kg/day was reached faster.

In a multicenter pediatric trial of 111 patients on ABLC, the only side effect noted in the 11 neonates was a mild rise in serum creatinine in 36% (four of the 11 neonates) [22]. Another trial observed 118 cases of neonatal candidiasis where L-AmB was given to eight neonates and ABLC was given to 29 [23]. No difference in mortality rate was observed between the two groups and efficacy was 94% and 86% with L-AmB and ABLC, respectively.

Flucytosine (5-FC)

Flucytosine is not recommended as monotherapy because resistance rapidly develops; however, the antifungal is occasionally given in combination with amphotericin B deoxycholate for meningo-encephalitis [24]. A review of 17 cases of *Candida* meningo-encephalitis (including 11 patients <12 months of age) observed improvement in 15 patients on combination therapy of amphotericin B deoxycholate and flucytosine [25]. However an evaluation of 320 ELBW neonates with candidiasis [1], including 27 with meningo-encephalitis, showed that time to clear infection was longer in neonates given combination flucytosine and amphotericin B than those treated with amphotericin B alone.

Flucytosine plasma concentrations in neonates are highly variable. In a study of 33 neonates who received intravenous or oral flucytosine, drug concentrations were low (trough <20 mg/L or peak <50 mg/L) in 40%; undetectable in 5%; high (trough level >40 mg/L or peak >80 mg/L) in 39%; and potentially toxic (>100 mg/L) in 10% of neonates [26].

The lack of availability of a parenteral formulation in the US limits the utility of flucytosine in neonates. Dosage of the drug is 50–150 mg/kg/day divided every 6 h. Bone marrow suppression is the predominant toxicity, seen largely with levels >100 μg/mL, so levels should be closely monitored in neonates with impaired renal function [27,28]. Because the benefits of flucytosine are unproven, the narrow therapeutic range, the need for therapeutic drug monitoring and need for oral administration in the US, the drug should only rarely be used in the young infant.

Azoles (fluconazole, voriconazole, and posaconazole)

Fluconazole is commonly used to treat candidiasis in neonates [29]. The drug may be given orally or intravenously and is nearly completely absorbed from the gastrointestinal tract [29,30]. The drug has a long half-life that decreases with increasing postnatal age [31]. Although fungistatic, fluconazole penetrates the CSF, kidneys, and liver well. Fluconazole is ideal for treating urinary tract infections because it is concentrated and excreted predominantly unchanged by the kidneys.

Fluconazole compared favorably with amphotericin B deoxycholate in one underpowered randomized trial of 23 very low birth weight (VLBW) neonates [32]. Other reports of fluconazole use are from uncontrolled prospective studies or retrospective reports. In one study that included 32 patients aged <3 months, 31 (97%) experienced successful treatment

with fluconazole [33]; two of 32 had elevated transaminases during treatment. In another study, 18 of 19 preterm infants treated with fluconazole cleared infection [34].

The recommended dosage of the intravenous or oral form of the drug in adult patients is approximately 4.5–6 mg/kg/day, but dosages of 10–12 mg/kg/day should be used for treatment in children and infants [35]. A small study of fluconazole in preterm infants reported prolonged plasma half-lives in the first 2 weeks of life [31]. A population pharmacokinetic study in 55 neonates and young infants (median weight 1.02 kg, gestational age at birth 26 weeks, and postnatal age 2.3 weeks) suggests that maintenance fluconazole doses of 12 mg/kg/day are necessary to achieve exposures similar to older children and adults [35]. Experts have also proposed the use of a loading dose, double the amount of the maintenance dose, to achieve steady-state concentrations sooner than the traditional dosing scheme [35]. This strategy is currently being evaluated in a Phase I clinical trial. The safety of fluconazole is well documented in older patients, and the product is thought to be safe in neonates.

The two most common species of *Candida* found in neonates, *C albicans* and *C parapsilosis*, are typically sensitive to fluconazole. However, 50% of *C glabrata* and 100% of *C krusei* isolates are reported to be resistant to fluconazole [36].

Owing to its pharmacokinetic properties, fluconazole is regarded as an excellent choice for prophylaxis. For this purpose, it has been the most widely studied antifungal agent in neonates. Fluconazole has a long half-life (allowing for broad dosing intervals), high CSF penetration, low protein binding (allowing optimal tissue penetration), and saliva and lung levels that are 1.3 and 1.2 times that of plasma levels, respectively, thereby providing higher levels at key areas of colonization [37,38].

In a randomized study of 103 preterm VLBW (<1500 g) neonates, intravenous fluconazole decreased rectal colonization, but did not decrease the incidence of IC [30]. Kaufman et al. randomized 100 neonates <1000 g birth weight (with either central vascular access or endotracheal tube) in a single-center study [39]. IC occurred in 20% (10 of 50) of the neonates in the placebo group and none (out of 50) of those in the fluconazole group (p=0.008). However, the placebo arm in this single-center study had one of the highest incidence rates of IC reported in neonates of <1000 g birth weight. A blinded trial conducted in eight neonatal intensive care units (NICUs) in Italy enrolled 322 neonates with birth weight <1500 g; fluconazole prophylaxis for 4–6 weeks reduced invasive fungal infections (2.7% in the 6 mg group [p=0.005 vs. placebo], 3.8% in the 3 mg group [p=0.02 vs. placebo], and 13.2% in the placebo group) [40]. Despite the findings from these studies, fluconazole prophylaxis has not become widely accepted practice as there remains concern regarding toxicity, development of resistance, diversification of *Candida* species, long-term neurodevelopmental outcome, and high rates of candidiasis among the placebo groups in the randomized controlled trials.

Voriconazole, a second-generation triazole, is also available in both intravenous and oral forms. The drug has a broader spectrum of antifungal activity against *Candida* than fluconazole. However, voriconazole should be used with caution in instances where fluconazole resistance is likely [41]. Voriconazole is not recommended in patients with renal insufficiency as its cyclodextrin carrier is renally cleared [42]. The drug is metabolized by the liver, and good CSF penetration has been observed. Other side effects include allergic reactions, elevated transaminases, and visual disturbances. Voriconazole has not been studied in neonates, but it has been used to treat premature neonates with refractory candidiasis and cutaneous aspergillosis [43,44]. In the preterm neonate with a developing retina and at risk for retinopathy of prematurity, the visual disturbances are especially

concerning [45]. The pharmacokinetics of voriconazole have not been studied in neonates. In children aged >2 years, voriconazole exhibits linear pharmacokinetics; elimination correlates with the CYP2C19 genotype; and higher doses are required to achieve exposures similar to those found in adults [46].

Posaconazole is a second-generation triazole available as a suspension for oral administration. The antimicrobial spectrum of posaconazole is similar to voriconazole; however, posaconazole is active against zygomycetes. The use of posaconazole in the pediatric population has been limited to children enrolled in adult salvage therapy trials [47,48]. There are no reports of its use in neonates, however, it is currently only available in an oral formulation in the United States.

Echinocandins (caspofungin, micafungin, and anidulafungin)

The echinocandins interfere with cell wall integrity as an inhibitor of 1→3 β-D-glucan synthase [49]. This drug class is available only in the intravenous preparation, and all are fungicidal for medically important *Candida* spp. in neonates, with the possible exception of *C parapsilosis* for which they may be fungistatic [50].

The first of these to be licensed, caspofungin, was unfortunately not tested in neonates prior to market approval. Odio et al. reported on a series of 10 neonates (nine preterm) in which caspofungin was used as salvage therapy after initial therapy with amphotericin B deoxycholate [49]. In that report nine of 10 (90%) neonates survived, and no adverse drug events were observed. The neonates were given a dose of 1 mg/kg/day for 2 days and increased to 2 mg/kg/day for the duration of treatment. A retrospective review of 13 neonates (median gestational age 27 weeks, range 24–28 weeks) treated with caspofungin (1–1.5 mg/kg/day) for refractory, disseminated candidiasis showed that 11 of the neonates achieved blood sterilization within a median of 3 days (range 1–21 days) [51]. In this cohort, two patients died within 2 days of starting caspofungin, one patient developed severe thrombophlebitis after the initial dose, two patients had hypokalemia, and four patients had a greater than three-fold elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels [51]. A single and multiple dose caspofungin sparse sampling PK study in infants < 3 mo of age (n=18, 72% premature) showed that a 25 mg/m^2 per day dose achieved lower peak and higher 24 h trough concentrations when compared to older infants, children, and adolescents receiving daily 50 mg/m^2. Peak and troughs concentrations were higher than those observed in adults receiving 50 mg per day.[1]

In pediatric cancer patients aged 2–17 years receiving 50 mg/m^2/day, the exposure following multiple doses of the drug was similar to that in adults receiving 50 mg/day and was consistent across age ranges whereas weight-based dosing using 1 mg/kg/day yielded suboptimal levels [52].

Side effects of caspofungin appear to be minimal as the target enzyme, 1→3 β-D-glucan synthase, is not present in humans [53]. In a trial of caspofungin versus amphotericin B deoxycholate for candidiasis in adult patients, only 3% of those on caspofungin therapy withdrew from the study due to side effects compared with 23% of patients receiving amphotericin B deoxycholate [54]. Until dosing is better established in the young infant, especially at levels expected to clear central nervous system (CNS) infections, this product should be used with caution in the nursery.

Micafungin was approved by the FDA in March 2005 for the treatment of esophageal candidiasis and prophylaxis of IC in patients undergoing stem cell transplantation. In February 2008, the FDA approved its use in adults with disseminated candidiasis, candidemia, *Candida* peritonitis, and abscesses.

Micafungin has been evaluated in a series of trials completed within the National Institute of Child Health and Human Development-sponsored Pediatric Pharmacology Research Network in premature and term infants. The first of which was a single dose pharmacokinetic study [55]. The AUC in neonates >1000 g was approximately 50% less than that observed in older children, and AUC was approximately 50% less in neonates 500–1000 g compared with neonates >1000 g. The substantially reduced AUC observed in neonates is extremely important because the echinocandins have shown a dose-response relationship. Data in 12 premature neonates (mean birth weight 851 g and mean gestational age 27 weeks) suggests that a micafungin dose of 15 mg/kg/day achieves similar exposures to adults receiving 5 mg/kg/day [56]. Micafungin doses of 7–10 mg/kg/day administered to 13 premature neonates (mean birth weight 1449 g and mean gestational age 27 weeks) was well tolerated provided adequate exposure to treat CNS candidiasis based on animal models [57,58].

The most common adverse events in a Phase I micafungin study of 77 children (aged 2–17 years) with fever and neutropenia were diarrhea (20%), epistaxis (18%), abdominal pain (17%), and headache (17%) [59]. No adverse events related to micafungin were reported among the 12 neonates administered 15 mg/kg [56]. Three (23%) of the neonates in the trial of the 7–10 mg/kg dose range experienced an adverse event felt related to micafungin (increased alkaline phosphatase, phlebitis, hypokalemia, and temperature elevation) [57].

Anidulafungin is the third echinocandin approved by the FDA. Anidulafungin exhibits slow degradation in the blood; it is not metabolized by the cytochrome P450 enzymatic system, and is not renally excreted. Therefore, its use in the clinical setting of the critically ill patient receiving multiple medications simultaneously is attractive. Adult dosages are 50 mg/kg/day for esophageal candidiasis and 100 mg/day for IC. The product has been studied in children with neutropenia and the pharmacokinetics described [60]. Twenty-five children aged 2–17 years were given anidulafungin (1.5–3 mg/kg loading dose, 0.75–1.5 mg/kg/day maintenance dose) for a mean duration of 8.7 days. Exposure to anidulafungin increased in a dose-proportional manner. Steady-state plasma concentrations were achieved after administration of the loading dose [60]. The anidulafungin concentration profiles in pediatric patients aged 2–17 years were similar to those of adult patients receiving 50 or 100 mg/day. The current anidulafungin formulation requires reconstitution in 20% dehydrated alcohol; therefore, its safety and pharmacokinetic profile in neonates younger than 2 years has yet to be determined.

Owing to its unique metabolic properties, anidulafungin dose not require dose adjustment in older patients with renal or hepatic impairment. The most common side effects observed in adults include nausea, emesis, and infusion reactions. In the pharmacokinetic study of neutropenic children, adverse events possibly related to anidulafungin included facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension [60].

Echinocandins and neonatal meningo-encephalitis

Meningo-encephalitis is a common component of neonatal candidiasis, and the echinocandins are likely to have minimal penetration into the CSF of neonates. However, several cases of the successful use of echinocandins in CNS infections have been published; and there are animal model data on the efficacy of echinocandins in CNS infections.

Similar to amphotericin B deoxycholate, micafungin was not detectable in the CSF in neutropenic rabbit models [58,61]. However, therapeutic drug levels of amphotericin B deoxycholate and micafungin have been documented in CNS infections in neutropenic rabbits as documented by successful treatment [62]. Moreover, at high doses, micafungin achieves therapeutic concentrations in several CNS compartments [58]. When these data

were extrapolated and modeled in the neonatal population, micafungin doses of 10–15 mg/kg/day were needed to adequately penetrate the CNS parenchyma of neonates [58].

Summary

For both prophylaxis and treatment of neonatal candidiasis, fundamental questions remain regarding dosing, safety, and efficacy. These questions require both multi-center collaborative efforts and basic knowledge in pharmacology, pathophysiology, and epidemiology. Prior research efforts have provided the field with much of the basic knowledge to move forward in multi-center collaborative research. It is now incumbent upon clinicians, clinical researchers, industry, and government agencies to collaborate to answer the clinical questions vital to the prevention and treatment of neonatal candidiasis.

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Table 1

Dosing of antifungal agents in neonates and children.

Drug	N (infants)	Suggested dose	Birth weight (g)	Gestational age (weeks)	Comments	Reference
Amphotericin B deoxycholate	13	1 mg/kg/day	1200 (800)*	27 (4.9)*	N/A	[10]
Lipid amphotericin B	28	5 mg/kg/day	1060 (480–4900)**	27 (24–41)**	Infant weight highest predictor of clearance	[21]
Fluconazole	55	12 mg/kg/day	1020 (451–7125)**	26 (23–40)**	Loading dose may be required.	[35]
Micafungin	43	10–12 mg/kg/day	1162 (530–4500)*	27 (23–40)*	N/A	[55–57]
Anidulafungin	0	1.5 mg/kg/day	Not studied in young infants	Not studied in young infants	Dose evaluated in pediatric patients aged 2–17 years. Loading dose (double the maintenance dose) required.	[60]
Voriconazole	0	4 mg/kg every 12h	Not studied in young infants	Not studied in young infants	Dose evaluated in pediatric patients aged 2–17 years. Loading dose (double the maintenance dose) required.	[47]
Caspofungin	0	50 mg/m^2/day	Insufficiently studied in young infants	Insufficiently studied in young infants	Dose evaluated in pediatric patients aged 2–17 years. Loading dose (double the maintenance dose) required.	[52]

*Mean (SD);

**Median (range);

CSF: cerebrospinal fluid; N/A: not applicable.

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