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Old and new: Appropriate dosing for neonatal antifungal drugs in the nursery

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Abstract

Candida infections are a source of significant mortality and morbidity in the neonatal intensive care unit. Treatment strategies continue to change as additional antifungals become available and studies in neonates are performed. Amphotericin B deoxycholate has been favored for many years, but fluconazole has the most data supporting its use in neonatal *Candida* infections and is often employed for prophylaxis as well as treatment. Voriconazole and posaconazole have limited utility in the nursery and are rarely used. The echinocandins are increasingly administered for invasive *Candida* infections, although higher doses are required in neonates than in older children and adults.

Invasive *Candida* infections cause significant morbidity and mortality in neonatal intensive care units (NICUs). Mortality approaches 30%, and sequelae of infection can be severe (neurodevelopmental impairment, chronic lung disease, retinopathy of prematurity) (1). In spite of the need for aggressive treatment, few antifungal drugs are specifically indicated for the treatment of invasive *Candida* in neonates. Amphotericin compounds and fluconazole are frequently used, and several newer antifungal agents have become available (2). There are few randomized trials comparing antifungal agents in neonates, and dosing techniques continue to change as more data become available (Table 1).

Amphotericin compounds

Amphotericin B deoxycholate was one of the earliest available antifungal agents and has been used extensively to treat many fungal infections, including candidiasis. Amphotericin B deoxycholate was the antifungal of choice for many years, with 88% of American specialists preferring it for treatment of invasive candidiasis in neonates (3). Typical dosing of 1 mg/kg daily is recommended (2). The risk of toxicity is thought to be low in neonates, but elevation of serum creatinine and hypokalemia have been observed (4).

Lipid formulations of amphotericin are thought to be associated with less renal toxicity in older patients. However, data are mixed regarding the renal protective advantage of lipid formulations in neonates. A large cohort study evaluating 730 infants <120 days old comparing amphotericin B deoxycholate to lipid products demonstrated both increased mortality and treatment failure for neonates with confirmed *Candida* infection treated with lipid formulations (5). This may be due to the propensity for *Candida* to affect both the urinary tract and the central nervous system (CNS) of young infants, both anatomic compartments that may achieve lower concentrations of amphotericin with the use of lipid products (6). If infection of these areas can reliably be excluded, lipid products may be

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considered. Standard dosing is 3–5 mg/kg daily, although higher doses may be needed to achieve therapeutic drug concentrations (6).

Triazoles

Since its licensure in 1990, fluconazole has become an important antifungal for neonatal candidiasis. Fluconazole is used in many NICUs for prophylaxis against invasive fungal disease in high-risk infants. The role of fluconazole prophylaxis is currently being evaluated in clinical trials, but most centers use 3–6 mg/kg every 24–72 hours for this purpose in high-risk infants (2). The criteria used to determine which neonates are at high risk for invasive fungal infection vary by center, but prophylaxis appears to be most useful in infants <1000 g in NICUs with a high incidence of invasive candidiasis.

Fluconazole is particularly useful for treatment of candidiasis due to its effective penetration into the CNS and the urinary tract, both important sites of invasive *Candida* infection in infants (1). Resistance to fluconazole appears to be increasing; some centers report fluconazole resistance among *Candida* isolates as high as 8%, mostly among non-*albicans* species (7). *Candida krusei* is generally considered to be inherently resistant to fluconazole, and up to 20% of *Candida glabrata* isolates are resistant (7). Most infants require higher doses of fluconazole for treatment than were used historically. Due to its long half-life, a therapeutic serum concentration may not be achieved until several days into therapy, even with 12 mg/kg/day dosing. An effective dosing strategy to reach therapeutic serum concentrations quickly is to give a loading dose of 25 mg/kg followed by 12 mg/kg/day (8). Due to its action on a fungal-specific enzymatic pathway, its toxicity is limited, even in premature neonates.

Voriconazole is structurally related to fluconazole and extends the spectrum of fluconazole to include *Aspergillus*. However, except for rare cases of *Aspergillus*, voriconazole has limited utility in the nursery. It has been successfully used for invasive *Aspergillus* disease in an infant, but the pharmacokinetics are not understood in young children, and there is no predictable relationship between dosage and serum concentrations in younger age groups (9). A dosing regimen of 9 mg/kg every 12 hours for 2 doses followed by 8 mg/kg every 12 hours has been suggested by pharmacokinetic models and clinical studies in older children (10). Therapeutic drug monitoring is recommended as trough levels <1 mg/L have been associated with increased mortality in older patients (11). Serum levels necessary for treatment success have not been determined in neonates.

Posaconazole has activity against *Candida*, *Aspergillus*, and zygomycete species. It is currently only available as an oral suspension and should be taken with high-fat meals to promote absorption, making it difficult to use for ill neonates. Dosing has yet to be well defined in older children. Posaconazole has been successfully used in 2 infants weighing 610 g and 580 g, respectively, with cutaneous *Aspergillus* infections following treatment with other antifungal agents (12). The dosing strategy for these infants was not described.

Echinocandins

There are currently 3 echinocandin antifungals—caspofungin, micafungin, and anidulafungin—that are marketed for use in the United States. The echinocandins are effective against *Candida albicans* isolates with high minimum inhibitory concentrations (MICs) to fluconazole, as well as often-resistant *Candida glabrata* and *Candida krusei*. Echinocandins were initially thought to be of limited use for fungal meningoencephalitis due to the large size and aqueous solubility of the molecule. An animal model of *Candida* meningoencephalitis suggested that higher doses of micafungin may overcome these characteristics to allow penetration into the CNS; dosing of 10–15 mg/kg/day was suggested

for neonates (13). Micafungin dosing of 10 mg/kg/day appears to be safe for use in premature infants and attains area under the curve concentrations suitable to treat most *Candida* isolates (14).

A small pharmacokinetic study suggests that a caspofungin dose of 25 mg/m²/day may provide neonates exposure similar to adults receiving 50 mg/day (15). Similarly, 1.5 mg/kg/day of anidulafungin may provide neonates with exposure similar to adults receiving 100 mg/day (16). However, neither of these agents has yet been demonstrated to effectively treat invasive *Candida* infections in neonates, and dosing adequate to penetrate the CNS has not been determined.

The new antifungal agents and a better understanding of proper dosing in neonates provide the means to limit the morbidity and mortality seen with invasive *Candida* infections. Research is ongoing to better define the role of antifungal prophylaxis in neonates and to better define treatment niches for each of the antifungal agents.

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Table 1

Recommended antifungal dosing in neonates

Antifungal	Recommended dosing	Studied in neonates	Neonatal indication
Amphotericin B deoxycholate	1 mg/kg/day	Yes (multiple)	No
Liposomal amphotericin	3 mg/kg/day	No	No
Amphotericin lipid complex	5 mg/kg/day	Yes (single)	No
Fluconazole	25 mg/kg load; 12 mg/kg/day Prophylaxis: 6 mg/kg twice weekly	Yes (multiple)	No
Voriconazole	9 mg/kg q 12h × 2 load 8 mg/kg q 12h	No	No
Posaconazole	Unknown	No	No
Micafungin	10 mg/kg/day	Yes (multiple)	No
Caspofungin	25 mg/m ² /day	Yes (single)	>3 months
Anidulafungin	1.5 mg/kg/day	Yes (single)	No