The Use of Antifungal Therapy in Neonatal Intensive Care

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KEYWORDS

• Invasive candidiasis • Amphotericin B deoxycholate
• Flucytosine • Fluconazole • Voriconazole • Posaconazole
• Micafungin • Anidulafungin • Caspofungin

Invasive candidiasis in extremely premature infants is the second most common cause of infectious disease-related death.[1] Birth weight is strongly related to the incidence of invasive candidiasis (1% of infants born weighing 1000–1500 g vs up to 12% of infants born weighing 401–750 g).[2] The morbidity and mortality of premature infants with invasive candidiasis are high.[3,4] In a cohort of 320 extremely-low-birth-weight (ELBW, <1000 g birth weight) infants with invasive candidiasis, 73% died or were neurodevelopmentally impaired at 18 to 22 months' corrected age.[3]

A unique characteristic of invasive candidiasis in infants is the frequent involvement of the central nervous system (CNS). The incidence of *Candida* meningitis among infants with candidemia varies from 5% to 25%.[3,5,6] Meningitis is not the only manifestation of CNS disease; parenchymal abscesses and vasculitis are also frequent in infants with invasive candidiasis.[7] Therefore, CNS involvement in invasive candidiasis among infants can best be termed meningoencephalitis. In meningoencephalitis due to *Candida*, cerebrospinal fluid (CSF) culture results are often negative, CSF parameters (eg, white blood cell count) are often normal,[5] and imaging is unreliable.

Given the high incidence of meningoencephalitis in the setting of candidemia and the lack of reliability of testing, the presence of meningoencephalitis should be assumed in the neonate with candidemia. This assumption influences length of therapy, dosing, and other key components of antifungal drug development and selection.

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Although antifungals have long been used in infants, their efficacy in this population is based on extrapolation from trials performed in adults.[8] Randomized trials to evaluate prophylactic systemic antifungal agents in very-low-birth-weight (VLBW, <1500 g birth weight) and ELBW infants exist, but no well-powered trials exist to guide treatment of invasive fungal infection in preterm infants.[9–13] However, several pharmacokinetic (PK) antifungal studies have been completed (**Table 1**). In this article, we summarize those findings.

POLYENES

Amphotericin B Deoxycholate

Amphotericin B deoxycholate was approved for use in adults in 1958 and is now approved for use in children and adults. It acts by binding to a cytoplasmic membrane ergosterol of the fungus, thereby creating pores in cell membranes.[14] Amphotericin B deoxycholate is poorly absorbed after oral administration and is highly protein bound (95%).[15] It is widely distributed in the body and can be detected in the liver, spleen, and kidneys.[15]

Amphotericin B deoxycholate has a longer half-life in infants (15 hours) than in adults and greater potential for drug accumulation.[16] The half-life, volume of distribution, and clearance are highly variable in infants.[16] CSF penetration in infants is higher than in

Table 1
Pediatric antifungal dosing

Drug	Formulation	Infants (31 d–2 y)	Neonates (0–30 d)	FDA Label
Polyenes				
Amphotericin B deoxycholate	IV	1 mg/kg/d	1 mg/kg/d	Children and adults
Amphotericin B lipid complex	IV	Unknown	Unknown	>16 mo
Amphotericin B colloidal dispersion	IV	Unknown	Unknown	Children and adults
Liposomal amphotericin B	IV	5 mg/kg/d	5 mg/kg/d	≥1 mo
Nucleoside analogues				
5-Flucytosine	PO	50–150 mg/kg/d q 6 h	50–150 mg/kg/d q 6 hr	Adults
Triazoles				
Fluconazole	IV, PO	12 mg/kg/d (25 mg/kg/loading dose)	12 mg/kg/d (25 mg/kg load)	≥6 mo
Voriconazole	IV, PO	Unknown	Unknown	≥12 y
Posaconazole	PO	Unknown	Unknown	≥13 y
Echinocandins				
Caspofungin	IV	50 mg/m^2/d	25 mg/m^2/d	>3 mo
Micafungin	IV	10 mg/kg/d	10 mg/kg/d	Adults
Anidulafungin	IV	1.5 mg/kg/d (3 mg/kg/loading dose)	1.5 mg/kg/d (3 mg/kg/load)	Adults

Abbreviations: IV, intravenous; PO, oral.
Data from Refs.[16,20,25,37,40,86,89,92,97,101,109,110]