Antifungal Drugs in Newborns and Children

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KEYWORDS

• Antifungal agents • Newborns • Children • Immunocompromised hosts

KEY POINTS

- Many studies of antifungals in children are small, dosing studies.
- There are minimal safety/ efficacy data, needed to support labeling.
- Dosing for infants and children with invasive fungal infections cannot be extrapolated from adults.

INTRODUCTION AND BACKGROUND

Invasive fungal infections continue to be a significant cause of morbidity and mortality in infants and children. The most common fungi affecting children and neonates are *Candida* and *Aspergillus*. Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States and much of the developed world.[1] *Candida* spp are the third most common pathogens in nosocomial blood stream infections among premature infants[2–4] and commonly isolated in hospitalized older pediatric patients.[5,6] Invasive *Candida* infections are associated with high mortality—34% in very low-birth-weight infants (<1500 g birth weight)[7,8] and 16% to 28% in older children.[9,10] Invasive infections caused by *Aspergillus* are common in severely immunocompromised children and associated with mortality as high as 50%.[11]

Invasive fungal infections are of increasing importance as physicians care for a growing number of immunocompromised infants and children. The options for treatment are evolving and therapeutic alternatives are more available as more is learned about the dosing of antifungals in infant and children.[12–14] Appropriate use of antifungals in this vulnerable population is important for both prevention and treatment of infection. Successful identification and treatment of invasive fungal infections are required to maximize the antifungal activity of the agents and minimize toxicity.

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Currently, there are 4 widely used classes of drugs in the treatment of invasive fungal infections in children and infants, including the polyenes, pyrimidine analogues, azoles, and echinocandins (**Table 1**).

POLYENES

The class of polyene macrolides is the oldest antifungal class. Included in this class are amphotericin B deoxycholate (AmB) and the later developed lipid-based formulations: amphotericin B liposomal complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AmB). Lipid formulations of amphotericin are associated with less nephrotoxicity.[15–17]

Amphotericin B Deoxycholate

For the past 6 decades, AmB has been one of the most used antifungals in infants and children. The mechanism of action is characterized by binding to fungal membrane ergosterols, which increases cell permeability and ultimately cell death.[18] With broad-spectrum coverage, AmB remained one of the most used antifungals for treatment of invasive infections, including *Candida* spp (excluding *Candida lusitaniae*), *Aspergillus* spp, and *Zygomycetes*. AmB is used for the treatment of *Candida* meningoencephalitis due to penetration of central nervous system (CNS) (but not the cerebrospinal fluid).[19]

Despite the lack of specific Food and Drug Administration (FDA) guidance in infants, AmB is frequently used to treat invasive candidiasis in this age group.[20,21] Safety and effectiveness have not been established in pediatrics. In infants, the risk of toxicity is low, with data suggesting transient elevation of creatinine and hypokalemia.[22] Infusion-related toxicities (fever and chills/rigors), nephrotoxicity, and electrolyte disturbances have been reported in older children.[23]

Most phamacokinetic (PK) studies in children suggest a dose of 1 mg/kg/d.[23,24] The recommended dose in infants is 1 mg/kg/d.[25]

Lipid-Based Amphotericin B Preparations

ABCD, ABLC, and L-AmB are FDA approved in infants and children aged 1 month to 16 years for neutropenic patients with persistent fever despite broad-spectrum antibiotic therapy and patients with invasive fungal infections who are refractory to or intolerant of conventional AmB therapy. 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. Dosing recommendations for ABCD are 3 mg/kg/d to 5 mg/kg/d,[26] for ABLC 2.5 mg/kg/d to 5 mg/kg/d,[27] and for L-AmB 3 mg/kg/d to 5 mg/kg/d.[26,28]

PYRIMIDINE ANALOGUES

Flucytosine is a fluorinated pyrimidine analogue that interferes with fungal nucleic acid synthesis.[29] Flucytosine has been shown to be active against *Candida* spp and *Cryptococcus neoformans*. Given the rapid development of resistance, it should be used in combination with other antifungal agents.[25] The combination therapy with AmB is supported by well-designed, randomized clinical trials for the treatment of cryptococcal meningitis.[30] Other than PK data included in the FDA label, flucytosine is not approved for use in neonates.[31]

Flucytosine is rarely used in children, and PK studies are limited in this population.[24,32] Given the limited PK, safety, and efficacy data in children and infants and the lack of safe target plasma concentrations, flucytosine use is discouraged.[33]