 10.1111/1469-0691.12040

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp.

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Abstract

Invasive candidiasis (IC) is a relatively common syndrome in neonates and children and is associated with significant morbidity and mortality. These guidelines provide recommendations for the prevention and treatment of IC in neonates and children. Appropriate agents for the prevention of IC in neonates at high risk include fluconazole (A-I), nystatin (B-II) or lactoferrin ± *Lactobacillus* (B-II). The treatment of IC in neonates is complicated by the high likelihood of disseminated disease, including the possibility of infection within the central nervous system. Amphotericin B deoxycholate (B-II), liposomal amphotericin B (B-II), amphotericin B lipid complex (ABLC) (C-II), fluconazole (B-II), micafungin (B-II) and caspofungin (C-II) can all be potentially used. Recommendations for the prevention of IC in children are largely extrapolated from studies performed in adults with concomitant pharmacokinetic data and models in children. For allogeneic HSCT recipients, fluconazole (A-I), voriconazole (A-I), micafungin (A-I), itraconazole (B-II) and posaconazole (B-II) can all be used. Similar recommendations are made for the prevention of IC in children in other risk groups. With several exceptions, recommendations for the treatment of IC in children are extrapolated from adult studies, with concomitant pharmacokinetic studies. Amphotericin B deoxycholate (C-I), liposomal amphotericin B (A-I), ABLC (B-II), micafungin (A-I), caspofungin (A-I), anidulafungin (B-II), fluconazole (B-I) and voriconazole (B-I) can all be used.

Keywords: Antifungal agents, candida disease, children, Europe, neonates

Clin Microbiol Infect 2012; **18** (Suppl. 7): 38–52

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This guideline was presented in part at ECCMID 2011.
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Introduction

The process of defining therapeutic recommendations in this document is consistent with paediatric development regulations and guidelines from the European Medicines Agency (EMA) [1,2]. The EMA has a relatively pragmatic approach to the licensure of pharmaceutical agents for neonates and children. The EMA accepts the requirement for extrapolation of evidence for efficacy from studies in adults to paediatric patients, or from older to younger paediatric patients when the following criteria are met: (i) a medicinal product is to be used for the same indication(s); (ii) the disease process or target sensitivity is similar; and (iii) the outcome of therapy is likely to be comparable [1,2].

Pharmacokinetic studies performed in all the age ranges of paediatric patients likely to receive a compound, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce drug exposure similar to those observed in adults. In situations where the comparability of the disease course or outcome of therapy is expected to be similar, but the relevant drug exposure in adults is not known, a pharmacokinetics/pharmacodynamics approach combined with safety and other relevant studies may avoid the need for clinical efficacy studies [1]. More complex disease–drug combinations may require specific studies.

The grading scheme used in this manuscript is consistent with guidelines developed for adults [141]. However, there are some subtle differences for paediatric patients. The Expert Group considered three components for grading of each drug–syndrome combination: (i) evidence for efficacy, which was frequently, but not invariably, obtained from studies in adults; (ii) the quality of the pharmacokinetic data and models performed in either neonates or children that enable an informed decision about an appropriate regimen for the specific population; and (iii) specific safety data obtained in neonates or children that support the use of a given compound in that specific population. These guidelines are intended to facilitate optimal antifungal therapy for neonates and children with invasive candidiasis. They are not necessarily exhaustive. Contraindications, drug–drug interactions and specific warnings for each compound should be considered by treating physicians. Furthermore, these guidelines should be coupled with diagnostic and therapeutic algorithms tailored to the specific case mix and local fungal epidemiology of each institution. The incorporation of these therapeutic guidelines with a risk stratification strategy is also recommended, especially for prophylaxis and empirical antifungal therapy.

Overview of syndromes and pathogenesis of invasive candidiasis in paediatrics

Neonates

Invasive candidiasis (IC) is a common and serious infection in premature neonates [3]. Invasive candidiasis may present as candidaemia, urinary tract infection and involvement of essentially any other tissue or structure. A syndrome that is particularly unique to premature infants is haematogenous *Candida* meningoencephalitis (HCME), where there is invasion of the central nervous system (CNS) by *Candida*. This syndrome occurs in 15–20% of cases of IC and may contribute to the increased mortality and long-term neurodevelopmental abnormalities [3,4].

The risk factors for development of IC in the neonatal intensive care unit (NICU) include prematurity, central vascular catheterization, abdominal surgery, necrotising enterocolitis (NEC), exposure to broad-spectrum antibacterial agents (e.g. third-generation cephalosporins and carbapenems), parenteral nutrition, antacids and endotracheal intubation. Infants with a smaller gestational age have a higher incidence of IC (e.g. neonates with gestational age of 23–24, 25–27 and ≥28 weeks have an incidence of 10–20%, 5–10% and <5%, respectively [5]). Similarly, smaller infants have a higher incidence of IC (e.g. neonates with birth weight <750 g, 750–1000 g and >1000 g have an incidence of IC of >10%, 5–10% and <5%, respectively).

Candida albicans is the most frequent *Candida* species causing IC in neonates [6,7]. *Candida parapsilosis, Candida tropicalis* and other *Candida* species are seen less commonly. Unlike adults, *Candida glabrata* and *Candida krusei* are infrequent causes of IC in the NICU.

Older children

The invasive *Candida* syndromes in older children closely resemble those seen in adults. *Candida* spp. are important causes of healthcare–associated infections in children and adolescents with indwelling central venous catheters, in paediatric cancer patients receiving treatment for haematological malignancies and in paediatric haematopoitic stem cell transplant (HSCT) recipients. Severe sepsis and/or septic shock occurs in approximately 30% [8,9]; mortality rates range between 10 and 25% in most series [9] and are close to 50% in patients admitted to the ICU [8,10,11]. IC is also an important syndrome in solid organ transplant recipients. The incidence in this setting remains relatively poorly defined, but is *c.* 5–10% in liver, small bowel and pancreas transplantation [12]. In the individual reports that are available, the incidence of IC for paediatric heart, lung and liver transplant recipients is 3.9%, 5% and 19%, respectively [10,13,14].