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Review article

Fluconazole prophylaxis in preterm infants: a systematic review

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ABSTRACT

Objective: This article aims to review the use of antifungal prophylaxis with intravenous fluconazole in premature newborns and the occurrence of Invasive Candidiasis.

Methods: This is a systematic review with search at databases: PubMed, Capes Portal, Virtual Health Library (BVS – Biblioteca Virtual em Saúde)/Lilacs, Scopus and Cochrane. The keywords used were: “Antifungal”, “Candida”, “Fluconazole prophylaxis” and “Preterm infants”.

Results: Invasive Candidiasis was evaluated in all the twelve items. In eleven of them, there was a statistically significant difference between the groups receiving prophylactic fluconazole, with lower frequency of Invasive Candidiasis, compared to placebo or no prophylaxis group. Colonization by *Candida* species was also evaluated in five studies; four of them presented statistically lower proportion of colonization in patients with Fluconazole prophylaxis, compared to placebo or no drugs. In one study, there was a significant difference, favoring the use of fluconazole, and reduction of death.

Conclusion: Studies indicate the effectiveness of prophylaxis with fluconazole, with reduction in the incidence of colonization and invasive fungal disease. The benefits of prophylaxis should be evaluated considering the incidence of candidiasis in the unit, the mortality associated with candidiasis, the safety and toxicity of short and long-term medication, and the potential for development of resistant pathogens.

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Introduction

The incidence of invasive fungal infection ranges from 2% to 4% in infants with very low birth weight (VLBW < 1500 g)¹ and may affect 4% to 16% of extreme-low birth weight newborns (EBPN < 1000 g).^{2–4} *Candida* species have a higher incidence of

invasive candidiasis (IC) in newborns and it is one of the most important causes of morbidity and mortality in the neonatal population.^{5,6}

The immaturity of the immune system and the use of invasive devices, such as mechanical ventilation and central venous catheter, are considered important risk factors for IC.^{7–9} Prior colonization by *Candida* sp., delivery route,

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and cross transmission by the hands of health professionals are also considered predisposing factors. Exposure to broad-spectrum antimicrobial drugs favors the selection of microbiome and the use of post-natal steroids and H2 inhibitors is a factor that favors translocation in the colonized patient to invasive infection.^{5,8,9}

Besides bloodstream infection (Candidemia) *Candida* may affect other organs, especially heart, urinary tract, retina, and central nervous system (CNS).⁹ CNS involvement may occur in around 50% of newborns with IC,^{10,11} and impaired neurological development after infection affects up to 60% of survivors.¹² The mortality rate reported in some studies is around 20%,^{11,13} but it can reach up to 40%.¹⁴

Despite evidences and recommendations favoring the use of intravenous fluconazole for prevention of invasive fungal infections (IFI) in neonates,¹⁵⁻¹⁷ universal use of antifungal prophylaxis is controversial in the literature. Currently, it is recommended in Neonatal Intensive Care Units (NICU) with fungal infections rates higher than 5%.^{18,19}

Thus, this study aimed to conduct a systematic review on the use of antifungal prophylaxis with intravenous fluconazole in premature newborns and the occurrence of IC (Fig. 1).

Methods

This was a systematic review which included virtual libraries: PubMed, EmBase, Portal Capes, Virtual Health Library (BVS – *Biblioteca Virtual em Saúde*)/Lilacs, Scopus, and Cochrane databases, without language restriction, with publications until February 2016 without previous date limit considering the first study was in 2001. It also included forward citation tracking. The keywords were “Antifungal”, “*Candida*”, “Fluconazole prophylaxis” and “Preterm infants” or “very low birth weight”. The search was performed in duplicate by two researchers.

PICO strategy²⁰ was performed considering: Population (P) – infants with birth weight lower than 1500 g; Intervention (I):

use of antifungal prophylaxis with fluconazole; Comparison (C): no antifungal prophylaxis or use of placebo; Outcome (O): occurrence of Invasive Candidiasis; Study type (S): comparative studies of case-control, cohort, or clinical trials.

A total of 168 articles were found: 54 PubMed articles, 52 Portal Capes articles, 31 BVS articles, 20 Scopus articles, 10 Cochrane articles, and a comparative study obtained in references cited in review articles. Of them, 85 were duplicates among the databases and 83 were chosen for the first selection.

Seventy one studies were excluded. Of them, 33 were reviews and five were experts' commentaries on articles published in journals indexed in the databases. Eight studies addressed the treatment of fungal infections, two included treatment of resistant *Candida* species and one was about diagnostic methods. Four were studies on the prevalence of fungal colonization in neonates and other four reports of infection by other fungal species. Three publications focused on epidemiological surveillance studies of invasive fungal infections. Four other studies evaluated prophylaxis of IC with a different antifungal and four addressed a pharmacokinetic evaluation of antifungal agents. In addition, one article examined the occurrence of side-effects with the use of Fluconazole. Furthermore, one article evaluated the adhesion of neonatologists to prophylactic fluconazole use protocol in NICU and one compared different doses of fluconazole.

Twelve studies were eligible for comparative and qualitative analysis, including four randomized clinical trials (RCT), five comparative studies, two case-control studies, and one cohort study.

Results

We selected 12 original articles which referred to the prophylaxis of IFI with intravenous use of fluconazole in premature infants, eight observational studies (comparative, cohort and case-control), and four clinical trials published between

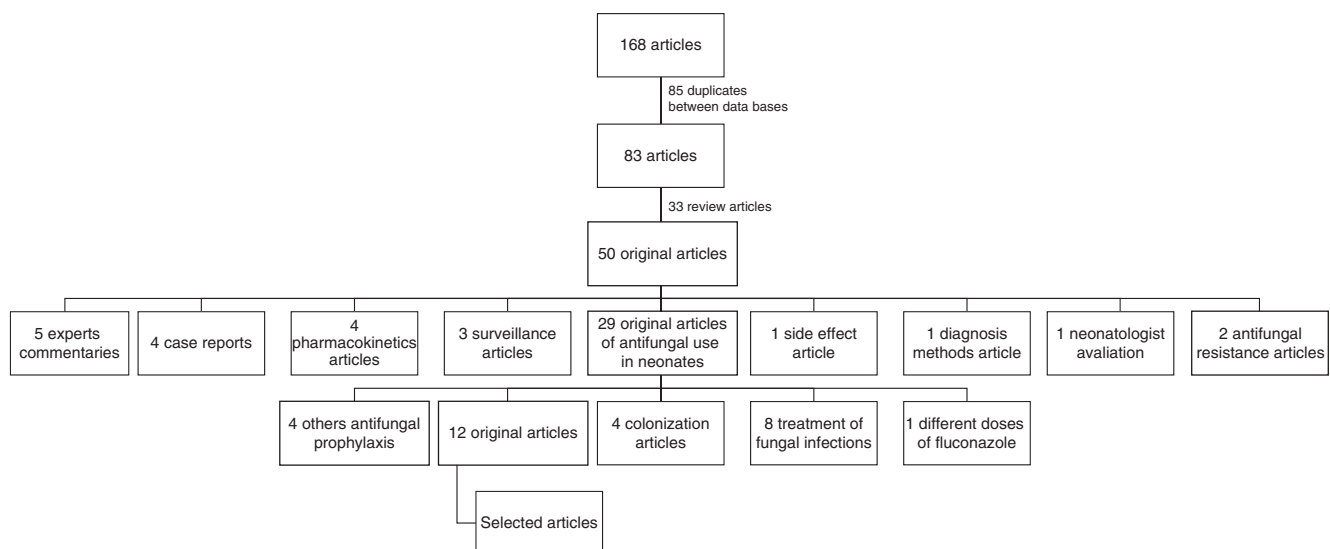


Fig. 1 – Flowchart.

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