# Fluconazole Doses Used for Prophylaxis of Invasive Fungal Infection in Neonatal Intensive Care Units: A Network Meta-Analysis

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**Objectives** To evaluate the safety and efficacy of different doses of fluconazole used for invasive prophylaxis of fungal infection in neonates.

**Study design** A systematic search was conducted with PubMed, Scopus, and Web of Science. A manual search was performed as well. Only randomized controlled trials of neonates in a neonatal intensive care unit (NICU) who received fluconazole prophylaxis for invasive fungal infection, regardless of the dose or therapeutic regimen, were included in this review. Data on baseline characteristics, outcomes incidence of proven invasive *Candida* infection, overall mortality, and invasive *Candida* infection-related mortality were extracted.

**Results** Eleven studies were included in the review, with fluconazole doses of 3, 4, or 6 mg/kg. When the incidence of invasive *Candida* and invasive *Candida*-related mortality were considered as outcomes, the 3 and 6 mg/kg fluconazole doses were found to be statistically superior to placebo (OR, 5.48 [95% credible interval, 1.81-18.94] and 2.63 [1.18-7.02], respectively, and 15.32 [1.54-54.31] and 9.14 [1.26-142.7], respectively), but data for the 3 doses were not statistically significantly different.

**Conclusions** Use of the lowest fluconazole dose (3 mg/kg) should be recommended for *Candida* prophylaxis in neonates, given that increasing the fluconazole dose is not associated with higher efficacy and has greater potential for toxicity and increased cost. *(J Pediatr 2017;185:129-35).*

Invasive fungal infections (IFIs) are serious health conditions that occur more frequently in vulnerable populations, such as in immunocompromised and critically ill patients (eg, hematologic, transplant, and intensive care unit patients) and in neonates being cared for in the neonatal intensive care unit (NICU).[1,2]

Cases of IFI in the NICU are associated with higher rates of morbidity and mortality. The incidence of IFI in very low birth weight (VLBW) infants is up to 3%, which can increase to 20% in extremely low birth weight neonates in some units.[2,3] The increased predisposition of infants in the NICU to IFI is due to their immature immune system and other risk factors, including prematurity, surgery, use of endotracheal intubation or catheters, variable infection prevention practices, and administration of antibiotics or corticosteroids. In neonates, fungal infections are mostly from *Candida*, especially *Candida albicans* and, more recently, *Candida parapsilosis*.[4-8]

The successful management of neonatal candidiasis requires effective treatment with appropriate antifungal therapy and supportive care, as well as the implementation of preventive measures to reduce the risk of invasive candidiasis (IC).[4,5]

Prophylaxis is one way to reduce the incidence of IC.[3] The prophylactic use of a systemic antifungal agent in nurseries with a high rate of IC (>10%) has been recommended in guidelines and used in clinical practice to improve outcomes.[9,10] The use of fluconazole for the prevention of IC in VLBW neonates is increasing.[11] Data from previous studies have suggested that fluconazole prophylaxis reduces the incidence of IC in neonates[3,11-15]; however, to date only 1 clinical trial has compared the safety and efficacy of different doses of fluconazole for these patients.[16]

High-dose antifungal prophylaxis may be associated with antifungal resistance and increased treatment cost, without providing any significant additional benefits. We performed a systematic review and network meta-analysis to compare the safety and efficacy of different doses of fluconazole as IFI prophylaxis in neonates.

## Methods

### Eligibility Criteria for the Systematic Review

We conducted our systematic review in accordance with PRISMA and Cochrane Collaboration recommendations.[17,18] Two reviewers individually performed all of

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| CrI | Credible interval | PK | Pharmacokinetic |
| IC | Invasive candidiasis | RCT | Randomized controlled trial |
| IFI | Invasive fungal infection | VLBW | Very low birth weight |
| NICU | Neonatal intensive care unit | | |

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the steps before reaching a consensus, and discrepancies were resolved by a third reviewer.

Randomized controlled trials (RCTs) were identified using PubMed, Scopus, and Web of Science. A manual search was performed as well. The search was conducted in May 2016, with no date restriction for the included studies. We used the descriptors "clinical trial", "random", "fluconazole", "infant*", "neonat*", and "newborn*", combined with the Boolean operators "AND" and "OR". Complete search strategies are illustrated in **Figure 1** (available at www.jpeds.com).

Studies were included if they met all of the following eligibility criteria: (1) neonates weighing <1500 g at birth who received fluconazole prophylaxis for IC, regardless of dose and therapeutic regimen, were included; (2) therapy was compared with a placebo or other antifungal agent (head-to-head study); and (3) outcomes of interest related to the incidence of IC or mortality were reported. Studies that did not address outcomes of interest, other types of studies (eg, cohort studies, case reports, and reviews), non-RCTs, and articles published in non-Roman characters were excluded.

### Data Extraction and Quality Assessment

The following data were extracted from each study: baseline characteristics (authors, year of publication, number of patients, gestational age, and characteristics of antifungal treatment) and the outcomes of interest (incidence of proven IC, overall mortality, and IC-related mortality). IC was defined as a positive culture for *Candida* spp from blood (venipuncture), urine (sterile bladder catheterization or suprapubic aspiration), and/or cerebrospinal fluid samples.

Two well-established tools were used to assess the methodologic quality of records included in this systematic review, the Jadad scale[19] and the Cochrane Collaboration's tool for assessing the risk of bias,[17] in which critical evaluations are performed for different factors (eg, blinding, randomization, data reporting). The Jadad scale has a maximum score of 5, with studies receiving at least 3 points if considered to be of good quality.[19] The Cochrane Collaboration classifies each study as having a low, unclear, or high risk of bias.[17]

### Statistical Analyses

Network meta-analysis, also called multiple-treatment meta-analysis, allows for the comparison of multiple treatments among all study arms by simultaneously combining direct and indirect evidence.[20] Usually based on Bayesian methods, this approach is recommended by the International Society for Pharmacoeconomics and Outcome Research for comparing efficacy and safety among different treatments.[21]

A random-effects model was created using the Markov chain Monte Carlo simulation method to generate pooled effect sizes. A consistency model was built for each outcome, and the relative effect size for each treatment was calculated as the OR and reported with the 95% credible interval (CrI). A common heterogeneity variable was assumed for all comparisons. To increase the precision of estimates for the relative effect size of comparisons, and to properly account for correlations between multiarm trials, rank probabilities involving all treatments were built for each outcome. These ranks estimate the probability of each dose to be the best, the second best, and so on.[22,23]

To estimate the robustness of the networks, we performed an inconsistency evaluation by node-splitting analysis. In this evaluation, the effects of direct and indirect evidence on a specific node of the network (the split node) were used to determine whether they were in agreement or not (with $P < .05$ indicating inconsistencies).[24,25] We performed the analyses using ADDIS version 1.16.6 (available from http://drugis.org/addis).[26]

## Results

The systematic search of all 3 databases retrieved a total of 1012 articles, 235 of which were excluded as duplicates. Articles that evaluated colonization instead of IFI also were excluded.[27] After screening the 777 remaining articles for title and abstract, we evaluated the full article for 16 studies, and deemed 11 RCTs, covering a total of 1578 subjects, suitable for inclusion in our meta-analysis.[16,28-37] (**Figure 2**; available at www.jpeds.com).

### Study Characteristics

The main characteristics of the 11 studies are presented in **Table I**. Five of the studies were conducted in the US (45.5%),[29,30,32,33,37] and 3 were multicenter studies.[16,29,35] One study included neonates weighting <750 g,[29] but the other 10 studies comprised infants with a minimum weight of 750 g and a maximum weight of 1500 g. Fluconazole was administered at doses of 3 mg/kg,[16,28,31-33] 4 mg/kg,[37] or 6 mg/kg.[16,29,30,34-36] In addition to fluconazole, 3 studies also investigated nystatin as antifungal therapy,[28,35,37] and 9 studies included a placebo for comparison. The duration of treatment varied from a minimum of 4 weeks to a maximum of 6 weeks.

### Quality Assessment

The quality assessment showed overall good quality, as demonstrated by a mean Jadad score of 3.36 (range, 2-4). All studies scored on randomization, and most studies correctly described this method, and accounted for patient withdrawal or dropout. None of the 7 studies classified as double-blind correctly described the blinding method, however. Regarding the risk of bias, the studies showed an overall low risk of bias, except for the blinding of caregivers and assessment of outcomes, for which many studies failed to provide sufficient detail. More than 70% of the studies (n = 8) were funded by industries or organizations, or presented a conflict of interest (**Table II** and **Figures 3** and **4**; available at www.jpeds.com).

### Network Meta-Analysis

We built a network meta-analysis, including 9 of the 11 reported trials and 13 comparison trials (**Figure 5**).[16,28-30,32,34-37] We used this network to analyze the incidence of confirmed IC. We also built other networks for overall mortality (6 trials and 10 comparisons) and IC-related mortality (9 trials and 12 comparisons). We obtained the pooled effect size for each outcome by performing multiple treatment comparison analyses with both direct and indirect comparisons (**Figure 6**). Using the node-splitting technique, we did not identify any