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MAJOR ARTICLE

Fluconazole Prophylaxis for the Prevention of Candidiasis in Premature Infants: A Meta-analysis Using Patient-level Data

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Background. Invasive candidiasis (IC) is an important cause of sepsis in premature infants and is associated with a high risk of death and neurodevelopmental impairment. Prevention of IC has become a major focus in very low birth weight infants, with fluconazole increasingly used as prophylaxis.

Methods. We identified all randomized, placebo-controlled trials evaluating fluconazole prophylaxis in premature infants conducted in the United States. We obtained patient-level data from the study investigators and performed an aggregated analysis. The occurrence of each endpoint in infants who received prophylaxis with fluconazole vs placebo was compared. Endpoints evaluated were IC or death, IC, death, *Candida* colonization, and fluconazole resistance among tested isolates. Safety endpoints evaluated included clinical and laboratory parameters.

Results. Fluconazole prophylaxis reduced the odds of IC or death, IC, and *Candida* colonization during the drug exposure period compared with infants given placebo: odds ratios of 0.48 (95% confidence interval [CI], .30–.78), 0.20 (95% CI, .08–.51), and 0.28 (95% CI, .18–.41), respectively. The incidence of clinical and laboratory adverse events was similar for infants who received fluconazole compared with placebo. There was no statistically significant difference in the proportion of tested isolates that were resistant to fluconazole between the fluconazole and placebo groups.

Conclusions. Fluconazole prophylaxis is effective and safe in reducing IC and *Candida* colonization in premature infants, and has no impact on resistance.

Keywords. fluconazole; candidiasis; premature infants; meta-analysis.

Invasive candidiasis (IC) is an important cause of sepsis in premature infants and is associated with a high risk of death and neurodevelopmental impairment [1]. The risk of IC is inversely related to birth weight, with those weighing <750 g at birth at highest risk [2]. IC is also associated with use of broad-spectrum antibiotics (especially third-generation cephalosporins), central venous lines, parenteral nutrition, and histamine-2 blockers [3, 4].

Fluconazole is increasingly used as prophylaxis for the prevention of IC in very low birth weight infants (<1500 g) [2, 5]. Previous studies comparing use of fluconazole prophylaxis with historical controls found that fluconazole prophylaxis was effective in reducing the incidence of IC [6,7]. However, many of these studies had a higher incidence of candidiasis in the control groups than is typically seen in clinical practice [8, 9].

Six randomized controlled trials have been conducted [10–15]. Four of these trials demonstrated a decreased incidence of IC in infants treated with fluconazole compared to those given placebo [11, 13–15]. The remaining 2 trials found similar incidences of IC but lower frequencies of *Candida* colonization in infants treated with fluconazole compared to those given placebo [10, 12]. Adverse events during fluconazole exposure were also documented. These studies enrolled between 26 and 362 infants.

The small sample sizes of the previous studies limited their ability to adequately evaluate the safety of fluconazole prophylaxis and the impact of fluconazole prophylaxis on the development of resistance. Widespread implementation of fluconazole prophylaxis in premature infants has not been adopted, likely due to these limitations. The objective of the present study was to analyze patient-level data from available randomized trials performed in the United States to evaluate the efficacy and safety of fluconazole prophylaxis in premature infants.

METHODS

We identified all randomized, placebo-controlled trials evaluating fluconazole prophylaxis in premature infants conducted in the United States. Due to potential differences in the epidemiology of *Candida* species' and fluconazole resistance patterns,

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Table 1. Included Studies

Trial [Reference]	Years	Birth Weight	Maximum Age at First Fluconazole Dose	Fluconazole Dose	Duration of Therapy	Exclusion Criteria
Trial 1 [10]	1998–1999	<1500 g	72 h	6 mg/kg every 72 h for first week, then daily	4 wk	Liver failure, congenital defect requiring surgery, chromosomal abnormality, expected survival <48 h
Trial 2 [11]	1998–2000	<1000 g	5 d	3 mg/kg every 72 h for 2 wk, every 48 h for 2 wk, then daily	6 wk	Liver failure
Trial 3 [14]	2001–2002	<1500 g (and <34 wk)	28 d	6 mg/kg every 72 h for 1 wk then every 48 h	6 wk	Lack of *Candida* colonization
Trial 4 [13]	2008–2013	<750 g	120 h	6 mg/kg twice weekly	6 wk	Liver or renal failure, candidiasis at the time of enrollment

we excluded studies that were conducted in other countries. Patient-level data were obtained from the primary investigators of each of the identified studies, integrated into a single master dataset, and reanalyzed in aggregate. The full analysis set was defined as all randomized infants (intent-to-treat analysis). All statistical comparisons were 2-sided with an α level of .05. No adjustments were made for multiple comparisons. All analyses were performed using SAS version 9.2 software (SAS Institute).

Four trials were identified that met study criteria (Table 1). Trial 1 was a single-center study in which 53 infants were enrolled in the fluconazole arm and 50 infants in the placebo arm [10]. Rectal cultures for *Candida* species were obtained at study entry and on days of life 7, 14, and 28 for all infants; infants <1250 g were also cultured on days 35, 49, and 56. Blood, urine, and cerebrospinal fluid (CSF) cultures were obtained at the discretion of the treating physician, and any cultures positive for *Candida* were noted. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were obtained on all infants at study entry and on days of life 7, 14, and 28. Necrotizing enterocolitis (NEC), chronic lung disease, intraventricular hemorrhage (IVH), and death were considered to have occurred if they were diagnosed during the study period. The primary outcome was *Candida* colonization.

Trial 2 was a single-center study that enrolled 50 infants in each of the 2 arms. Infants were excluded if they had liver failure [11]. Fungal surveillance cultures were obtained from the nasopharynx or endotracheal tube if intubated, groin, umbilicus, and stool or rectum at study entry and weekly thereafter. Blood, urine, and CSF cultures were obtained at the discretion of the treating physician, and any cultures positive for *Candida* were noted. All surveillance and clinical *Candida* isolates had susceptibility testing. AST, ALT, direct bilirubin, and alkaline phosphatase levels were collected at study entry and after 6 weeks of study participation. NEC, spontaneous intestinal perforation (SIP), retinopathy of prematurity (ROP), grade III or IV IVH or periventricular leukomalacia (PVL), and death were considered to have occurred if they were diagnosed during hospitalization. The primary outcome was IC.

Trial 3 randomized infants from a single center who had *Candida* colonization demonstrated by positive cultures obtained from rectal, oropharyngeal, or tracheal samples to receive either fluconazole or placebo [14]. The primary outcome was IC. Safety data were not collected.

Trial 4 was a multicenter trial conducted at 32 sites with 189 infants randomized in the fluconazole arm and 173 infants in the placebo arm [13]. Infants were excluded if they had liver failure, had congenital candidiasis or IC at the time of enrollment, or had liver or renal failure. Fungal surveillance cultures were obtained from the nasopharynx, groin, and stool or rectum. Blood, urine, and CSF cultures were obtained at the discretion of the treating physician, and any cultures positive for *Candida* were noted. AST, ALT, alkaline phosphatase, direct bilirubin, and γ-glutamyl transpeptidase concentrations were collected weekly. NEC, SIP, ROP, grade III or IV IVH or PVL, chronic lung disease, and death were considered to have occurred if they were diagnosed during hospitalization. The primary outcome was death or definite or probable IC.

The primary outcome of this meta-analysis was the composite outcome of IC or death. Secondary outcomes were

Table 2. Demographic Characteristics

Characteristic	Fluconazole (n = 299)	Placebo (n = 279)	*P* Value
Gestational age, wk[a]	25 (24, 27)	26 (25, 27)	.10
Birth weight, g[a]	680 (600, 745)	680 (595, 760)	.91
<750	226 (76)	202 (72)	
750–1000	45 (15)	53 (19)	
>1000	28 (9)	24 (9)	
Race			.98
White	126 (42)	120 (43)	
African-American	158 (53)	145 (52)	
Other	15 (5)	14 (5)	
Male	132 (44)	126 (45)	.81
Inborn	254 (85)	240 (86)	.72
Cesarean delivery	191 (64)	196 (70)	.10
Intubated at randomization	200/239 (84)	182/223 (82)	.56
Prolonged rupture of membranes	61/294 (21)	63/274 (23)	.52
Antenatal steroids	227 (76)	227 (81)	.11
Prenatal antibiotics	140/246 (57)	127/229 (55)	.75

Data are presented as No. (%) unless otherwise indicated.

[a] Median (25th, 75th percentile).

death, IC, *Candida* colonization, and prespecified safety outcomes (NEC, SIP, chronic lung disease, grade III or IV IVH or PVL, ROP, and abnormal liver laboratory values). Because trial 3 required colonization with *Candida* as a requirement of study entry, participants from this study were not included in the aggregated analysis comparing *Candida* colonization following fluconazole prophylaxis vs placebo. Liver laboratory values evaluated were elevation of AST, ALT, alkaline phosphatase, and bilirubin.

Baseline characteristics of infants given fluconazole and placebo were compared using χ^2 and Fisher exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. The odds of death or IC, death, IC, and *Candida* colonization were determined for each treatment group at the end of the study drug exposure period and compared using logistic regression adjusted for gestational age and study of origin. The time to the first event from randomization and cumulative event rates for death or IC, death, and IC were also calculated through the end of the study follow-up period, and compared between treatment groups using a Cox proportional hazards regression adjusted for gestational age and trial of origin.

The incidences of laboratory abnormalities for infants receiving fluconazole vs placebo were compared using logistic regression. The incidences of clinical adverse events were determined for infants receiving fluconazole or placebo and compared using a χ^2 test. When a given laboratory or clinical adverse event was not collected in a trial, the infants from that trial were not included in the analysis.

For infants with a positive culture for *Candida*, trials 1 and 4 performed resistance testing on some of the isolates. The data for this endpoint were combined across the 2 trials. Among infants who had atleast 1 isolate tested, the proportion of total isolates that were resistant to fluconazole (minimum inhibitory concentration ≥8 μg/mL) for infants treated with fluconazole was compared to that of infants given placebo using a χ^2 test.

Because trial 3 included a small number of infants and collected less information on each participant, we repeated the logistic regression analysis for the primary endpoint of death or candidiasis at the end of the drug exposure period with the infants from trial 3 excluded as a sensitivity analysis.

RESULTS

Baseline characteristics for infants receiving prophylaxis with fluconazole were similar to those given placebo (Table 2). Most infants (74%) weighed <750 g at birth, were born at the hospital where enrollment occurred (85%), and required ventilator support (83%) at the time of enrollment. Most infants who received prophylaxis with fluconazole (83%) were given 6 mg/kg/dose; the remainder received 3 mg/kg/dose.

Fluconazole prophylaxis decreased the odds of the composite outcome of death or IC and the odds of IC at the end of the

Table 3. Outcomes During Study Drug Exposure

Outcome	Trial 1		Trial 2		Trial 3		Trial 4		All Trials		
	Fluconazole (n = 53)	Placebo (n = 50)	Fluconazole (n = 50)	Placebo (n = 50)	Fluconazole (n = 7)	Placebo (n = 6)	Fluconazole (n = 189)	Placebo (n = 173)	Fluconazole (n = 299)	Placebo (n = 279)	Fluconazole vs Placebo[a], OR (95% CI)
Death or candidiasis	3 (6)	5 (10)	3 (6)	15 (30)	0 (0)	2 (33)	30 (16)	33 (19)	36 (12)	55 (20)	0.48 (.30–.78)
Death	3 (6)	5 (10)	3 (6)	7 (14)	0 (0)	2 (33)	27 (14)	25 (14)	33 (11)	39 (14)	0.68 (.40–1.13)
Invasive candidiasis	1 (2)	0 (0)	0 (0)	10 (20)	0 (0)	1 (17)	5 (3)	12 (7)	6 (2)	23 (8)	0.20 (.08–.51)
Candida colonization	8 (15)	21 (42)	11 (22)	30 (60)			34 (18)	60 (35)	53 (18)[b]	111 (41)[c]	0.28 (.18–.41)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for gestational age and trial.

[b] N = 292.

[c] N = 273.

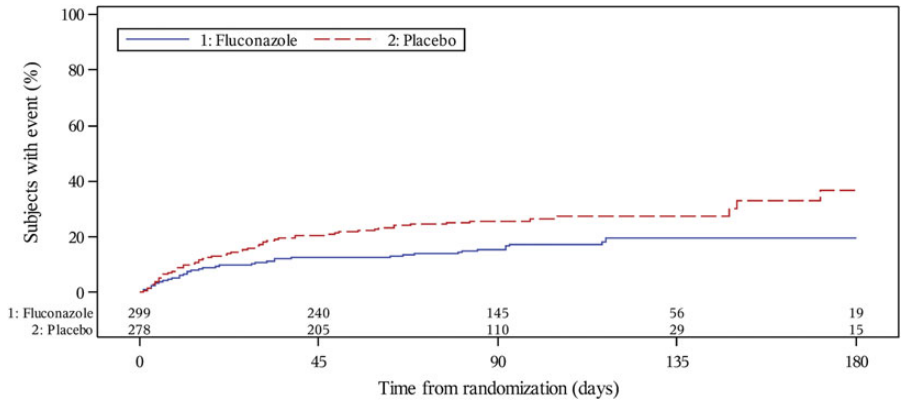

Figure 1. Cumulative incidence for the first occurrence of candidiasis or death by study group.

study drug exposure period: odds ratio (OR), 0.48 (95% confidence interval [CI], .30–.78), $P = .003$; and OR, 0.20 (95% CI, .08–.51), $P < .001$, respectively (Table 3). The odds of the composite outcome were similar when the trial 3 infants were excluded (OR, 0.51 [95% CI, .32–.83], $P = .007$). The frequency of death, however, was not significantly different between groups (11% fluconazole vs 14% placebo; OR, 0.68 [95% CI, .40–1.13], $P = .14$). *Candida* colonization occurred less often in infants receiving fluconazole than with placebo (53/292 [18%] and 111/273 [41%], respectively; OR, 0.28 [95% CI, .18–.41], $P < .001$).

In the survival analysis, infants who received fluconazole prophylaxis also had a lower cumulative incidence of the composite outcome of death or IC through the end of the evaluation period, compared with infants who received placebo (hazard ratio [HR], 0.52 [95% CI, .37–.75], $P < .001$) (Figure 1). The cumulative incidences of IC and death at the end of the evaluation period were also lower in infants who received fluconazole vs placebo (HR, 0.28 [95% CI, .14–.54], $P < .001$; and HR, 0.63 [95% CI, .42–.94], $P = .023$, respectively).

Clinical safety events were similar between infants given fluconazole prophylaxis and those treated with placebo (Table 4). SIP was the least common clinical safety event, occurring in 8% of infants receiving fluconazole compared with 6% of placebo patients ($P = .60$). Abnormal AST and ALT values were uncommon for infants in both groups. Abnormal alkaline phosphatase and direct bilirubin levels were more common but occurred in a similar number of infants in each group.

Resistance testing was performed on *Candida* isolates in trials 1, 2 and 4. Across the 3 studies, the proportions of isolates that were resistant to fluconazole among infants treated with fluconazole compared to those given placebo were similar (9/292 [3.1%] and 12/273 [4.4%], respectively, $P = .41$). Among infants who had at least 1 *Candida* isolate tested, resistant isolates occurred in 9 of 57 (15.8%) of the fluconazole-treated vs 12 of 112 (10.7%) of the placebo patients ($P = .34$).

DISCUSSION

Prevention of IC is an important way to reduce morbidity and mortality among premature infants. We demonstrated that the

Table 4. Safety Events

	Trial 1		Trial 2		Trial 4		All Trials		
Safety Event	Fluconazole (n = 53)	Placebo (n = 50)	Fluconazole (n = 50)	Placebo (n = 50)	Fluconazole (n = 189)	Placebo (n = 173)	Fluconazole	Placebo	*P* Value[a]
Necrotizing enterocolitis	4 (8)	6 (12)	2 (4)	6 (12)	25 (13)	23 (13)	31/292 (11)	35/273 (13)	.42
Spontaneous intestinal perforation	. . .	. . .	2 (4)	5 (10)	16 (8)	9 (5)	18/239 (8)	14/223 (6)	.60
Chronic lung disease	31 (58)	25 (50)	. . .	. . .	114 (60)	93 (54)	145/242 (60)	118/223 (53)	.13
Grade III/IV IVH or PVL	7 (13)	7 (14)	8 (16)	9 (18)	37 (20)	34 (20)	52/292 (18)	50/273 (18)	.88
Retinopathy of prematurity	. . .	. . .	15 (30)	11 (22)	29 (15)	25 (14)	44/239 (18)	36/223 (16)	.52
Abnormal ALT	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1/292 (<1)	1/273 (<1)	.96
Abnormal AST	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	1 (1)	3/292 (1)	1/272 (<1)	.38
Abnormal alkaline phosphatase	. . .	. . .	0 (0)	1 (2)	18 (10)	20 (12)	18/239 (8)	21/223 (9)	.43
Abnormal direct bilirubin	. . .	. . .	0 (0)	4 (8)	32 (17)	31 (18)	32/239 (13)	35/223 (16)	.44

Data are presented as No. (%) or no./No. (%). Safety data not available for trial 3.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

[a] All *P* values for fluconazole vs placebo.

prophylactic use of fluconazole reduces IC, the composite outcome of death or IC, and *Candida* colonization in a large cohort of premature infants enrolled in randomized controlled clinical trials. Despite the reduction in IC, there was no effect on mortality during the period of drug exposure. Safety events did not occur more frequently with fluconazole therapy than with placebo, and fluconazole resistance was not significantly higher among infants exposed to fluconazole.

While the incidence of death was not reduced by fluconazole prophylaxis, the reduction in IC is clinically meaningful. IC is associated with significant short- and long-term morbidity. Infants with IC often develop shock, meningitis, and renal failure at the time of the IC episode [16]. Infants with candidiasis have an increased incidence of ROP, PVL, and chronic lung disease [16]. A Neonatal Research Network study of 1317 infants <1000 g birth weight with IC found increased odds of neurodevelopmental impairment at 18 months compared with uninfected infants (OR, 1.83 [95% CI, 1.01–3.33]) [17]. Mortality in infants with IC was also increased (OR, 4.76 [95% CI, 2.24–10.14]) in the same study. These complications may be decreased if IC is prevented. Two randomized trials that were of sufficient duration to assess the impact of fluconazole prophylaxis on neurodevelopmental impairment did not demonstrate a difference between infants treated with fluconazole (31%) and those given placebo (27%) ($P = .60$) [13, 18]. This may be because these trials were not powered to detect a difference in neurodevelopment.

While several previous studies using historical controls found fluconazole prophylaxis to be effective at preventing IC, few evaluated the safety of fluconazole exposure. A single-center study found that cholestasis was similar for 163 infants given fluconazole prophylaxis as for 99 control infants [7]. A larger single-center study found that the 127 (31%) infants with cholestasis had received significantly more doses of fluconazole than the 282 infants without cholestasis ($P < .001$) [19]. However, multivariable logistic regression found that NEC and increasing days of total parenteral nutrition but not increasing day or number of doses of fluconazole were significantly associated with the development of cholestasis [19].

The current study provides the most complete analysis of the safety of fluconazole prophylaxis for premature infants. We found that there was no difference in the frequency of clinical adverse events for infants treated with fluconazole compared with placebo. There was also no difference in the number of infants with abnormal ALT, AST, alkaline phosphatase, or conjugated bilirubin levels.

Another theoretical concern about using fluconazole prophylactically is the potential for a shift in the susceptibility patterns, with widespread use resulting in more resistant *Candida* species in the event of a breakthrough infection. A retrospective study found that all 22 cases of IC occurring after the implementation of a fluconazole prophylaxis protocol were susceptible to fluconazole [19]. They did note an increase in the proportion of IC infections due to non-*albicans Candida* species, but this was due to a decrease in the number of *C. albicans* infections rather than an actual increase in infections due to non-*albicans* species [19]. Isolates with azole resistance did not differ if patients were receiving placebo or fluconazole in our study, and the absolute proportion of isolates that were resistant to fluconazole was low. As we did not analyze resistance by *Candida* species, this may also represent intrinsic resistance of some *Candida* species (eg, *C. glabrata* and *C. krusei*). The number of *Candida* isolates that underwent susceptibility testing was low and may not have been adequate to detect a difference between the groups. One infection control study had resistance emerge when higher doses of fluconazole were used for both prophylaxis and treatment of fungal infections [20]. Fluconazole prophylaxis used at the doses we studied was not associated with emergence of resistance in our study. When using fluconazole for antifungal prophylaxis, a different antifungal should be used for empiric therapy or treatment of documented infections.

Different dosing schedules were used in these studies. While 6 mg/kg was most commonly used, the frequency ranged from daily to twice weekly. Manzoni et al, in a multicenter randomized placebo-controlled trial in Italy, found 3 mg/kg and 6 mg/kg to be equally effective in preventing IC [15]. Other studies have considered various dosing intervals. In one study, twice-weekly dosing was as effective as more frequent dosing [22]. In addition to benefits in costs of using twice-weekly dosing [21], more frequent dosing may increase resistance when used for ≥4 weeks [22].

A limitation of this study is that not all endpoints were collected in exactly the same manner in every trial. Similarly, the trials had different inclusion and exclusion criteria and used slightly different dosing strategies. The trials also took place over a period of several years, and changes in medical practices may have occurred to make the trials more heterogeneous. However, a strength of this study is that data were collected prospectively as part of placebo-controlled randomized clinical trials. Additionally, patient-level data were used in this study, which allowed us to increase the sample size without making inappropriate assumptions. A similar analysis using patient-level data was used to evaluate treatment of IC in adult patients, which increased the strength of the findings compared to each study alone [23]. To our knowledge, the current study represents the largest analysis of patient-level data for premature infants receiving fluconazole prophylaxis and demonstrates the consistency of effectiveness and safety information across trials.

In conclusion, fluconazole prophylaxis is safe and effective at reducing IC and *Candida* colonization in premature infants <1500 g birth weight when given at 3 or 6 mg/kg twice weekly.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, which had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

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APPENDIX

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