

# Fluconazole Prophylaxis in Neonates (Non-Systematic) Literature Review

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## Abstract

**Background:** Nosocomial infection remains an important contributing factor for morbidity and mortality in neonates. Coagulase-negative staphylococci have emerged as the predominant pathogens of late onset sepsis. This is followed by staphylococcus aureus, gram negative bacilli, and fungi. Old studies noted that mortality due to candidemia was higher in infants weigh less than 2000 g after being exposed to risk factors. The prophylactic use of fluconazole for the prevention of IC in extremely low birth weight was first reported in 2001. **Methods:** Current guidelines from Europe and North America that refer to the treatment of fungal infections are included. Literature search was performed using Medline, Scopus and Cochrane Central Register of Controlled Trials through March, 2016. **Conclusion:** Mortality was not different in early studies. However, recent studies concluded that mortality was reduced in the fluconazole arms. Risk-based approach towards fluconazole prophylaxis seems to be safe and effective.

## Keywords

Invasive Candidiasis, Neonates, Preterm, Fluconazole Prophylaxis, Central Venous Catheters

## 1. Introduction

Nosocomial infection remains an important contributing factor for morbidity and mortality. Neonatal sepsis is divided into two classifications: early onset and late onset sepsis. Early onset sepsis occurs within the first 72 hours of life, while late onset sepsis occurs after 72 hours of birth. The incidence of late onset sepsis is inversely related to birth weight and gestational age [1]. Coagulase-negative staphylococci have emerged as the predominant pathogens of late onset sepsis. This is followed by staphylococcus aureus, gram negative bacilli, and fungi. Different risk factors were found to predispose

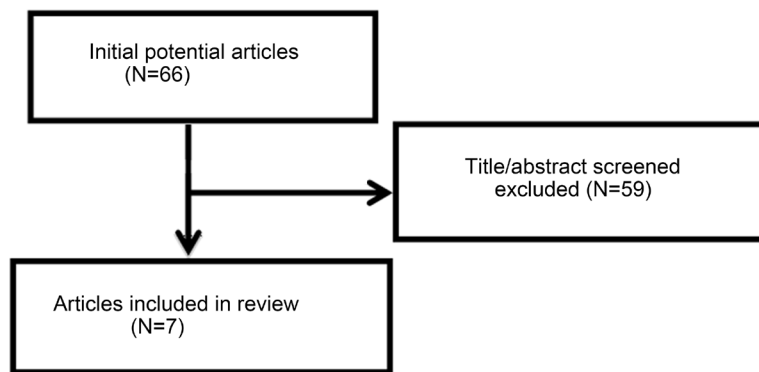
neonates to invasive candidiasis. According to published data, colonization with candida species increases the risk of candidemia (OR 5.1% 95% CI 1.01 - 25.6) [2]. Neonates in the NICU may be colonized with candida species after birth through two different mechanisms. First, vertical transmission from maternal flora. Second, horizontal transmission from the hands of health care workers [3]. Old studies noted that mortality due to candidemia was higher in infants weighed less than 2000 g after being exposed to risk factors [4]. Mechanisms that put preterm neonates at fungal infections are multifactorial that include but may not be limited to immature immune cells, use of broad-spectrum antibiotics, and frequent breeches of the skin [5]. Studies found that candida species colonizing GI tract are identical to candida species isolated from blood in patients with candidemia [6]. *Haematogenous Candida meningoenephalitis* (HCME) is a unique syndrome in preterm infants, where candida invades the central nervous system. This syndrome occurs in 15% - 20% of patients with invasive candidiasis and may contribute to long-term neurodevelopmental abnormalities [7]. In addition to that, sepsis in general was found to be associated with increase neurodevelopmental impairment among survivals [6]. *Candida albicans* by far are the most common species colonizing GI tract and causing invasive infection followed by candida parapsilosis [3] [8]. The European Society of Medical Infectious Diseases recommends fluconazole as the drug of choice in extremely low birth weight infants in centers where the incidence of invasive candidiasis (IC) is more or equal to 2%, while centers where the incidence of IC is less than 2% should be made on a case-by-case basis and embedded in a risk stratifications strategy [7]. On the contrary, the most recent guidelines from the Infectious Disease Society of America recommended initiating fluconazole prophylaxis in centers where the incidence of IC is 10% or more. The prophylactic use of fluconazole for the prevention of IC in extremely low birth weight was first reported in 2001 [5].

## 2. Methods

Current guidelines from Europe and North America that refer to the treatment of fungal infections are included. Literature search was performed using Medline, Scopus and Cochrane Central Register of Controlled Trials through March, 2016, that reported on fluconazole prophylaxis in neonates restricted to English language. The following searching strings were used [Fluconazole AND prophylaxis AND preterm AND neonates AND invasive candidiasis AND central venous catheters]. Only clinical trials and meta-analysis reported on fluconazole prophylaxis in neonates were reviewed for analysis (Figure 1).

## 3. Literature Review

Kaufman *et al.* conducted the first prospective study to evaluate the efficacy of fluconazole prophylaxis in preterm neonates. The birth weight at baseline was 717 +/- 150 in the fluconazole group and 744 +/- 157 in the placebo group. All neonates were preterm with mean gestational age of 25.5 +/- 1.6 in fluconazole group and 25.7 +/- 2 in placebo group. They were randomized to receive Intravenous fluconazole 3 mg/kg every



**Figure 1.** Studies included in review.

third day for 2 weeks, then every other day for the third and fourth week, then daily during the fifth and sixth week vs. placebo. They limited their study for the first 6 weeks of life of preterm neonates with extreme low birth weight and fluconazole was discontinued once central venous catheters are removed and neonates are extubated. Unfortunately, the incidence of IC at their facility was not stated in this study and was not specified if fluconazole will continue if other risk factors were still existed (**Table 2**) [5].

Rolnitsky *et al.* conducted a retrospective study to evaluate the efficacy of fluconazole prophylaxis in VLBW neonates. The incidence of candidiasis in their institution is low so they developed a risk based approach to initiate fluconazole in high risk neonates. They considered neonates with ELBW, gestational age of less than 28 weeks, and broad-spectrum antibiotics as major criteria and fluconazole will be discontinued once the risk factor is no longer available. Central venous catheters, endotracheal intubation, Total parenteral nutrition were considered minor criteria and a VLBW neonate will not receive fluconazole prophylaxis if he had only one risk factor (**Table 2**) [9].

Manzoni *et al.* conducted a randomized controlled trial to evaluate the prophylactic use of fluconazole in VLBW and ELBW preterm infants. The mean weight was 1065 +/- 280 in the 6 mg/kg group, 1060 +/- 245 in the 3 mg/kg group, and 1120 +/- 270 in the placebo group. The mean gestational age was 28.9 +/- 2.3. The primary outcome in this study was the incidence of colonization, and the incidence of IC. Colonization occurred less frequently in the 6-mg group (9.8%) and the 3-mg group (7.7%) than in the placebo group (29.2%);  $P < 0.001$  for both comparisons. Lastly, invasive fungal infection occurred in 2.7% in the 6-mg group and in 3.8% in the 3-mg group, as compared with 13.2% in the placebo group;  $P 0.005$  and  $P 0.02$ , respectively (**Table 2**) [10]. Kirpal *et al.* conducted a randomized controlled trial to evaluate the safety, an efficacy of fluconazole prophylaxis in VLBW (**Table 1**) neonates. The mean weight was 1250 +/- 0.36 in the fluconazole group and 1220 +/- in the control group. The primary outcome in this study was the development of IC (**Table 1**). All cause mortality was considered a secondary outcome. The incidence of IC was significantly lower in the fluconazole group compared to placebo 21% versus 43.2%, 95% CI 0.09 - 0.37,  $P 0.04$ . All cause mortality was also lower in the fluconazole group compared to

**Table 1.** Abbreviations.

|      |                            |
|------|----------------------------|
| VLBW | Less than 1500 g           |
| ELBW | Less than 1000 g           |
| IC   | Invasive candidiasis       |
| NICU | Neonatal ICU               |
| TNA  | Total parenteral nutrition |

placebo, however, it didn't reach statistical significance 2.6% versus 18.9% > P 0.05 (**Table 2**) [11].

Ericson *et al.* conducted a meta-analysis for four clinical trials conducted in United States that looked at the efficacy of fluconazole in preventing IC. 72% of the enrolled neonates had a birth weight of less than 750 g in the placebo group and 75.58% had a birth weight of less than 1000 g in the fluconazole group. The primary outcome of this meta-analysis was the composite endpoint of IC and death. The OR for the composite end point was 0.48, P < 0.003, and the OR for IC was 0.2, P < 0.001. The incidence of death was not significantly different between placebo group and fluconazole group OR.68, P 0.14 [12].

### Risk Factors for Invasive Candidiasis (IC) Infection

- 1) Very low birth weight and extremely low birth weight (**Table 1**).
- 2) Central venous catheter/Umbilical catheter.
- 3) Third generations cephalosporins and broad spectrum antibiotics.
- 4) Corticosteroids therapy.
- 5) Candida colonization.
- 6) Mechanical ventilation.
- 7) TNA.

## 4. Results

Fluconazole prophylaxis was effective in reducing the incidence of colonization and the incidence of IC in neonates with risk factors. The primary and secondary outcomes were not similar between studies (**Table 2**) [10] [11]. Some studies measured the difference between candida colonization with or without fluconazole prophylaxis and found significant reduction in the incidence of colonization, which was translated to reduction in the incidence of IC as well (**Table 2**) [5] [10] [13]. Only one trial reported the incidence of IC in their center and designed a risk-based approach for fluconazole eligibility [9]. Fluconazole was associated with transient elevation in liver transaminases that returned to baseline after discontinuation [10] [11] [13].

## 5. Discussion

Literature of the recent years supports the prophylactic use of fluconazole in ELBW and in VLBW preterm neonates with one or more risk factors (**Table 1**). Risk-based ap

**Table 2.** Selected studies evaluated the prophylactic use of fluconazole in preterm neonates.

| Author                          | Study design  | Inclusion criteria  | Drug/dose   | Results   | Conclusion/Comments  |
|---------------------------------|---|---|---|---|--|
| Kaufman <i>et al.</i> 2001 [5]  | Prospective, randomized, double-blind clinical trial, 100 infants (50:50) (May 5, 1998, and October 10, 2000)   | ELBW, Preterm neonates, and/or Central venous catheter, endotracheal intubation | IV fluconazole 3 mg/kg every third day for 2 weeks, then every other day for the third and fourth week, then daily during the fifth and sixth week vs. placebo (Schedule A) | <p><b>Primary outcome:</b><br/>Colonization<sup>‡</sup>: Fungal colonization at one or more sites occurred in 30 of placebo group vs. 11 in the fluconazole group P 0.002</p> <p>Infection developed in 10 in placebo group (20%) and none in fluconazole arm. (Risk difference: 0.20% P 0.008)</p> <p><b>Secondary outcome:</b> No difference in mortality between groups P 0.22</p> | <p>Due to the concern of azole resistance fluconazole was limited to preterm infants who required central venous catheters and intubation during the six weeks of life</p> <p>Author didn't specify if additional risk factors are needed to be present in addition to ELBW, preterm and/or central venous catheter, endotracheal intubation</p> <p>**Candiduria was considered IC in this study**</p> <p>**&gt;Number of sites colonized &gt;IC incidence**</p> |
| Kaufman <i>et al.</i> 2005 [13] | Prospective, randomized, double-blind clinical trial, 82 infants (41:40)  | ELBW, Preterm, and/ or central venous catheter, endotracheal intubation         | Regimen above (Schedule A) vs. Twice weekly (Schedule B)  | <p>Colonization<sup>‡</sup>: Fungal colonization at one or more sites developed in 5 in group A vs. 4 in group B P 0.83</p> <p>Infection: Two developed (Schedule A) IC vs. 1 in Schedule B. P value 0.68</p> <p><b>Secondary outcome:</b> No significant difference in mortality P 1.00</p>  | <p>Twice weekly fluconazole is as effective as conventional regimen. No adverse effects except reversible elevation in transaminases</p> <p>Serum aminotransferases were elevated in 2 of group A and in 4 of group B</p>  |
| Manzoni <i>et al.</i> 2007 [10] | Multicentre, prospective randomized, double-blind, placebo controlled trial, 322 infants (112 in 6 mg/kg group, 104 in 3 mg/kg group, 106 in placebo group) | VLBW, ELBW  | IV fluconazole 3 mg/kg vs. 6 mg/kg vs. 1 ml NS every third day for 2 weeks, then every other day for the third and fourth week, then daily during the fifth and sixth week  | <p><b>Primary outcome:</b><br/>Colonization occurred less frequently in the 6-mg group 9.8% (11/112) and the 3-mg group 7.7% (8/104) than in the placebo group 29.2% (31/106) P &lt; 0.001 for both comparisons.</p> <p>IC occurred in 2.7% (3/112) of 6 mg/kg, 3.8% (4/104) of 3 mg/kg, and 13.2% (14/106) in placebo group P 0.005 and P value 0.02, respectively</p>               | <p>Selection of fluconazole should be directed to high risk patients to minimize the overgrowth of fluconazole resistant candida strains.</p> <p>Elevation in serum aminotransferases was reported in 4 neonates in fluconazole group and no elevation in placebo group P 0.31</p> <p>**Candiduria was considered IC if &gt;10,000 organisms/milliliter</p>  |

## Continue

|                                  |  |  |  |  |  |
|----------------------------------|--|--|--|--|--|
| Healy <i>et al.</i> 2008 [14]    | Retrospective, 3012 (2000-2001) and 6393 (2002-2006) (Cohort)<br>**2000-2001 didn't implement fluconazole prophylaxis protocol**   | ELBW, BW close to 1 kg, other risk factors in the opinion of neonatologist   | IV fluconazole 3 mg/kg every third day for 2 weeks, then every other day for the third and fourth week, then daily during the fifth and sixth week | <p><b>Primary outcome:</b><br/>Incidence of IC reduced from 0.6% (19 of 3012) to 0.3% (22 of 6393) P value 0.05</p> <p><b>Secondary outcome:</b> IC related mortality was reduced from 0.1% to 0%, P 0.004</p>   | Fluconazole prophylaxis should be strongly recommended in ELBW and others with VLBW additional risk factors to limit total exposure to fluconazole<br><br>**Urine candida was not considered IC**  |
| Rolnitsky <i>et al.</i> 2012 [9] | Retrospective cohort study<br>VLBW-ELBW cohort infants received risk-based fluconazole (2007-2008 vs placebo (2002-2004)<br>Treatment group number = 130<br>Placebo group number = 319 | <p>VLBW + 1 major risk factor or 2 minor risk factors, ELBW</p> <p>Major risk factor: ELBW, Gestational age less than 28 weeks, Broad spectrum antibiotics (3<sup>RD</sup> generation cephalosporins, Carbapenems etc.)</p> <p>Minor risk factors: CVC, Endotracheal intubation, H2 blockers, Steroid therapy, TNA</p> | IV fluconazole 6 mg/kg every other day until risk factors are removed in VLBW, 6 weeks in ELBW   | <p><b>Primary outcome:</b><br/>Invasive candidiasis in 1 out of 130 in fluconazole group, and 19 out of 319 in control group<br/>P 0.016</p> <p>Incidence of Blood stream fungal infection reduced from 5.96% in control group to 77% in fluconazole group</p> <p><b>Secondary outcome:</b> No difference in mortality between the groups P 0.77</p> | VLBW infants received fluconazole only if one or more risk factors were present e.g. central catheter, preterm, antibiotics etc.<br><br>Consider in high risk patients with combined risk factors, no adverse effects reported<br><br>The incidence of Candida infection was low in their institute , and they used risk-based strategy        |
| Kirpal <i>et al.</i> 2016 [11]   | Randomized double-blinded randomized controlled trial Total (80) (40:40)   | <p>1-Broad spectrum antibiotics (vancomycin, Azosyn, carbapenems, fluoroquinolones)</p> <p>2-VLBW</p> <p>3-Preterm neonates</p>  | IV fluconazole 6 mg/kg every third day for 2 weeks, then every other day for the third and fourth week, then daily during the fifth and sixth week | <p><b>Primary outcome:</b> IC 21% (8/38) in fluconazole group vs. 43.2% (16/37) in placebo group (ARR:22.2%, NNT:5) P 0.04 **Incidence of IC in larger infants (&gt;1500 g) was not different**</p> <p><b>Secondary outcome:</b> Fungal attributed mortality was 2.6% (1/37) in fluconazole group vs 18.9% (7/37) in placebo group) P 0.02</p>       | Elevation of transaminases in 2 of fluconazole arm and 1 of placebo arm P of >0.05<br><br>**Central venous catheters, IV lipids, intubation** were not included in baseline characteristics**<br><br>**Analyzed data from last 3 years: candida rectal colonization in 30%, candida infection in 23% (Retrospective review of hospital data)** |

proach towards fluconazole prophylaxis seems to be safe and effective. Mortality was not different in early studies. However, recent studies concluded that mortality was reduced in the fluconazole arms [10]. In addition to that, due to the morbidity associated with systemic fungal infections, prophylaxis may be warranted in institutions where IC is at least 2% until the risk factors are no longer available. On the contrary, the most recent IDSA guidelines recommend using fluconazole prophylaxis in centers where the incidence of IC is more than 10%. Neurodevelopmental complications were similar in the fluconazole group compared to placebo in patients who already developed IC. The inclusion criteria in some trials included patients with VLBW and didn't evaluate the presence of other risk factors evaluated in the previous trials [11].

Two dose regimens were used in the clinical trials and both of them showed similar outcomes:

- Fluconazole 3 - 6 mg /kg every third day for 2 weeks, then every other day for the third and fourth week, then daily during the fifth and sixth week.
- Fluconazole 3 - 6 mg/kg twice weekly for 6 weeks.

This literature review has some limitations. First, trials that investigated the safety and efficacy of oral non-absorbable antifungal agents were excluded (Figure 1). Second, research was restricted to English, which may result in missing studies investigated fluconazole prophylaxis in neonates published in different languages. Finally, larger randomized trials are needed to evaluate fluconazole safety and efficacy in Neonatal intensive care units where incidence of IC is low or unknown.

## 6. Conclusion

Fluconazole prophylaxis in preterm neonates and/or neonates with ELBW seems to be safe and effective in reducing IC. Important to remember that only IV fluconazole was tested in clinical trials for 6 weeks or as long as risk factors are available.

## 7. Conflict of Interest

Author declares that he has no conflict of interest.

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