



Prevention of Invasive Candidiasis in Premature Neonates: Administering Fluconazole or Not?

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Abstract

Purpose of the Review Fluconazole prophylaxis (FP) for invasive candidiasis (IC) in preterm newborns is still a debated topic. In this review, we describe the most important papers on the topic, and we discuss pros and cons of the use FP in newborns according to these paper's findings.

Recent Findings Since 2001, several studies have been published on the use of FP to prevent IC. While most of them agree on the effectiveness of FP in reducing IC, especially in NICUs with high IC rates, the lack of evidence of decrease in overall mortality, and the risks associated with fluconazole administration both concerning neurodevelopmental impairment and the increase in *Candida* resistances still pose great concern against the universal implementation of FP.

Summary A local risk-based selection strategy could represent the best choice to optimize the benefits of FP and minimize the potential long-term toxicity and the development of resistant pathogens.

Keywords Fluconazole prophylaxis · Premature · Invasive candidiasis

Introduction

Invasive candidiasis (IC) is a serious infection with significant morbidity and mortality. Central nervous system is involved in around 50% of newborns with IC [1, 2], and up to 60% of survivors may present neurological impairment [3].

The incidence of IC varies according to birth weight and it has been estimated that the risk of IC is threefold higher for infants < 750 g compared to infants with birth weight of 750–1000 g [4]. The immaturity of the immune system of very low birth weight (VLBW) and extremely low birth weight (ELBW) neonates is the most important risk factor [5]; the

presence of invasive devices, prior colonization by *Candida* spp., cross transmission by hands, and use of broad-spectrum antibiotics use, as well as recent abdominal surgery are all considered predisposing conditions [6, 7]. Indeed, the difference in IC incidence between single NICUs reflects the differences in central line policies, infection control, and antimicrobial stewardship programs [7, 8].

Owing to its pharmacokinetic characteristics, fluconazole represents an attractive agent for prophylaxis. It has a good enteral absorption, long half-life, excellent CSF penetration, and it is mostly eliminated unchanged in the urine [9].

Effectiveness of Fluconazole Prophylaxis

There is some evidence supporting fluconazole prophylaxis (FP) as a safe and efficacious strategy to prevent colonization and IC in VLBW and ELBW infants.

The use of fluconazole for prophylaxis was first explored in 2001 by two randomized controlled trials. The first, by Kaufman et al., was a prospective, randomized, double-blind trial of 100 ELBW infants randomly assigned to receive either intravenous fluconazole or placebo for 6 weeks. Although the study had small numbers of neonates included in each arm this trial showed a significant reduction in *Candida* colonization

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and a decrease in IC [10]. The second one, conducted by Kicklighter et al., was a single-center randomized control trial investigating if FP administration for the first 28 days of life could result in a reduced incidence of *Candida* colonization in the VLBW infant. This trial, that involved 103 patients, showed that FP is safe and able to decrease the risk of rectal colonization by *Candida* species [11].

In 2007 Manzoni et al. conducted a robust multicenter, randomized, double-blind, placebo-controlled trial regarding fluconazole prophylaxis including 322 VLBW infants. Patients were randomly assigned to receive either fluconazole (at a dose of either 6 mg or 3 mg/kg) or placebo, from birth until day 30 (if VLBW) or day 45 of life (if ELBW). In this case, a significant reduction in both colonization and IC in the fluconazole arms was reported.

In addition to this evidence, other retrospective comparative studies with pre- and post-exposure analysis support the use of FP [12]. Healy et al., in 2008 reported a reduction of IC from 0.6% (19/3012) to 0.3% (22/6393) with the use of FP, with a 3.6-fold decrease in ELBW infants in particular. Similarly, Rueda and colleagues in 2010 published a study that described a reduction in the incidence of IC among VLBW neonates, from 7.7% (21/271) in the pre-FP period to 1.1% (3/252) in the post-FP period [13].

On the other hand, some studies question the effectiveness of FP in preventing neonatal IC. A randomized, double-blind placebo-controlled study conducted by Parikh et al. in 2007 [14], reported no difference between the incidence of IC between intervention and placebo groups. Likewise, a retrospective analysis by Lee and colleagues on 423 children, reported no reduction of incidence in IFIs in ELBW infants receiving FP [15].

In 2014 Benjamin et al., conducted a multicenter randomized blinded, placebo-controlled trial of fluconazole in premature infants including 361 infants weighing less than 750 g at birth [16]. The aim of the study was to evaluate the safety and efficacy of fluconazole in preventing IC or death among ELBW infants and to determine the effect of FP on neurodevelopment in surviving infants. They concluded that among infants with a birth weight of less than 750 g, FP compared with placebo was not associated with a statistically significant difference in the incidence of the composite outcome of death or IC. These findings do not support the universal use of prophylactic fluconazole in extremely low birth weight infants [16] (Table 1).

The lack of consistency in these results may be a consequence of differences in baseline incidence of colonization and IC: many studies reporting an effective reduction of IC come from centers with high incidence of IC (15–20%), while it is unclear if FP has a real impact in low incidence settings [24].

Moreover, as underlined by Ericson and Benjamin in their review, all studies regarding FP that used historical controls as comparator group are affected by other factors (e.g., central line policies) that might have changed over time, and it is

impossible for these studies to fully determine the effect of fluconazole on the incidence of IC. In fact, a reduction in the incidence of *Candida* central line-associated bloodstream infections has been reported even in birth weight cohorts that are not considered for FP (e.g., > 1000 or > 1500 g birth weight) [24].

As a consequence, universal FP is not recommended for all neonates. Current recommendations include the use of FP only for infants with a birth weight of less than 1000 g in NICUs with high rates of IC [25, 26]. However, differences in the threshold for starting a FP still persist. Indeed, ESCMID guidelines suggest a cut-off IC rate of 2% [26] differently from the 5% proposed by the IDSA guidelines [25]. Moreover, the lack of evidence of decrease in overall mortality, and the risks associated to fluconazole administration both concerning neurodevelopmental impairments and an increase in *Candida* resistances still represent important concerns against the use of FP.

Open Issues

Reduction of Mortality

Literature findings reporting a reduction of mortality associated with IC in neonates receiving FP are scarce. A recent review conducted by Ferrera da Silva Rios et al. [27], included 12 original articles on antifungal prophylaxis in premature infants. They identified six studies that assessed IC-related mortality: four comparative studies with pre-prophylaxis period and FP period, [13, 18, 19, 22] and two trials comparing fluconazole to placebo [10, 14]. They found that in only one of these studies [13], there was a significant reduction of IC-associated deaths, with 21% mortality in the pre-prophylaxis group versus no deaths in the post-prophylaxis group.

Similarly, a meta-analysis conducted in 2015 by Clerihew et al., including data from four trials comparing FP to placebo did not demonstrate any statistically significant effect on overall mortality rate, even if with a wide confidence interval (95%) [28].

Neurodevelopmental Disorders

Other concerns regarding widespread application of FP are long-term consequences of fluconazole administration and neurodevelopmental impairment. To our knowledge, two studies assessed neurodevelopmental consequences in neonates receiving FP.

The first one is the aforementioned trial conducted by Benjamin et al. [2] that evaluated neurodevelopment at 18–22 months of age in 118 infants who were randomized to use FP or placebo. The authors concluded that the use of fluconazole did not impair the neurodevelopment of these neonates. However, as stated in the study, these results are biased, since

Table 1 Main studies on antifungal prophylaxis with fluconazole in the NICU

Author	Year	Study	Population	Outcome
Kaufman D et al. [10]	2001	RCT	50 NB < 1000 g: placebo 50 NB < 1000 g: fluconazole	Colonization IC Mortality
Kicklighter et al. [11]	2001	RCT	50 NB < 1500 g: placebo	Colonization
Bertini et al. [17]	2005	Cohort study	136 NB < 1500 g: placebo 119 NB < 1500 g + central catheter: fluconazole	IC Mortality
Uko Set et al. [18]	2006	Cohort study	206 NB < 1500 g: no fluconazole 178 NB < 1500 g: fluconazole	CI (after 30 day) Mortality
Manzoni P et al. [19]	2006	Cohort study	240 NB < 1500 g: no fluconazole 225 NB < 1500 g: fluconazole	Colonization IC Mortality
Manzoni P et al. [12]	2007	RCT	106 NB < 1500 g: placebo 112 NB < 1500 g: fluconazole 6 mg/kg group 104 NB < 1500 g: fluconazole 3 mg/kg group	Colonization IC Overall mortality
Parikh TB et al. [14]	2007	RCT	60 NB < 1500 g: placebo 60 NB < 1500 g: fluconazole	Colonization IC Mortality
McCossan et al. [20]	2007	Cohort study	33 NB < 1500 g: placebo	IC
Weitkamp J-H et al. [21]	2008	Cohort study	44 NB < 750 g or < 26 GA: no fluconazole 42 NB < 750 g or < 26 weeks of GA: fluconazole	IC
Healy CM et al. [13]	2008	Cohort study	3012 NB: no fluconazole 6393 NB: fluconazole	IC IC associated Mortality Overall mortality
Rueda K et al. [22]	2010	Cohort study	271 NB < 1250 g: no fluconazole 252 NB < 1250 g: fluconazole	IC IC associated Mortality Overall mortality
Rolnitsky A et al. [23]	2012	Cohort study	130 NB < 1000 g, or risk factors: fluconazole 319 historical controls: no fluconazole	IC
Benjamin Jr. DK et al. [16]	2014	RCT	188 NB < 750 g: fluconazole 173 NB < 750 g: placebo	IC Mortality Neurodevelopmental impairment
Lee et al. [15]	2016	Cohort study	264 NB < 1000 g: fluconazole 159 NB < 1000 g: placebo	IC Mortality

RCT randomized control trial

many factors affected neurodevelopmental impairment in pre-term neonates, and the study was not powered for differences in neurodevelopmental impairment alone.

The second study, by Kaufmann et al. [29•], assessed long-term consequences, considering neurodevelopmental and behavioral impairments at 8–10 years of age. The complete follow-up and assessment was possible only for 20 children

who had received fluconazole as infants, and it showed that outcomes of the children who received fluconazole was not different from the ones who did receive placebo. Even if this result is encouraging, the high number of patients lost in follow-up, as well as the possible biases related to the long period of follow-up represent significantly limit the strength of the evidence.

Moreover, while these results show that FP administration does not result in neurodevelopmental impairments, they also show that it provides no advantage compared to placebo either.

Antifungal Resistances

Although it has not been reported in NICUs yet, resistance to fluconazole has appeared in recent years, with some centers reporting ~8% of resistance among *Candida* isolates both in adults and children [30]. Furthermore, it has been demonstrated that the application of non-targeted FP leads to a change in the distribution of the different species of *Candida*, resulting in a decrease of *C. albicans*, and an increase of *C. krusei*, which is inherently resistant to fluconazole, and *C. glabrata*, that has resistance rates > 50% [31, 32]. Indeed, the aforementioned study by Lee et al. [15], reported an increase in incidence of invasive infections involving fluconazole-resistant *C. parapsilosis* even though it was not statistically significant (41.7 vs. 0%, $P = 0.11$).

On the other hand, a single-centered study conducted by Manzoni et al. over a 5-year period, found no increase in fluconazole inherently resistant *Candida* species after the implementation of routine FP for VLBW infants [33]. Likewise, a study by Healy and colleagues [13], compared resistance patterns of isolates causing IC before and after the implementation of FP, and showed no difference in the epidemiology in the two study periods.

However, both these are single-center studies, and have relatively small number of patients and short duration, and the effect of FP on larger scale and longer period is yet to be evaluated.

In addition to the concerns about current resistances, there is rising attention about the emergence of a new, highly resistant species, *Candida auris*, that is a new species that was first described in 2009 and has been demonstrated to be multidrug resistant, with fluconazole resistance rates > 90%. Even if the report of *C. auris* are still occasional, it is interesting to underline that among the 12 first reported cases in India, 3 were neonates, as reported by Chowdhary et al. [34].

One last factor to consider is the cost-effectiveness of FP: according to Swanson et al. [35], if the incidence of IC is below 2.8%, FP loses its cost-effectiveness in NICU. However, as indicated by the authors, many factors affect the incidence of IC in NICUs, and in low incidence centers the cost-benefit may only be seen in selected population (i.e., < 27 weeks gestation or < 750 g). This analysis provides evidence of the need for targeted use of FP in preventing IC.

Targeted Prophylaxis

To optimize the benefits of FP in preterm neonates, some authors proposed a risk-stratification strategy.

In an observational study by Bertini et al. [17], FP was administered only to VLBW infants with a central venous line. A reduction of fungal infection was reported in the fluconazole group in comparison to the baseline group (9/119 vs. 0/136, $P = 0.003$).

In 2006, Uko et al. conducted an observational study of two subsequent periods of inborn VLBW and ELBW infants, one before and one after targeted-FP implementation. In this study, the main factor for starting a FP in VLBW and ELBW infants was a concomitant broad-spectrum antibiotic therapy for more than 3 days. IFI was observed in 6.3% (13/206) in the control period and 2/178 (1.1%) after targeted-FP implementation, with a common odds ratio of 0.166. Moreover, this intervention was cost-effective and the number needed to treat to prevent 1 IFI was 10 [18]. Differently, McCrossan et al. suggested few conditions which could request a FP in VLBW babies [20]. In their analysis, the additional risk factors were colonization of *Candida* species from surface sites with a central venous catheter, third-generation cephalosporin treatment, or total duration of antibiotic treatment > 10 days. The results showed that selective FP reduced invasive fungal sepsis without evidence of fluconazole resistance emerging [20].

Martin et al. in 2012 further stratified the high-risk population proposing targeted FP to all VLBW infants who had received broad-spectrum antibiotics for more than 2 days and having at least one additional risk factor for IC. The authors reported a significant decrease in IC from 15.3 to 6.2% during the FP period [36].

Another study, by Weitkamp et al. applied a different targeted approach to FP, including only < 750 g birth weight or < 26 weeks gestational age with a central line in the prophylaxis group. Again, a reduction in IFI was demonstrated, in comparison with historic controls (9/44 vs. 0/42, $p = 0.004$), with no significant rates of adverse effect recorded. In addition, the targeted approach allowed to reduce the number of infants > 1000 g requiring prophylaxis from 80 to 42 (48% reduction), without missing any preventable infection [21].

One more recent analysis was conducted by Rolnitsky et al., 2012, in Israel. In their retrospective cohort study with historical controls, they categorized many different risk factors into major (birth weight < 1000 g, corrected gestational age < 28 weeks, and use of broad-spectrum antibiotics) and minor (the presence of a central venous line, respiratory support, inotropic support, use of parenteral nutrition, use of a histamine-2 blocker or systemic steroids, confirmed necrotizing enterocolitis, or recent abdominal surgery), and applied FP only to neonates presenting with one major or two minor criteria. With this approach, they reported a significant reduction in the rate of fungal infections in the fluconazole prophylaxis group (1 of 130 vs. 19 of 319, $p = 0.016$). Furthermore, they calculated that this selective approach reduced the number of infants treated from 247 to 130 [23].

Alternatives to Fluconazole Prophylaxis

Oral nystatin prophylaxis was the first antifungal studied in preventing IC, and many studies report its efficacy [37–39]. FP is preferred because of its greater efficacy and cost-benefit, but nystatin prophylaxis has been proven to reduce mortality as well as IC [38].

Furthermore, since many factors impact IC incidence in NICUs, other infection control measures may reduce IC and IC-related mortality. In their study, Chen et al. [40], evaluated the effect of integrated measures (with a particular emphasis on hand hygiene), in reducing IC in a Chinese hospital's NICU. They found that integrated measures, combined to FP can be much more effective than FP only: the reported incidence of IC in the group to which integrated measures (together with FP) were applied was 2.9% (2/68), while in the group that received only FP it was 18.2% (18/99) and in the control group was 22.3% (22/94).

Conclusion

Currently, many studies suggest efficacy of FP in reducing IC and colonization by *Candida* species; however, literature findings are not consistent with recommending universal use of FP, and many aspects of this topic need to be further clarified by scientific evidence.

From what we know at this moment, FP should be implemented in NICUs with an IC rate > 5%, while in those with IC rate between 2 and 5% an approach based on additional risk factors seems to be the best choice to optimize the benefits of FP and to minimize the potential long-term toxicity and the development of resistance.

Compliance with Ethics Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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