Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 02/28/2024
Approved on: 09/13/2024

REVIEW ARTICLE

Fluconazole prophylaxis in susceptible newborns: a systematic review

Lidiane França Cabral[1], Ronaldi Gonçalves dos Santos[2]

Keywords:
Disease prevention,
Fluconazole,
Infant,
newborn.

Abstract

Fungal infections in newborns represent a major problem for the health of the population. It has been observed that in hospital environments, neonates are susceptible to infections, especially those born preterm and with extreme low birth weight. The general objective is to review and evaluate the efficacy of the prophylactic use of fluconazole in very and extremely low birth weight (VLBW/EBW) patients against the development of systemic fungal infection (SFI). Searches were carried out on the PubMed®, Scopus and Embase research platforms for articles from May 2012 to October 2021. The following descriptors were used: "fluconazole", "prophylaxis" and "neonates" in the databases. Studies that addressed prophylactic use in susceptible individuals were included. A total of 1649 patients who took part in the studies were reviewed. There was no significant difference between the sexes, the length of prophylactic treatment was 4-6 weeks, the dose varied between the studies, but 3 mg/kg was the most commonly used. The results analyzed included complications and risk factors such as low birth weight, lower gestational age, longer duration of total parenteral nutrition, necrotizing enterocolitis, use of broad-spectrum antibiotic therapy, use of pulmonary surfactant and use of postnatal steroids. The prophylactic approach should be started before 72 hours, since after that its outcome is more relevant to reducing complications than the incidence of SFI. Prophylaxis with fluconazole has been shown to reduce the incidence of SFF and other complications such as length of hospital stay, oxygen therapy and mortality in newborns with EBP.

[1] HUJM- Hospital Universitário Júlio Muller, Departamento de Pediatria - Cuiabá - Mato Grosso - Brazil.
[2] UFMT-Universidade Federal de Mato Grosso, FM-Faculdade de Medicina - Cuiabá - Mato Grosso - Brazil.

Correspondence to:
Ronaldi Gonçalves dos Santos.
Universidade Federal de Mato Grosso. Rua Quarenta e Nove, nº 2367, Boa Esperança, Cuiabá, MT, Brazil. CEP: 78060-900. E-mail: ronaldi.goncalves.s02@gmail.com

Resid Pediatr. 2025;15(2). DOI: 10.25060/residpediatr-2025.v15n2-1249

Este trabalho está licenciado sob uma Creative Commons Attribution 4.0 International License.

INTRODUCTION

Fungal infections are the third leading type of infection worldwide and are more prevalent in individuals with compromised or developing immune systems, such as neonates.[1] Approximately 2 to 20% of premature newborns are affected, and 10% of sepsis cases occur in extremely low birth weight (ELBW) newborns, with Candida spp. being the third most common pathogen.[2-5] Although the epidemiology of the infection has changed with an increase in cases related to other species of the genus, such as C. tropicalis, C. parapsilosis, C. glabrata, and C. krusei, the species Candida parapsilosis and Candida albicans stand out.[2] Fungal infections can be acute or chronic, presenting with superficial or deep lesions. Immunosuppressed individuals may develop oligosymptomatic disease or severe symptoms.[1,3] The transmission forms are considered vertical (15%) through contact with the pathogen in the birth canal; the horizontal mode (85%) occurs through contact with infected hospital equipment and/or healthcare workers.[3,4]

In candidemia, Candida spp. have a greater tropism for the central nervous system (10-64%), kidneys (37-57%), liver, spleen, heart, and retina (6-50%).[4-6] The presence of invasive devices (such as endotracheal tube, venous catheter, bladder catheter), prolonged and excessive use of broad-spectrum antibiotics, steroids, H2 receptor blockers, congenital malformation, and abdominal surgery are risk factors for neonatal candidemia.[7,8]

Clinical diagnosis is challenging due to nonspecific systemic signs and symptoms, but the gold standard method remains isolating the agent using sterile cultures.[9,10] Given the importance of early diagnosis and immediate intervention to control the infection while reducing morbidity and mortality, this systematic review on neonatal candidemia highlights the significance of using fluconazole in susceptible neonates as a prophylactic strategy, assessing its efficacy and safety.

METHODOLOGY

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Articles were searched on the digital platforms PubMed®, Scopus, and Embase. The prophylactic use of fluconazole against fungal infections was evaluated based on selected randomized and non-randomized trials.

Search strategy and selection criteria

The search for articles was based on the following descriptors: "fluconazole," "prophylaxis," and "neonates." A total of 289 articles were found. Boolean operators were added to the following search phrases: "fluconazole" AND "prophylaxis" AND "neonates"; "fluconazole" AND "neonates"; and "prophylaxis" AND/OR "neonates." The search for articles was initiated on December 5, 2023, and ended on January 12, 2024. The search included studies carried out in the last fifteen years, with articles published between May 2012 and October 2021. Initially, screening included all studies discussing the prophylactic use of fluconazole in newborns selected according to the criteria. The inclusion criteria were: a) studies that evaluated the use of fluconazole in very low and extremely low birth weight newborns; b) articles that used fluconazole in the prophylaxis against systemic fungal infection; c) studies with follow-up periods longer than four weeks; d) neonatal survival longer than 72 hours; and e) newborns undergoing treatment in an intensive care unit.

The exclusion criteria were: a) studies with no control group; b) trials that used fluconazole for treatment rather than prophylaxis; c) studies that did not exclusively evaluate very and extremely low birth weight newborns; d) systematic reviews; e) case studies.

The articles were also selected based on the Population, Intervention, Comparison, Outcome (PICO) strategy.

Population: extremely and very low birth weight newborns treated in an intensive care unit.

Intervention: analysis of fluconazole prophylaxis to reduce systemic fungal infections.

Comparison: analysis of groups treated with fluconazole versus controls concerning the incidence of infection and complications.

Outcome: indication of whether prophylactic fluconazole reduces infections, hospital stay length, and complications in extremely and very low birth weight newborns.

Data extraction

The abstracts of the studies selected based on the search criteria were read, and the articles deemed relevant were reviewed in full. Two independent reviewers extracted the data. Any disagreements among reviewers regarding the inclusion or exclusion of a study were resolved through consensus. The variables collected included birth weight, time to initiate treatment, duration of treatment, target dose, and interventions performed.

Quality assessment

The Newcastle-Ottawa scale was utilized to evaluate the quality of the included studies. This scale assigns scores ranging from 0 to 9 across eight categories, which include selection criteria, comparability, and control group outcomes.

RESULTS

Literature search and study characteristics

Database searches yielded a total of 289 articles. Of these, 155 were excluded because they fell outside the period of interest. From the remaining 134 articles, 126

were excluded based on the inclusion criteria. The abstracts of the eight remaining articles were reviewed. In the end, eight articles were included in this review: six selected using the above method, and two added by the review's authors. Three multicenter, two randomized, and one retrospective comparative studies were identified. Among the articles, citations were interlinked among the authors; only one article presented a conflict of interest due to sponsorship by the pharmaceutical company Pfizer®. The distribution is illustrated in Flowchart 1.

Reference characteristics

The studies involving fluconazole prophylaxis involved 1649 patients. There was no significant difference between the sexes. The prophylactic treatment lasted 4 to 6 weeks; there was no consensus on the dosage, but 3mg/kg was the most common. The analyzed results included complications and risk factors.

Use and results

Among the references studied based on the inclusion criteria, prophylaxis is relevant for very low-weight and extremely low-weight newborns; treatment should begin after the first two days of life, continuing for 4-6 weeks. There is still no consensus in the literature regarding the prophylactic use of fluconazole, although treated individuals fared better than controls. The elements covered in the studies are described in Table 1.

DISCUSSION

The academic community has not reached a consensus on fluconazole's use and management, with differences arising in dosage and the timing for initiating prophylactic care. Generally, prophylaxis is considered beneficial only for a subset of at-risk patients for whom the medication is suitable. This group includes preterm newborns with very low or extremely low birth weight.

The studies included in this review enrolled very low and extremely low birth weight newborns. Other criteria were considered, such as surviving at least 72 hours after birth at 32 weeks of gestation or less.[3,11] The remaining studies followed similar criteria described in Table 1.

There was disagreement among the studies regarding when to start treatment, with some initiating prophylactic care within 72 hours of birth and others beginning after that period. This decision is relevant from the perspective of risk factors. Fluconazole may not protect individuals repeatedly exposed to various risk factors during this time. Early colonization of newborns may relate to maternal factors, gestational factors, maternal pathogens, and characteristics of the fungus, rather than gestational age or birth weight, since Candida colonizes newborns regardless of these factors.

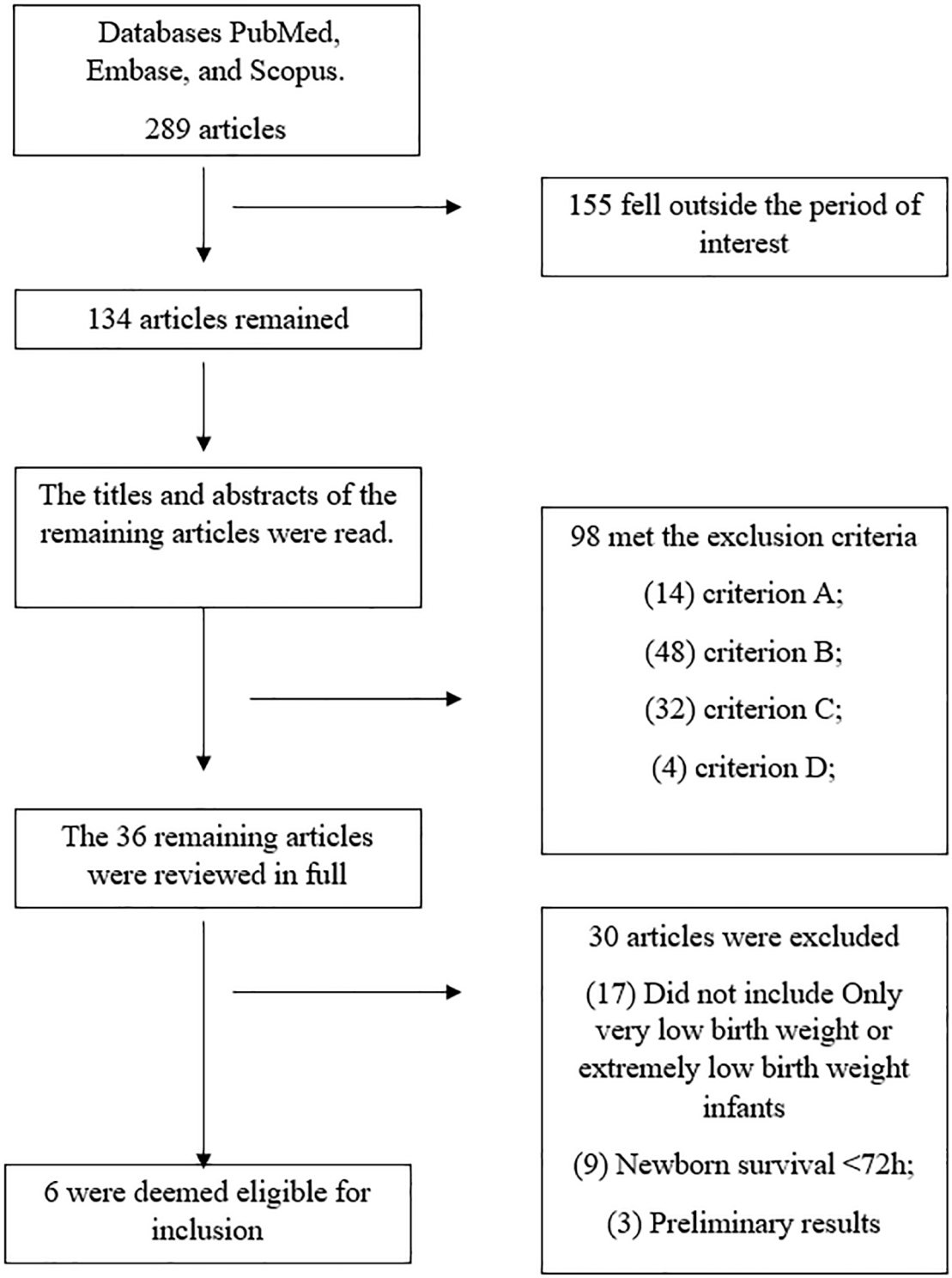
When newborns were divided into baseline colonization (BC) and acquired colonization (AC), it became clear that 21 cases of systemic fungal infection occurred in a group of 54 colonized individuals (38.8%), with 6 out of 16 belonging to the BC subgroup and 15 out of 38 to the AC subgroup. In other words, all episodes of systemic fungal infection occurred in newborns with prior colonization. The progression rate to systemic fungal infection was lower in the group receiving prophylaxis with fluconazole, with treatment initiation within 72 hours yielding better outcomes.[3] Studies in which prophylaxis was started after 72 hours of birth examined similar variables, such as the active search for risk factors for sepsis.

The target dose used for prophylaxis was also heterogeneous among the studies. Among the studies prescribing 3mg/kg, there were no significant differences in gestational age, birth weight, or use of steroids and surfactants; however, time on oxygen therapy was 7.86±11.33 days in the fluconazole group and 11.86±10.26 days in the control group, while time on a ventilator was 3.7±7.82 days in the fluconazole group and 8.5±52 days in the control group.[12] The length of hospitalization between the groups also varied, with 35.16±16.43 days in the fluconazole group and 43.03±19.07 days in the control group. There were nine deaths in the fluconazole group and 15 in the control group.

Patients administered 3 mg/kg of fluconazole had a lower risk of fungal infection and reduced use of H2 blockers (39% vs. 69%, p <0.001), third-generation cephalosporin (5% vs. 26%, p <0.001), and vancomycin (49% vs. 60%, p = 0.03). They also required fewer days of parenteral nutrition (26 ± 16 vs. 31 ± 17 days, p = 0.001) and antibiotic therapy (19 ± 20 vs. 28 ± 26 days, p <0.001). The percentage of patients needing oxygen therapy more than 48 hours after birth was significantly lower in the fluconazole group (87% vs. 94%, p=0.02).[13]

Studies in which patients were prescribed 6mg/kg also found that individuals receiving prophylactic care had a lower risk of developing nosocomial infections and clinical complications than controls. A significant difference was noted in the incidence of systemic fungal infection between the groups, with 21% in the prophylaxis group versus 43.2% in the control group (95% CI 0.09-0.37, p-value 0.04). This equates to a risk reduction of 22.2% and a relative risk of 0.48 (95% CI 0.09-0.37).[14,15]

Prophylactic fluconazole dosages typically ranged from 3 mg/kg to 6 mg/kg. However, due to the heterogeneity of the populations and studies, it is not possible to determine which dosage provides the best prophylactic results, as the methods employed varied even when the same doses were used, such as in the study describing fluconazole administration from every two days to twice a week.



Fluxograma 1. Screening and selection of analyzed studies.

Table 1. Characteristics of eligible articles, containing inclusion criteria, start of treatment, dose, and outcomes.

Article	Year	Type	Country	Population	Inclusion criteria	Start of treatment	Dose alvo	Duration of treatment	Outcome
Manzoni et al.[3]	2012	Randomized trial	Italy	225 individuals on fluconazole 111 controls	Survival >72h.	<72h	3mg/kg (50%) and 6mg/kg (50%) every 48h	Not indicated	Newborns with com BC given fluconazole had less SFI.
Kaufman et al.[11]	2014	Multicenter trial	United States of America	127 individuals on fluconazole 399 controls	BW 500-1200g; Survival > 4 weeks; Venous access for 10-14 days.	<24h	3mg/kg (97.5%) and 6mg/kg (2,5%), twice a week.	6 weeks	Infection in 0.8% (1/127) of the individuals given fluconazole and in 7.3% (29/399) of controls.
Jannatdoust & Imani[12]	2015	Multicenter trial	Iran	43 individuals on fluconazole 50 controls	BW <1250g; GA < 32 weeks	<24h	3mg/kg every 72h on 1st and 2nd weeks, every 48h in the 3rd and 4th weeks, and every 24h in the 5th and 6th weeks.	6 weeks	Hospitalization: 7.86±11.33 and 3.7±7.82 among individuals given fluconazole and 11.86±10.26 and 8.5±52 among controls.
Lee et al.[13]	2016	Multicenter trial	Korea	264 individuals on fluconazole 159 controls	ELBW newborns in an ICU	>72h	3mg/kg twice a week	4 weeks	Decreased need for oxygen therapy > 48h and less SFI.
Kirpal et al.[14]	2016	Randomized trial	India	38 individuals on fluconazole 37 controls	BW <1500g and ICU stay within 72 hours of birth	>72h	6mg/kg every other day in 1st week, daily onwards.	4 weeks	Incidence of SFI of 21% in newborns given fluconazole versus 43% in controls.
Zhang et al.[15]	2021	Comparative retrospective study	China	113 individuals on fluconazole 83 controls	VLBW and ELBW newborns	>72h	6mg/kg twice a week	4 weeks (VLBW) 6 weeks (ELBW)	Decrease in nosocomial infections and complications.

Key: BW, birth weight; GA, gestational age; VLBW, very low birth weight; ELBW, extremely low birth weight; BC, baseline colonization; SFI, systemic fungal infection; ICU, intensive care unit.

Birth weight was a significant risk factor for systemic fungal infection. Other risk factors included lower gestational age (adjusted OR = 0.87, 95% CI = 0.80-0.95, P = 0.002), longer duration of total parenteral nutrition (adjusted OR = 1.06, 95% CI = 1.02-1.09, P = 0.001), and necrotizing enterocolitis (adjusted OR = 7.34, 95% CI = 2.00-26.95, P = 0.003).[15] Among the neonates with Candida systemic fungal infection, 90% had ELBW, a proportion equal to that of the individuals given prophylaxis with fluconazole, indicating that birth weight is a vital variable in analyzing the conversion of colonization to systemic fungal infection in the reviewed population.[11]

Regarding invasive Candida infections diagnosed in blood, urine, and cerebrospinal fluid tests, a significant difference was found between individuals given fluconazole and the controls, with an incidence of 0.8% versus 5.5%.[11] A retrospective multicenter study on neonatal candidemia included 1,395 cases and found a median gestational age of 27 weeks.[8] Among the 422 newborns admitted to the ICU, Candida albicans was isolated in 60% of cases, followed by Candida parapsilosis in 27.7%. The mortality rate in this group was 18.3%. Additionally, Candida tropicalis infection was observed, with an incidence of 37%.[14]

Considering maternal colonization, a study evaluating 102 cases of premature newborns admitted to the NICU found a significant positive correlation between vaginal delivery and prolonged labor with early rupture of membranes and Candida colonization.[16] This correlation may relate to a longer interval of fetal contact with the maternal microbiota compared to cesarean sections or faster-progressing vaginal deliveries. The Candida genus identified in neonatal colonization was identical to that in pre-delivery samples taken from the maternal vagina, so screening for Candida in mothers experiencing preterm labor may help prevention the disease.[12,16]

Prophylaxis resulted in reduced mortality across all studies. However, one study found no significant difference between the groups regarding systemic fungal infection incidence and key clinical differences.[13]

Most studies described considerable differences between neonates receiving fluconazole prophylaxis and those who did not, both in the incidence of systemic fungal infections between the groups and in the length of hospitalization, time to complete enteral nutrition, time on oxygen therapy, duration on a ventilator, and mortality rates. Only one study did not report significant differences between the fluconazole and control groups. An important difference was also found among newborns outside the risk group, particularly those with birth weights above 1500g, a group in which no statistically significant benefit was identified with the administration of fluconazole.

Prophylaxis should be initiated based on each patient's risk factors. Studies indicate that prophylactic care should be introduced within 72 hours of birth. When commenced after 72 hours of birth, fluconazole is more effective at reducing the incidence of complications than at preventing systemic fungal infection.

CONCLUSION

Administering fluconazole to susceptible newborns as a prophylactic strategy for neonatal candidemia is scientifically valid when considering variables such as oxygen therapy, length of hospital stay, and mortality. Newborns with extremely low birth weight benefit the most from prophylactic care. Neonates with very low birth weight also experience decreases in complications like systemic fungal infection and length of hospital stay due to fluconazole therapy. However, the results are not as strong as those observed in newborns with very low and extremely low birth weight.

REFERENCES

1. Arendrup MC. Candida e candidemia. Suscetibilidade e epidemiologia. Dan Med J. 2013;60(11):B4698.
2. Mantadakis E, Tragiannidis A. Invasive fungal infections in the pediatric intensive care unit. Pediatr Infect Dis J. 2019;38(9):e216-e218.
3. Manzoni P, Farina D, Leonessa ML, Priolo C, Mostert M, Saia OS, et al. Clinical characteristics and response to prophylactic fluconazole of preterm VLBW neonates with baseline and acquired fungal colonisation in NICU: data from a multicentre RCT. Early Hum Dev. 2012;88(Suppl 1):S60-S64.
4. Auriti C, De Gasperis MR, Di Profio E, Ronchetti MP, Orzalesi M, Toma E, et al. High-dose micafungin for preterm neonates and infants with invasive and central nervous system candidiasis. Antimicrob Agents Chemother. 2016;60(12):7333-9.
5. Araújo MAS, Silva MT, Medeiros SM, Melo MM, Oliveira JG, Souza LB. Candida spp. isolados da urina de recém-nascidos de uma Unidade de Terapia Intensiva Neonatal. Rev Bras Anal Clin. 2013;1(11):35-7.
6. Martins JM. Doença invasiva por fungos no recém-nascido pré-termo [Tese de Doutorado]. Lisboa: Universidade de Lisboa; 2015.
7. Vasileiou E, Tsioutis C, Roussos N, Karageorgopoulos DE, Daikos GL. Invasive candidiasis and candidemia in pediatric and neonatal patients: A review of current guidelines. Curr Med Mycol. 2018;4(3):28-35.
8. Warris A, Pana ZD, Oletto A, Launay E, Castagnola E, Velegraki A, et al. Etiology and outcome of candidemia in neonates and children in Europe: An 11-year multinational retrospective study. Pediatr Infect Dis J. 2020;39(2):114-20.
9. Staniszewska M, Bondaryk M, Siennicka K, Kocyla J, Wroblewska M. Virulence factors in Candida species. Curr Protein Pept Sci. 2020;21(3):313-23.
10. Hamula CL, Hughes K, Gajee R, Kwong CH, Li A, Leung V, et al. T2Candida provides rapid and accurate species identification in pediatric cases of candidemia. Am J Clin Pathol. 2016;145(6):858-61.
11. Kaufman DA, Cuff AL, Ward RM, Boyle RJ, Gurka MJ, Grossman LB, et al. Fluconazole prophylaxis in preterm infants: a multicenter case-controlled analysis of efficacy and safety. Early Hum Dev. 2014;90(Suppl 1):S87-S90.
12. Jannatdoust A, Imani V. The effect of prophylactic intravenous fluconazole on the clinical outcome of preterm infants during hospitalization. Int J Womens Health Reprod Sci. 2015;3(4):212-6.
13. Lee J, Kim HS, Shin SH, Choi CW, Kim EK, Kim BI, et al. Efficacy and safety of fluconazole prophylaxis in extremely low birth weight infants: multicenter pre-post cohort study. BMC Pediatr. 2016;16(1):1-9.

14. Kirpal H, Mitra S, Rath S, Agarwal S, Deorari AK, Paul VK. Prophylactic fluconazole in very low birth weight infants admitted to neonatal intensive care unit: randomized controlled trial. J Matern Fetal Neonatal Med. 2016;29(4):624-8.
15. Zhang D, Wang L, Zhu R, Li Y, Hu Y, Wang Y. Prophylactic use of fluconazole in very premature infants. Front Pediatr. 2021;9:1-7.
16. Hsieh E, Smith PB, Benjamin DK Jr. Neonatal fungal infections: when to treat? Early Hum Dev. 2012;88(Suppl 1):S6-S10.