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Fluconazole Effectiveness in Preventing Invasive Fungal Infection in Very Low Birth Weight Infants: Systematic Review and Meta-analysis

(Efektivitas Flukonazol dalam Mencegah Infeksi Jamur Invasif pada Bayi dengan Berat Lahir Sangat Rendah: Tinjauan Sistematis dan Meta-analisis)

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Abstract: Fungal infections in neonates, especially in Very Low Birth Weight (VLBW) infants, are mostly caused by *Candida species* and may lead to morbidity and mortality. A systematic review and a meta-analysis were conducted to determine the extent to which fluconazole, an antifungal prophylactic, was effective and safe to use in VLBW or premature infants in preventing Invasive Fungal Infection (IFI), by including Randomized Controlled Trials (RCTs) carried out worldwide. The investigation started with searching process through publication databases: MEDLINE, Cochrane, ScienceDirect, and Garuda, for Randomized Controlled Trials (RCTs) that compared the prophylactic effects of fluconazole and placebo on IFI in VLBW infants. The selected eight RCT studies indicated that, compared to placebo, fluconazole accounted for 68% risk reduction of overall fungal colonization (RR=0.32; 95% confidence interval [CI]=0.24-0.42, p=0.00001, I-square=0%) and 60% risk reduction of IFI (RR=0.40; 95%[CI]=0.22-0.72, I-square=56%, p=0.002). However, fluconazole did not significantly reduce mortality in VLBW infants (RR=0.79; 95%[CI]=0.60-1.03; p=0.08, I-square=0%). Also, regarding its safety, fluconazole prophylaxis did not result in significant elevations of SGOT/SGPT levels (RR=1.22; 95%[CI]=0.50-3.00, p=0.66, I-square=0%) nor cause intestinal perforation (RR=0.96; 95%[CI]=0.25-3.68, p=0.96, I-square=59%). Fluconazole is an effective prophylaxis agent against invasive fungal infection when given to preterm infants with birth weight <1500, but not proven in reducing the mortality incidence in VLBW infants.

Keywords: antifungal, fluconazole, infant, invasive fungal infection, prevention and control, very low birth weight.

Abstrak: Infeksi jamur pada neonatus, terutama pada bayi dengan Berat Badan Lahir Sangat Rendah (BBLSR), sebagian besar disebabkan oleh jamur jenis *Candida*, dan dapat menyebabkan morbiditas dan mortalitas. Kami melakukan tinjauan sistematis dan meta-analisis untuk melihat besarnya efektivitas dan keamanan, khususnya penggunaan flukonazol sebagai profilaksis infeksi jamur invasif pada BBLSR atau bayi prematur menggunakan *Randomized Controlled Trials* (RCT) secara global. Peneliti mencari melalui MEDLINE, Cochrane, ScienceDirect, dan Garuda untuk mengidentifikasi RCT yang membandingkan efek profilaksis infeksi jamur invasif dari flukonazol dan plasebo pada bayi BBLSR. Delapan artikel RCT yang dimasukkan dalam meta-analisis ini menghasilkan 68% pengurangan risiko kolonisasi jamur (RR=0,32; interval kepercayaan 95% [CI]=0,24-0,42, p=0,00001, I-square=0%) dan 60% pengurangan risiko infeksi jamur invasif (RR=0,40; CI95%=0,22-0,72, p=0,002, I-square=56%) dengan penggunaan flukonazol. Namun demikian, flukonazol tidak signifikan menurunkan angka kematian pada bayi BBLSR (RR=0,79; CI95%=0,60-1,03; p=0,08, I-square=0%). Berkaitan dengan masalah keamanan, tidak terjadi elevasi SGOT / SGPT (RR=1,22; CI95%=0,50-3,00, p=0,66, I-square=0%) dan perforasi usus (RR=0,96; CI95%=0,25-3,68, p=0,96, I-square=59%) yang signifikan pada kelompok flukonazol. Flukonazol merupakan agen profilaksis yang efektif terhadap infeksi jamur invasif bila diberikan pada bayi prematur dengan berat lahir <1500 g, namun belum terbukti bermanfaat dalam mengurangi kematian pada bayi BBLSR.

Kata kunci: antijamur, bayi, berat badan lahir sangat rendah, flukonazol, infeksi jamur invasif, pencegahan dan pengendalian.

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INTRODUCTION

FUNGAL infections in neonates are caused chiefly by *Candida species*[1]. *Candida*, a genus of yeasts, can live in the skin, throat, vagina, and esophagus and often survives in the human body without causing any diseases or problems. However, a fungal infection in premature or Very Low Birth Weight (VLBW) infants can be fatal. Premature infants admitted to the Neonatal Intensive Care Unit (NICU) are at significant risks of contracting a fungal infection, which, according to studies, has an incidence rate of up to 50%. Further, it can develop into an invasive fungal infection (IFI), which is a systemic infection that potentially leads to morbidity and mortality.

Therefore, many NICU healthcare professionals are looking for a solution to prevent fungal colonization from occurring in infants by, among others, administering fluconazole. Fluconazole is widely used in treating infections of various types of fungi, including the *Candida* type. Fluconazole is not only used for medicinal purposes. It is also used in preventing the colonization of fungi[2,3].

Several studies have compared levels of effectiveness of fluconazole in the prophylaxis of invasive fungal infections due to various *Candida species*, namely *Candida albicans* and other *Candida* fungi. In those studies, fluconazole has been found to effectively reduce colonization in different parts of the human body, such as the skin, digestive tract, and respiratory tract. Up to now, systematic reviews and meta-analysis have been conducted to see the effectiveness of antifungal generally, while other studies focusing on fluconazole use only in a specific region (United States of America)[4–6].

McQuire, *et al*. studied meta-analysis of fluconazole usage as preventive in VLBW infants using before-after study design and found that publication bias may occur using this study design, compared to Randomized Controlled Trial (RCT) design[7]. Therefore, the current research conducted both systematic review and meta-analysis to determine the extent to which fluconazole was effective and safe to use in the prophylaxis of IFI in VLBW or premature infants by pooling individual RCTs worldwide.

METHODS

We analyzed RCT comparing the prophylactic effect of fluconazole and placebo or no drug in very low birth weight infants weighing <1500 g at birth. This study used two different groups: the group using fluconazole and the group using a placebo.

Data Sources and Searches. We examined all data from references using RCT for fluconazole prophylactic effect in VLBW or preterm infants. We searched through four databases, in MEDLINE using keywords of the following MeSH terms: ((("Premature Birth"[Mesh]) OR "Infant, Very Low Birth Weight"[Mesh]) AND "fluconazole"[Mesh]) AND "prevention and control" [Subheading]; database Cochrane Library using keywords of the following text words: Fluconazole AND very low birth weight infant AND prevention; database ScienceDirect using keywords of the following text words: Fluconazole AND very low birth weight infants AND prevention and control; and database Garuda using keywords of the following text words: flukonazol DAN bayi DAN pencegahan. We also searched for articles manually, through related research articles, related reviews, and also looked for relevant proofreading. We did not apply any language and year of publication restrictions.

Study Selection. The individual RCTs obtained from the database searches were then selected using several inclusion criteria. First, the participants consisted of VLBW infants weighing less than 1500 g or preterm infants born at less than 34 weeks. Second, the intervention was with fluconazole prophylaxis through the intravenous route, enteral route, or both. In addition, the primary outcomes evaluated in the study were fungal colonization, confirmed invasive fungal infections, and mortality, while the secondary outcomes were elevated SGOT/SGPT levels and intestinal perforation. Meanwhile, irrelevant studies and major uncertainty caused by methodological weaknesses were excluded from meta-analysis.

Data Extraction and Quality Assessment. Three investigators assessed the suitability of the topic on the abstracts and then checked the quality of the trials using the The Critical Appraisal Skills Program (CASP) checklist for RCT studies. A good quality trial means all the criteria are met. When the criteria are not fully met but are classified as almost fully met, it can be said that the quality of the study is fair. Thus, studies that are classified as poor are those that hardly or do not meet the criteria.

Data Synthesis and Analysis. A meta-analysis was conducted to identify the effects and effectiveness of fluconazole from various RCT studies, as evidenced by the overall incidence of fungal colonization (at least at one site), invasive fungal infections, death due to any cause, and side effects like increased SGOT/SGPT levels and intestinal perforation. The effectiveness was evaluated using the RevMan v.5.4 program. Also, the relative risk for all cases was analyzed based on

the number of events and the absence of events. The Mantel-Haenszel random effect method was used to generalize the results globally. In addition, a sensitivity analysis was performed to evaluate the effectiveness of fluconazole prophylaxis in all of the included trials and compared to excluding those with poor or unidentified quality. Subgroup analysis was conducted on dose variety and infants with Extremely Low Birth Weight (ELBW), i.e., less than 1,000 g.

RESULTS AND DISCUSSION

Global searches through the databases and other sources came back with 35 studies and one study, respectively. However, among these 36 studies, two were duplicates and were hence removed. Then, of the 32 studies, 23 were irrelevant for the meta-analysis (as shown by the abstracts) and were thereby excluded. Eventually, as seen in Figure 1, eight RCT studies, including one conference abstract, were analyzed qualitatively and quantitatively in the current research. In those studies, the trial population size ranged from 26 to 361 infants with a birth weight of <750 to <1,500 g, and the fluconazole was administered at different dosages: from 3 to 6 mg/kg twice weekly or every 24 hours for 28 to 42 days[8-15]. The characteristics of the eight RCTs are summarized in Table 1.

Qualitative Assessment. We identified the quality of each paper included using the CASP checklist. From the eight RCT trials, 7 hadave acceptable quality, and 1 trial from the conference abstract wasis unidentified. The significant limitations of trials included, which mightay lead to bias, can be seen in Table 2, and the summary of quality assessment can be seen in Figure 2.

The meta-analysis of eight individual RCTs revealed that, compared with the placebo group, fluconazole could significantly reduce overall fungal colonization (RR=0.32; 95% confidence interval [CI]=0.24 to 0.42, p=<0.00001, I-square=0%, Figure 3) and invasive fungal infections (RR=0.40; 95% confidence interval [CI]=0.22 to 0.72, p=0.002, I-square=56%, Figure 4) but had no significant effect on mortality (RR=0.79; 95% confidence interval [CI]= 0.60 to 1.03, p=0.08, I-square=0%, Figure 5). The subgroup analysis of ELBW infants also showed similar results on invasive fungal infections (RR=0.30 95%; confidence interval [CI] 0.13 to 0.70, p=0.005, I-square = 0%).

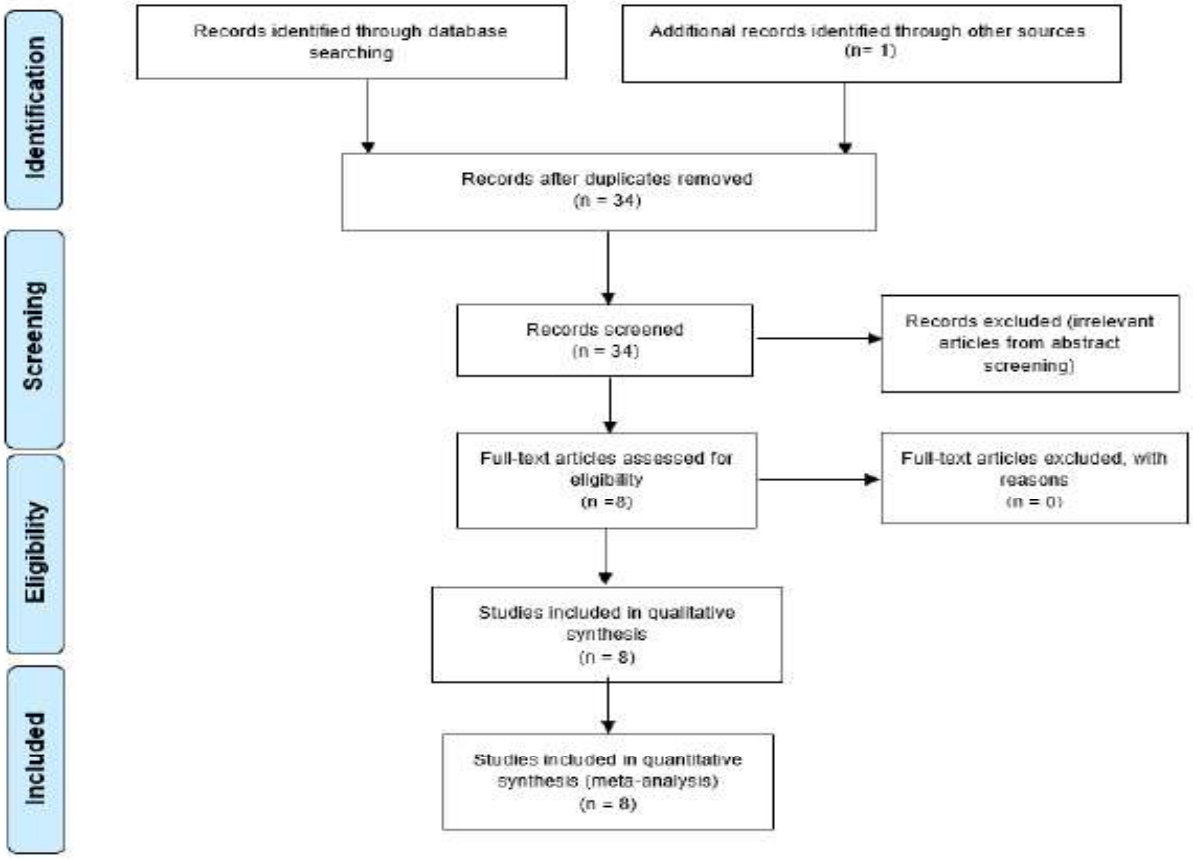

Figure 1. Provisional PRI.

Table 1. General characteristics of the included studies.

Study (Reference)	Study Design	Dose	Treatment Duration	Participants, n	IFI Definition
Kirpal et al.[8]	RCT	6 mg/kg	28 days or discharge whichever was earlier	80 infants with birth weight < 1500 g	Candida isolation from blood and/or cerebrospinal fluid.
Benjamin et al.[9]	RCT	6 mg/kg of body weight, twice weekly	42 days	361 with birth weight of less than 750 g.	Definite candidiasis was defined as a positive *Candida* culture from a normally sterile body fluid such as blood, cerebrospinal fluid, peritoneal fluid, or urine obtained via suprapubic aspiration or in/out catheterization. Probable invasive candidiasis was defined as receipt of more than 5 days of consecutive antifungal therapy and both thrombocytopenia (<150,000/103 μL) and a positive *Candida* culture from a non-sterile site (e.g., bag urine).
Aydemir et al.[10]	RCT	3 mg/kg body weight, every third day	30 days (45 days for neonates weighing)	184 infants with birth weight less than 1500 g	A positive culture from the blood (peripheral venipuncture), urine (≥10 000 or more colony-forming U/ml from sterile bladder catheterization or suprapubic aspiration), or cerebrospinal fluid.
Parikh et al.[11]	RCT	6 mg/kg/day as a single dose every 72 hours till day 7 and subsequently every 24 hours	28 days or less if, discharged or died earlier	120 infants with birth weight 1500 g	Fungal growth in blood
Manzoni et al.[12]	RCT	either 6 mg or 3 mg per kilogram of body weight)	30 days (45 days for neonates weighing)	336 infants with birth weight less than 1500 g	A positive culture from the blood (a peripheral site), urine (collected by sterile suprapubic puncture or bladder catheterization, with the growth of ≥10,000 organisms per milliliter), or cerebrospinal fluid
Kaufman et al.[13]	RCT	3 mg per kilogram of body weight every third day	6 weeks	100 infants with birth weight less than 1000 g	A positive culture of blood, urine, or cerebrospinal fluid

Table 2. Majority limitations of papers included.

Checklist	Limitations
Clearly focused issue	Based on the exclusion criteria of 1 paper, there is a chance of patients with IFI before enrollment. This paper did not mention the baseline criteria for any colonization or IFI events.
Allocation concealment	● Two papers did not give enough information, which may lead to the risk of bias during the allocation process ● One unclear piece of information from the conference abstract.
Blinding	● No detailed description of the blinding mechanism in the four papers, 1 of them provided different appearances of drugs, and it's impossible to do the blinding. ● One unclear piece of information from the conference abstract.
The similarity of two groups at the beginning	● In 1 paper, the use of corticosteroids is significantly higher in the fluconazole group ($p<0.05$). In 1 other paper, there were differences in steroid use and cesarean section. In the end, the multivariate analysis had been done to adjust this confounding. ● One unclear piece of information from the conference abstract.
Treatment equality	One unclear piece of information from the conference abstract.
Intention-to-treat	● One paper had incomplete data due to a randomization error that occurred ● One other paper had 14 incomplete data, including four incorrect drug administrations. ● One unclear piece of information from the conference abstract.
Selective-reporting possibility	None
The precision of treatment effects	Three papers did not mention confidence interval level.

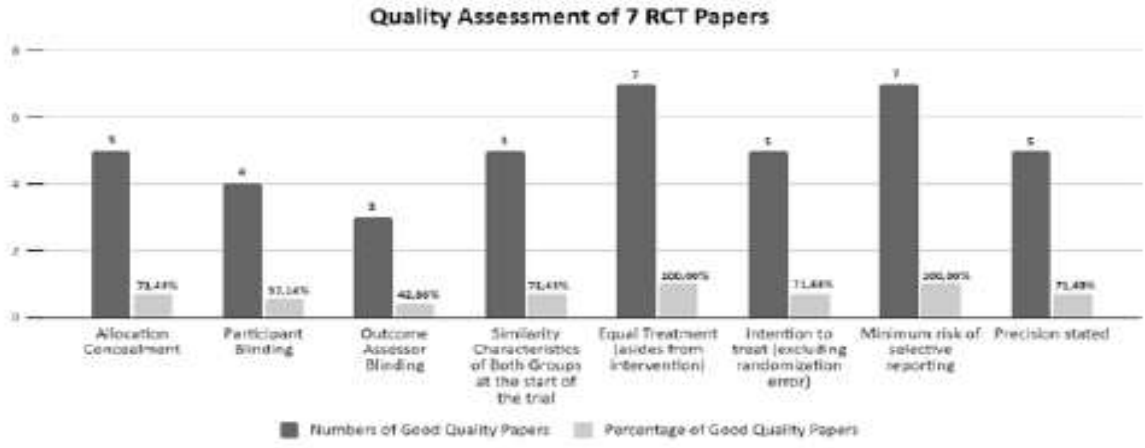

Figure 2. Summary of quality assessment.

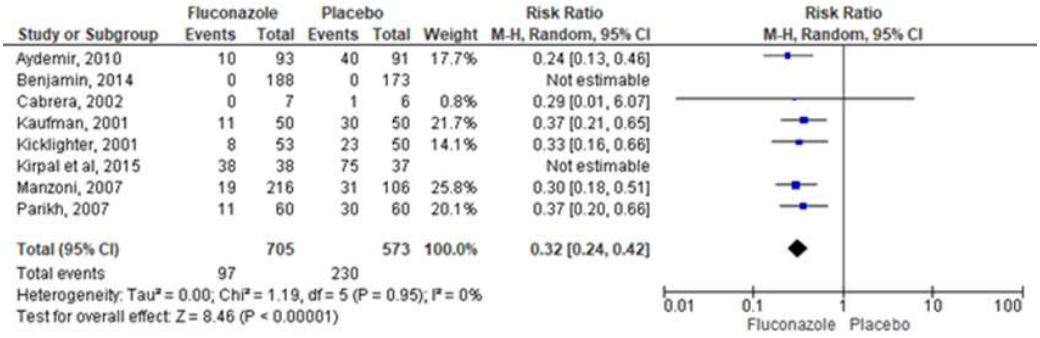

Figure 3. Forest plot of the efficacy of fluconazole compared to placebo based on overall fungal colonization (at least one site). M-H, Mantel-Haenszel; CI, confidence interval.

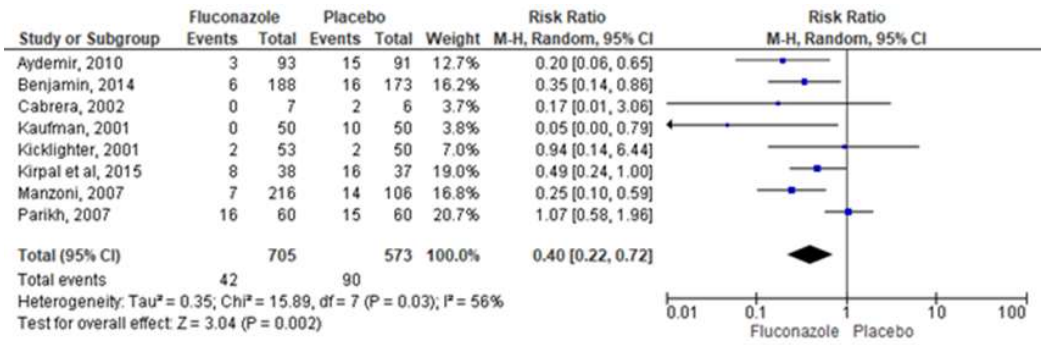

Figure 4. Forest plot of the efficacy of fluconazole compared to placebo based on invasive fungal infection. M-H, Mantel-Haenszel; CI, confidence interval.

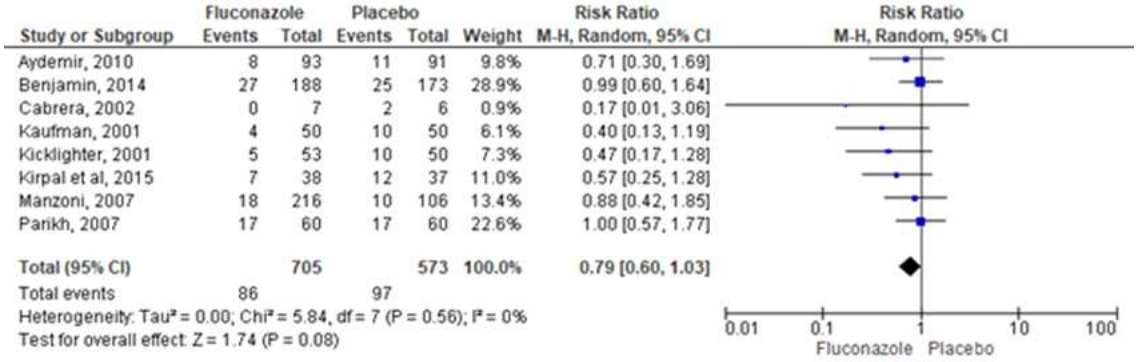

Figure 5. Forest plot of the efficacy of fluconazole compared to placebo based on death from any cause. M-H, Mantel-Haenszel; CI, confidence interval.

Safety of Fluconazole. Fluconazole is considered safe to use for VLBW or premature infants. It was concluded from the absence of any significant elevation of SGOT/SGPT levels (RR=1.22; 95% confidence interval [CI]=0.50 to 3.00, p=0.66, I-square = 0%, Figure 6) and intestinal perforation (RR = 0.96; 95% confidence interval [CI]=0.25 to 3.68, p=0.96, I-square = 59%, Figure 7) in the two groups.

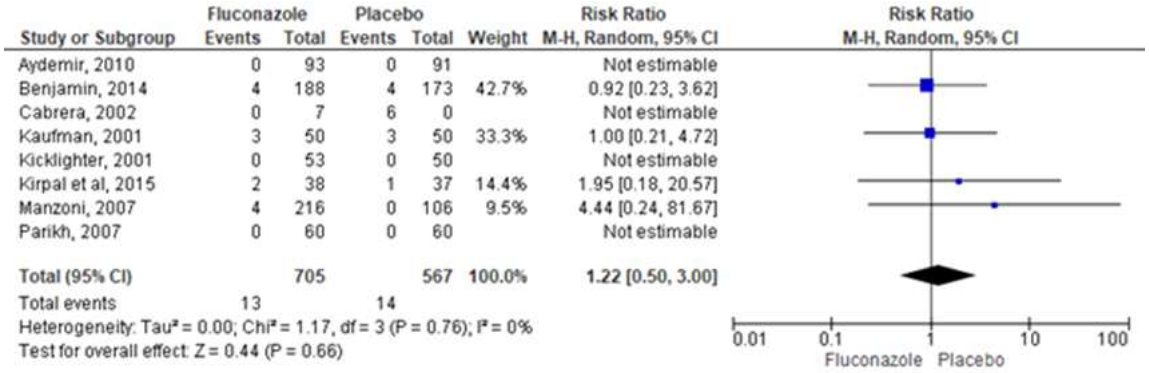

Figure 6. Forest plot of safety of fluconazole compared to placebo based on elevated of SGOT/SGPT. M-H, Mantel-Haenszel; CI, confidence interval.

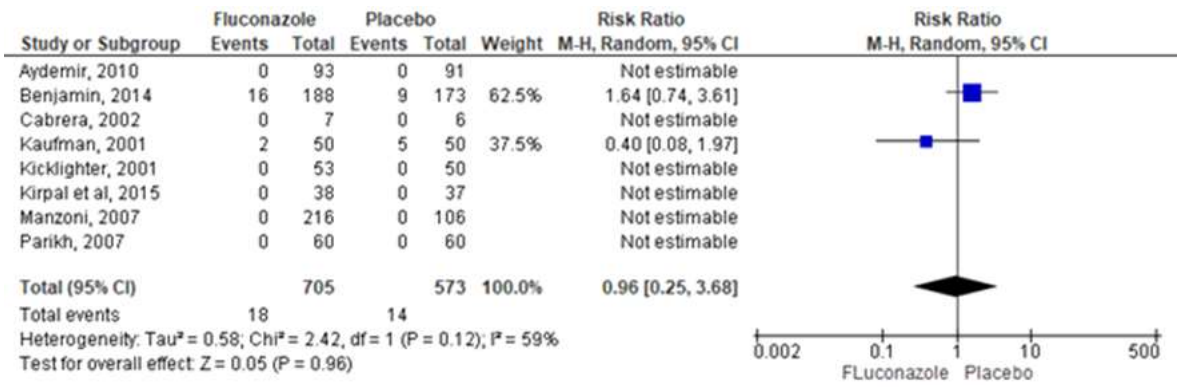

Figure 7. Forest plot of safety of fluconazole compared to placebo based on intestinal perforation. M-H, Mantel-Haenszel; CI, confidence interval.

Subgroup and Sensitivity Analysis. A subgroup analysis was also performed on different doses to overcome heterogeneity. It revealed that the doses 3 mg/kg and 6 mg/kg showed similar primary and secondary outcomes. At 6 mg/kg, fluconazole administration was associated with a relative risk (RR) of 0.29 for overall fungal colonization (95% confidence interval [CI] 0.20 to 0.42, p<0.00001, I-square=0%), RR=0.21 for invasive fungal infections (95% confidence interval [CI]=0.10 to 0.45, p <0.0001, I-square=0%), and RR=0.66 for deaths (95% confidence interval [CI]=0.39 to 1.13, p=0.13, I-square=0%). Similarly, when given at 3 mg/kg, it was associated with RR=0.34 for overall fungal colonization (95% confidence interval [CI]=0.24 to 0.50, p<0.00001, I-square=0%), RR=0.52 for invasive fungal infections (95% confidence interval [CI]=0.36 to 0.76, p<0.0006, I-square=47%), and RR=0.81 for deaths (95% confidence interval [CI]=0.60 to 1.10, p=0.18, I-square=0%).

Excluding one conference abstract, the sensitive analysis revealed no different results from the eight RCT studies for all the primary and secondary outcomes, i.e., overall fungal colonization (RR=0.31; 95% confidence interval [CI]=0.24 to 0.41, I-square=0%, p=<0.00001), invasive fungal infections (RR=0.42; 95% confidence interval [CI]=0.30 to 0.59, p=<0.00001, I-square=61%), mortality (RR=0.78; 95% confidence interval [CI]=0.60 to 1.03, p=0.08, I-square=0%), elevation of SGOT/SGPT levels (RR=1.33; 95% confidence interval [CI]=0.56 to 3.19, p=0.52, I-square=0%), and intestinal perforation (RR=1.21; 95% confidence interval [CI]=0.61 to 2.38, p=0.59, I-square=59%).

This review included eight RCTs that assessed the benefits and harms of using fluconazole as a prophylactic agent against fungal colonization, invasive fungal infections, and all-cause mortality in a total participant of 1,310 VLBW infants. Consistent evidence with previous systematic reviews and meta-analyses was found. McQuire et al. reviewed eleven before-and-after studies and pointed out a significant reduction of invasive fungal infections in the fluconazole group. However, a small study size with large effects from these observational studies may contribute to publication bias[7]. Cleminson et al. also identified a significant reduction of invasive fungal infections (RR=0.43, 95% confidence interval [CI]=0.31–0.59) in the antifungal group and no significant all-cause mortality (RR=0.79, 95% CI=0.61–1.02) in the antifungal and placebo groups; the antifungals were fluconazole and oral non-absorbed agents, such as nystatin and miconazole[4]. Reviewing four RCTs conducted in the United States, Ericson et al. found that the fluconazole group exhibited significantly reduced fungal colonization and invasive candidiasis, but the contrary for mortality. The odds ratio of these three outcomes were 0.28 (95% CI=0.18–0.41), 0.20 (95% CI=0.08–0.51), and 0.68 (95% CI=0.40–1.13)[6].

In terms of safety, Ericson et al. suggested that fluconazole was safe to use as a prophylactic agent in VLBW infants, as indicated by the absence of differences in the elevation of SGOT/SGPT levels and intestinal perforation between the fluconazole and placebo groups (P>0.05 for all events). Furthermore, no significant difference was found in the other safety events measured, i.e., necrotizing enterocolitis, chronic lung disease, retinopathy, abnormal alkaline phosphatase, and abnormal direct bilirubin (P>0.05 for all events)[6]. Nevertheless, it has been reported that, with prolonged treatment, the use of this antifungal could develop into cases with fluconazole-resistant *Candida species* through various mechanisms[16].

However, other studies such as Kaufman et al. and Manzoni et al. found that the Minimum Inhibitory Concentration (MIC) of fluconazole did not differ significantly throughout the 30 months of their study periods, suggesting no variability in the sensitivity patterns and resistances of the fungi observed to the

medication[12,13]. Similarly, Kicklighter et al. also reported no significant differences in the MIC of the isolates between the fluconazole and the control groups during the treatment period[14].

Of the eight RCTs, only two examined the effects of fluconazole on neurodevelopmental impairment. Benjamin et al. demonstrated no differences between the fluconazole and placebo groups regarding neurodevelopmental impairment, as evaluated in a follow-up at 18-22 months corrected age. Their study defined developmental impairment as a Bayley-III cognitive scale of less than 70[9].

Correspondingly, Kaufman et al. found that the developmental impairment did not differ between the groups receiving fluconazole prophylaxis and placebo after evaluating the enrolled premature infants at 8-10 years of age using the Vineland Adaptive Behavior Scales-II (VABS-II). Further, using the Child Health Questionnaire for Parents-Completed Form 28 (CHQ-PF28), it was concluded that their quality of life also did not differ significantly[17]. As evident in these trials, fluconazole is considered safe for antifungal prophylaxis because it is not linked to any long-term effects on neurodevelopment. The trials included in this study prescribed two different regimens of fluconazole prophylaxis: 3 mg/kg and 6 mg/kg. Based on the subgroup analysis results, there were no differences between their clinical outcomes. In 2005, Kaufman et al. found that, instead of the regular dosing schedule, a twice-weekly regimen may be beneficial in lowering not only Candida colonization and invasive fungal infection in infants weighing less than 1,000 g at birth but also cost[18].

In 2012, Manzoni et al. revealed baseline characteristics of the enrolled VLBW infants as a potential contributing factor to the results of prophylactic fluconazole regimens. Infants with baseline and actual colonization might show a different progression of fungal infection and a different response to the fluconazole regimen[19]. However, not all of the trials included in this study factored in and discussed the baseline criteria for colonization or IFI events.

Aside from the revelation of baseline characteristics in only some of the included trials, this review also has another limitation related to unexplained heterogeneity. Subgroup analysis was performed for the different doses used in the selected trials, but the root of the heterogeneity in the invasive fungal infection data was unable to be identified. Moreover, most of the trials included a follow-up less than a decade after the completion, making it difficult to distinguish the effects of fluconazole on neurodevelopmental impairment and quality of life in the long term.

CONCLUSIONS

Fluconazole is an effective prophylaxis agent against invasive fungal infection and fungal colonization when given to preterm infants with birth weight <1500 g. Fluconazole does not reduce the incidence of mortality in VLBW infants.

REFERENCE

1. Agarwal V, Tomer P, Gupta P, Upadhyay A. Epidemiology, Clinical Spectrum and Outcomes of Fungal Sepsis in Neonates in Neonatal Intensive Care Unit:AProspective Observational Study. 2018;5(1):5.
2. Nobile CJ, Johnson AD. Candida albicans Biofilms and Human Disease. Annu Rev Microbiol. 2015 Oct 15;69(1):71–92.
3. Yoo JR, Shin BR, Jo S, Heo ST. Evaluation of the early fluconazole treatment of candidemia protocol with automated short message service alerts: a before-and-after study. Korean J Intern Med [Internet]. 2020 Jul 9 [cited 2020 Dec 22]; Available from: http://kjim.org/journal/view.php?doi=10.3904/kjim.2019.259
4. Cleminson J, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2015 Oct 24;(10):CD003850.
5. Austin N, Cleminson J, Darlow BA, McGuire W. Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. Cochrane Neonatal Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Oct 24 [cited 2020 Dec 17]; Available from: http://doi.wiley.com/10.1002/14651858.CD003478.pub5
6. Ericson JE, Kaufman DA, Kicklighter SD, Bhatia J, Testoni D, Gao J, et al. Fluconazole Prophylaxis for the Prevention of Candidiasis in Premature Infants: A Meta-analysis Using Patient-level Data. Clin Infect Dis. 2016 Sep 1;63(5):604–10.
7. McGuire W, Clerihew L. The effect of fluconazole prophylaxis in very low birthweight infants is overestimated by before-after studies. Arch Dis Child - Fetal Neonatal Ed. 2010 May 1;95(3):F182–7.
8. Kirpal H, Gathwala G, Chaudhary U, Sharma D. Prophylactic fluconazole in very low birth weight infants admitted to neonatal intensive care unit: randomized controlled trial. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2016;29(4):624–8.
9. Benjamin DK, Hudak ML, Duara S, Randolph DA, Bidegain M, Mundakel GT, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. JAMA. 2014 May 7;311(17):1742–9.
10. Aydemir C, Oguz SS, Dizdar EA, Akar M, Sarikabadayi YU, Saygan S, et al. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal

infection in very low birth weight infants. Arch Dis Child - Fetal Neonatal Ed. 2011 May 1;96(3):F164–8.
11. Parikh TB, Nanavati RN, Patankar CV, Rao S, Bisure K, Udani RH, et al. Fluconazole prophylaxis against fungal colonization and invasive fungal infection in very low birth weight infants. Indian Pediatr. 2007 Nov;44(11):830–7.
12. Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. N Engl J Med. 2007 Jun 14;356(24):2483–95.
13. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med. 2001 Dec 6;345(23):1660–6.
14. Kicklighter SD, Springer SC, Cox T, Hulsey TC, Turner RB. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. Pediatrics. 2001 Feb;107(2):293–8.
15. Cabrera et al. AAP-Section on Perinatal Pediatrics. J Perinatol. 2002 Oct;22(7):594–622.
16. Berkow E, Lockhart S. Fluconazole resistance in Candida species: a current perspective. Infect Drug Resist. 2017 Jul;Volume 10:237–45.
17. Kaufman DA, Cuff AL, Wamstad JB, Boyle R, Gurka MJ, Grossman LB, et al. Fluconazole Prophylaxis in Extremely Low Birth Weight Infants and Neurodevelopmental Outcomes and Quality of Life at 8 to 10 Years of Age. J Pediatr. 2011 May;158(5):759-765.e1.
18. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. J Pediatr. 2005 Aug;147(2):172–9.
19. Manzoni P, Mostert M, Latino MA, Pugni L, Stolfi I, Decembrino L, 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 May;88 Suppl 2:S60-6.