Chemoprophylaxis of Neonatal Fungal Infections in Very Low Birth Weight Infants: Efficacy and Safety of Fluconazole and Nystatin

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STUDY QUESTION
To review the efficacy of anti-fungal chemoprophylaxis to prevent neonatal invasive fungal infections (IFI) in very low birth weight infants (VLBW <1500 g).

MATERIALS AND METHODS
Eligibility
All randomized controlled trials and quasi-randomized trials that compared the effect of prophylactic anti-fungal therapy with placebo, no drug, another anti-fungal agent or anti-fungal dose regimen in VLBW infants was included.

Types of interventions
Fluconazole versus placebo, nystatin versus placebo and fluconazole versus nystatin.

Inclusion
All studies that compared the effect of fluconazole with placebo, nystatin with placebo, and fluconazole with nystatin were included.

Exclusion
All studies of anti-fungal agents other than fluconazole and nystatin were excluded. In addition, studies that did not perform data analysis stratified by birth weight, thereby precluding us from determining outcomes specific for babies <1500 g, were also excluded.

Outcomes
1. Incidence of invasive fungal infection (IFI)
2. Death from all causes prior to hospital discharge
3. Anti-fungal resistance
4. Adverse drug reactions.

Search
Standard search strategy of the Cochrane Neonatal Review Group was used to search the literature for studies on neonatal fungal prophylaxis. This included searches of the Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, 2011), MEDLINE (1966–July 2011), EMBASE (1980–July 2011), conference proceedings, and previous reviews.

Data collections
Methodological quality was assessed using standardized methods. Summary estimates of incidence of fungal infection, death, relative risks (RR), and 95% confidence intervals (CI) comparing subjects in the treatment groups with subjects in the control groups were driven using random effect meta-analyses.

Studies were weighted according to a measure proportional to their sample size and number of events using the inverse of the standard error for measures of incidence and the inverse of the variance of the logRR for RRs. The I^2 statistics were derived to estimate the fraction of variability between
studies RRs due to heterogeneity rather than chance. Publication bias was assessed using the Egger test.

**Population**
Very low birth weight infants.

**RESULTS**
Nine trials were identified enrolling 2029 infants. Five eligible trials were comparing fluconazole with placebo, and 2 studies were comparing oral nystatin with placebo. In addition, there was one published randomized controlled trial, in which babies received fluconazole, nystatin, or placebo and 1 randomized controlled trial, which compared fluconazole and nystatin.

When data from 6 trials comparing fluconazole with placebo (840 infants) were examined, the incidence of IFI in babies with birth weight <1500 g was significantly lower with fluconazole compared with placebo in 3 trials.

Significant heterogeneity was observed among studies. The mortality was 10.9% (95% CI: 6.0-15.9%) for babies receiving fluconazole compared with 16.7% (10.2-23.1%) with placebo (RR 0.76, 95% CI 0.54-1.08). The RR reduction for infection observed with fluconazole was 10.9% with a number needed to treat (NNT) of 9 babies to prevent one IFI.

Three trials compared nystatin with either placebo or no drug (1200 infants). All demonstrated significant reductions in IFIs with nystatin prophylaxis. In the meta-analysis, the incidence of IFI in babies with birth weight <1500 g treated with prophylactic oral nystatin was 5.3% (95% CI: 3.5-7.1%) compared to 28.0% (13.7-42.7%) in babies receiving placebo [RR=0.16, 95% CI 0.11-0.23]. Mortality was 7.5% (95% CI: 5.4-9.6%) with nystatin and 10.9% (4.9-16.7) with placebo (RR 0.86, 95% CI 0.59-1.26). The RR reduction observed with nystatin was 22.7% with a NNT of 4.

When the two studies comparing fluconazole with nystatin were combined, there was no significant difference in incidence of IFI between fluconazole and nystatin. The incidence of IFI with prophylactic fluconazole was not significantly different compared with nystatin (3.6% vs. 8.0%, RR=0.54, 95% CI 0.19-1.56). Mortality was 4.6% (0.0-11.7%) with fluconazole and 9.8% (4.5-14.8%) with nystatin (RR 0.43, 95% CI 0.43). There was no significant toxicity reported from fluconazole and oral nystatin in the studies reviewed, and no babies were withdrawn from the studies because of adverse events.

**CONCLUSION**
This meta-analysis demonstrates that both fluconazole and nystatin prevent neonatal IFI in VLBW infants at high risk of IFI. The choice of anti-fungal agent should be influenced by the incidence of IFI, local epidemiology of colonizing *Candida* species, and relative cost.

**COMMENTARY**
Invasive fungal infections (IFI) are an important cause of late-onset disease in very low birth weight infants. Prophylactic fluconazole and oral nystatin are both highly effective in preventing IFI in VLBW infants, and both agents are safe without significant toxicities. Despite this significant finding, application of prophylactic fluconazole and oral nystatin remain controversial. Given the use of anti-fungal prophylaxis is associated with the potential risk of selecting resistant organisms and the paucity of data comparing fluconazole with nystatin, either anti-fungal prophylaxis may be used in VLBW infants who are at highest risk for fungal infection. In addition to the very low birth weight, other risk factors include the presence of a central vascular catheter (CVC) or endotracheal tube, in infants who are exposed to broad-spectrum antibiotics and parenteral nutrition. In addition, CVC colonization and multiple-site colonization are risk factors that can predispose to invasive fungal infection in this population. Moreover, if these criteria are applied, almost all infants admitted in the NICU will have the fungal prophylaxis. Therefore, these criteria can be restricted to infants with a birth weight of 1000 g or less and those who are positive for fungal colonization.

Future research should be directed to identify other risk factors for invasive fungal infection and interventions to prevent these infections. In addition, larger multicenter randomized trials are required to determine the long-term neurodevelopment outcomes of infants received chemoprophylaxis for fungal infection.

**Abstracted from**
Blyth CC, Barzi F, Hale K, Isaacs D. Chemoprophylaxis of neonatal fungal infections in very low birth weight infants: Efficacy and safety of fluconazole and nystatin. J Paediatr Child Health 2012 Sep;48(9):846-51. DOI: 10.1111/j.1440-1754.2012.02543.x.