Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin

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CRD summary
The authors concluded that both fluconazole and nystatin prevented neonatal invasive fungal infections in very low birthweight infants. Poor reporting of some aspects of the review process means that it is difficult to be certain of the reliability of the conclusions.

Authors' objectives
To review the use of antifungal chemoprophylaxis to prevent neonatal invasive fungal infections in very low birthweight infants.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from inception to July 2011; search terms were not specified. There was a manual search of conference proceedings and previous reviews.

Study selection
Randomised controlled trials and quasi-randomised controlled trials that compared prophylactic antifungal therapy (fluconazole or nystatin) with placebo, no drug, another antifungal agent or antifungal dose regimen in very low birthweight infants (lower than 1,500g at birth) were eligible for inclusion. The primary outcome was incidence of fungal infections defined as isolation of fungus from a normally sterile site such as the blood or cerebrospinal fluid but also could include urine collection using an appropriate sterile technique. Analysis had to be stratified by birthweight so that data could be assessed for very low birthweight infants.

The included studies were conducted in USA, Italy, India and Turkey. The authors noted that the rate of invasive fungal infections was very high in several trials (higher than typical in a country such as Australia and New Zealand). Dosages, frequency and duration were reported for each trial.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed using Cochrane Collaboration criteria to evaluate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias.

The authors did not state how many reviewers assessed study quality.

Data extraction
Outcomes (fungal infections, all-cause death prior to hospital discharge) were extracted from each study to calculate relative risks (RR) with 95% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were pooled in a meta-analysis using a random-effects model. Heterogeneity was assessed using the I² statistic. Publication bias was assessed using the Egger test.

Results of the review
Nine trials (2,029 infants) were included in the review. Seven of the nine trials reported an adequate sequence generation, five reported adequate allocation concealment, four reported blinding on all outcomes, eight addressed incomplete outcome data and were free of selective reporting.

Fluconazole significantly reduced the incidence of invasive fungal infection in very low birthweight babies compared to...
placebo (RR 0.36, 95% CI 0.15 to 0.89; six trials, 840 infants; significant heterogeneity I²=66%). The number needed to treat was nine babies (95% CI 6.7 to 16.3) to prevent one invasive fungal infection. Mortality was not significantly different between treatment groups (RR 0.76, 95% CI 0.54 to 1.08). No significant toxicity was reported from fluconazole and no babies were withdrawn from the studies due to adverse events.

Nystatin significantly reduced the incidence of invasive fungal infection in very low birthweight babies compared to placebo or no drug (RR 0.16, 95% CI 0.11 to 0.23; three trials, 1,200 infants; no significant heterogeneity). The number needed to treat was four babies (95% CI 3.1 to 4.3) to prevent one invasive fungal infection. Mortality was not significantly different between treatment groups (RR 0.86, 95% CI 0.59 to 1.26). No significant toxicity was reported from oral nystatin and no babies were withdrawn from the studies due to adverse events.

There was no significant difference in the incidence of invasive fungal infections (RR 0.54, 95% CI 0.19 to 1.56) or mortality (RR 0.43, 95% CI 0 to 4.31; two trials, 257 infants) when fluconazole was compared with nystatin. No significant toxicity was reported from either agent in the studies reviewed.

The results of the publication bias test were not reported.

**Authors’ conclusions**
Both fluconazole and nystatin prevented neonatal invasive fungal infections in very low birthweight infants at high risk of invasive fungal infections.

**CRD commentary**
The review question and inclusion criteria were clear. Three databases, conference proceedings and previous reviews were searched. Any language restrictions and searches for unpublished data were unclear so some studies may have been missed. It was unclear whether study selection, study quality assessment and data extraction were carried out with sufficient attempts to minimise error and bias. It appeared that data were appropriately pooled in a meta-analysis and suitable methods were used to assess heterogeneity.

Poor reporting of some aspects of the review process means that it is difficult to be certain of the reliability of the conclusions.

**Implications of the review for practice and research**
**Practice:** The authors stated that antifungal prophylaxis should be used in all very low birthweight infants babies. Choice of antifungal agent should be influenced by incidence of invasive fungal infections, local epidemiology of colonising *Candida* species and relative cost.

**Research:** The authors did not state any implications for research.

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