A review of Candida prophylaxis in the neonatal intensive care population
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CRD summary
This review concluded that antifungal prophylaxis appeared to be effective in reducing incidence of Candida colonisation and invasive Candida infections in the neonatal intensive care unit. Potential for missed studies, the lack of quality assessment, inadequate reporting of study details and limited synthesis of study results mean that the authors’ conclusions should not be considered as reliable.

Authors' objectives
To assess the efficacy and safety of antifungal prophylaxis in the neonatal intensive care unit setting.

Searching
The authors searched MEDLINE from January 1988 to December 2010; search terms were reported. Only studies in English were sought and preference was given to published research. Reference lists of retrieved articles were searched for additional relevant studies.

Study selection
Original studies of use of prophylactic antifungals in neonatal intensive care unit patients aged from birth to six months were eligible for inclusion. The authors stated a preference for controlled trials.

The studies included very low birth weight infants (birth weight of 1,500g or less) or extremely low birth weight infants (birth weight of 1,000g or less). Most studies used fluconazole as the prophylactic antifungal; some studies used nystatin. The fluconazole regimen varied between studies: dosages were 3mg/kg or 6mg/kg per dose and included both intravenous and oral methods of administration. Nystatin was administered at a dose of 100,000 units enterally every eight hours or 100,000 units (or 1mL) orally every six hours. Treatment durations ranged from four weeks to approximately six weeks, where stated. Fluconazole and nystatin were compared against each other, placebo, an unspecified control group or an unspecified historical control group. It was not clear whether all studies had a control group.

All three authors evaluated studies for inclusion but did not report whether this was done independently or how discrepancies were resolved.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
The proportion of patients in intervention and control groups who had fungal colonisation and invasive fungal infection was extracted from the included studies.

The authors did not state how many reviewers undertook data extraction.

Methods of synthesis
The number of studies that demonstrated a reduction in incidence of fungal colonisation and invasive fungal infection in the intervention was reported.

Results of the review
Twenty-two studies (more than 10,000 neonatal intensive care unit patients, range 13 to 719) were included in the review.

All seven studies that evaluated the impact of antifungal prophylaxis with fluconazole on Candida colonisation demonstrated a reduction in incidence of fungal colonisation. Twelve out of 16 studies that evaluated the impact of fluconazole prophylaxis on the incidence of invasive fungal infection demonstrated a reduction in invasive fungal
infection.

All three studies that evaluated the impact of antifungal prophylaxis with nystatin on Candida colonisation and/or invasive fungal infection demonstrated a reduction in colonisation/invasive infection in the nystatin group.

Two randomised controlled trials found no statistically significant difference between fluconazole and nystatin in terms of invasive fungal infection and/or fungal colonisation.

In one study there were more deaths in the nystatin group than in the fluconazole group. Although none of the deaths were associated with an invasive fungal infection they may have been linked to nystatin use. Six studies reported that no adverse reactions to fluconazole were observed. One study reported that no hepatotoxicity associated with fluconazole use was observed. One study reported a higher incidence of conjugated hyperbilirubinaemia in the fluconazole group than the control group and one study reported a higher incidence of direct hyperbilirubinaemia and elevated liver transaminases in the control group than the fluconazole group.

**Authors' conclusions**

Antifungal prophylaxis appears to be effective in reducing the incidence of Candida colonisation and invasive Candida infections in the neonatal intensive care unit.

**CRD commentary**

The review question was generally clear. Inclusion criteria were vague in relation to study design and outcomes of interest. The search strategy was limited and language restrictions were applied so language bias may have been present and some relevant studies may have been missed. It was unclear whether adequate attempts were made to minimise reviewer error and bias in study selection and data extraction procedures. The authors did not appear to assess the quality of the included studies.

Reporting of study details was inadequate. The study design and control treatment was not reported for many studies. Reporting of participant characteristics was limited. Synthesis of effectiveness results was limited and no synthesis of safety data was presented. There was no formal assessment of heterogeneity.

Potential for missed studies, the lack of quality assessment, inadequate reporting of study details and limited synthesis of study results mean that the authors' conclusions should not be considered as reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that further research was required before widespread antifungal prophylaxis can be recommended.

**Research:** The authors stated that further research was required regarding which antifungal was best for prophylaxis and the optimal dosing regimen. The long term impact of antifungal prophylaxis on resistance patterns needed to be determined.

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