Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis

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CRD summary

This review evaluated the effects of fluconazole prophylaxis on fungal infections and mortality in critically ill surgical patients. The authors concluded that prophylactic fluconazole appeared to reduce fungal infections but had no effect on mortality, and that further research is required. Overall, this was a reasonably well-conducted review and the authors' cautious conclusions are likely to be reliable.

Authors' objectives

To evaluate the effects of fluconazole prophylaxis on fungal infections and mortality in critically ill surgical patients.

Searching

MEDLINE (1966 to December 2004), EMBASE (1990 to December 2004) and the Cochrane Library were searched using the reported search terms. No language restrictions were applied. In addition, abstracts from the meetings of five specified societies (1998 to 2004) and reference lists were handsearched and experts in the field were contacted.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review

Studies that compared fluconazole prophylaxis with placebo were eligible for inclusion. Studies in which fluconazole prophylaxis was administered for another reason (immunosuppression, chemotherapy or organ transplantation) were excluded, as were studies that used fluconazole as part of a treatment regimen for selective digestive decontamination solely for the prevention of nosocomial pneumonia. The included studies used different fluconazole regimens, such as 100 mg/day combined with other agents, 400 mg/day, and 800-mg loading dose followed by 400 mg/day; fluconazole was also given by different routes (e.g. oral, enteral and intravenous).

Participants included in the review

Studies in critically ill surgical patients were initially eligible for inclusion, but these criteria were subsequently broadened to include studies in which at least 50% of the participants were critically ill surgical patients. The included studies were based in intensive care units (ICUs) but used different inclusion criteria for the participants (e.g. duration of ICU stay greater than 48 or 72 hours and recurrent perforation or gastric leak after major abdominal surgery; one study included medical ICU patients). Where reported, most of the participants required mechanical ventilation (range: 87.6 to 100%). Across studies, varying proportions of patients were receiving parenteral nutrition at baseline (range: 8.5 to 53.8%). The rates of baseline fungal colonisation also varied (range: 39.5 to 76.9%).

Outcomes assessed in the review

The main review outcomes were fungal infections and mortality. The review also assessed the type of fungal infection, distribution of candida species isolated, ICU length of stay and adverse events. The included studies generally assessed only ICU mortality. Similar definitions for bloodstream infection, but not other types of fungal infection, were used. Some studies excluded funguria from the outcomes.

How were decisions on the relevance of primary studies made?

Two reviewers independently selected the studies.

Assessment of study quality

Validity was assessed using the Jadad scale. Two reviewers independently selected the studies; inter-rater agreement

was measured using the kappa statistic.

Data extraction

Two reviewers independently extracted the data. For each study, the numbers of events of interest were extracted and odds ratio (ORs) of events were calculated with 95% confidence intervals (CIs). Risk differences were computed on the basis of the ORs and their respective 95% CIs.

Methods of synthesis

How were the studies combined?

Pooled ORs with 95% CIs were calculated for fungal infections and mortality using the random-effects model of DerSimonian and Laird. Publication bias was assessed using Begg's statistic and by visual examination of a funnel plot.

How were differences between studies investigated?

Differences between the studies were discussed in the text. Statistical heterogeneity was assessed using the Q statistic and by visual examination of a Galbraith plot. The meta-analysis of mortality was repeated after including two other studies: one study included patients with a gastric perforation regardless of the severity of the illness, while the other included both surgical and nonsurgical patients (only data from patients with intra-abdominal processes were extracted from the second study).

Results of the review

Four RCTs (n=626) were included in the review. Two additional RCTs (n=143) were included in the sensitivity analysis.

The studies were of a high quality (median Jadad score 6); the authors of the review did not report the range of possible scores for their scoring system. All four RCTs and two additional RCTs were double-blinded. Inter-rater agreement for the quality assessment was good (kappa 0.95).

There was no evidence of publication bias from either the funnel plot or Begg's statistic (p=0.734).

The meta-analysis showed that prophylactic fluconazole significantly reduced the risk of fungal infection compared with placebo (OR 0.44, 95% CI: 0.27, 0.72, p<0.001). No statistically significant heterogeneity was detected (p=0.692).

There was no significant difference between treatments in terms of candidaemia, although there were few actual cases of candidaemia (14 cases in 626 patients: 11 cases in fluconazole-treated groups and 3 cases in placebo-treated groups).

Prophylactic fluconazole was associated with a significant reduction in the risk of candida albicans (OR 0.51, 95% CI: 0.30, 0.87, p=0.014) but there was no significant difference between treatments in terms of nonalbicans candida infections (p=0.10).

There was no significant difference between treatments in terms of mortality (OR 0.87, 95% CI: 0.59, 1.28). The meta-analysis that included two additional studies also showed no significant difference between treatments.

Neither of the two studies assessing ICU length of stay reported any significant difference between treatments.

Three studies assessed adverse events and reported that fluconazole was generally well-tolerated with no difference between fluconazole and placebo in rates of laboratory abnormalities. No deaths were attributed to fluconazole and few patients had treatments discontinued due to suspected toxicity (two receiving fluconazole and three receiving placebo).

Cost information
The review also sought to assess costs but none of the included studies assessed this outcome.

Authors' conclusions
Prophylactic fluconazole appeared to reduce fungal infections but had no effect on mortality. There was insufficient evidence to determine the effects of fluconazole on rates of fungaemia and duration of hospital stay. Further research is required.

CRD commentary
This review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise language and publication bias; appropriate methods were used to examine the potential for publication bias and no evidence of this was found. Two reviewers independently selected studies, assessed validity and extracted the data, thus reducing the potential for reviewer bias and errors. Validity was assessed using specified established criteria but only aggregated scores and the level of blinding were reported; this means it is not possible for readers to adequately judge study quality for themselves. There was adequate information on the characteristics of the participants and interventions. Statistical heterogeneity was assessed and the studies appear to have been appropriately combined in meta-analyses, although the review's authors did discuss clinical heterogeneity between the studies. Overall, this was a well-conducted review and the authors' cautious conclusions are likely to be reliable. The stated need for future research appears reasonable.

One of the authors had previously received funding from Intrabiotics and is currently receiving funds from Pfizer, Merck Bard and Elan. A second author is on the speakers bureau of Pfizer and Merck.

Implications of the review for practice and research
Practice: The authors stated that clinicians should make decisions about the use of prophylactic fluconazole based on local rates of fungaemia. Further research is required before prophylaxis with fluconazole becomes routine.

Research: The authors stated the need for further studies to identify patients at high risk of fungal infections and to examine the effects of fluconazole on mortality, the distribution of Candida species in the ICU and the use of resources (including length of stay and duration of mechanical ventilation).

Bibliographic details
Shorr A F, Chung K, Jackson W L, Waterman P E, Kollef M H. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. Critical Care Medicine 2005; 33(9): 1928-1935

PubMedID
16148461

Indexing Status
Subject indexing assigned by NLM

MeSH
Antifungal Agents /administration & dosage /therapeutic use; Candidiasis /prevention & control; Critical Illness /mortality; Double-Blind Method; Drug Resistance, Fungal; Drug Resistance, Microbial; Fluconazole /administration & dosage /therapeutic use; Fungemia /prevention & control; Humans; Intensive Care Units; Multicenter Studies as Topic; Mycoses /prevention & control; Postoperative Complications /prevention & control; Randomized Controlled Trials as Topic

AccessionNumber
12005004632

Date bibliographic record published
30/04/2007

Date abstract record published
30/04/2007

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.