Prophylactic action of oral fluconazole against fungal infection in neutropenic patients: a meta-analysis of 16 randomized, controlled trials


Authors' objectives
To assess the efficacy of fluconazole prophylaxis during chemotherapy-induced neutropenia.

Searching
MEDLINE, Cancerlit and a company database (Pfizer) were searched; the last search was performed in April 1999. No details were given of the keywords used. Studies reported in any language were considered, and both published and unpublished studies were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Studies comparing oral fluconazole with placebo, no treatment, or oral polyenes as prophylaxis for fungal infections, were eligible if no intravenous antifungal prophylaxis was used. The use of intravenous fluconazole for patients who could not receive oral medication was permitted. Fluconazole was given orally in doses ranging from 50 to 400 mg, and intravenously in doses ranging from 200 to 400 mg; children received 3 mg/kg orally. The control treatments were placebo, no treatment, oral nystatin (4,000,000 to 24,000,000 units, or 50,000 to 200,000 units/kg), oral amphotericin-B (800 to 2,400 mg), or clotrimazole troche (20 mg). In some studies, empiric intravenous amphotericin-B was given to patients with persistent neutropenic fever that was resistant to antibacterial agents.

Participants included in the review
Studies of patients with neutropenia (less than 1,000/microL) were eligible. The participants included adults and children with the following conditions: bone marrow transplant; haematological malignancies including acute leukaemia and refractory myelogenous leukaemia; and cancer.

Outcomes assessed in the review
Studies that allowed the determination of the number of patients with pathologically or microbiologically proven, systemic fungal infections were eligible. The primary outcomes were the occurrence of fungal-related deaths and proven systemic fungal infection. Fungal-related death was defined as the death of a patient related to the neutropenic period, which was attributable to proven systemic fungal infection. A systemic fungal infection was defined as one in which there was both clinical evidence of blood and tissue infection, and a culture or biopsy specimen from the involved site showing a pathogenic fungal organism.

The other outcome measures were: superficial fungal infections; the use of amphotericin-B; systemic fungal infection caused by Aspergillus species, and by Candida krusei or Torulopsis glabrata species; and colonisation by C. krusei and T. glabrata, as detected by surveillance cultures from mucous membranes.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The included studies were restricted to RCTs. However, a formal validity assessment was not undertaken.
Data extraction
Two independent reviewers extracted the data, and any discrepancies were resolved by reinspection of the original papers. The following information was tabulated in the review: author; year; patients' condition; control and experimental intervention; the number of patients per treatment arm; and the number of patients with bone marrow transplant. The authors of eligible studies were asked to provide the following information: the method of randomisation; the accuracy of the extracted data; and any data missing from the reports.

Methods of synthesis
How were the studies combined?
The pooled odds ratios (OR) and 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.1). The fixed-effect model (Mantel-Haenszel) was used for the meta-analysis when the heterogeneity P-value exceeded 0.10 (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Homogeneity for each outcome was assessed statistically, and was also demonstrated graphically in forest plots. Studies were classified as either high-dose (400 mg/day) or low-dose fluconazole trials (50 to 200 mg/day), and were analysed separately. Separate analyses were also conducted for studies containing non-bone marrow patients and those containing bone marrow patients, and for studies in which the incidence of systemic fungal infection in the control group was either less than or greater than 15%. A sensitivity analysis was performed by recalculating the results after omitting each trial sequentially.

Results of the review
Sixteen RCTs (3,734 patients) were included. Of these, 6 RCTs (1,373 patients) did not involve any bone marrow transplant patients.

Significant statistical heterogeneity was found across studies for the outcomes of the empiric use of amphotericin-B and the colonisation of T glabrata. A random-effects model was used to pool the data for these outcome, whilst a fixed-effect model was used for all other outcomes.

Fungal-related deaths. Fungal-related deaths were significantly less frequent for those patients receiving fluconazole; the pooled OR was 0.45 (95% CI: 0.29, 0.72). There was no significant difference between the treatment groups in non-bone marrow transplant trials; the pooled OR was 0.91 (95% CI: 0.30, 2.82).

Proven systemic fungal infection. Systemic fungal infections were significantly less frequent in those patients receiving fluconazole; the pooled OR was 0.42 (95% CI: 0.31, 0.57). There was no significant difference between the treatment groups in non-bone marrow transplant trials; the pooled OR was 0.85 (95% CI: 0.47, 1.55). Systematic fungal infection was reduced only in those studies with an incidence of fungal infection in the control group of greater than 15%. The ORs were 0.78 (95% CI: 0.50, 1.21) and 0.23 (95% CI: 0.15, 0.36) for an incidence of less than 15% and greater than 15%, respectively.

Superficial fungal infections.

Empiric use of amphotericin-B.

The criteria for use varied between studies. Empiric use of amphotericin-B was significantly less frequent for those patients receiving fluconazole; the pooled OR was 0.76 (95% CI: 0.60, 0.96). There was no significant difference between the treatment groups in non-bone marrow transplant trials; the pooled OR was 0.90 (95% CI: 0.56, 1.45), but after excluding one study, this was changed to 0.70 (95% CI: 0.53, 0.92). The use of amphotericin-B was reduced in high- and low-dose fluconazole studies, albeit not significantly.
Systemic fungal infection caused by Aspergillus species.

There was no significant difference between the treatment groups for the following: all studies combined; non-bone marrow studies only; and high- or low-dose fluconazole studies. The overall pooled OR was 1.24 (95% CI: 0.71, 2.18).

Systemic fungal infection caused by C. krusei or T. glabrata.

The overall pooled OR for C. krusei or T. glabrata was 0.88 (95% CI: 0.46, 1.68).

Colonisation by C. krusei and T. glabrata. C. krusei and T. glabrata were significantly more common in patients treated with fluconazole. The pooled OR was 2.01 (95% CI: 1.30, 3.12) for C. krusei and 2.18 (95% CI: 1.17, 4.08) for T. glabrata. There was no significant difference in the detection rates of C. krusei between the treatment groups for high- or low-dose fluconazole trials. T. glabrata was significantly more common in patients treated with low-dose, but not high-dose, fluconazole; the OR for low-dose fluconazole was 6.30 (95% CI: 3.87, 10.35). There was no significant difference between the treatment groups in terms of T. glabrata colonisation; the OR was 2.61 (95% CI: 0.64, 10.72). After excluding one study, the OR for colonisation by T. glabrata in non-bone marrow studies was 6.39 (95% CI: 1.53, 26.6).

Adverse effects.

The definition of adverse effects differed between the trials. Generally, the overall frequency was similar in the control and experimental groups. Fluconazole patients developed abnormalities in liver enzyme tests more frequently, but these were reversible. Patient compliance exceeded 90% in the fluconazole groups, compared with 70 to 90% in the control groups.

The authors reported that the major shortcoming of this review was the heterogeneity between trials in terms of drug dosage and patient populations, especially in the degree of immunosuppression.

Authors' conclusions

The current review failed to find an effect of fluconazole on both fatal fungal infection and systemic fungal infection in non-bone marrow transplant patients.

CRD commentary

This was a good, clearly presented review. The aims were stated and the inclusion criteria were defined in terms of the study design, participants, interventions and outcomes. Several relevant databases were searched and no language restrictions were applied. In addition, both unpublished and published material was eligible for inclusion in the review. However, the keywords used were not reported, and the methods used to select the studies were not described.

The included studies were restricted to RCTs although no formal validity assessment was undertaken. Relevant information was tabulated, and the methods used to extract the data were described. Statistical homogeneity was assessed and illustrated graphically in forest plots for each outcome. However, the authors used a random-effects model to control for heterogeneity, which was inappropriate, and the results of the heterogeneity tests were not presented. The influence of various factors on the results was examined. The factors investigated included the patients' condition, the prevalence of infection in control group, and the contribution of each study. The evidence presented supports the authors' conclusions.

Implications of the review for practice and research

Practice: The authors state that high-dose fluconazole prophylaxis (400 mg/day) should be provided for bone marrow transplant recipients, and that prophylactic fluconazole seems to be effective when the incidence of systemic fungal infection is expected to exceed 15%. They further state that prophylactic fluconazole clearly decreases superficial fungal infections and that it may improve the quality of life for patients during neutropenia. For this purpose, lower doses of fluconazole (50 to 200 mg/day) may be effective. Colonisation by C. krusei and T. glabrata should be carefully followed during fluconazole prophylaxis.
Research: The authors state that further studies on severely neutropenic non-bone marrow transplant patients are required.

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