Fluconazole vs. amphotericin B for the management of candidaemia in adults: a meta-analysis
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Authors' objectives
To answer two questions.

1. In candidaemic adult patients, does therapy with fluconazole differ from amphotericin B in terms of total mortality, infection-specific mortality, response, late complications, and toxicity?

2. How do the two drugs compare in the treatment of candidaemia caused by various non-albicans Candida species?

Searching
MEDLINE was searched from January 1966 to May 1999 using the MeSH terms 'candidaemia', 'candidiasis', 'fluconazole', 'amphotericin B', 'antifungal therapy' and 'prospective studies'. The search was restricted to studies published in the English language. References, review articles and abstracts from international conferences were manually searched. In addition, an expert in candidal infections was contacted to ensure that all studies of relevance to the review, published or otherwise, were identified.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled studies, prospective observational studies and matched-paired cohort studies with more than 5 patients were eligible for inclusion. To be eligible for inclusion, the studies had to clearly describe their design, the severity of the underlying illness, the degree of immune suppression of the affected patients, portal of entry of candidaemia, and causative Candida species. Studies comparing fluconazole and amphotericin B for the treatment of antibiotic-refractory neutropenic fever were excluded.

Specific interventions included in the review
Studies comparing fluconazole with amphotericin B were eligible for inclusion. Studies comparing fluconazole with the combination of amphotericin B and 5-fluorocytosine, and studies of episodes of candidaemia that received sequential therapy with two agents (e.g. fluconazole prophylaxis of therapy followed by amphotericin B or vice versa), were excluded.

The median dose of amphotericin B ranged from 0.5 to 0.6 mg/kg per day, and the median duration of treatment ranged from 9 to 25 days. The mean dose of fluconazole ranged from 200 to 466 mg/day, and the median duration of treatment ranged from 9 to 21 days.

Participants included in the review
Adults with candidaemia. The proportion of patients with Candida albicans in the included studies ranged from 51 to 70%.

Outcomes assessed in the review
Six outcome measures were defined: efficacy, total mortality, candidaemia-attributable mortality, toxicity, and microbiological failure according to all Candida species and to non-albicans Candida species for each drug. Each study's own predefined criteria for diagnosis of candidaemia, response or failure, Candida-attributable mortality, relapse or superinfection, and toxicity were used.

How were decisions on the relevance of primary studies made?
Two of the authors reviewed each study independently. Although there were no disagreements between the two reviewers, if there had been, these would have been resolved by discussion or consensus with the other collaborator.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two of the authors reviewed each study independently. Although there were no disagreements between the two reviewers, if there had been, these would have been resolved by discussion or consensus with the other collaborator.

The data extracted included: study period; study setting; study design; the dose and duration of treatment with amphotericin B; the dose and duration of treatment with fluconazole; intravenous catheter management; severity of illness at the onset of candidaemia; the degree of immune suppression; Candida species; portal of entry; the type of Candida infection; the numbers of evaluable and enrolled patients; and the length of follow-up. When data were available for both mycological and clinical responses, only the clinical data were used.

Methods of synthesis
How were the studies combined?
The results of the meta-analysis were presented as odds ratios (ORs). The corresponding 95% confidence intervals (CIs) were also determined. The ORs of all six outcome measures were combined to obtain summary estimates of the log(OR). The 95% CI of the OR was also estimated for each of the above parameters.

Two separate analyses were performed for each outcome: one for randomised studies (primary analysis) and the other for all selected studies (secondary analysis). The authors reported the statistical results for evaluable patients only.

How were differences between studies investigated?
Potential heterogeneity among the different studies was evaluated using two approaches: (1) the with- and between-studies variations were calculated and the Q statistics were computed (see Other Publications of Related Interest no.1); and (2) heterogeneity was evaluated by comparing the results of the fixed-effect and random-effects (DerSimonian and Laird) models (see Other Publications of Related Interest nos.1-2).

Results of the review
Six studies were eligible for inclusion (862 evaluable patients). Three studies were open randomised controlled trials (RCTs), two were prospective non-randomised studies, and one was a matched-paired cohort study.

The ORs for total mortality of treatment with amphotericin B versus fluconazole were 1.06 (95% CI: 0.89, 1.20) and 1.08 (95% CI: 0.94, 1.24) based on data from the 3 RCTs and all 6 studies, respectively.

The ORs for candida-specific mortality were 1.00 (95% CI: 0.70, 1.45) and 0.90 (95% CI: 0.66, 1.96) for the 3 RCTs and all studies, respectively.

The ORs for clinical response were 1.14 (95% CI: 0.93, 1.39) and 1.09 (95% CI: 0.91, 1.31) for the 3 RCTs and all studies, respectively.

The ORs for microbiological failure were 0.99 (95% CI: 0.78, 1.26) and 1.03 (95% CI: 0.86, 1.23) for the 3 RCTs and all studies, respectively.

No statistically-significant difference in mycological eradication was found according to whether the Candida species was ‘any species’ or ‘non-albicans Candida’ in either the primary or secondary analysis. However, the authors reported that a trend favouring amphotericin B was seen in the mycological eradication of non-albicans Candida species (random-effects OR 0.71, 95% CI: 0.46, 1.07).

With regard to toxicity, the pooled estimate showed that compared with amphotericin B, fluconazole therapy resulted in reduced drug-related toxicity (random-effects OR 2.95, 95% CI: 2.24, 3.89) based on data from all 6 studies. Renal toxicity was significantly more likely to occur in the amphotericin B group than the fluconazole group (random-effects OR 3.20, 95% CI: 1.61, 5.01).
Both methods used to evaluate heterogeneity revealed that the studies were homogeneous with respect to all outcomes measures examined, with the exception of microbiological failure due to non-albicans Candida species and renal toxicity.

**Authors' conclusions**
Fluconazole was as efficacious as amphotericin B, but less toxic, in stable, non-severe immunosuppressed candidaemia patients at low risk for death. However, fluconazole may be less effective than amphotericin B in candidaemias caused by some non-albicans Candida species.

**CRD commentary**
The authors posed a clear question for the review but the inclusion and exclusion criteria could have been reported in more detail. The literature search was inadequate; by limiting the search to English language studies and searching only one database, it makes it highly likely that important studies were missed. The authors did not assess the validity of the included studies. Details of the studies were reported adequately, and the studies were pooled appropriately. However, the authors chose to report data from the evaluable-patient analysis rather than the intention to treat data for their primary analysis. The authors statistically assessed heterogeneity, although further discussion regarding differences between the included studies was warranted but not undertaken. Generally, the authors' conclusions follow on from the data presented, but should be interpreted with caution due to the methodological problems outlined.

**Implications of the review for practice and research**
Practice: The authors state that fluconazole at a dose of 400 mg/day is a safe and less toxic alternative to amphotericin B in stable non-neutropenic candidaemic patients.

Research: The authors state that large studies that include sufficient candidaemic patients at high risk of death, such as patients with neutropenia or acute disseminated candidiasis, are needed. These are in addition to large studies addressing, in a randomised fashion, the role of catheter exchange and the optimal therapy of candidaemias caused by various non-albicans Candida species.

**Bibliographic details**

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**Other publications of related interest**

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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.