Treatment of invasive candidal infections: systematic review and meta-analysis
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CRD summary
The review concluded that fluconazole was microbiologically inferior to amphotericin B and anidulafungin, but that amphotericin B was associated with a higher rate of adverse events when compared with fluconazole and echinocandins in patients with invasive candidiasis. The review was generally well conducted, but the reliability of the conclusions was unclear.

Authors' objectives
To compare the efficacy and safety of antifungal treatments for invasive candidiasis (IC).

Searching
The Cochrane Cancer Network Register of Trials (in 2007), the Cochrane Central Register of Controlled Trials (in 2007), EMBASE (1980 to 2007), PubMed (1966 to 2007) and conference proceedings (2005 to 2007) were searched without language restriction; search terms were reported. Retrieved articles were also cross checked for relevant studies.

Study selection
Studies were eligible if they were randomised controlled trials (RCTs) that compared different types of antifungal treatments for confirmed invasive candidiasis. Invasive candidiasis was defined as one or more positive results on blood culture for Candida species or culture from a normally sterile site during the previous three to four days and clinical sign of infection. Trials were excluded if they addressed treatment of either oesophageal, oropharyngeal, chronic disseminated candidiasis or neutropenia associated with prolonged fever despite antibacterial therapy. Trials that compared different doses of the same drug and trials assessing an investigational biological agent were also excluded. The primary outcome was all cause mortality. Secondary outcomes included treatment failure, microbiological failure and adverse events.

In the included studies, the antifungal treatments included fluconazole, amphotericin B, itraconazole, amphotericin B plus fluconazole, echinocandins (anidulafungin, caspofungin, micafungin) and voriconazole. All patients were hospitalised and in six studies they were in an intensive care unit. Most participants were adults with mean or median age ranging from 53 to 65 years, although some studies were of newborns or young children. Duration of treatment ranged from one to 89 days. Mean or median Acute Physiology and Chronic Health Evaluation (APACHE) score ranged from 8 to 20. Most participants had candidemia. Other conditions included pneumonia and other organ infections. Many participants had comorbidities. All cause mortality was assessed at different time points ranging from 28 to 98 days, during therapy or at the end of therapy. Definitions for microbiological and treatment failure also differed between the trials.

Two reviewers independently performed selection of trials. Disagreement was resolved by close inspection of the full publication and discussion.

Assessment of study quality
Methodological quality in the included studies was assessed by grading allocation concealment, generation of allocation sequence and blinding as either adequate, unclear or inadequate according to definitions specified in the Cochrane Handbook for Systematic Reviews of Interventions.

Two reviewers independently performed the validity assessment, but it was not stated how disagreement was resolved.

Data extraction
Data were extracted on outcomes for three subgroups of patients: those with candidemia; those with Candida albicans; and those with other Candida species. Trial authors were contacted for further information when necessary.
Two reviewers independently extracted data. Where there was disagreement, a third reviewer also extracted data.

**Methods of synthesis**

Pooled relative risks (RR) with 95% confidence intervals (CIs) were calculated using a Mantel-Haenszel fixed-effects meta-analysis. Results were presented as two main comparisons: fluconazole versus any other fungal agent stratified according to type; and echinocandins stratified by type versus any other antifungal agent stratified by type. Intention to treat analysis was performed, where possible. Statistical heterogeneity was assessed by calculating a $\chi^2$ test statistic and the $I^2$. Where statistically significant heterogeneity was found, a random-effects model was used. Clinical heterogeneity was investigated by subgroup analyses according to type of Candida infection. Sensitivity analysis was performed by comparing results of all trials with trials that had adequate allocation concealment for mortality.

**Results of the review**

Fifteen RCTs (n=3,265) were included.

Seven studies had adequate generation of allocation. Nine studies had adequate allocation concealment. Eight studies had unclear generation of allocation. Six studies had unclear allocation concealment. Six studies had no blinding. One study had blinding (unspecified). Eight studies had double blinding.

**Efficacy**

**Fluconazole versus other fungal agent**

There was no evidence of a significant difference between groups in all-cause mortality (seven trials) or treatment failure (eight trials), but there were significantly higher microbiological failure rates with fluconazole compared to amphotericin B (six trials, RR 1.52, 95% CI 1.12, 2.07) and combined amphotericin B plus fluconazole (one trial, RR 2.69, 95% CI 1.17, 6.18).

When subgroup analysis was undertaken, there was no evidence of a significant difference in any of the efficacy outcomes assessed, except that patients with candidemia taking fluconazole had significantly higher rates of treatment failure (two trials) (RR 1.42, 95% CI 0.96, 2.09) than those taking amphotericin B.

**Echinocandins versus any other fungal agent**

There was no evidence of a significant difference between groups in all-cause mortality for any comparison (four trials). Treatment failure and microbiological failure decreased significantly with anidulafungin versus fluconazole (one trial) (treatment failure RR 0.61, 95% CI 0.42, 0.89 and microbiological failure RR 0.5, 95% CI 0.29, 0.86).

There was no evidence of a significant difference in treatment and microbiological failure between caspofungin versus amphotericin B or micafungin versus liposomal amphotericin B (one or two trials). Subgroup analysis confirmed a lower microbiological failure rate for patients with Candida albicans who took anidulafungin versus fluconazole (one trial), but there was no evidence of significant differences in any of the other subgroup comparisons.

There was no evidence of a significant difference in the outcomes between micafungin versus caspofungin or amphotericin B plus fluconazole versus voriconazole (one trial in the comparisons).

**Safety**

There was no evidence of a difference in the rates of adverse events requiring discontinuation between fluconazole versus other agents (four trials), but fluconazole caused less nephrotoxicity than amphotericin B or combined amphotericin B plus fluconazole (five trials) (RR 0.11, 95% CI 0.03, 0.48; RR 0.12, 95% CI 0.04, 0.39).

All echinocandins had significantly lower rates of adverse events requiring discontinuation when compared with other agents (anidulafungin versus fluconazole RR 0.52, 95% CI 0.29, 0.92, one trial; caspofungin versus amphotericin B: RR 0.11, 95% CI 0.04, 0.36, one trial; micafungin versus liposomal amphotericin B: RR 0.45, 95% CI 0.26, 0.80, two trials).

No evidence of differences in adverse events requiring discontinuation was found when micafungin was compared with...
caspofungin (one trial).

Adverse events requiring discontinuation were significantly lower (RR 0.47, 95% CI 0.23, 0.93, one trial) and nephrotoxicity was significantly higher (RR 2.64, 95% CI 1.57, 4.44, one trial) for combined amphotericin B plus fluconazole when compared with voriconazole.

Authors' conclusions
The antifungal agents assessed had similar efficacy, but the rate of microbiological failure increased with fluconazole when compared with amphotericin B or anidulafungin. Amphotericin B was associated with a higher rate of adverse events than fluconazole or echinocandins.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. The authors searched five relevant databases without language restriction. Attempts were made to identify unpublished data. Methods were used to minimise bias and reviewer error in the selection of studies, extraction of data and quality assessment. Approximately half of the included studies had adequate generation of allocation and/or allocation concealment and/or were blinded.

Multiple comparisons were made between different types of antifungal agent, so the power of the analyses may be limited. Only one or two trials contributed data to the comparisons (except for the comparison of fluconazole with amphotericin B). Subgroup analyses were undertaken for three types of patients, but not of other high-risk groups such as patients with a high APACHE score or neutropenia or rarer types of invasive candidiasis.

The authors’ conclusions reflected the evidence presented, although the reliability of the conclusions was unclear and lack of power may have limited the ability to find real differences between types of antifungal agent.

Implications of the review for practice and research
Practice: The authors stated that echinocandins and liposomal amphotericin B should be considered as first-line treatment, but where cost and availability are barriers, combined amphotericin B plus fluconazole was an effective alternative.

Research: The authors stated that further trials comparing echinocandins and polyenes were needed. Further trials should define a uniform time for the assessment of mortality, effects of treatment should be assessed in specific subgroups of patients and rare forms of invasive candidiasis should be assessed.

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