Efficacy and safety of micafungin for invasive candida infections: a meta-analysis of randomized controlled trials

Chen Q, Lin MH, Chen ML, Liu ZY, Chai D, Wang R

CRD summary
This review found that micafungin may offer a better safety and tolerability profile than several other antifungal agents in the prevention and treatment of invasive candida infections. The authors' conclusions were based on the evidence presented and are likely to be reliable.

Authors' objectives
To determine the efficacy and safety of micafungin compared to other antifungal agents for treating infections associated with invasive candidiasis.

Searching
PubMed, EMBASE, CAJ and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2011 for relevant published studies in English or Chinese; one search term was reported. References from relevant articles and reviews were checked for additional references.

Study selection
Randomised controlled trials (RCTs) that evaluated micafungin compared to other antifungal agents for treatment of invasive candida infections were eligible for inclusion. Trials needed to report data on effectiveness, toxicity or mortality.

The included patients in the trials presented with invasive candidiasis (including oesophageal candidiasis and candidaemia). Some of the included patients had HIV or were adult and paediatric patients undergoing haematopoietic stem cell transplantation. Micafungin doses ranged from 50mg/day to 150mg/day. The comparators were fluconazole (200 to 400mg/day or 8mg/kg for patients who weighed less than 50kg), caspofungin (70mg followed by 50mg daily) and liposomal amphotericin B (3mg/kg/day).

Overall therapeutic efficacy was defined as overall treatment success including clinical (complete or partial resolution of symptoms) and mycological response (eradication or presumed eradication of the infection) at the end of intravenous therapy. For the analysis of prophylaxis, treatment success was the absence of proven, probable or suspected systemic fungal infection at the end of prophylactic administration of the antifungal medication and at the end of the four-week post-treatment period. Median duration of treatment ranged from 14 days to 19.2 days across the trials.

Two reviewers performed the study selection.

Assessment of study quality
Two reviewers independently assessed methodological quality using a five-point modified Jadad scale of randomisation, generation of randomisation sequence, double-blinding, information on withdrawals and allocation concealment. One point was awarded for fulfilling each criterion. Trials that scored 3 or more were judged to be high quality trials; RCTs that scored 2 or less were judged to be low quality trials.

Data extraction
Data were extracted using a modified intention-to-treat approach to calculate odds ratios (OR) and 95% confidence intervals for clinical and safety outcomes.

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

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using the Mantel-Haenszel fixed-effect model and the DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using the X² test. Where there was no
heterogeneity between the included trials for any outcome the results from the fixed-effect model were presented; where there was significant statistical heterogeneity the results from the random-effect model were presented.

**Results of the review**

Seven RCTs (2,946 patients, range 106 to 889) were included in the review. Six studies received a quality score of 4 points; one trial was allocated a score of 3 points.

Statistically significant treatment effects were observed with micafungin compared to other antifungal agents (OR 1.20, 95% CI 1.00 to 1.44; I²=0%; 2,851 patients) and for antifungal prophylaxis of patients who underwent haematopoietic stem cell transplantation (OR 1.47, 95% CI 1.08 to 2.00; I²=0%; 982 patients). No significant differences were observed for comparisons of micafungin with liposomal amphotericin B (592 patients; I²=0%) or when micafungin was used for treatment of invasive fungal infections (I²=0%; 1,870 patients). A marginal result was observed for micafungin with fluconazole (OR 1.27, 95% CI 0.99 to 1.64; I²=0%; 1,682 patients).

There were no significant differences between micafungin and comparator antifungal medications in overall adverse drug reactions (OR 0.94, 95% CI 0.77 to 1.11; I²=23%; 2,732 patients). Significantly fewer patients treated with micafungin withdrew due to adverse events than patients treated with other antifungal treatments (OR 0.64, 95% CI 0.44 to 0.94; I²=10%; 2,732 patients).

Visual appraisal of funnel plots revealed no evidence of publication bias.

**Authors' conclusions**

Micafungin may offer a better safety and tolerability profile than several other antifungal agents in the prevention and treatment of invasive candida infections and was an emerging option for treatment of seriously ill or critical patients.

**CRD commentary**

The review addressed a clearly defined question. Criteria for inclusion of studies were stipulated and reproducible. Appropriate databases were searched for relevant studies. Although the review was restricted to published studies, the authors evaluated potential for publication bias using validated methods. The authors took steps to minimise reviewer error and bias for study selection and assessment of methodological quality; no such steps were reported for data extraction. Methodological quality of the included trials was assessed and the trials were found to be of good quality.

All the included trials were supported by the manufacturer of micafungin, which the authors acknowledged may have generated bias in outcome assessment. The authors’ decision to combine the results in a meta-analysis appeared justified, particularly as little statistical heterogeneity was observed across the trials for each result. Limitations of the review from differences in outcome definition and times of outcome assessment were acknowledged in the discussion.

The authors’ conclusions were based on the evidence presented and are likely to be reliable.

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

**Practice:** The authors stated that micafungin was an emerging option for treatment of seriously ill or critical patients. In particular, micafungin appeared to have some advantages for antifungal prophylaxis and this may be a more appropriate use of micafungin than treatment for invasive candida infections.

**Research:** The authors did not state any implications for research.

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