Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection

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CRD summary
This review concluded that fluconazole and echinocandins were generally associated with lower risks of treatment termination and adverse liver events. Itraconazole and voriconazole was associated with a higher risk of liver injury. Limitations in the analysis mean that these conclusions are unlikely to be reliable.

Authors' objectives
To evaluate the tolerability and liver safety profiles of systemic antifungal agents commonly used for the treatment of invasive fungal infections.

Searching
MEDLINE, EMBASE, The Cochrane Library and ClinicalTrials.gov were searched to August 2009 for studies published in English. Search terms were reported. Reference lists of relevant review articles were screened.

Study selection
Randomised controlled trials (RCTs) that assessed empirical, pre-emptive or definitive standard antifungal therapy mostly in adults with suspected or documented invasive fungal (Aspergillus, Candida) infections or persistent febrile neutropenia were eligible for inclusion. Studies conducted exclusively in children, asymptomatic patients and patients with superficial or mucocutaneous fungal infections were excluded. Studies of infusion-related or renal toxicity and studies of combination antifungal treatments were excluded. Data from non-randomised studies, cohort studies and case series were included in an auxiliary analysis.

The primary outcome was incidence of patients who withdrew due to adverse reactions. Secondary outcomes were cumulative incidence of patients who stopped treatment due to abnormal liver function tests and the cumulative incidence of patients who developed abnormal liver function tests during treatment but not require discontinuation. Studies had to report data on one such outcome to be included in the review. Thresholds for abnormal liver function were based on values reported in the primary studies.

Included studies were head-to-head comparisons of various antifungal agents or different doses of the same agent. The most commonly assessed antifungal agent was amphotericin B. Other agents included itraconazole, fluconazole, voriconazole, anidulafungin, caspofungin and micafungin. Mean age ranged from 18 to 61 years. The proportion of patients with neutropenia ranged from zero to 100%. The proportion of patients with leukaemia ranged from zero to 100%. The proportion of transplant patients ranged from zero to 69%.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed allocation concealment, sequence generation, blinding of patients and investigators and availability of data on an intention-to-treat basis.

Data extraction
Two reviewers independently extracted data on the proportion of patients with each outcome of interest in each treatment arm. No measures of effect that compared results between trial treatment groups were calculated. Disagreements were resolved through discussion.

Methods of synthesis
Summary cumulative incidence rates and 95% confidence intervals (CIs) were estimated using the maximum likelihood method and beta-binomial method and used to account for heterogeneity. Data were pooled for each treatment arm.
stratified according to treatment indication (empirical versus definitive and yeast versus mould infection). In situations where few adverse events occurred, there were only one or two studies of the treatment regimen or that had no significant heterogeneity, the beta-binomial distribution was collapsed to a simple binomial distribution and Wald CIs were calculated. For risks corresponding to no events, the adjusted Wald method was used to calculate point estimates and 95% CIs. For rare outcomes, the lower bounds of the 95% CI were set to be no smaller than zero. When the beta-binomial model was used, the likelihood ratio test and Tarone's Z-test were used to assess heterogeneity.

**Results of the review**

Thirty-nine RCTs (number of patients reported as 8,745, range 28 to 1,111) were included. Thirteen studies were double blinded, 13 had adequate concealment of treatment allocation, 12 had adequate allocation generation and 31 were analysed on an intention-to-treat basis.

Treatment discontinuation due to adverse events was most common for itraconazole (18.8%, 95% CI 14.3% to 23.2%; three treatment arms) and Amphotericin B formulations (13.4%, 95% CI 8.9% to 17.8%; 41 treatment arms). Rates were less than 10% for all other agents and were lowest for fluconazole (2.2%, 95% CI 0 to 4.6%; 10 treatment arms).

The proportion of patients who discontinued treatment due to elevated liver enzyme tests was highest for micafungin (2.7%, 95% CI 0.7% to 4.6%; three treatment arms) and itraconazole (1.5%, 95% CI 0 to 4%; three treatment arms). Summary rates were less than 1% in all other studies.

The proportion of patients with elevated liver enzyme levels that did not require stopping treatment was highest for voriconazole (19.7%, 95% CI 16.8% to 22.6%), itraconazole (17.4%, 95% CI 3.9% to 31%; three treatment arms) and amphotericin B formulations (14.1%, 95% CI 10.3% to 18%). Values were less than 10% for all other agents.

An auxiliary analysis was conducted for an additional 37 non-randomised studies (n=3,191). The order of the safety profiles of the different antifungal agents was generally the same as for the RCTs.

**Authors’ conclusions**

Fluconazole and echinocandins were generally associated with lower risk of treatment termination and adverse liver events. Use of itraconazole and voriconazole was associated with a higher risk of liver injury.

**CRD commentary**

The review addressed a clear question and inclusion criteria were defined. The search was adequate for published studies. The restriction to studies published in English risked language and publication biases. Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was assessed using appropriate criteria for RCTs. However, randomisation was broken in the analysis and so other potential sources of bias that were not addressed in this assessment (such as controlling for confounding factors) may have been more relevant to consider. The loss of randomisation limited the validity of the analysis and the conclusions that could be drawn from this review. Each treatment arm was in effect analysed as a single case series. Any differences in summary estimates across the different antifungal agents may have been the result of confounding rather than true differences between agents. A more informative analysis would have compared the different agents within the RCTs. A network meta-analysis would have been particularly informative in this review.

Limitations in the analysis make the authors’ conclusions are to be reliable.

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

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

**Practice:** The authors stated that users of itraconazole and voriconazole, especially those at high risk for hepatic dysfunction, needed to be monitored closely during antifungal therapy.

**Funding**

National Institutes of Health; Harvard Pharmacoepidemiology Program.
Bibliographic details

PubMedID
20308378

DOI
10.1128/AAC.01657-09

Original Paper URL
http://aac.asm.org/cgi/content/abstract/54/6/2409

Indexing Status
Subject indexing assigned by NLM

MeSH
Amphotericin B /adverse effects /therapeutic use; Antifungal Agents /adverse effects /therapeutic use; Clinical Trials as Topic; Humans; Liver /drug effects /injuries; Mycoses /drug therapy; Risk Factors

AccessionNumber
12010004373

Date bibliographic record published
10/11/2010

Date abstract record published
20/07/2011

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.