Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis

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CRD summary
This review concluded that antifungal prophylaxis significantly reduced all-cause mortality in patients at high risk for fungal infections. Antifungal prophylaxis should be used for patients undergoing allogeneic HSCT and possibly with high-risk acute leukaemia patients. This was a generally well-conducted review, but certain considerations – in particular wide confidence intervals – should be taken into account when interpreting the authors' conclusions.

Authors' objectives
To assess the effects of antifungal prophylaxis compared with placebo, no treatment or other antifungal agents on all-cause mortality, invasive fungal infections (IFIs) and adverse events in patients with cancer, following chemotherapy.

Searching
PubMed and Cochrane Central Register of Controlled Trials were searched up to 2007. Search terms were reported. Conference proceedings in oncology, haematology and infectious diseases, and references of included studies and relevant reviews were also searched.

Study selection
Randomised controlled trials (RCTs) comparing a systemic antifungal agent with either placebo, no treatment or another antifungal agent for the prevention of fungal infections in afebrile patients with cancer after chemotherapy or haematopoietic stem-cell transplantation (HSCT) were eligible for inclusion. The primary outcome was all-cause mortality at the end of follow-up (as defined in each study) and 30-day mortality at the end of treatment. Secondary outcomes included IFIs, fungal-related death and use of empiric antifungal therapy (as defined in the review).

The majority of studies were of adults, were inpatients and had acute leukaemia. Treatment doses and durations, and follow-up periods varied between studies. Systemic antifungal agents included fluconazole, itraconazole, ketoconazole, voriconazole and liposomal amphotericin.

Two reviewers independently screened references for inclusion. Where there were disagreements between reviewers, full articles were inspected independently.

Assessment of study quality
Two reviewers independently assessed methodological quality, including criteria on allocation generation and concealment (graded as adequate, unclear or inadequate), and blinding. Exclusions after randomisation and method of analysis – intention-to-treat (ITT) or per protocol (PP) – were also assessed.

Data extraction
Two reviewers independently extracted rates of all-cause mortality, ultimately to calculate relative risk (RRs) with 95% confidence intervals (CIs). Where data were missing, study authors were contacted. Disagreements were resolved by consensus.

Methods of synthesis
A fixed-effect model was used to pool RRs. Where there was significant statistical heterogeneity in studies a random-effects model was used. Heterogeneity was assessed using the $X^2$ and $I^2$ tests. Heterogeneity was investigated using subgroup analyses by patient group: those with haematological malignancies; those who underwent bone marrow transplant; and patients with other malignancies. Meta-regression was conducted to assess the effects of various factors on outcomes including age, neutropenia duration, percentage of patients with acute leukaemia and study year. Sensitivity analyses were conducted to assess the effect of methodological quality. Publication bias was assessed using
funnel plots and the Begg test.

**Results of the review**

Sixty four RCTs (n=13,015; 6,517 receiving treatment and 6,498 controls) were included in the review. Allocation generation and concealment was adequately reported in 16 studies. Twenty six studies were double blind.

**Systemic antifungals versus placebo/no treatment/non systemic antifungals**

All-cause mortality was reported in 31 studies. Mortality at the end of follow-up and 30-day mortality were significantly reduced when patients were treated with systemic antifungals: RR 0.84 (95% CI: 0.74, 0.95, p=0.007) at the end of follow-up and RR 0.79 (95% CI: 0.68, 0.92) for 30-day mortality. Subgroup analyses reported different outcomes. The authors reported that meta-regression showed only one significant association, which was between the percentage of patients with acute leukaemia (with or without HSCT) and RR for mortality at the end of follow-up (RR 1.006, p=0.29). Thirty three studies reported significant differences between fungal-related mortality, favouring systemic antifungals: RR 0.55 (95% CI: 0.41, 0.74, p<0.0001).

There was no evidence of heterogeneity or publication bias. Secondary outcomes were reported.

**Comparison of two systemic antifungal agents (19 studies)**

Seven studies comparing fluconazole with itraconazole reported significant increases in adverse events with itraconazole, resulting in the study being discontinued: RR 2.50 (95% CI: 1.89, 3.33). No other significant differences were reported. Subgroup analyses and indirect comparison of drugs versus placebo or no treatment, or two systemic antifungals were also reported.

Significant reductions in IFIs were reported with fluconazole versus amphotericin B (three studies): RR 0.49 (95% CI: 0.28, 0.86). More adverse events were reported in amphotericin B: RR 6.67 (95% CI: 2.6, 16.7).

Two studies compared posaconazole with fluconazole or itraconazole, reporting: borderline significant reductions in all-cause mortality (RR 0.77; 95% CI: 0.59, 1.01); a significant reduction in fungal-related mortality (RR 0.25; 95% CI: 0.11, 0.57); documented or probable IFIs (RR 0.47; 95% CI: 0.3, 0.74); and documented invasive Aspergillus infections (RR 0.22; 95% CI: 0.11, 0.42).

Outcomes for fluconazole versus antifungals with antimould activity and other trials were also reported in the review.

**Authors' conclusions**

Antifungal prophylaxis significantly reduced all-cause mortality in patients at high risk for fungal infections, and should be used in patients undergoing allogeneic HSCT. Prophylaxis should probably be administered to patients with acute leukaemia during induction chemotherapy and to other high-risk leukaemia patients. However, there was insufficient evidence to allow conclusions to be drawn regarding the use of antifungal prevention in patients with solid tumours and autologous HSCT.

**CRD commentary**

The review question and supporting inclusion criteria were clear. A reasonable search of the literature was undertaken and attempts were made to minimise the potential for language and publication bias. Validity was assessed and attempts were made at each stage of the process to minimise reviewer error and bias. Appropriate methods were used to synthesise the data and investigate heterogeneity. However, the majority of individual studies appeared to have wide confidence intervals and a ratio greater than one, which reduced the reliability of the results. This was a generally well-conducted review. The evidence appeared to support the authors' conclusions, but the considerations above should be taken into account when interpreting the conclusions.

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

Practice: the authors stated that consideration needed to be given to the pros and cons of using the different antifungal agents, including local factors such as local epidemiology of fungal infection, availability of diagnostic tools and their performance in the early diagnosis of fungal infections, and the local expertise in carrying out each strategy.
Research: the authors stated that further well-designed studies using risk-stratification protocols were required to further assess the use of antifungal prophylaxis in patients with acute leukaemia and patients undergoing autologous HSCT. Further studies were also needed to investigate the combination of fluconazole prophylaxis and pre-emptive therapy versus prophylaxis with antimould active agents. Observational studies were warranted to monitor the epidemiology of fungal infections in places where antifungal prophylaxis was implemented.

**Funding**
Young Investigator Research Grant of the Rabin Medical Centre.

**Bibliographic details**

**PubMedID**
17909198

**DOI**
10.1200/JCO.2007.12.3851

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Antifungal Agents /therapeutic use; Child; Hematopoietic Stem Cell Transplantation; Humans; Mycoses /etiology /prevention & control; Neoplasms /drug therapy /microbiology /therapy; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**
12008009045

**Date bibliographic record published**
03/11/2008

**Date abstract record published**
31/03/2009

**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.