# Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patients receiving chemotherapy or haematopoietic stem-cell transplantation: a systematic review and meta-analysis of randomised controlled trials

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## CRD summary

Compared with fluconazole prophylaxis, mould-active prophylaxis significantly reduced the number of proven or probable invasive fungal infection, invasive aspergillosis and invasive fungal infection-related mortality in patients who received chemotherapy or haematopoietic stem cell transplantation. Despite limitations in study quality and uncertainty about heterogeneity for the secondary outcomes, the conclusions reflected the evidence and are probably reliable.

## Authors' objectives

To compare mould-active versus fluconazole prophylaxis in cancer patients who receive chemotherapy or haematopoietic stem cell transplantation.

## Searching

MEDLINE and EMBASE (up to August 2011) and Cochrane Central Register of Controlled Trials (CENTRAL) (third quarter of 2011) were searched for eligible studies. Reference lists of relevant articles and ClinicalTrials.gov were searched. Conference abstracts from 2005 to 2011 were searched. The full search strategy was reported.

## Study selection

Randomised controlled trials (RCTs) that compared mould-active with fluconazole prophylaxis in patients who received cancer chemotherapy or underwent haematopoietic stem cell transplantation were eligible for inclusion. Mould-active agents were included if administered systemically.

Primary outcome was proven/probable invasive fungal infections. Secondary outcomes were: incidence of invasive aspergillosis (culture-proven or diagnosed by microscopic examination); number of invasive fungal infections or invasive aspergillosis-related deaths; all-cause mortality; and adverse events that required discontinuation or modification of antifungal prophylaxis. Mortality was measured at three months.

Studies of pre-emptive or empiric therapy or anti-fungal treatment and studies in which more than one systemic prophylactic anti-fungal drug was given within a study arm were excluded.

Mean age ranged from 0.6 to 82 years. Most studies focused on stem cell transplantation patients; several studies included patients who underwent chemotherapy alone or mixed with stem cell transplantation patients. Children were included in a fifth of the trials; one trial included only children. Antibiotic prophylaxis was recommended in 40% of studies. Study regimens varied and included itraconazole (half of the studies) as well as amphotericin B formulations, micafungin, posaconazole or voriconazole. All studies that evaluated echinocandins used micafungin. Fungal prophylaxis was generally started at the beginning of chemotherapy.

Abstracts and titles were screened by two reviewers. Full texts of potentially eligible articles were screened by two reviewers independently. Disagreements were resolved through consensus or with a third reviewer.

## Assessment of study quality

Study quality was assessed based on the Cochrane risk of bias tool for generation of sequence allocation, allocation concealment, blinding, incomplete outcome data and intention-to-treat analysis.

Two reviewers performed the quality assessment.

## Data extraction

Data on primary and secondary outcomes were extracted to calculate risk ratios (RRs). Where needed and where sufficient data were available, invasive fungal infection data were reclassified using revised standard criteria. Study

authors were contacted as needed.

Two reviewers independently extracted the data. Disagreements were resolved through consensus or with a third reviewer.

### Methods of synthesis
Studies were pooled using a Mantel-Haenszel random-effects meta-analysis. Heterogeneity was assessed using $I^2$ and forest plot inspection. Analyses were performed on an intention-to-treat basis. Prespecified subgroup analyses and meta-regressions were performed to assess the effects of age (children versus adults), study population (stem cell transplantation versus chemotherapy), drug used in the comparison group, dose of fluconazole and study design items (blinding and ITT analysis). Sensitivity analyses were performed. Funnel plots were used to assess publication bias.

### Results of the review
Twenty RCTs (5,725 patients) were included in the review. Most studies did not report adequate information on sequence allocation and allocation concealment. Only four out of 20 studies were blinded and six out of 20 (30%) conducted an intention-to-treat analysis. Half of the studies were conducted in multiple centres.

Compared with fluconazole, mould-active prophylaxis significantly reduced the number of proven/probable invasive fungal infections (RR 0.71, 95% CI 0.52 to 0.98; 18 trials). There was evidence of some heterogeneity ($I^2$=33%). Risk of invasive aspergillosis was lower in the mould-active group (RR 0.53, 95% CI 0.37 to 0.75; 15 trials) as was risk of invasive fungal infection-related mortality (RR 0.67, 95% CI 0.47 to 0.96; 15 trials).

There was a significantly increased risk of adverse events leading to antifungal discontinuation in the mould-active group (RR 1.95, 95% CI 1.24 to 3.07; 16 trials). There was no statistically significant difference in aspergillosis-related mortality and no evidence of any difference in overall mortality between the groups.

Results of subgroup analyses, meta-regression and sensitivity analyses were reported. There was no evidence of publication bias.

### Authors' conclusions
Compared with fluconazole prophylaxis, mould-active prophylaxis significantly reduced the number of proven or probable invasive fungal infection, invasive aspergillosis and invasive fungal infection-related mortality in patients who received chemotherapy or haematopoietic stem cell transplantation. It also increased the risk of adverse events leading to antifungal modification or discontinuation. It did not impact on overall mortality.

### CRD commentary
The review question and inclusion criteria were clearly stated. Several bibliographic sources were consulted, including conference abstracts and trials registers. Appropriate attempts were made to minimise the risk of error and bias at the study selection, data extraction and quality assessment stages of the review.

Validity assessment showed several limitations in the quality and reporting of the studies. The methods of synthesis appeared appropriate. Attempts to explore heterogeneity were made. Forest plots and results of test for heterogeneity were reported only for the primary outcome so levels of heterogeneity were unclear for secondary outcomes. Several confidence intervals nearly reached non-significance. The number and size of the trials were relatively significant and sensitivity analyses suggested that the results were robust.

Despite limitations in the quality and reporting of the studies and uncertainty about heterogeneity for the secondary outcomes, the conclusions reflected the evidence and are probably reliable.

### Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: More RCTs should be performed in children to evaluate the effect of mould-active prophylaxis in this population. Future research should focus on better understanding of the benefits and downsides of individual classes of mould-active antifungals through individual patient meta-analysis and RCTs focused on treatments considered less toxic. Patient preferences and costs should be explored further.

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